VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

Veterans Health Affairs
Department of Defense

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VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

Introduction

INTRODUCTION
Diabetes in the Department of Veterans Affairs (VA) and Department of Defense (DoD)

Diabetes is the sixth leading cause of death by disease in the United States. Approximately 17 million Americans - 6.2 percent of the population - have diabetes. (NIDDK, 2002) Much of the cost of diabetes treatment is attributed to long-term complications, such as heart disease, blindness, kidney disease, stroke and even death. With appropriate and timely screening and management, this burden can be reduced significantly (NHLB, 2002). Diabetes-related costs (direct and indirect) totaled nearly 100 billion dollars in 1997 (American Diabetes Association [ADA], 1997 & 1998) and accounted for approximately 14 percent of healthcare expenditures in the United States in 1992 (Rubin et al., 1994).

Diabetes in the United States is common, costly, and complicated, but controllable (National Cholesterol Education Program [NCEP], 1994). The burden of diabetes in the VA is among the highest of any national healthcare system, as evidenced by the following data:

COMMON: The prevalence of diabetes among all veteran clinical users in 2001 was nearly 20 percent. This figure is based upon a combination of at least one outpatient prescription for oral antihyperglycemic medications and/or insulin, at least two outpatient 250.xx ICD-9CM codes, or an inpatient discharge (PTF file) using the VA Healthcare Analysis and Information Group Diabetes registry. During Fiscal Year (FY) 01 there were 764,603 veterans with diabetes out of 3,843,832 unique veteran users, for a 20 percent prevalence; this compares to 639,323 (19 percent prevalence) for FY 00; 503,321 (16 percent prevalence) for FY 99, and 420, 486 patients (14 percent prevalence) in FY 98.

COSTLY: In FY 94, 12 percent of all veterans from participating facilities received diabetes-related prescriptions and therefore, were identified as having diabetes. These patients were responsible for 24 percent of the total Veterans Health Administration (VHA) direct pharmaceutical and supply costs. In FY 98 and FY 00 respectively, using the pharmacy-derived database, patients identified as having diabetes were approximately 12.5 percent (n=348,339) and 18 percent (n=535,016) of the total VHA pharmacy user population. These veterans received 28 percent and 30 percent of all pharmacy prescriptions respectively, which represented 25 percent and 28 percent, respectively, of all pharmacy dollars expended. These expended dollars included all pharmacy costs, not only medications related to diabetes. The mean total pharmacy cost during FY 00 for veterans with diabetes was 79 percent higher than those without diabetes. The total health costs of veterans with diabetes are not known.

COMPLICATED: Diabetes accounts for approximately 40 percent of patients with end-stage renal disease receiving dialysis, over 70 percent of amputations performed at VA hospitals, and 50 percent of cerebrovascular events in the VHA. Approximately two-thirds of veterans have hypertension, over 30 percent have mental health conditions, and

over a quarter have congestive heart failure. A 1994 Optometry Service study indicated that 0.9 percent of veterans with diabetes, sequentially examined in an Optometry Service multi-site field study, had severe visual loss. The annual mortality rate is about 5 percent.

CONTROLLABLE: Despite the high prevalence and even higher direct and indirect economic costs of diabetes, there is now incontrovertible scientific evidence that effective antihyperglycemic, antihypertensive, and hypolipidemic treatments decrease the risk of both microvascular and macrovascular complications of diabetes. As a result of the VA/DoD Guideline and accompanying performance measures that date back to 1997, the VHA has assumed a national leadership role in the quality of care provided to veterans with diabetes (Fleming et al., 2001) and is recognized as a benchmark organization in the treatment of diabetes.

Office of Quality and Performance/External Peer Review Program

In FY 02, the Office of Quality and Performance (OQP), through its External Peer Review Program (EPRP), collected data from a random sample of 23,561 charts of veterans with diabetes. A patient, to be established in the "plan" (not just enrolled as a veteran), must have accessed the VHA for any type of care at least once two years ago and at least once during the previous 12 months.

OQP data analysis showed that the percentage of patients having Diabetes Quality Improvement Project (DQIP) measures documented in their charts, using DQIP abstraction criteria, within 12 months (or as noted) of the chart review is as follows:

HbA_1c test (94%); HbA_1c values less than 9.5% (87%); less than 9% (78%); less than 8.0% (65%); less than 7% (41%); greater than 9.5% (17%)
Lipid profile within 2 years (94%); LDL-C values less than 130 mg/dL (70%); less than 120 mg/dL (64%); less than 100 mg/dL (43%)
Blood pressure control less than 140/90 (58%)
Dilated retinal examination (72%)
Nephropathy screening within 2 years (78%)
Visual examination of feet (92%); palpation of pedal pulses (86%); sensory examination of feet (82%); referral of patients with "high-risk feet" to a foot care specialist (84%)

Since the VHA uses DQIP measures, comparison to the private sector is possible. In FY 01, VHA national adherence to most measures was at the 90th percentile of the individual private sector plans included in the The State of Health Care Report [http://www.ncqa.org/Communications/News/sohc2002.htm] of the National Committee for Quality Assurance (NCQA).

Office of Policy and Planning/VA Healthcare Analysis and Information Group

Based on registry data analysis for patients with A1c performed in VA laboratories, the mean HbA_1c for FY 01 was 7.37 compared with 7.61 in FY 00; and the mean LDL was 104 mg/dL compared with 108 mg/dL in FY 01. In collaboration with the Centers for Disease Control and Prevention (CDCP) Division of Diabetes Translation, a 12 year Lower Extremity Amputation (LEA) Registry was created. From FY 97 to FY 00, the age-adjusted rate (standardized to the VHA 1998 user population) of LEA in the entire veteran population had decreased from 2.18 (0.78 major amputations [e.g., below knee or above knee]) to 1.42 (0.65 major amputations) per 1000 VHA users in FY 00.

On the other hand, the hemoglobin A1c average remains significantly higher among younger individuals and African Americans, and the number of diabetes-related major amputations has not trended downwards. As previously noted, a significant number of veterans would benefit from improvement in blood pressure control, the most important risk factor for both micro and macrovascular disease. Thus, while we can applaud our improvement, we must recognize the need for continued improvement. The VHA is in the process of updating its data through 2002.

It is incumbent on each healthcare provider to be aware of the comprehensive preventive care needs of the entire person at the time of each encounter. For example, a podiatrist should be alert as to whether an eye exam has been performed within the past year; and an optometrist or ophthalmologist should be concerned whether there is evidence of clinical nephropathy in a person with retinopathy. Each should be aware of the symptoms of uncontrolled hyperglycemia and be able to make appropriate referrals back to the primary care provider or subspecialist team. Expanded roles for nurse practitioners, nurses, physician assistants, dietitians, and pharmacists should be considered. Treating diabetes in the home, in the workplace, and by remote encounters should become more commonplace. Diabetes is an epidemic, and its recognition and control must be a shared responsibility.

Overview of the Diabetes Mellitus Guideline Update (v3.0)

This clinical practice guideline on the ambulatory assessment and treatment of diabetes mellitus is intended to promote evidence-based management of individuals with diabetes. Although veterans with diabetes have a disproportionate number of hospitalizations relative to veterans without diabetes, diagnosis, education, preventive screening, risk factor reduction, and pharmaceutical treatment of diabetes (including microvascular and macrovascular complications) occur mostly in the outpatient primary care setting. This guideline encompasses the critical decision points in patient management such as glycemic control, evaluation of the eyes and feet, and early recognition and treatment of co-morbid conditions including hypertension, hyperlipidemia, and renal disease. At the same time, it is designed to be flexible so that local options and policies for implementation, such as those regarding referrals to or consultation with diabetes teams, ophthalmology, optometry, podiatry, nephrology, and endocrinology (lipids) can be accommodated. It should be recognized that this series of algorithms, as is true for most, cannot be used as a linear guideline for the recognition and management of diabetes

mellitus and is not intended to supersede the clinical judgment of the provider caring for an individual. Medication usage guidelines have been adapted from the Pharmacy Benefits Management Strategic Health Group Medical Advisory Panel Guidelines for Non-Insulin Dependent Diabetes Mellitus (NIDDM), Hypertension and Cholesterol.

The VA/DoD Diabetes Mellitus Working Group builds on the 1999 VA/DoD Guideline, as well as incorporating information from other evidence-based guidelines/reports (see Appendix A - Guideline Development Process) including:

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. American Diabetes Association: clinical practice recommendations 2002. Diabetes Care 2002 Jan;25 Suppl 1:S1-147

Key Changes to the Guideline Update (v3.0)

New Recommendations

Module S: Screening and Prevention [new module in this update]

Screening for impaired glucose
Prevention intervention for patients at risk (exercise, Medical Nutrition Therapy [MNT] & weight loss)

Changes in Recommendations

Module E: Screening for Retinopathy
Frequency of dilated eye exam for no risk patient changed to every 2 years

Module G: Glycemic Control
New medications with more efficacy of combination
Non-pharmacologic intervention (e.g., weight loss and exercise)
Detailed evidence tables on efficacy of pharmacotherapy

Deleted Modules

Module H: Hypertension Management; Refer to the VA/DoD Hypertension guideline (Summary is included in Module D: Core)

Module L: Lipid Control; Refer to the VA/DoD Dyslipidemia guideline (Summary is included in Module D: Core)

Changes in Format

Evidence is clearly presented in Evidence tables and specific recommendations are formulated in a Recommendations section.

The Diabetes Mellitus Guideline Update (v3.0) is organized into seven major modules. Module D contains an algorithm that provides an overview of the relationship between the modules.

Module D - Core
Module S - Screening and Prevention [NEW]
Module G - Glycemic Control
Module E - Eye Care
Module F - Foot Care
Module R - Kidney Function
Module M - Self-Management and Education

Each module uses a risk stratification approach to identify persons with diabetes who have a greater probability of developing complications and who therefore, would benefit from more intensive intervention. Despite the costs and morbidity associated with diabetes, there is a general consensus that preventive care can delay, if not prevent, a significant percentage of the instances of visual loss, chronic renal failure, foot ulcers and lower extremity amputations, as well as hospital admissions for metabolic control. Providers should recognize that the major cause of morbidity and mortality in persons with diabetes is cardiovascular disease-myocardial infarction, stroke, and peripheral vascular disease. Cardiovascular disease accounts for over 70 percent of hospitalizations and deaths. Therefore, an aggressive approach to evaluating and reducing cardiovascular risk factors-including smoking cessation, management of hyperlipidemia, treatment of hypertension, and promotion of a healthy lifestyle-should reflect the general goal for all providers.

While each module is designed for use by primary care providers in an ambulatory care setting, the modules can also be used to coordinate and standardize care within subspecialty teams and as teaching tools for students and house staff.

Performance Measurement

The inability of consumers and healthcare purchasers to determine if medical care is appropriate and effective has given rise to the concept that the healthcare system should be held accountable for what is done and the outcomes achieved. This principle of accountability has resulted in the development of so-called "performance and outcome measures" which are administered through "report card" systems. Measures must be seen as fair and reasonable and must be achievable in various practice settings, when carried out either by diabetes experts and/or generalists.

Performance measures are indicators or tools to assess the level of care provided within systems of care to populations of patients with diabetes. The measures are constructed to best utilize the available evidence for assessing care or outcomes of care in systems where test reliability, patient characteristics, (co-morbidity), and compliance cannot be easily determined and taken fully into consideration (i.e., the measures are not case-mix adjusted). The current state of the art measurement system does not allow full adjustment for factors outside the control of the healthcare system.

The VHA instituted performance measures for diabetes in FY 97 based upon the recommendations of the VHA Diabetes Advisory Field Group. Subsequent to the publication of the first version of the VHA Diabetes Mellitus Guideline in March 1997, the VHA hosted a conference at the National Institutes of Health (NIH) to develop recommendations for performance measures. Participants included representatives of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), CDCP, DoD, Rand, The Health Care Financing Administration (HCFA) and private sector experts. The recommended measures were derived from the guideline and were evidence-based. In this context, the VHA Chronic Disease Performance Measures for Diabetes foreshadowed, and were very similar to, the Diabetes Quality Improvement Project (DQIP) both in content areas and recommended target values.

Results of performance monitoring by VHA's EPRP are presented, both for diabetes specific measures and general preventive measures pertinent for persons with diabetes in Table 1. The cohort was defined as veterans with at least three primary care or selected subspecialty visits during the year. The significance level was determined by calculating the correlation coefficient between the year and intervention status. When two years of data were available, the significance of any difference was determined by a standard chi square test for 2x2 tables. There was significant improvement ($P<0.001$) in all measures whether determined over two or three sampling years.

Table 1. VHA's External Peer Review Program Specific Measures

MEASURE	1995 (n=9578)	1997 (n=13557)	1998 (n=8513)	1999	2002
HbA_1c performed	59	85	91	93	94
HbA_1c <10%	72	82	87		
HbA_1c < 9%	*	*	*	*	78
HbA_1c <7	*	*	*	38	41
HbA_1c <8	*	*	*	61	65
Dilated retinal examination by eye specialist	44	55	62	66	72
Foot visual examination	77	90	95	91	92
Foot sensation checked	38	69	78	78	82
Foot pulses checked	51	74	84	83	86
Blood pressure (BP) <140/90 if hypertension diagnosed	N/A	40	44		58
Low density lipoproteins-cholesterol (LDL-C) measured	N/A	47	64		94

LDL-C <130 mg/dL	N/A	62	68	70
Urine protein evaluated	N/A	23	36	
Influenza immunization	34	58	70	
Pneumococcal vaccine	29	56	68	
Nutritional counseling if body mass index (BMI) >27	68	92	95	
Smoking cessation intervention	39	78	90	

* Not measured during this FY

Disease Management

Disease state management can be defined as the continuous process of identifying and delivering, within selected patient populations, the most efficient combination of resources for the treatment of or prevention of disease. The rationale assumes there are systematic ways to deliver healthcare to a population that will be more efficient than the status quo. The guideline is appropriate for population-based medicine. There is no intent to prevent providers from using their best judgment in the care of an individual patient. Rather, the intent is to establish verifiable treatment objectives for patients with diabetes that will lead to a reduction in limb loss, visual loss, chronic renal insufficiency, and cardiovascular disease. The Pharmacy Benefits Management Strategic Health Group/Medical Advisory Panel Guidelines and Headquarters External Peer Review Program Performance Measures collaboration has resulted in reaching for these goals in this clinical guideline, which should be viewed as the cornerstone for Diabetes Chronic Disease State Management Program in the VA and DoD. The Employee Education System published templates for the elements of a diabetes management program in January 1999.

Implementation

The guideline and algorithms are designed to be adapted to the individual facility's needs and resources. They will be updated periodically or when relevant research results become available. They should be used as an impetus for administrators at each Veterans Integrated Services Network (VISN) facility or Department of Defense (DoD), medical center or medical treatment facility (MTF), and other care access sites to develop innovative plans to remove barriers that prevent primary care providers, subspecialists, and allied health professionals from working together, and barriers that prevent patients from gaining prompt access to preventive care. The ultimate goal is to improve local management of patients with diabetes and thereby, improve patient outcomes.

	KEY POINTS
Primary Prevention	Consider screening all adults (age >45) for impaired glucose tolerance.
	Consider aerobic exercise and diet to achieve weight loss and prevent the progression of impaired fasting glucose.
Secondary Prevention	Achieve individualized HbA_1c target through diet, exercise, medication, and patient education.
	Reduce and control blood pressure to improve quality and length of life, and prevent micro- and macrovascular complications.
	Control cholesterol to reduce risk for cardiovascular disease
Tertiary Prevention	Screen annually for kidney disease.
	Screen for retinopathy using a dilated eye examination.
	Screen annually for lower extremity complications and risk stratification
Health Preventive Measures	Consider aspirin therapy to reduce the risk of cardiovascular fatal events.
	Advise about tobacco use cessation.
	Provide influenza vaccination in season.
	Provide pneumonia vaccine, if indicated.
	Empower patients to make informed decisions about their self-care of diabetes.

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VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

MODULE D – CORE

ALGORITHMS AND ANNOTATIONS

Completion Date: March, 2003
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SUMMARY OF RECOMMENDATIONS

General

1. Children with diabetes should be referred to a pediatric diabetic team for consultative care.
2. All female patients of reproductive potential with pre-existing diabetes should be counseled to plan and prepare for each pregnancy.
3. All female patients of reproductive potential with pre-existing diabetes should be counseled on the need for optimal glycemic control.
4. Diabetes mellitus (DM) management should be evaluated in the context of the patient's total health status.
5. Urgent or semi-urgent medical conditions, including severe hypo- or hyperglycemia, must be treated before long-term disease management principles are applied.
6. Determine and document if diabetes mellitus is type 1 or 2.

Aspirin Therapy

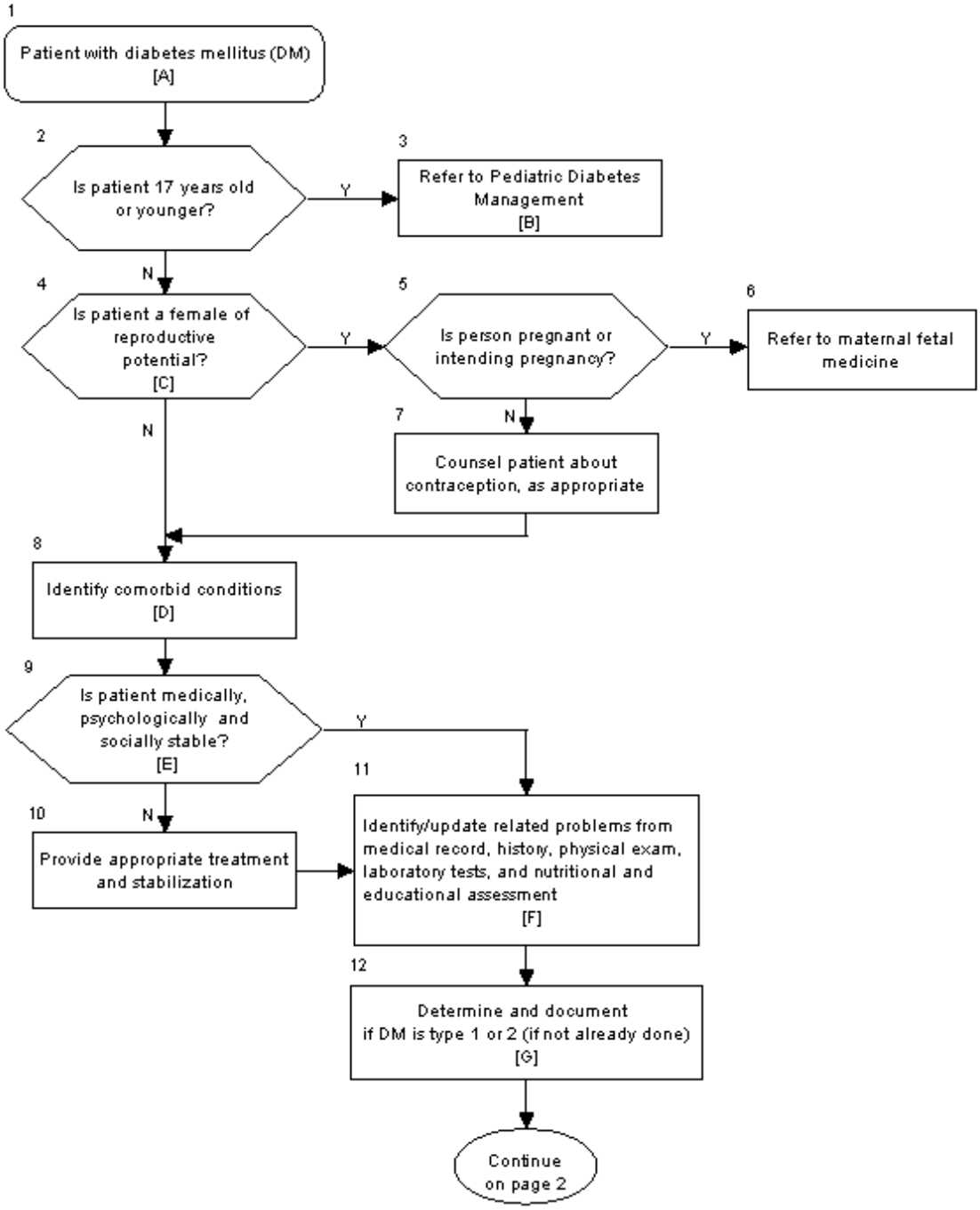
7. Prescribe aspirin therapy (75 to 325 mg/day) for all adult patients with diabetes type 2 and evidence of cardiovascular disease.
8. Consider beginning aspirin therapy (75 to 325 mg/day) for primary prevention in patients age >40 with type 2 diabetes and one or more other cardiovascular risk factors.
9. Consider individual evaluation for aspirin therapy for patients age 30 to 40 with type 2 DM, particularly those with other cardiovascular risk factors, or with type 1 DM and long duration of disease.

Management of Diabetes

1. If the individualized HbA_1c is not at target, refer to **Module G – Glycemic Control**
2. If systolic blood pressure (SBP) $\geq$140 or diastolic blood pressure (DBP) is $\geq$80 mmHg, refer to the VA/DoD Clinical Practice Guideline for the Management of **Hypertension. (Also see Annotation J)**
3. If a lipids evaluation was not done within one year or the patient has elevated cholesterol or lipids, refer to the VA/DoD Clinical Practice Guideline for the Management of **Dyslipidemia (Lipids). (Also see Annotation K)**
4. If a renal evaluation was not done within one year or the patient has micro-/macroalbuminuria or elevated creatinine, refer to **Module R – Renal Disease.**
5. If an eye evaluation was not done within two years, the patient has symptoms, or a previous exam showed a high-risk for visual loss or retinopathy, refer to **Module E – Eye Care**.
6. If a foot-risk assessment was not done within one year or the patient has risk factors or an active lesion, refer to **Module F – Foot Care.**
7. If the patient needs additional nutritional or lifestyle education, refer to **Module M – Self-Management and Education.**
8. If the patient is a candidate for an **influenza vaccine**, administer it in season.
9. Administer **pneumonia vaccine** if indicated. (See VA/DoD Preventive Index Guideline).
10. If the patient is using tobacco, refer to the VA/DoD Clinical Practice Guideline for the Management of **Tobacco Use Cessation.**

Management of Diabetes Mellitus
Module D - Core Algorithm

D



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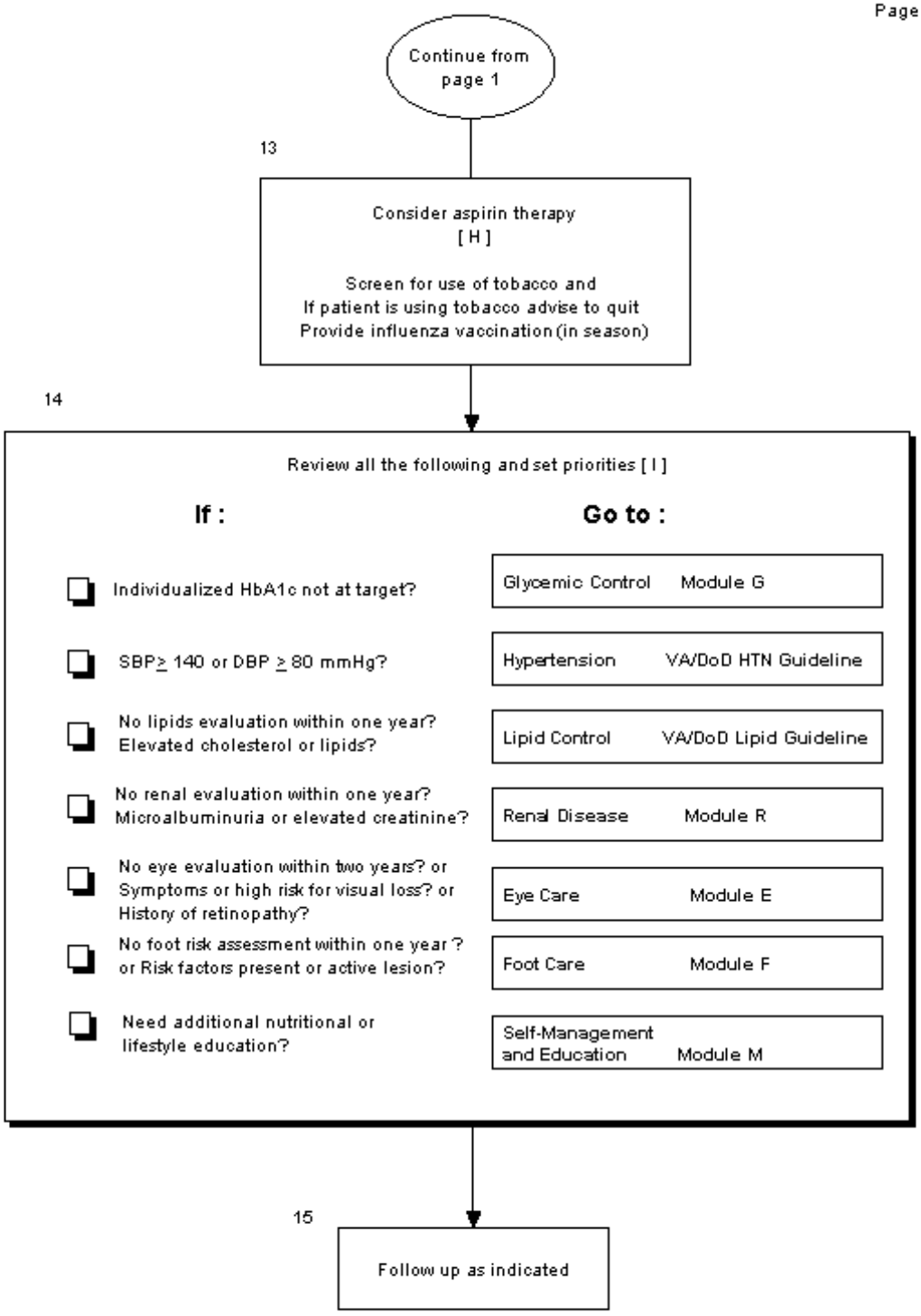

Continue from page 1
13
Consider aspirin therapy [H]
Screen for use of tobacco and
If patient is using tobacco advise to quit
Provide influenza vaccination (in season)
14
Review all the following and set priorities [I]
If :
Go to :
Individualized HbA1c not at target?
Glycemic Control Module G
SBP≥ 140 or DBP ≥ 80 mmHg?
Hypertension VA/DoD HTN Guideline
No lipids evaluation within one year?
Elevated cholesterol or lipids?
Lipid Control VA/DoD Lipid Guideline
No renal evaluation within one year?
Microalbuminuria or elevated creatinine?
Renal Disease Module R
No eye evaluation within two years? or
Symptoms or high risk for visual loss? or
History of retinopathy?
Eye Care Module E
No foot risk assessment within one year ?
or Risk factors present or active lesion?
Foot Care Module F
Need additional nutritional or lifestyle education?
Self-Management and Education Module M
15
Follow up as indicated

Feb-03

ANNOTATIONS

The core module provides an overview of the important components of diabetes care that should be considered at each visit and the interventions that should be performed at appropriate intervals. This module will assist the provider to organize and prioritize a care plan for persons with diabetes mellitus (DM).

A. Patient With Diabetes Mellitus

Diabetes mellitus (DM) is a state of absolute or relative insulin deficiency resulting in hyperglycemia. This algorithm applies to adults only (age 17), both diabetes type 1 and type 2 (formerly referred to as insulin-dependent and non-insulin dependent diabetes mellitus), but not to gestational diabetes mellitus (GDM).

Biochemical Criteria for Diagnosis

The criterion for the diagnosis of DM is either two fasting plasma glucose (FPG) readings with results 126 mg/dL or two random blood sugars with values 200 mg/dL, if symptoms of DM are present.

Oral glucose tolerance testing is no longer recommended in clinical practice. Hemoglobin A_1c (HbA_1c) measurement is not recommended as a screening test. An individual with a casual plasma glucose level 200 mg/dL, but without symptoms, should have his or her fasting blood glucose measured.

Individuals with impaired glucose tolerance (IGT) have an increased risk of developing DM and should receive counseling regarding weight control, exercise, and future screening.

Table D1. Diagnosis of Diabetes Mellitus

Status	Fasting Plasma Glucose (FPG) Preferred Level (a), (b)	Casual Plasma Glucose (c)
Diabetes Mellitus	FPG $\geq$126 mg/dL (7.0 mmol/L)	Casual plasma glucose 200 mg/dL (11.1 mmol/L) plus symptoms of diabetes
Impaired Glucose Tolerance	Impaired fasting glucose (IFG) FPG 110; <126 mg/dL	—
Normal	FPG <110 mg/dL	—

(a) Fasting is defined as no caloric intake for at least 8 hours.
(b) FPG is the preferred test for diagnosis, but either of the two listed is acceptable. In the absence of unequivocal hyperglycemia with acute metabolic decompensation, one of these two tests should be done on a different day to confirm the diagnosis.
(c) Casual means any time of day without regard to time since the last meal; classic symptoms include polyuria, polydipsia, and unexplained weight loss.

DISCUSSION

Patients with one or more of the following risk factors have a higher risk of being diagnosed with diabetes (*Major risk factors for DM are adapted from ADA, 2002)*:

Age 45 years
Family history (parents or siblings with DM)
High-density lipoprotein cholesterol (HDL-C) level 40 mg/dL (0.90 mmol/L) and triglyceride (TG) level 250 mg/dL (2.82 mmol/L)

History of GDM; or women delivering babies weighing >9 pounds
Hypertension (blood pressure [BP] 140/90 mmHg)
Obesity (20 percent above ideal body weight, or body mass index (BMI) 25 kg/m^2)
Habitual physical inactivity
History of IFG or IGT
Race/ethnicity—African American, Hispanic American, Native American, Asian American, and Pacific Islander

Oral glucose tolerance testing (OGTT) is no longer recommended in clinical practice because it is an imprecise test with poor reproducibility. Nonetheless, it would be of value to list the criteria for the diagnosis of diabetes using the OGTT for those providers who decide to continue to use the OGTT. The World Health Organization suggests continued use of the OGTT for patients with blood glucose values in the "uncertain range." Also, the OGTT does seem to better predict macrovascular complications.

OGTT diagnostic criteria (per ADA):

Normal glucose tolerance: 2-h postload glucose (2-h PG) <140 mg/dL (7.8 mmol/l)
Impaired glucose tolerance: 2-h PG 140 (7.8 mmol/l) and <200 mg/dL (11.1 mmol/l)
Provisional diagnosis of diabetes (the diagnosis must be confirmed): 2-h PG 200 mg/dL (11.1 mmol/l)

Because the 2-h OGTT cutoff of 140 mg/dL (7.8 mmol/l) will identify more people as having impaired glucose homeostasis than will the fasting cutoff of 110 mg/d (6.1 mmol/l), it is essential that investigators always report which test was used.

B. Refer To Pediatric Diabetes Management

OBJECTIVE

Provide appropriate management for diabetic children.

ANNOTATION

Approximately three-fourths of all newly diagnosed cases of type 1 DM occur in children (below the age of 18). Children's healthcare needs are different from those of adults in several ways. Providing healthcare to children not only must involve meeting their physical needs, but must address their changing developmental stages. It is important to remember that young children have a limited ability to communicate their needs and to indicate if they are in pain. Therefore, they should not be expected to understand specific clinical interactions.

Primary care providers should refer children with diabetes to a pediatric diabetic team for consultative care. Team members must be knowledgeable and experienced in meeting the medical, psychosocial, and developmental needs of children with diabetes. The team should include, at a minimum, a pediatrician, certified diabetes educator, registered nurse, registered dietitian, and social worker, all with expertise and specialized training in the comprehensive care of children with diabetes.

C. Is Patient A Female Of Reproductive Potential?

OBJECTIVE

Assess the risk of maternal and fetal complications of an unintended pregnancy and implement prevention strategies.

ANNOTATION

Primary care providers should strongly recommend to all patients with pre-existing diabetes that they plan and prepare for each pregnancy. Primary care providers should also counsel all diabetic female patients of reproductive potential on the need for optimal glycemic control.

Because of the high-risk nature of a diabetic pregnancy and the need for intensive multidisciplinary monitoring and patient support, referral of women with diabetes to an expert high-risk perinatal team at the earliest possible opportunity must be considered as the standard of care. Ideally, such a referral should be made during the period of planned conception.

DISCUSSION

The risk of fetal congenital anomalies is directly related to the periconceptual HbA_1c values. The major determinant of outcome is the degree of maternal glycemic control in the preconceptual, periconceptual, and gestational periods.

Nondiabetic pregnancies with maternal HbA_1c levels below 7.0 mg/dL translate into a 1 to 2 percent risk of fetal anomalies; for diabetic pregnancies, maternal levels of HbA_1c above 11 percent result in anomalies in 25 percent of these pregnancies.

Abnormalities related to deficient control of maternal diabetes include:

- Congenital anomalies: overall risk of 13 to 18 percent
- Central nervous system anomalies: 8.5 percent
- Cardiac anomalies: 5.3 percent

Fetal complications of maternal hyperglycemia, besides congenital malformations, include:

- Macrosomia
- Neonatal delivery-related trauma
- Neonatal hypoglycemia
- Stillbirth

Maternal complications that occur at above average rates in diabetic pregnancies include:

- Preeclampsia
- Hypertension
- Preterm labor
- Need for cesarean section

In addition to providing intensive glycemic control, the primary care provider should:

- Prescribe supplemental folic acid and a dietetic regimen to ensure appropriate caloric intake during pregnancy
- Screen for autoimmune thyroid disease, hypertension, and renal disease

D. Identify Comorbid Conditions

OBJECTIVE

Evaluate DM management in the context of the patient's total health status.

ANNOTATION

DM may not be the patient's only disease, nor is it necessarily the condition that needs to be prioritized for immediate treatment. Persons with DM are at risk for multiple comorbid conditions including:

Coronary artery disease (CAD)
Peripheral vascular disease (PVD)
Hypertension (HTN)
Hyperlipidemia

The following are examples of conditions that affect the management of DM:

Chronic obstructive pulmonary disease (COPD)
Substance use disorder (SUD)
Depression

Among the more frequently encountered precipitating factors resulting in secondary diabetes are:

Pancreatic disease (e.g., due to alcoholism and pancreatic insufficiency secondary to chronic pancreatitis, malignancy, and hemochromatosis)
Drug induced disease (especially thiazide diuretics, steroids, and phenytoin)
Cushing's disease
Acromegaly

E. Is the Patient Medically, Psychologically, and Socially Stable?

OBJECTIVE

Stabilize the patient before initiating long-term disease management.

ANNOTATION

Urgent or semiurgent medical conditions, including hypo- or hyperglycemia, and deficient renal function must be treated before long-term disease management principles are applied.
The urgency of medical treatment, including the necessity for hospitalization, will depend upon the presence of ketoacidosis, dehydration, hyperosmolarity, infections, etc.
Psychiatric illness and marked socioeconomic hardship (e.g., homelessness, absence of a support system or reliable transportation, and unemployment) pose significant barriers to diabetic management. If such circumstances are identified, involvement of mental health, social services, and case management professionals may enhance patient compliance with treatment and follow-up.
The determination of stability is up to the judgment of the provider.

F. Identify/Update Related Problems from Medical Record, History, Physical Examination, Laboratory Tests, And Nutritional and Educational Assessment

OBJECTIVE

Obtain and document a complete medical evaluation for the patient with DM, annually.

ANNOTATION

In addition to a general medical examination, a complete evaluation of patients with DM will include:

Information regarding the onset and duration of DM
History of hospitalization(s) for diabetic events
Review of glycemic control

Measurement of serum lipids
Identification of foot complications
Identification of eye complications
Screening for hypertension
Screening for kidney disease
Identification of macrovascular disease
Identification of neurovascular disease
Assessment of psychosocial status (including family support)
Appraisal of self-management skills

On a follow-up visit, the evaluation should focus on updating new information and/or changes to the patient record (see Table D2 for a listing of the components of the evaluation).

Table D2. Evaluation of the Diabetic Patient

Evaluation Component	History-Patient/Family	Physical Examination	Laboratory
Glycemia	Home glucose monitoring records Hyperglycemia Ketoacidosis Hypoglycemia Lifestyle Nutrition Current and past medications Also consider secondary etiologies: - Cushing's disease - Acromegaly - Hemochromatosis - Medications	Weight Height Body mass index (BMI) BMI = Wt(kg)/(Ht[m])squared	HbA_1c Fasting glucose
Foot	Symptoms of neuropathy: - Pain - Paresthesia Symptoms of peripheral vascular disease Symptoms of systemic or local infection Previous episodes of foot complications: - Foot deformity - Skin breakdown - Ulcers - Amputations	Visual inspection including: - Nails - Web spaces - Ulcers - Calluses - Deformities Palpation of pulses and determination of sensation (consider using a 5.07 monofilament)	N/A
Eye	Changes in vision Laser treatment Glaucoma Dilated retinal exam by eye care provider within last year	Visual acuity, if changes in vision are reported	N/A
Kidney	Known history of diabetic disease Family history of hypertension and renal disease	Edema	Routine urinalysis Test for micro-albuminuria and serum creatinine level, if indicated
Hypertension	Previous diagnosis of hypertension Current and previous medications	Blood pressure	N/A
Coronary and Peripheral Arterial Disease/	Atherosclerotic disease: Myocardial infarction (MI)/angina Stroke	Cardiac examination: Heart Peripheral circulation including pulses and bruits	Electrocardiogram (EKG) Fasting lipid profile, if not

Evaluation Component	History-Patient/Family	Physical Examination	Laboratory
Hyperlipidemia	Transient ischemic attack (TIA) Claudication Surgical history of revascularization Atherosclerotic risks other than diabetes: Smoking history Family history Previous diagnosis of hyperlipidemia; triglycerides Current and previous medications: Aspirin Estrogen therapy Hypolipidemics	Cutaneous or tendinous xanthomata	done within the last year
Neurovascular	Sensory state of: Hands and feet	Interosseous muscle wasting Deep tendon reflexes	N/A
Self-management education	Knowledge, understanding and self-described behaviors of: Use of medication Goals of treatment Diet and self management skills What to do in case of complications	Observation: Home glucose monitoring, if indicated Foot self-examination	N/A
Other	Dental history and oral exam Dental and gingival health	Oral examination	N/A
	Infections Insulin injection sites Immunizations: flu and pneumovax	N/A	N/A

Educational Assessment

The following questions were developed based on expert opinion and are believed to reflect the patient's general knowledge and ability to adequately self-manage his or her diabetes:

> Is there anything you do or have been advised to do because of your diabetes that you have difficulty with or are unable to do?
>
> Do you know what to do when your sugar is high/low (describe both hyperglycemia and hypoglycemia symptoms)? Who and when do you call?
>
> Do you remember your target goals: HbA_1c, low-density lipoprotein (LDL), weight, exercise, and BP?
>
> Which food affects your blood sugar the most—chicken breast, salad, or potato?

The patient's inability to answer these questions indicates a possible deficiency in knowledge and self-management skills. Module M (Self-Management and Education) provides the clinician with additional assessment information and action plans.

Patients with DM who have more immediate medical or psychiatric problems should still undergo an educational needs assessment. This evaluation will determine whether they have sufficient skills to manage their glycemic control during a period of concurrent illness, with a goal of avoiding symptomatic hypo- or hyperglycemia.

G. Determine And Document If Diabetes Mellitus Is Type 1 Or 2 (If Not Already Done)

OBJECTIVE

Determine what treatment components are needed for a particular patient.

ANNOTATION

Patients with type 1 DM are insulinopenic (i.e., virtually absent insulin secretion), often due to autoimmune or toxic (e.g., alcohol) destruction of the pancreatic beta cells. Patients with type 2 DM have underlying insulin resistance and relative insulin deficiency.

In a primary care setting, the patient's age at the time diabetes is diagnosed, plus the BMI and level of urinary ketones, are usually sufficient to classify the patient.

Table D3. Clinical Classification of DM

	Likely Type 1	Indeterminate	Likely Type 2
Age	<30 years	30 - 40 years	>40 years
BMI	<25 BMI*	25 - 27	>27
Urinary ketones	Moderate to large	Low to moderate	None to low

**For Asian/Pacific Islanders the BMI threshold should be 23.*

The increasing prevalence of obesity has translated to an earlier onset for type 2 diabetes. Therefore, using age alone as a discriminator for the diagnosis of type 1 or type 2 diabetes may be misleading.

DISCUSSION

Because patients with type 2 or initially indeterminate DM can present with ketoacidosis (especially with concomitant alcohol use) they should be reevaluated after stabilization to assess continued need for insulin therapy.

CLINICAL CLASSIFICATION OF TYPE 1 OR 2

Patients with type 1 DM require insulin and will develop ketoacidosis if not treated with insulin or if insulin requirement increases during stress. Patients with type 1 DM are generally more prone to develop hypoglycemia or ketosis, especially during times of stress.

Patients with type 2 DM may need to be treated with insulin to improve glycemic control but will not usually develop ketoacidosis if they do not receive insulin. Patients with DM adequately treated with medical nutritional therapy (MNT), physical activity, and/or oral agents are classified as having type 2 DM.

H. Consider Aspirin Therapy

OBJECTIVE

Prevent cardiovascular disease.

BACKGROUND

Patients with type 2 DM are at increased risk for cardiovascular events. The antiplatelet action of aspirin therapy has been evaluated as primary prevention and secondary prevention of cardiovascular outcomes (i.e., MI and stroke). As primary prevention, there is some evidence that aspirin therapy prevents cardiovascular events. For secondary prevention—to prevent additional cardiovascular outcomes and/or progression of disease among diabetics diagnosed with atherosclerosis—there is strong evidence to support aspirin therapy.

RECOMMENDATIONS

1. Prescribe aspirin therapy (75 to 325 mg/day) for all adult patients with type 2 diabetes and evidence of cardiovascular disease.
2. Consider beginning aspirin therapy (75 to 325 mg/day) for primary prevention in patients ≥ age 40 with type 2 diabetes and one or more other cardiovascular risk factors.
3. Consider individual evaluation for aspirin therapy for patients age 30 to 40 with type 2 DM, particularly those with other cardiovascular risk factors, or with type 1 DM and long duration of disease.

DISCUSSION

The Antiplatelet Trialists Collaboration (1994) addresses the value of antiplatelet therapy for prevention of cardiovascular outcomes. Although this meta-analysis covers a broad range of patients, seven studies included patients with DM and examined them as a separate subgroup. Patients with DM were also analyzed as members of the "high-risk" group, along with other high-risk patients.

When patients with DM are considered as a separate subgroup, the results of antiplatelet therapy are not statistically significant. When patients with DM are considered as part of the general group of "high-risk" patients, however, they are considered to benefit from antiplatelet therapy. The "high-risk" group as a whole (i.e., patients with some vascular disease or other condition implying an increased risk of occlusive vascular disease) experienced a relative reduction of vascular events that are similar to those seen in patients with known cardiac disease — approximately 25 percent (Antiplatelet Trialists Collaboration, 1994). The authors of the meta-analysis argue that although patients with DM, when analyzed as a subgroup, did not seem to benefit from antiplatelet therapy, the outcome may be misleading. For most other risk factors, a homogenous pattern of relative benefit was demonstrated. Additionally, in trials involving high-risk patients (where data for each individual were available), the benefit of antiplatelet therapy in preventing vascular events was similar and statistically significant in patients with and without DM.

The results of the meta-analysis suggested that there may be no benefit in administering routine antiplatelet therapy to all persons with DM, but that patients with DM and other cardiovascular risk factors should be considered for antiplatelet therapy. In high-risk patients with diabetes (i.e., those with a history of cardio- or cerebrovascular disease), however, there was a clear statistical and clinical benefit to antiplatelet therapy.

Three randomized controlled trials (RCTs) are relevant to the question of routine antiplatelet therapy for persons with DM (de Gaetano, 2001; The Early Treatment Diabetic Retinopathy Study [ETDRS], 1992; Hanson et al., 2000). de Gaetano (2001) reported efforts by the Collaborative Group of the Primary

Prevention Project to determine the value of low-dose aspirin and vitamin E in people at cardiovascular risk. In this study, DM was considered to be a cardiovascular risk factor. The results indicated that aspirin lowered the frequency of all clinical endpoints and was significant for cardiovascular death (from 1.4 to 0.8%; relative risk 0.56 [95% CI 0.31-0.99]) and total cardiovascular events (from 8.2 to 6.3%; 0.77 [0.62-0.95]. Vitamin E, however, showed no statistically significant benefit. Although bleeding events were more frequent in the aspirin group than the no-aspirin group (1.1% vs. 0.3%; p <0.0008), the investigators concluded that "in women and men at risk of having a cardiovascular event because of the presence of at least one major risk factor, low-dose aspirin, given in addition to treatment of specific risk factors, contributes an additional preventive effect, with an acceptable safety profile" (de Gaetano, 2001).

The ETDRS Investigators (1992) was designed to evaluate the effects of photocoagulation and aspirin on ocular events. Because of the five-year follow-up period of the study, it also provided an opportunity to evaluate the effects of aspirin use on cardiovascular events in a population with DM. The study included 3,700 persons with type 1 and type 2 DM and with diabetic retinopathy. In this study, those patients with type 2 DM randomized to receive a 650 mg dose of aspirin per day, had no significant improvement in cardiovascular outcomes. In considering this result, however, the issue of generalizability arose. This group of patients with diabetes with retinopathy may have represented a population with more severe diabetes that perhaps puts them at higher risk of cardiovascular complications. Because of the insufficient power of this study, the lack of demonstrated benefit of antiplatelet therapy in this group should be taken as only a tentative suggestion that such therapy may not be useful as a routine practice among persons with type 2 DM.

When considering the value of antiplatelet therapy in persons with DM, the opposite question is also valid: what are the potential dangers of such therapy for persons with DM? de Gaetano (2001) reported that aspirin users experienced more bleeding episodes, but concluded that the safety profile was acceptable. Hansen et al. (2000) investigated a possible contraindication to the use of aspirin in persons with DM. They conducted a small study to determine whether the use of aspirin interfered with the classification of AER or monitoring of antiproteinuric treatment in such patients. They found that "treatment with 150 mg ASA daily did not have any impact on albumin excretion rate (AER) or glomerular filtration rate (GFR) in patients with type 1 diabetes with macroalbuminuria." This initial evidence suggests that aspirin does not jeopardize antiproteinuric treatment monitoring in persons with DM.

The findings of the studies suggest that these recommendations may be applicable for patients with type 1 DM; however, there is no evidence to support this intuitively appealing observation. Patients with type 1 DM may be individually evaluated for aspirin therapy, with consideration of both duration of disease and the presence of other cardiovascular risk factors.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Aspirin therapy for patients with type 2 DM and evidence of large vessel disease.	Antiplatelets Trialists' Collaboration, 1994 de Gaetano, 2001	I	Good	A
2	Aspirin therapy for patients with type 2 DM.	Antiplatelets Trialists' Collaboration, 1994 de Gaetano, 2001 EDTRS, 1992	I	Fair	B
3	Aspirin therapy for younger patients (age 30 to 40) with type 2 DM or with type 1 DM and other cardiovascular risk factors	Working Group Consensus	III	Poor	I
4	Aspirin therapy for patients age <40 with type 1diabetes:, in particular, those with longer duration of disease.	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

I. Review All Diabetes-Related Complications And Set Priorities

OBJECTIVE

Identify DM-related complications requiring special attention.

RECOMMENDATIONS

1. If the individualized HbA_1c is not on target, refer to **Module G – Glycemic Control**
2. If SBP ≥140 or DBP is ≥80 mmHg, refer to the VA/DoD Clinical Practice Guideline for the Management of **Hypertension. (Also see Annotation J)**
3. If a lipids evaluation was not done within one year or the patient has elevated cholesterol or lipids, refer to the VA/DoD Clinical Practice Guideline for the Management of **Dyslipidemia (Lipids). (Also see Annotation K)**
4. If a renal evaluation was not done within one year or the patient has microa-/macrolbuminuria or elevated creatinine, refer to **Module R – Renal Disease.**
5. If an eye evaluation was not done within two years, the patient has symptoms, or a previous exam showed a high-risk for visual loss or retinopathy, refer to **Module E – Eye Care**.
6. If a foot-risk assessment was not done within one year or the patient has risk factors or an active lesion, refer to **Module F – Foot Care.**
7. If the patient needs additional nutritional or lifestyle education, refer to **Module M – Self-Management and Education.**
8. If the patient is a candidate for an **influenza vaccine**, administer it in season.
9. Administer **pneumonia vaccine,** if indicated. (See VA/DoD Preventive Index Guideline).
10. If the patient is using tobacco, refer to the VA/DoD Clinical Practice Guideline for the Management of **Tobacco Use Cessation.**

Management of Hypertension in Diabetes Mellitus

For complete management of hypertension see: VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care Setting at http://www.oqp.med.va.gov/cpg/cpg.htm or http://www.qmo.amedd.army.mil .

Patients with Diabetes with SBP ≥140 or DBP ≥80 mmHg

BACKGROUND

The incidence of hypertension (HTN) among those with type 1 DM rises steadily from 5 percent at 10 years, to 33 percent at 20 years, and 70 percent at 40 years (Epstein & Sowers, 1992), and there is a correlation between the onset of HTN and the presence of diabetic nephropathy (DN). The association of HTN and DN is less strong among patients with type 2 DM, because up to 50 percent of patients have HTN before the onset of microalbuminuria. Therefore, early treatment of HTN in patients with diabetes, particularly type 2 DM, is important to delay the onset and/or retard the progression of cardiovascular disease and DN.

RECOMMENDATIONS

1. Patients with diabetes with hypertension (BP ≥140/90 mm Hg) or with isolated hypertension (ISH) (defined as pretreatment SBP greater than 140 and DBP less than 90) should:
   Begin anti-hypertensive therapy with an angiotensin converting enzyme inhibitor (ACEI)
   Switch to an angiotensin receptor blocker (ARB) if ACEI induced side-effects occur
   Use other agents as necessary to achieve BP target <140/80 mm Hg
2. Patients with diabetes with SBP less than 139 and DBP between 80 and 89 with or without microalbuminuria would benefit from ACEI therapy. However, there is no clinical trial evidence that indicates a preferred target level of BP.
3. In patients with diabetes with renal insufficiency (i.e., serum creatinine >1.5 mg/dL) or proteinuria (i.e., >1 g/24h) there are some data suggesting that further BP lowering (<125/75 mm Hg) may further slow progression of renal disease. Lower BP should be achieved, if feasible and practical, depending on the tolerance of medications and side effects of BP lowering.

DISCUSSION

Blood Pressure Targets

Diabetics with HTN are at high-risk for cardiovascular disease. Lower BP, per se, reduces cardiovascular events (Gaede et al., 1999; Hansson et al., 1998; Lindholm et al., 2002; UKPDS 1998). However, despite using aggressive treatment protocols, clinical trials have been unsuccessful in achieving SBP <140 mm Hg. There are no published intervention studies in patients with diabetes in which achieved SBP was <130 mm Hg. Thus, there are no data on which to conclude that lower systolic levels will achieve further benefits. Diastolic blood pressure (DBP) levels may be more readily controlled and there is evidence from clinical trials that <80 mm Hg is achievable and likely beneficial. In studies in which achieved DBP was 82 mm Hg or less diabetes-related outcomes were significantly improved (Brenner et al., 2001; Estacio et al., 2000; Hansson et al., 1998; Lewis et al., 2001; Lindholm et al., 2002; UKPDS, 1998).

Blocking the renin-angiotensin system offers specific advantages in patients with diabetes (Estacio et al., 2000; HOPE, 2000; Lewis et al., 1993) and particularly when renal disease is present (Brenner et al., 2001; Lewis et al., 2001; Parving et al., 2001). Adding an ACEI to an existing medical regimen (even in the setting of BP <140/80 mm Hg) is associated with fewer cardiovascular events and delay in the progression of microalbuminuria to overt nephropathy (HOPE, 2000).

Pharmacotherapy

Patients with diabetes, particularly those with nephropathy, may have HTN that is difficult to control, often requiring combinations of several agents to achieve lower BP. ACEIs, ARBs, beta-blockers, diuretics, and nondihydropyridine calcium channel blockers (NCCB) may be used to treat hypertensive patients with DM.

ACEI

1. ACEIs have several advantages including protection against cardiovascular events, few adverse effects, and a safety track record. There is a compelling indication to use ACEIs for patients with type 1 DM and nephropathy, based on the reduced risk of doubling the serum creatinine and a 50 percent reduction in the risk of the combined endpoints of death, dialysis, and transplantation (Lewis et al., 1993).
2. ACEIs compared to placebo decreased the risk of combined MI, stroke, and cardiovascular death in hypertensive patients with type 2 diabetes with high-risk for cardiovascular disease (HOPE, 2000).
3. ACEIs may also be beneficial in normotensive patients with type 1 or 2 DM and microalbuminuria (Laffel et al., 1995; Ravid et al., 1993; Viberti, 1994).

ARB

1. ARBs appear to have similar short-term effects as ACEIs in patients with diabetes and nephropathy, with fewer side-effects (Anderson et al., 2000; Lacourciere et al., 2000; Muirhead et al., 1999; Nielsen

et al., 1997). However, there are no long-term outcome trials comparing an ACEI to an ARB to determine if these agents provide similar long-term benefits in patients with DM.
2. ARBs are effective in patients with type 2 DM with nephropathy (Brenner et al., 2001; Lewis et al., 2001) or microalbuminuria (Morgensen et al., 2000: Parving et al., 2001). Treating patients with type 2 DM and nephropathy with an ARB resulted in a reduction in the composite endpoint of doubling of serum creatinine, progression to end-stage renal disease, and all-cause mortality when compared to placebo (Brenner et al., 2001; Lewis et al., 2001).
3. Patients with HTN and type 2 DM with microalbuminuria experienced a significant reduction in the primary endpoint of time to onset of overt DN with an ARB compared to placebo (Parving et al., 2001).
4. Compared to treatment with a beta-blocker, an ARB reduced the composite endpoint of cardiovascular death, MI, and stroke in a subgroup of patients with DM, HTN and left ventricular hypertrophy (Lindholm et al., 2002).
5. Few studies have evaluated the effects of ARBs, ACEIs, or their combination. In one study of patients with HTN, type 2 DM, and microalbuminuria, BP and urinary albumin excretion were reduced with the ARB, the ACEI, and further reduced with the combination. However, there are no long-term safety or efficacy studies showing that this combination offers specific advantages over other combinations of anti-hypertensive medications in patients with nephropathy.

Calcium Channel Blockers (CCB)
1. For patients with type 1 or 2 DM with proteinuria, the NCCB reduce proteinuria and provide renoprotection (Bakris et al., 1996; Kasiske et al., 1993; Salvetti et al., 1999; Vivian & Goebig; 2001).
2. Combination ACEI and NCCB may provide additive protection in patients with inadequate response to an ACEI alone (Bakris et al., 1998; Vivian & Goebig; 2001).
3. Use of long-acting dihydropyridine calcium channel blockers (DHCCB) in the absence of an agent that blocks the renin-angiotensin system may worsen proteinuria and/or progression of renal disease (Lewis et al., 2001).
4. Studies with a long-acting DHCCB in patients with HTN and type 2 DM showed an increased risk of major vascular events (Tatti et al., 1998) and a higher incidence of fatal and nonfatal MI (Estacio et al., 1998) compared to patients treated with an ACEI (Opie & Schall, 2002; Pahor et al., 2000).

Beta Blockers
1. Treatment with captopril versus atenolol in patients with HTN and type 2 DM had similar effects on preventing the primary endpoints of macrovascular and microvascular complications (UKPDS 1998).
2. Beta-blockers offer clear benefits in patients after a MI and in some patients with congestive heart failure. Small changes in insulin sensitivity induced by beta-blockers should not be considered a contraindication to their use in patients with diabetes.
3. Beta-blockers may worsen insulin resistance. In hypertensive non-diabetic patients this may be associated with an increased risk for developing type 2 diabetes when compared with no treatment, thiazides, CCBs, or ACEIs (Gress et al., 2000). Some of this adverse effect on insulin resistance is not seen with beta-blockers that also contain alpha-blocking properties.

Diuretic
1. Dietary salt restriction and/or diuretics may counteract the tendency for volume expansion in patients with diabetes and may enhance BP lowering.
2. Diuretics enhance the anti-hypertensive and anti-proteinuric effects of ACEIs and may reduce the occurrence of hyperkalemia with ACEI, ARBs and beta-blockers.
3. Treatment with a diuretic resulted in a reduction in major cardiovascular disease rate compared to placebo, in both patients with and without DM. The absolute risk reduction was twice as great in patients with DM compared to those who did not have DM (Curb et al., 1996).

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
GENERAL RECOMMENDATIONS					
1	Treatment of HTN in patients with diabetes to retard progression of macrovascular complications and DM.	Epstein & Sowers, 1992 Gaede et al., 1999 Hansson et al., 1998 UKPDS , 1998	I	Good	A
2	Target BP of <140/80 mm Hg for patients with diabetes with HTN, due to high-risk for cardiovascular disease.	Gaede et al., 1999 Hansson et al, 1998 Lindholm et al., 2002 UKPDS, 1998	I	Good	A
3	Consideration of lower BP targets (<125/75 mm Hg) to slow the progression of renal disease for patients with diabetes with elevated serum creatinine and/or urinary protein excretion above 1 g/day.	Lazarus et al., 1997	II-2	Fair	B
GENERAL THERAPEUTIC RECOMMENDATIONS					
4	Antihypertensive therapy with ACEI for patients with diabetes with BP >140/80 mm Hg. Switch to ARB if ACEI-induced side-effects occur, then use other agents to achieve BP target <140/80 mm Hg.	Anderson et al., 2000 Hansson et al, 1998 HOPE Study Investigators, 2000 Lacourciere et al., 2000 Lindholm et al., 2002 Mogensen et al., 2000 Muirhead et al., 1999 Nielsen et al., 1997	I	Good	A
SPECIFIC THERAPEUTIC RECOMMENDATIONS					
5	ACEI for normotensive patients with type 1 DM and proteinuria and for patients with type 2 DM and microalbuminuria or a high-risk for cardiovascular disease.	HOPE Study Investigators, 2000 Lewis et al., 1993	I	Good	A
6	Consideration of ACEI for normotensive patients with type 1 DM.	Laffel et al., 1995 Viberti et al., 1994	I	Fair	B
7	Treatment with ARBs for patients with type 2 DM and nephropathy, microalbuminuria, or HTN and left ventricular hypertrophy.	Brenner et al., 2001 Lewis et al., 2001 Lindholm et al., 2002 Mogensen et al., 2000 Parving et al., 2001	I	Good	A
8	Combination ACEI and NCCB to provide renal protection in patients with inadequate response to an ACEI alone.	Bakris et al., 1998 Vivian & Goebig, 2001	II-2	Fair	B
9	Diuretics to enhance the BP lowering effects of other antihypertensive agents.	Brenner et al., 2001 Curb et al., 1996 Lewis et al., 2001 Lindholm et al., 2002	I	Good	A
THERAPEUTIC CAUTIONS					
10	Use caution in prescribing long-acting DHCCBs without an ACEI or ARB because of the risk of less renal protection and/or adverse cardiovascular outcomes.	Estacio et al., 1998 Lewis et al., 2001 Opie and Schall, 2002 Pahor et al., 2000 Tatti et al., 1998	I	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix A)

Management of Lipids in Diabetes Mellitus

For complete management of hypertension see: VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Dyslipidemia in the Primary Care Setting at http://www.oqp.med.va.gov/cpg/cpg.htm or http://www.qmo.amedd.army.mil

Diabetes Patient With No Lipids Evaluation Within One Year Or Elevated Cholesterol Or Lipids

BACKGROUND

DM is associated with a two-fold to four-fold increase in atherosclerotic cardiovascular disease (ASCVD). The morbidity and mortality from coronary events in patients with diabetes are substantial, and exceed those in non-DM patients.

RECOMMENDATIONS

1. Patients with diabetes and patients with established coronary heart disease (CHD) should be screened for lipid abnormalities. A fasting lipid profile is required at least once every two years (triglycerides and HDL-C or LDL-C).
2. All patients with diabetes should be given lifestyle counseling. Lifestyle change is indicated in all patients with LDL-C > 100 mg/dL. Strategies include diet (dietary/nutritional management of fat and/or cholesterol intake or MNT consult), exercise, smoking cessation, cessation of excessive use of alcohol, and weight control.
3. Patients with diabetes with elevated triglyceride (TG) level should receive drug therapy. Elevated TG level (>400 mg) may be due to poor glycemic control. The most common secondary causes of hypertriglyceridemia are alcohol, diabetes, and hypothyroidism. Addressing these underlying conditions can improve or normalize triglyceride levels and failing to address these conditions can render therapy ineffective. Once glycemic control is improved, the TG level should be reassessed.
4. Patients with diabetes who do not reach LDL target and whose LDL-C level is >130 mg/dL should begin pharmacotherapy.

DISCUSSION

Table D4. summarizes the thresholds and goals for dyslipidemia treatment.

Table D4. LDL-C Thresholds for Initial Dyslipidemia Treatment in Patients with Diabetes

	Baseline LDL-C [mg/dL]	
	≥100	≥130
Diabetes (with or without known CHD)	Diet/exercise Consider drug	Diet/exercise Initiate drug therapy

- ***Initial Therapy:*** Evidence clearly supports initiation of pharmacotherapy when LDL is >130 mg/dL in patients with CHD (Scandanavian Simvastatin Survival Study Group [4S], 1994). For CHD and CHD equivalents (i.e., type 2 DM) and patients with HDL >40 mg/dL and LDL <130 mg/dL, there is insufficient evidence on which to base a recommendation for pharmacotherapy. Individual clinicians may choose to initiate drug therapy for LDL >100mg/dL for secondary CHD prevention, based on consensus opinion. However, the CARE study, a prospective secondary prevention trial, found no outcomes benefit when high-dose pravastatin was initiated at a baseline LDL < 125mg/dL (Sacks, 1996).

Choice of Drug: Statins are the best studied and show most benefit, in terms of absolute LDL reduction and patient outcome. Older trials with niacin and bile acid resins have shown modest reduction in LDL (10 to 20 percent) and CHD event rates, with some evidence of small mortality benefit. Fibrates, which have minimal effect on LDL, have shown reduced CHD event rates but not mortality (Frick et al., 1987; Rubins et al., 1999). Statin-based outcome trials have included lovastatin, pravastatin, and simvastatin. There is no convincing evidence that one statin is better than another. Choice and starting dose should be dictated by the required LDL reduction, as statins differ in their potency. The dose should be adjusted at six to eight week intervals until the LDL reduction goal is achieved.

Aggressiveness of LDL Reduction: There is no direct evidence from RCTs that demonstrates a net benefit (in terms of clinically relevant endpoints) of treating to an LDL goal of less than 130 mg/dL. Indirect evidence from the 4S Trial (1994) demonstrated that in patients with previous CHD, treated with simvastatin to an average LDL of 118 mg/dL, the benefits clearly outweighed the harms. NCEP III recommends lowering LDL to <100 mg/dL in the secondary CHD and CHD equivalents (i.e., type 2 diabetes mellitus) prevention setting. Trials are now underway to determine whether even more aggressive treatment produces additional benefit. An angiographic trial in coronary artery bypass grafting (CABG) patients showed that patients treated to a target LDL <140mg/dL had worse outcomes than those treated more aggressively to a target LDL <85mg/dL (Post CABG Trial, 1997). After four years, angiographic progression for the aggressive and moderate groups was 27 percent and 39 percent, respectively. Revascularization was reduced by 29 percent in the lower LDL group. Some experts argue that it is the percentage drop in LDL, not the absolute LDL achieved, that is important in achieving benefit. Treating to New Targets (TNT) is a five year RCT currently under way looking at lowering LDL to very low target levels in patients with CHD, who are randomizing to atorvastatin 10 mg versus 80 mg/day. The results of the 4S Trial suggest that there may be additional benefits of lowering LDL to less than 130 mg/dL. The VA/DoD Working Group for the management of dyslipidemia and diabetes recommend a treatment goal of <120 mg/dL, while waiting for a more definitive answer.

HDL Cholesterol <40 mg/dL with LDL <130 mg/dL

Large epidemiologic trials have shown that a low HDL is associated with an increased risk for cardiovascular events (Gordon, 1989). In the VA-HIT trial (1999), patients with established cardiovascular disease, an HDL <40 mg/dL and an LDL <140 mg/dL were randomized to treatment with gemfibrozil versus placebo. The mean entry HDL of the treatment arm was 32 mg/dL and the mean entry LDL level was 111 mg/dL. Following a mean follow-up of five years, the gemfibrozil treatment arm saw a 22 percent relative risk reduction in the combined end point of nonfatal myocardial infarction or death due to cardiovascular disease, and a 25 percent reduction in stroke. Subgroup analysis of VA-HIT strongly suggests that CHD patients with low HDL, triglycerides >200 mg/dL, hypertension, or impaired fasting glucose were particularly likely to benefit from gemfibrozil therapy. The study was not powered to detect an overall mortality benefit.

Pharmacologic Therapy

Drug therapy is indicated for patients who remain above LDL thresholds with non-pharmacologic measures. HMG-CoA reductase inhibitors (statins) are first line agents in most situations. They are cost-effective in secondary prevention and high-risk primary prevention risk groups. *The dose should be adjusted at 4 to 6 week intervals until the individually-determined LDL-C goals are met.* Other agents have been shown to reduce CHD events and angiographic progression, but have had minimal impact on total mortality. The first line drugs and alternatives for lipid disorders are summarized in Table D5.

Table D5. Dyslipidemia Drug Therapy Recommendations

Lipid Disorder	Monotherapy	Efficacy		Considerations
LDL-C Initial	Statins	**LDL** -22 to -60%		Use statins with caution in hepatic disease. Niacin is contraindicated in hepatic disease and relatively contraindicated in DM, gout, and history of complicated/active peptic ulcer disease. Resins may increase TG.
Alternate	Niacin	-13 to -21%		
	Bile acid resin (resin)	-10 to -20%		
LDL-C and TG Initial	Niacin	**LDL** -13 to -21%	**TG** -10 to -24%	For high TG, use fibrates or niacin. For high LDL, use statins.
	or statin	-22 to -60%	-06 to -37%	
Alternate	Fibrates	+10 to -35%	-32 to -53%	
LDL and HDL	Niacin	**LDL** -13 to -21%	**HDL** +10 to +24%	No preferences in terms of efficacy.
	or statin	-22 to -60%	+2 to +12%	
	or fibrates	+10 to -35%	+2 to +34%	
TG 400-1000 mg/dL	Consider gemfibrozil if HDL-C < 40 mg/dL[a]			For high TG, use direct LDL-C measurement or non-HDL-C to guide therapy.

Adapted from PBM-MAP, 1997.
[a] VA-HIT, 1999.

For CHD/ASCVD Patients

For patients with known CHD/ASCVD who have HDL <40 mg/dL, pharmacotherapy with gemfibrozil is recommended (VA-HIT, 1999).

Table D6. Dyslipidemia Drug Therapy Recommendations

Lipid Disorder	Monotherapy	Efficacy		Considerations
LDL-C >130 mg/dL *and* HDL-C <40 mg/dL	Gemfibrozil	**LDL** +10 to –35%	**HDL** +2 to 34%	Outcome data for secondary prevention only.

Adapted from PBM-MAP, 1997.

Some special conditions apply to lipid-lowering drug treatment for persons with DM. Treatment options for the patients with diabetes exhibiting "diabetic dyslipidemia" (i.e., low HDL, elevated triglycerides, normal-to-slightly elevated LDL) include aggressive LDL lowering, as in secondary CHD prevention in non-diabetic patients, or triglyceride-lowering therapy with a fibrate drug (such as gemfibrozil), which usually also raises HDL. Clinicians should exercise caution in the use of niacin in dyslipidemia. Niacin is contraindicated in hepatic disease and relatively contraindicated in DM, gout, and history of complicated/active peptic ulcer disease (PUD). It has been known to cause glucose intolerance in some individuals with DM.

After commencing drug treatment, the clinician should monitor the patient's progress toward a goal lipid level. The VA/DoD Dyslipidemia Guideline recommends a target LDL-C goal of <120 mg/dL for patients with DM and without known CHD. The NCEP III recommends an LDL-C goal of <100 mg/dL in patients with known CHD and CHD equivalents (i.e., type 2 DM).

For patients who have reached targets of LDL-C <130 and TG <400, an annual reassessment is recommended. Because total and LDL cholesterol tend to increase with advancing age, patients with initially borderline LDL values may evolve to frankly elevated LDL with the passage of 1 year or may develop concurrent health conditions (nephritic syndrome, hypothyroidism, DM) that can declare as hyperlipidemia. Patients known to be at high-risk for CAD based on multiple risk factors other than hyperlipidemia are candidates for early and aggressive dietary and pharmacologic therapy; thus annual reevaluation of serum lipid status is prudent and cost-effective.

Failure to Reach LDL Goal with Statins: Some patients will not achieve their LDL target with full dose statins. What should be done? It is not clear. Adding niacin/bile acid-binding resins will further lower LDL, and may provide clinical benefit (Canner et al., 1986). Gemfibrozil will not substantially change the LDL and so is not indicated in this situation. Until further evidence is available, the addition of niacin or resins could be considered. In combination with statins, niacin increases the risk of hepatitis and rhabdomyolysis, but will raise HDL and lower triglycerides. Frequent monitoring of liver function tests is prudent when combination therapy is used.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Lifestyle modification.	Ebrahim & Davey Smith, 2000 Wilson et al., 1998	I	Good	A
2	Primary prevention.	Downs et al., 1998 Shepherd et al., 1995	I	Good	A
3	Secondary prevention.	4S, 1994 Canner et al., 1986 Frick et al., 1987 Leng et al., 2000 NCEP III, 2001 Post CABG Trial, 1997 Sacks et al., 1996	I	Good	A
4	Treatment of low HDL.	Gordon et al., 1989 Rubins et al., 1999	I	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix A)

VA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

MODULE S - SCREENING FOR DIABETES

ALGORITHMS AND ANNOTATIONS

Completion Date: March, 2003
Release Date: October, 2003
Version 3.0

SUMMARY OF RECOMMENDATIONS

SCREENING

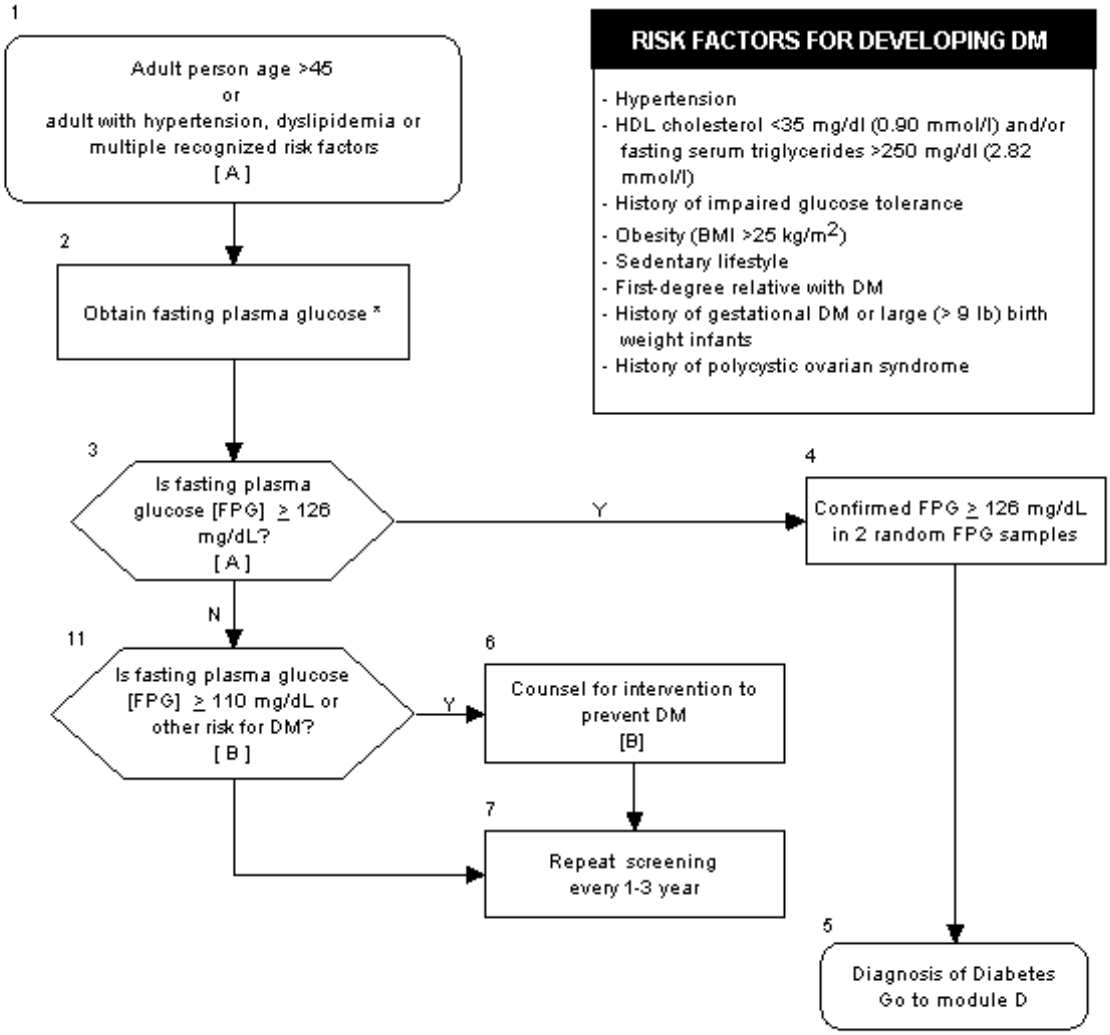
1. Screening for diabetes mellitus (DM), should be considered for adults **age 45 at 1 to 3 year intervals**.
1. Screening should be considered in **younger non-pregnant adults who have hypertension or dyslipidemia or multiple other recognized risk factors** for diabetes. Risk factors include history of impaired glucose tolerance (IGT), body mass index (BMI) >25 kg/m^2, sedentary lifestyle, first-degree relative with DM, history of gestational diabetes mellitus (GDM) or large (>9 lb) birth weight infants, hypertension, high density lipoproteins - cholesterol (HDL-C) <35 mg/dL (0.90 mmol/l) and/or fasting serum triglycerides >250 mg/dL (2.82 mmol/l), history of polycystic ovarian syndrome, member of a high-risk ethnic population (e.g. African-American, Latino, Native American, Asian-American, and Pacific Islander), impaired fasting glucose (IFG) on previous testing, or other clinical conditions associated with insulin resistance.
2. **Fasting plasma glucose (FPG) is the preferred screening test** for DM and is also a component of diagnostic testing. DM is diagnosed if the value is 126 mg/dL on at least two occasions (see Module D, Annotation A). A normal FPG is <110 mg/dL. An FPG ≥110 and <126 mg/dL (7.0 mmol/l) is an indication for retesting, which should be done on a different day.
3. Although not recommended as a first-line screening test, **casual non-fasting plasma glucose** >200 mg/dL (on at least two occasions) is sufficient to diagnose DM, and <110 mg/dL is sufficient to exclude it. Random (non-fasting) plasma glucose in the range 111 to 199 mg/dL should be followed up with fasting plasma glucose.

PREVENTION

1. Patients with IGT (i.e., a FPG ≥110 mg/dL and <126 mg/dL) should be **counseled about prevention of** DM. Intensive lifestyle interventions to prevent diabetes include both regular aerobic exercise and a calorie-restricted diet to promote and maintain weight loss.
2. Patients with a BMI >25 are at high-risk for DM and should achieve and sustain **weight loss** of 5 percent or more.
3. **Modification of lifestyle** may be beneficial for all patients and may be considered in patients with risk factors for diabetes (other than IGT).

Management of Diabetes Mellitus
Module S - Screening for DM

S



* Note:
Random non-fasting plasma glucose is not recommended as first line screening. However, non-fasting plasma glucose >200 mg/dl (on at least two occasions) is sufficient to diagnose DM, and <110 mg/dl is sufficient to exclude it. Random (non-fasting) plasma glucose in the range 111-199 mg/dl should be followed up with a fasting plasma glucose.

Jan - 03

ANNOTATIONS

A. Screening for Diabetes Mellitus

OBJECTIVE

Diagnose type 2 diabetes mellitus (DM) at a stage early enough that effective treatment can minimize the risk of severe microvascular and macrovascular complications.

BACKGROUND

Individuals at risk for type 2 DM can be identified on the basis of numerous, readily identifiable risk factors. Early identification of these individuals provides the opportunity for several aggressive interventions in accordance with population health practices. Lifestyle interventions (e.g., nutritional therapy and regular aerobic exercise leading to sustained weight loss) reduced the rate of diabetes in several small studies and most recently, in the NIH-funded Diabetes Prevention Program (DPP) *(*Knowler et al., 2002*).* The DPP also demonstrated reduced incidence of diabetes among trial participants who were treated with metformin, although the magnitude of benefit was significantly less than that of lifestyle interventions.

Additional pharmacologic agents which have been associated with reduced incidence of type 2 DM in clinical trials include acarbose and ramipril, and there is considerable interest in the pre-emptive use of thiazolidinedione drugs for prevention of DM. The results of randomized clinical trials (RCTs) need to be completed before accurate estimates of benefit can be established.

RECOMMENDATIONS

1. Screening for DM, should be considered for adults age 45 at 1 to 3 year intervals.
2. Screening should be considered in younger non-pregnant adults who have hypertension or dyslipidemia or multiple other recognized risk factors for diabetes. Risk factors include history of impaired glucose tolerance (IGT), dysmetabolic Syndrome X, body mass index (BMI) >25 kg/m^2, sedentary lifestyle, first-degree relative with DM, history of gestational DM or large (>9 lb) birthweight infants, hypertension, high density lipoproteins - cholesterol (HDL-C) <35 mg/dL (0.90 mmol/l) and/or fasting serum triglycerides >250 mg/dL (2.82 mmol/l), history of polycystic ovarian syndrome, member of a high-risk ethnic population (e.g. African-American, Latino, Native American, Asian-American, and Pacific Islander), impaired fasting glucose (IFG) on previous testing, or other clinical conditions associated with insulin resistance.
3. Fasting plasma glucose (FPG) is the preferred screening test for DM and is also a component of diagnostic testing. DM is diagnosed if the value is 126 mg/dL on at least two occasions (see Module D, Annotation A). A normal FPG is <110 mg/dL. An FPG ≥110 and <126 mg/dL (7.0 mmol/l) is an indication for retesting, which should be done on a different day.
4. Although not recommended as a first-line screening test, casual non-fasting plasma glucose >200 mg/dL (on at least two occasions) is sufficient to diagnose DM, and <110 mg/dL is sufficient to exclude it. Random (non-fasting) plasma glucose in the range 111 to 199 mg/dL should be followed up with fasting plasma glucose.

DISCUSSION

It is estimated that 3.2 percent of the U.S. population aged 25 to 65 has undiagnosed DM, and that type 2 DM is present for about 10 years prior to its diagnosis in unscreened populations. Microvascular complications of DM begin to appear 3 to 5 years after the onset of diabetes, and their incidence and prevalence increase up to 30 years duration. Up to 20 percent of patients have retinopathy, and as many as 10 percent have nephropathy at the time of diagnosis of type 2 DM. Macrovascular complications occur variably owing to individual risks, in addition to DM.

There is evidence from the UK Prospective Diabetes Study (1998) that the natural history of type 2 DM includes worsening glycemic control over time, despite increasingly intensive drug therapy. There is evidence from the DPP research group (Knowler et al., 2002) that persons at risk for future type 2 DM who participate in intensive lifestyle modification which includes regular aerobic exercise and calorie-restricted diet, and which results in sustained modest weight loss, develop DM at a lower rate than untreated individuals at risk. Collectively, these observations suggest that early identification and treatment of DM may be beneficial in delaying the severity and treatment resistance of hyperglycemia. Two recent reviews, including Monte Carlo modeling, concluded that screening for type 2 DM in high-risk persons age <34 may be cost-effective, particularly in African-Americans (CDC, 1998; Chen et al., 2001).

The Guideline Working Group is aware of the recent US Preventive Services Task Force (USPSTF) evidence based review "Screening for Type 2 Diabetes" (Annals Internal Medicine 2003, 138: 212-214, 215-229). The USPTSF concluded that the evidence was insufficient to recommend screening except for individuals with hypertension and hyperlipidemia. The VA-DOD recommendation to consider screening, based on expert opinion, is consistent with the USPSTF report in that clinicians will need to make their best judgment for their individual patients.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Screening of persons age ≥45 for DM.	Centers for Disease Control and Prevention (CDC), 1998 Rao, 1999 Tuomilehto et al., 2001	II-2	Good	B
2	Screening of persons age <45 with DM risk factors.	American Diabetes Association (ADA), 2002 Working Group Consensus	III III	Fair Poor	C
3	FPG - preferred screening test	ADA, 2002 Engelgau et al, 2000	III II-3	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)
Evidence Appraisal Report Question #2

B. Prevention Of Diabetes

OBJECTIVE

Prevent or delay onset of type 2 DM in high-risk patients.

BACKGROUND

Individuals with IGT are at high-risk for type 2 diabetes. Therapeutic lifestyle modification leading to weight loss, with frequent and ongoing professional monitoring and supervision, has been shown to benefit patients with IGT.

RECOMMENDATIONS

1. Patients with IGT (i.e., a FPG ≥110 mg/dL and <126 mg/dL) should be counseled about prevention of DM. Intensive lifestyle interventions to prevent diabetes include both regular aerobic exercise and a calorie-restricted diet to promote and maintain weight loss.
2. Patients with a BMI >25 are at high-risk for DM and should achieve and sustain weight loss of 5 percent or more.
3. Modification of lifestyle may be beneficial for all patients and may be considered in patients with risk factors for diabetes (other than IGT).

DISCUSSION

Two high quality RCTs addressed the impact of weight loss/exercise on the development of type 2 diabetes in adults with IGT (Swinburn et al., 2001; Tuomilehto et al., 2001). Both studies concluded that *diet and/or exercise, as compared to placebo, delayed the onset of diabetes in patients with glucose intolerance.* In addition, Knowler et al. (2002) found that *diet and exercise were significantly more effective than metformin in prevention of diabetes in glucose intolerant patients.*

Two lower quality RCTs also showed that *diet and/or exercise will delay the onset of diabetes in glucose-impaired individuals (*Knowler et al., 2002; Pan et al., 1997).

Institution of a well-designed dietary and exercise program can delay the development of type 2 DM in high-risk individuals. Whether similar results can be achieved in a primary care setting remains to be seen. On the basis of these results, physicians should recommend such programs to patients with IGT.

S1. Prevention of Diabetes Reference Table

Reference	Design/Patients	Intervention / Comparison	Outcomes/Conclusions
KNOWLER et al., 2002	RCT of 3,234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations; Mean age 50.6; Mean BMI 34.0; 65% females, 45% minorities.	Three groups: placebo, metformin, lifestyle modification program with goals of at least 150 minutes of physical activity per week, and at least 7% weight loss. Average follow-up was 2.8 years.	Incidence of diabetes was 11.0 cases per 100 person-years in placebo group, 7.8 in metformin, and 4.8 in lifestyle intervention group. Lifestyle intervention group reduced incidence by 58% (95%CI, 48-66%) as compared with placebo; Metformin reduced incidence by 31% (95% CI, 17-43%). The incidence of diabetes was 39 percent lower in the lifestyle-intervention group than in the metformin group (95% CI, 24-51%). Number needed to treat (NNT) 6.9 persons for 3 years to prevent 1 new case of diabetes.
TUOMILEHTO et al., 2001	RCT of 522 nondiabetic persons with IGT; Mean age 55; BMI 31; 172 men, 522 women.	Intervention group received individualized counseling aimed at weight reduction, total intake of fat, increased fiber, and increased physical activity Control group received general oral and written information about diet and exercise at base line and subsequent annual visits, but no individual program.	Mean weight loss in intervention group at end of 1 year was 4.2 5.1 kg in the intervention group and 0.8 3.7 kg in the control group. Net loss at the end of year 2 was 3.5 5.5 kg in the intervention group and 0.8 4.4 kg in the control group. (P<0.001 for both comparisons). The cumulative incidence of diabetes after 4 years was 11% (95% CI, 6-15%) in the intervention group and 23% (95% CI, 17-29%) in the control group. During the trial, the risk of diabetes was reduced by 58% (P<.001) in the intervention group. NNT 22 adults with IGT for one year to prevent 1 case of diabetes.

Reference	Design/Patients	Intervention / Comparison	Outcomes/Conclusions
SWINBURN et al., 2001	5 year follow-up of a 1-year RCT; 176 patients with IGT entered with 103 completing at 5 years.	Reduced-fat ad-lib diet and monthly educational sessions on reduced-fat eating for 1-year vs. a usual diet and no education.	Weight decreased in the reduced-fat diet group compared to the control group (P<0.0001) greatest difference at year 1 (-3.3 kg), at 2 years (-3.2 kg), and at 3 years (-1.6 kg), and was no longer present at 5 years (1.1 kg). Glucose tolerance also improved. At 1 year 47% of the intervention group developed diabetes/glucose intolerance as compared to 67% of the control group (P<0.05). In subsequent years, there was no difference between groups.
PAN et al., 1997	RCT of 577 Chinese individuals with IGT.	Randomized by clinic into a control group or one of 3 treatment groups: diet only, exercise only, diet plus exercise. Follow-up at 2-year intervals over a 6-year period.	Cumulative incidence of diabetes at 6 years in the control group was 67.7% (95% CI, 59.8-75.2) compared to 43.8% (95% CI, 35.5-52.3) in the diet group, 41.1% 95% CI, 33.4-49.4) in the exercise group, and 46.0% (95% CI, 37.3-54.7) in the combined diet-exercise group. Each of the active intervention groups differed significantly from the control clinics (P<0.05). The relative decrease in rate of diabetes in the active treatment groups was similar when subjects were stratified as lean or overweight (BMI>25). The diet, exercise and diet-plus exercise groups were associated with 31% (P<0.03), 46% (P<0.0005), and 42% (P<0.005) reductions in risk of diabetes, respectively.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Weight loss and exercise counseling of patients with FPG ≥110.	Working Group Consensus	III	Poor	I
2	Diet and exercise leading to weight loss may slow progression to diabetes.	Knowler et al., 2002 Tuomilehto et al.,2001 Pan et al., 1997	I	Good	A
3	Weight loss for patients with a BMI >25.	Knowler et al., 2002 Tuomilehto et al., 2001 Pan et al., 1997	I	Good	A
4	Lifestyle modification for patients with other risk factors.	Field et al., 2001 Manson et al., 1992	II-2	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

MODULE G - GLYCEMIC CONTROL

ALGORITHMS AND ANOTATIONS

Completion Date: March, 2003
Release Date: October, 2003
Version 3.0

SUMMARY OF RECOMMENDATIONS

ASSESSMENT

1. Measure **HbA_1c** periodically to assess glycemic control over time.
2. Assess the postprandial plasma glucose (**PPG**) level for patients with:
   - Elevated HbA_1c (not at target) but a normal fasting plasma glucose level
   - Frequent troublesome hypoglycemic symptoms during waking active hours

   Use the PPG level to modify the therapy.
3. Patients with recurrent or severe **hypoglycemia** should be evaluated for precipitating factors that may be easily corrected (e.g., missed meals, incorrect administration of insulin [dosage or timing], and exercise).
4. Patients with diabetes should be assessed for **knowledge, performance skills, and barriers** (e.g., psychosocial, personal, or financial) to full compliance.

GLYCEMIC CONTROL TARGET RANGE

1. Each patient's glycemic target range must be individualized, based on the provider's appraisal of the risk-benefit ratio for that individual, and the patient's medical, social, and psychological status. The risk of hypoglycemia should be specifically considered in recommending the target goal.
   - HbA_1c target should be kept **<9 percent** for all patients to avoid symptoms of hyperglycemia.
   - For patients with very mild or no microvascular complications of diabetes, and those free of major concurrent illnesses and with a reasonable life expectancy, the HbA_1c target should be **<7 percent**.
   - For patients with advanced microvascular complications and/or major comorbid illness, or who have a shortened life expectancy (5 to 10 years), **aggressive glucose lowering** may not be warranted because of limited benefit in reducing the absolute risk of microvascular complications.
   - Individual **treatment goals** must be established with the patient based on the extent of the disease, comorbid conditions, and patient preferences.

TREATMENT OPTIONS

1. Patients with type 1 diabetes mellitus (DM) should receive **insulin replacement therapy**.
2. On at least a temporary basis, the use of **intermediate- or long-acting insulin** for controlling fasting plasma glucose, alone or in addition to oral agents, should be considered for patients with type 2 DM in whom:
   - Oral agents have proven ineffective, intolerable, or are contraindicated.
   - Rapid restoration of euglycemia is desirable (e.g., patients with persistent symptoms of diabetes or with hyperglycemia in perioperative and/or critical care settings).
   - Pregnancy is desired or has already occurred.
   - HbA_1c is >1.5 percent above target.
   - Relative insulin deficiency is suggested by weight loss and persistent, non-fasting ketosis.
3. **Diet** and **exercise** and **lifestyle modification** should be encouraged.
   - Institution of diet and exercise is usually the appropriate initial management in patients with new onset type 2 diabetes, depending upon the severity of the symptoms, psychosocial evaluation, and overall health status.
4. If treatment goals are not achieved with diet and exercise alone, drug **monotherapy** should be initiated.

   Initial monotherapy with a sulfonylurea or biguanide (i.e., metformin) should be used as first line drug therapy. Sulfonylurea can be considered for most patients with type 2 diabetes; however, for those who are significantly overweight (body mass index [BMI] >25), initial monotherapy with a biguanide may be preferable.

   Thiazolidinediones (TZDs) are NOT recommended as monotherapy for patients with type 2 DM, unless there is documented and unacceptable intolerance to metformin and available sulfonylurea agents.

   Other oral agents, while less effective, are still appropriate first line agents if the desired increase in HbA_1c is proportionally less or if there are additional contraindications to the other first line medications.

5. If the glycemic target level is not achieved with one oral agent alone, **combination oral and/or insulin therapy** is recommended.

Combination Oral Agent Therapy

A **biguanide** (i.e., metformin) may be combined with a **sulfonylurea**.

Alpha-glucosidase inhibitors may be used in conjunction with a sulfonylurea or sulfonylurea/biguanide combination in patients whose postprandial blood glucose is inadequately controlled, but whose fasting glucose is in the desired range on sulfonylurea or sulfonylurea/biguanide regimens.

Addition of a **thiazolidinedione** (TZD) in failed monotherapy with a sulfonylurea should be considered only if the addition of metformin has failed and HbA_1c is within 1.5 percent of the target level. Addition of insulin to a sulfonylurea should be considered if a >1.5 percent decrease in HbA_1c is desired.

Addition Of Oral Agents To Insulin Therapy

Addition of **bedtime insulin therapy** to an existing combination oral agent regimen may be a treatment option when the glycemic control target is not achieved by an all-oral regimen. Intermediate-acting insulin in a single bedtime dose may be used in conjunction with oral monotherapy with either sulfonylurea or biguanide, or in addition to combined sulfonylurea/biguanide therapy.

Biguanide (i.e. metformin) or **TZDs** can be considered as an adjuvant therapy to insulin for the purpose of achieving glycemic target goals. Metformin is the preferred agent to add to an existing insulin regimen because of equal efficacy to glitazones and a known safety profile. **Thiazolidinedione** are an alternative if metformin is contraindicated or a trial of metformin has failed to achieve the target HbA_1c. Addition of oral agents with existing insulin may be considered in the following circumstances:

- Patient is on >1unit per kg of insulin in divided dosages, AND
- Insulin dose has been actively adjusted in an attempt to improve glycemia, AND
- HbA1c >1 percent above the target, AND
- There is documented adherence to MNT or a referral to MNT

Baseline and follow-up efficacy (at 6 months) are necessary for continuation of oral therapy. A referral to a diabetes care team for assistance with patient management should be considered.

In patients treated with **large doses of insulin**, addition of a TZD may reduce the insulin requirement and produce improved glycemia, with reduction of HbA_1c by 1 percent.

Carefully selected individuals may benefit from **three-drug oral hypoglycemic therapy**. In general, these patients may benefit from referral to a diabetes care team.

6. Insulin therapy may also be used when given in multiple daily doses, if the glycemic control target has not been reached with oral therapy.

The use of insulin lispro or glargine is not recommended for routine use in the treatment of type 2 DM, as there is no evidence that it has any inherent superiority to more established insulin preparations in lowering HbA1c levels.

Insulin glargine may be considered in the following settings:

- In the insulin-treated patient with frequent, severe nocturnal hypoglycemia.
- As a basal insulin for patients on multiple daily insulin injections.

In patients treated with insulin, regular insulin is recommended for most patients that require mealtime coverage.

Dietary counseling and individualized education should accompany initiation or change of mealtime insulin in response to hyperglycemia or hypoglycemia.

In patients treated with insulin, alternatives to regular insulin include aspart and lispro, and should be considered in the following settings:

- Demonstrated requirement for pre-meal insulin coverage due to postprandial hyperglycemia AND concurrent frequent hypoglycemia
- Patients using an insulin pump (Note: aspart is FDA-approved for use in an insulin pump: satisfactory outcomes have also been reported using lispro in pumps.)

7. Patients who fail to attain the target glycemic control goal despite ongoing care, education, and medication adjustment in the primary care setting may benefit from **referral to a diabetes care team** for comprehensive assessment and intensified management.

FOLLOW-UP

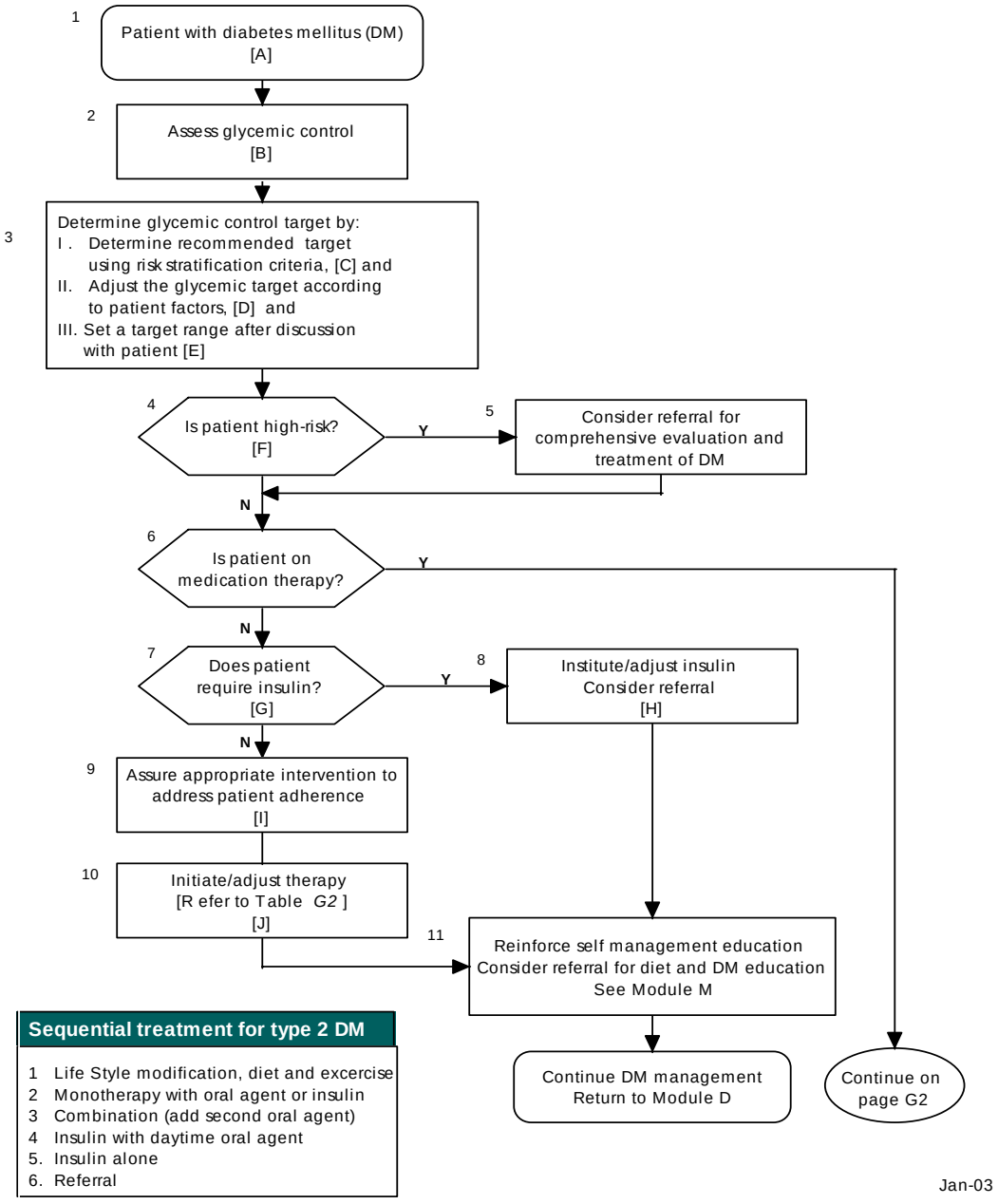
1. Patients should be scheduled for **appropriate follow-up** to evaluate response, tolerability to therapy, goal re-assessment and management of acute and chronic problems.

   The frequency of primary care provider visits for patients with diabetes who are meeting treatment goals and who have no unstable chronic complications should be individualized.

   When there is a sudden change in health status or when changes are made to the treatment regimen, follow-up within one month or sooner may be appropriate.
2. Treatment goals should be **periodically reassessed** based upon patient-specific factors, including changes in the patient's health status, adverse drug reactions, adherence to therapy, and preferences.

MANAGEMENT OF DIABETES MELLITUS
Module G - Glycemic Control

G1



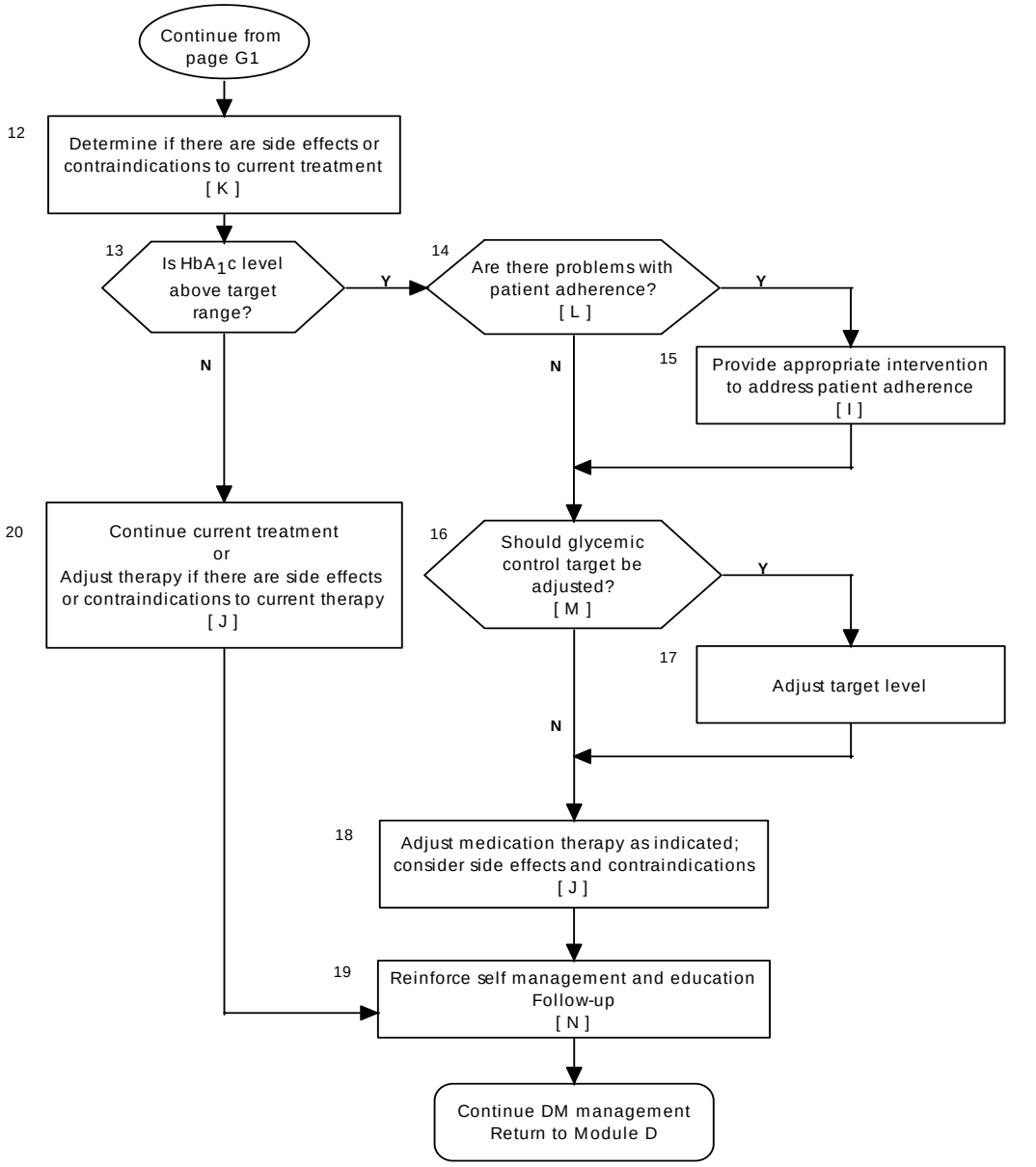
Sequential treatment for type 2 DM

1 Life Style modification, diet and excercise
2 Monotherapy with oral agent or insulin
3 Combination (add second oral agent)
4 Insulin with daytime oral agent
5. Insulin alone
6. Referral

Jan-03

MANAGEMENT OF DIABETES MELLITUS
Module G - Glycemic Control

G2



Jan-03

ANNOTATIONS

A. Patient With Diabetes Mellitus (DM)

Every patient with DM, regardless of its duration, needs to negotiate an appropriate goal for glycemic control target with his or her provider, and plan a treatment strategy to achieve this goal.

Glycemic control should be reevaluated at every regular interim visit or in the context of visits that relate to other concurrent problems that could affect glycemic control.

B. Assess Glycemic Control

OBJECTIVE

Determine the patient's level of glycemic control.

BACKGROUND

Glycosylated hemoglobin, measured or reported as hemoglobin A_1c (HbA_1c), is the only laboratory test measure validated in randomized controlled trials (RCTs) as a predictor of risk for microvascular complications. Hence, periodic measurement of HbA_1c is recommended to assess glycemic control over time.

RECOMMENDATIONS

1 HbA_1c should be measured periodically to assess glycemic control over time.
2 Postprandial plasma glucose (PPG) level should be assessed in patients with:
    Elevated HbA_1c (not at target) but a normal fasting plasma glucose level
    Frequent troublesome hypoglycemic symptoms during waking active hours
3 The PPG level should be used to modify the therapy.

DISCUSSION

Assessment of glycemic control requires an understanding of the assessment methods, as well as their accuracy (see Appendix G-1, Measurements of Glycemic Control).

Normalization of HbA_1c has been shown to substantially reduce the microvascular and neuropathic complications of diabetes. The measurement of HbA_1c is subject to inter-laboratory variability, red cell survival, and the composition of red cell hemoglobin. The HbA_1c reflects average blood glucose over a period of time. Hence, an HbA_1c of 7 percent may indicate that the blood glucose level is <140 mg/dL throughout the day, but may also indicate that the blood sugar is >250 mg/dL for half of the day and <50 mg/dL for the remaining half of the day.

Assessment of Postprandial Plasma Glucose

Glycemia can be assessed through the measurement of PPG, normal fasting plasma glucose level (FPG), and HbA_1c. The HbA_1c level best correlates with the severity of hyperglycemia over time. However, HbA_1c is an integrated value. Some patients have normal fasting glucose levels and high HbA_1c; others have normal HbA_1c but high fasting blood glucose levels. Troubleshooting poor glycemic control requires more than a measurement of HbA_1c.

There are insufficient data to accurately determine the relative contribution of the FPG and PPG to HbA_1c. It appears that FPG is somewhat better than PPG in predicting the level of HbA_1c, especially in patients with type 2 diabetes. The only setting in which PPG monitoring has been shown to improve outcomes is gestational diabetes. Regardless of whether the FPG or PPG level is determined, it is not the collection of the data, but

rather the use of the data to make clinical decisions, that lead to improvements in diabetes control. Dose adjustment of short-acting insulin may be impractical without the measurement of PPG.

Elevated glucose values post challenge of 2-h oral glucose tolerance test [OGTT] have been associated in some epidemiological studies with increased cardiovascular risk, independent of fasting plasma glucose. PPG levels >140 mg/dL are unusual in nondiabetic individuals, though large evening meals can be followed by plasma glucose values up to 180 mg/dL. Pharmacological agents are available that primarily modify PPG and thereby reduce HbA_1c in parallel. Therefore, in individuals who have pre-meal glucose values within targets, but who are not meeting HbA_1c targets, consider monitoring PPG 1 to 2 hours after the start of the meal and treating to reduce average PPG values <180 mg/dL, which may lower HbA_1c. However, it should be noted that this approach has not been shown to reduce complications in outcome studies in patients with either type 1 or type 2 diabetes (ADA, 2002).

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Measurement of PPG.	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

C. Determine Recommended Glycemic Control Target Using Risk Stratification Criteria

OBJECTIVE

Determine the recommended target based on the patient's absolute risk for developing microvascular complications.

BACKGROUND

Lowering HbA_1c has been associated with a reduction in microvascular and neuropathic complications of diabetes. Determination of an optimal target HbA_1c level is based upon the risk for developing microvascular complications. The individual risk is dependent on life expectancy, absence or presence of pre-existing microvascular complications, and genetic factors. The likelihood of developing microvascular complications is largely dependent on how high the individual's glucose level has been and for how long. The duration of glycemic exposure is similar to smoking duration for cancer risk; the severity of hyperglycemia is similar to the number of packs of cigarettes smoked daily. The HbA_1c level is the best measure of the severity of hyperglycemia over time. The presence and stage of microvascular complications reflects prior duration and severity of hyperglycemic exposure and individual susceptibility to development of complications.

RECOMMENDATIONS

1. Each patient's glycemic target range must be individualized, based on the provider's appraisal of the risk-benefit ratio for that individual.
2. HbA_1c target for any patient with diabetes should be kept <9 percent to avoid symptoms of hyperglycemia.
3. The patient with very mild or no microvascular complications of diabetes, and who is free of major concurrent illnesses and has a reasonable life expectancy, should have an HbA_1c target of $\leq$7 percent.
4. The patient with advanced microvascular complications and/or major comorbid illness, or short life expectancy is less likely to show survival benefit; therefore, aggressive glucose lowering may not be warranted.

5. Risk of hypoglycemia should be considered in recommending a target goal.

DISCUSSION

The glycemic target range must be individualized for each patient based on the provider's appraisal of the risk-benefit ratio for that individual. Additionally, following counseling, the patient's own preferences should be factored into the decision-making. The provider and the patient must mutually determine the target value after considering the risks, benefits, the proposed therapeutic regimen, and patient preference.
In general, patients with very mild or no microvascular complications of diabetes, and those free of major concurrent illnesses adversely affecting quality of life and survival, are most apt to benefit from intensive treatment intended to achieve near-normoglycemia ($\leq$ 7%). Conversely, patients with advanced microvascular complications and/or a major comorbid illness may be less likely to show survival benefit, may continue to show progression of microvascular disease, and frequently may be at increased risk for severe hypoglycemic morbidity when normoglycemic control is attempted.

In the absence of a readily available mechanism to assist the provider in the estimation of life expectancy, Table G-1 is intended to provide an overall perspective that considers microvascular complications and comorbid illness and that can aid the provider in counseling patients with diabetes about individual glycemic control goals.

Table G-1. Determination of Target HbA_1c Level

Major Comorbidity (d) or Physiologic Age	**Microvascular Complications**		
	Absent or Mild (a)	**Moderate (b)**	**Advanced (c)**
Absent >15 years of life expectancy	7% (<1% above upper normal range)	<8% (<2% above upper normal range)	<9% (<3% above upper normal range)
Present (e) 5 to 15 years of life expectancy	<8 % (<2% above upper normal range)	<8% (<2% above upper normal range)	<9% (<3% above upper normal range)
Marked (f) <5 years of life expectancy	<9% (<3% above upper normal range	<9% (<3% above upper normal range	<9% (<3% above upper normal range)

(a) Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria, and/or mild neuropathy.
(b) Moderate microvascular disease is defined by pre-proliferative (without severe hemorrhage, intra-retinal microvascular anomalies [IRMA], or venous bleeding) retinopathy or persistent, fixed proteinuria (macroalbuminuria) and/or demonstrable peripheral neuropathy (sensory loss).
(c) Advanced microvascular disease is defined by severe non-proliferative (with severe hemorrhage, IRMA, or venous bleeding) or proliferative retinopathy and/or renal insufficiency (serum creatinine level > 2.0 mg/dL) and/or insensate extremities or autonomic neuropathy (e.g., gastroparesis, impaired sweating, or orthostatic hypotension).
(d) Major comorbidity includes, but is not limited to, any or several of the following conditions: cardiovascular disease, chronic obstructive pulmonary disease, chronic liver disease, stroke, and malignancy.
(e) Moderate degree of major comorbid condition.
(f) Severe degree or end-stage major comorbid condition.

Reduction in the incidence of microvascular complications of diabetes is primarily a function of glycemic control (HbA_1c level) and duration of diabetes (life expectancy), modified by the presence of complications, and family history. See Appendix G-2, Estimating Benefit and Risk of Glycemic Control.

Treatment that reduced average HbA_1c to approximately 7 percent (approximately 1 percent above the upper limits of normal) was associated with fewer long-term, microvascular complications; however, intensive control has been found to increase risk of hypoglycemia and weight gain. Epidemiological analyses suggest that there is no threshold or lower limit of HbA_1c above normal levels at which further lowering has no benefit. An average HbA_1c >8 percent is associated with a higher risk of complications, at least in patients with reasonably long life expectancies. The relative benefit of achieving an A_1c of 7 percent is documented in RCTs with relative risk reductions of 15 to 30 percent per 1 percent absolute reduction in HbA_1c.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Progression to non-proliferative retinopathy.	DCCT Research Group, 1993 Klein, 1995a Ohkubo et al., 1995	I	Good	A
2	Progression to proliferative retinopathy.	Klein et al., 1994	I	Fair	B
3	Progression to microalbuminuria.	DCCT Research Group, 1993 Kawazu et al., 1994 Krolewski, 1995 Ohkubo et al., 1995	I	Good	A
4	Progression to proteinuria.	DCCT Research Group, 1993 Ohkubo et al., 1995	I	Good	A
5	Progression to blindness.	DCCT Research Group, 1993 Ohkubo et al., 1995	I	Good	A
6	Progression to end-stage renal disease.	DCCT Research Group, 1993 Klein, 1995a Ohkubo et al., 1995	I	Fair	B
7	Progression to neuropathy.	DCCT Research Group, 1993 DCCT Research Group, 1995	I	Good	A
8	Progression to amputations.	Klein et al., 1994 Mayfield et al., 1996	I	Fair	B
9	Myocardial infarction, stroke.	Abraira et al., 1997 Anderson et al., 1995 DCCT Research Group, 1993 Klein, 1995a Ohkubo et al., 1995 Singer et al., 1992	I	Good	A
10	Effect of DM on life expectancy.	Goodkin, 1975 Panzram et al., 1987 Singer, 1992	I	Fair	B
11	Duration of DM and incidence of end-stage microvascular complications.	Humphrey et al., 1989 Klein et al., 1994, 1995a Palmberg et al., 1981 UKPDS, 1995	I	Fair	B
12	Effect of ethnicity on glycemic target levels.	Haffner et al., 1988 Hamman et al., 1989 Lee et al., 1992 Nelson et al., 1988 Rabb et al., 1990	II-1	Fair	B
13	Pre-existing retinopathy or	DCCT Research Group, 1993	I	Good	A

	microalbuminuria as a risk factor for progression.	Ohkubo et al., 1995			
14	Progression to microvascular complication (primary laser therapy).	UKPDS, 1998	I	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix A)

D. Adjust The Glycemic Target According To Patient Factors

OBJECTIVE

Ensure that the recommended target value for HbA_1c can be safely achieved by the patient, taking into consideration individual risk, benefit, and preference.

BACKGROUND

The risks of therapy are different for each patient, depending upon the individual's medical, social, and psychological status. Thus, the risks of a proposed therapy must be balanced against the potential benefits.

RECOMMENDATIONS

1. Risks of a proposed therapy should be balanced against the potential benefits, based upon the patient's medical, social, and psychological status.

DISCUSSION

Factors to consider in lowering the HbA_1c target include, but are not limited to:

Appropriate medical support and psychosocial environment
Pregnancy or the intention to become pregnant
Willingness and ability to self monitor blood glucose and to make appropriate lifestyle change

Factors to consider in raising the HbA_1c target include, but are not limited to:

History of severe, recurrent hypoglycemia
The possible consequence of adverse effects associated with hypoglycemia (e.g., consider cardiovascular disease, anticoagulation, and use of dangerous equipment)
Alcohol or substance abuse
The presence of multiple end-stage microvascular complications, including macular edema, proliferative retinopathy and macroproteinuria, especially with elevated serum creatinine
Symptomatic cardiovascular disease

Factors that demonstrate patient preference:

Quality of life
Specific risks of patient therapeutic options

E. Set A Glycemic Target Range After Discussion With Patient

OBJECTIVE

Establish the patient's readiness and willingness to achieve the target.

RECOMMENDATIONS

1. A specific target range of glycemic control should be negotiated by the patient and provider after discussing the risks and benefits of therapy.
2. If necessary, the patient should be referred to an endocrine/diabetes clinic or a case manager to meet glycemic control target goals.

DISCUSSION

A target range of HbA_1c based upon life expectancy, microvascular complications, and familial history, is a starting point for negotiation with the patient. It does not mean that a lower HbA_1c level will not be beneficial, nor does it mean that the provider and the patient should not negotiate a lower one. Rather, it implies that there is a decreased benefit of excellent glycemic control in the setting of limited survival expectation or pre-existing moderate-to-advanced microvascular complications of diabetes. These factors should be taken into account when evaluating the risks and benefits of pharmacological therapy, as well as patient preferences. In addition, it should be recognized that reduction in risk from decreasing HbA_1c is a continuum, so a negotiated target level does not have to be exactly 7.0, 8.0, or 9.0 percent. The patient should make the final decision about a specific target value of glycemic control after a full discussion of the risks and benefits of therapy with his or her provider.

Providers should consider that some patients may require more immediate, urgent, or aggressive management in primary care. Some cases may require referral to an endocrine/diabetes clinic or to a case manager, in order to meet glycemic control target goals.

F. Is Patient High-Risk?

OBJECTIVE

Identify the high-risk patient for whom subspecialty consultation would be appropriate to assist in the development of a treatment plan and/or supervise ongoing care.

RECOMMENDATIONS

1. The patient with HbA_1c >9.5 percent should be considered for aggressive management on an expedited basis.
2. The patient who is on high-dose multiple agents should be considered for referral.

High-risk DM patients include those who:

- Have type 1 DM (especially patients with history of hospitalizations for metabolic complications and/or patients who are receiving intensive insulin therapy)
- Have recurrent episodes of incapacitating hypo- and/or hyperglycemia
- Have poor recognition of hypoglycemia and who have a history of severe hypoglycemic reactions (including coma, seizures, or frequent need for emergency resuscitation)
- Have new-onset insulin-requiring DM
- Have visual and/or renal impairment
- Have psychosocial problems (including alcohol or substance abuse) that complicate management
- Have HbA_1c > 9.5 percent

DISCUSSION

The Diabetes Quality Improvement Project (DQIP), a federal/private sector coalition, reached the consensus that HbA_1c >9.5 percent represents high-risk glycemic control even in the absence of case mix adjustment.

Consequently, providers should consider a patient with HbA_1c >9.5 percent for aggressive management on an expedited basis. Patients who are on high-dose multiple agents should also be considered for referral.

G. Does Patient Require Insulin?

OBJECTIVE

Identify the patient for whom insulin treatment is the only viable alternative.

RECOMMENDATIONS

1. The patient with type 1 DM should receive insulin replacement therapy.
2. The patient with type 2 DM or DM of undetermined cause who exhibits significant or rapid weight loss and/or persistent non-fasting ketonuria has at least severe relative insulin deficiency and will likely require insulin therapy on an indefinite basis.

DISCUSSION

All patients with type 1 DM by definition must receive insulin therapy. Additionally, patients with type 2 diabetes or diabetes of undetermined cause who exhibit significant or rapid weight loss and/or persistent non-fasting ketonuria have at least severe relative insulin deficiency and will require insulin therapy on an indefinite basis.

Weight loss and ketonuria are indications of a catabolic state for which insulin is the preferred therapy in type 2 DM. Insulin is an anabolic hormone, and is often beneficial in such circumstances, especially if there is a concurrent illness.

H. Institute/Adjust Insulin; Consider Referral

OBJECTIVE

Improve/achieve glycemic goals using insulin.

RECOMMENDATIONS

1. All patients with type 1 DM should be referred to a diabetic clinic with multidisciplinary resources (e.g., diabetologist, diabetic nurse, educator/manager, and registered dietitian) for institution and adjustment of insulin therapy.
2. If expeditious referral is not possible, the primary care provider should institute "survival" insulin therapy.
   Calculate total daily dose (TDD) of 0.5 units/kg body weight/day.
   Two-thirds of the TDD administered 30 minutes prior to breakfast as two-parts human neutral protamine Hagedorn insulin (NPH) insulin and one-part human regular insulin.
   Remaining third of the TDD can be split equally, as human regular insulin 30 minutes before supper and as human NPH insulin at bedtime.

DISCUSSION

Because type 1 DM is caused by absolute insulin deficiency, insulin replacement therapy is the only viable treatment option. Insulin therapy for patients with type 1 DM must be individualized and customized according to multiple lifestyle factors. Institution and adjustment of insulin therapy is most efficiently accomplished by

referral to a diabetic clinic with multidisciplinary resources including diabetologists, diabetic nurses, educator/managers, and registered dietitians. If expedient referral cannot be accomplished, the primary care provider should institute "survival" insulin therapy. This can be initiated at a calculated TDD of 0.5 units/kg body weight/day. Two-thirds of the TDD administered 30 minutes prior to breakfast as two-parts human NPH insulin and one-part human regular insulin. The remaining third of the TDD can be split equally, as human regular insulin 30 minutes before supper and as human NPH insulin at bedtime (see Annotation J-3, Insulin Therapy).

I. Assure Appropriate Intervention To Address Patient Adherence

OBJECTIVE

Assure proper patient monitoring and contact with the healthcare team.

RECOMMENDATIONS

1. Patients with diabetes should be assessed for knowledge, performance skills, and barriers to full compliance.
2. If psychosocial, personal, or financial barriers are identified, additional resources should be consulted, as applicable (e.g., mental health, medical social work, or financial counselors).

DISCUSSION

An important touchstone for successful management of type 2 diabetes is comprehensive patient education and internalization of diabetes self-management knowledge and performance skills (see Module M). Ongoing professional contact allows for feedback, answering questions, reinforcing positive skills and behaviors, and improving suboptimal skills and behaviors. Ideally, the diabetes nurse, educator/manager, and dietetic consultant will be involved as partners with the primary care provider. Together they should assess the patient's knowledge, performance skills, and barriers to full compliance. If psychosocial, personal, or financial barriers are identified, additional resources, such as mental health, medical social work, or financial counselors can be consulted as applicable.

J. Initiate/Adjust Therapy

OBJECTIVE

Achieve glycemic target goals by the most cost-effective and least invasive means.

BACKGROUND

Long-term outcomes of treatment of DM (i.e., microvascular complications) are related to the degree of glycemic control but not to the means used to achieve it (i.e., diet/exercise versus oral hypoglycemic agent versus insulin, or any known combination therapy). Based on this principle, therapy should be tailored to individual preferences, needs, and pragmatic considerations, such as cost and ease of compliance.

RECOMMENDATIONS

1. Individual treatment goals must be established with the patient based on the extent of the disease, comorbid conditions, and patient preferences.
2. Institution of diet and exercise is usually the appropriate initial management in patients with new onset type 2 diabetes, depending upon severity of symptoms, pyschosocial evaluation, and overall health status. Encourage diet and exercise and lifestyle modification.
3. If treatment goals are not achieved with diet and exercise alone, drug therapy should be initiated.
4. There is no evidence that blood glucose monitoring in stable type 2 DM patients is of clinical benefit. If self-monitoring is to be done, a twice-weekly regimen is usually sufficient. Special situations, such as acute intercurrent illness, frequent hypo- or hyperglycemia, or changes in medication regimen, may justify more frequent monitoring on a temporary basis.

The concept of sequential treatment is commonly employed in clinical management of chronic diseases. The sequential steps for glycemic control therapy are summarized in Table G-2 and Diagram G1.

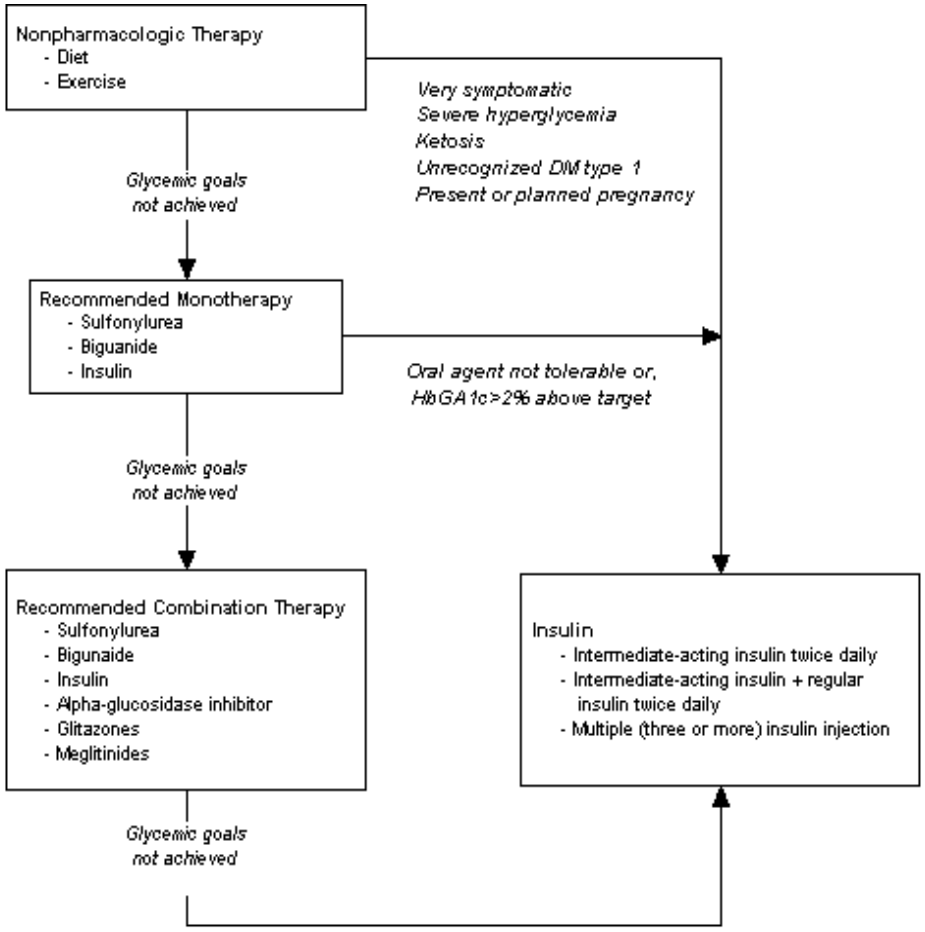
Table G-2: Sequential Treatment for Type 2 DM

	Therapy	**Drugs**	**Expected reduction in HbA_1c ****
1	Lifestyle modification, diet, and exercise.	None	—
2	Lifestyle modification, diet, and exercise *and* **Monotherapy** with oral agent or insulin.	Sulfonylurea or biguanide	1 to 2%
3	Lifestyle modification diet and exercise *and* **Combination** (add a second oral agent).	Sulfonylurea + biguanide Sulfonylurea/biguanide + alpha-glucosidase inhibitor Sulfonylurea/biguanide + thiazolidenedione Biguanide + repaglinide/ nateglinide	1 to 2% 0.5 to 1% 0.7 to 1.75% 0.1 to .3%
4	**Insulin** with oral agent.	Biguanide + insulin thiazolidenedione + insulin Sulfonylurea + insulin	0.2 to 2.6%

5	Insulin.	Insulin alone	2%
6	Referral.	None	—

*** Over a 2 to 3 month period of follow-up*

Diagram G1. Stepwise Approach to Glycemic Control



DISCUSSION

Non-Pharmacologic Therapy

Each patient with newly diagnosed DM should attempt non-pharmacological treatment with diet and lifestyle modification prior to the use of medications. Lifestyle changes include diet (see Module M, Self-management and Education), exercise for at least 30 minutes per day on most days of the week (as appropriate, after a detailed medical examination), weight loss if indicated, and smoking cessation. Limit alcohol to no more than 2 drinks per day for men and 1 drink per day for women (1 drink=12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits). Diet and exercise should be given at least a 3 month trial before drug therapy is started, unless fasting glucose $\geq$250 mg/dL or $\leq$250 mg/dL with symptoms of hyperglycemia.

Pharmacotherapy

When selecting an agent, consideration must be given to efficacy, contraindications, drug interaction, side effects, cost, and patient preferences. . There is considerable evidence from the UKPDS 28 (1998) that type 2 DM is a progressive disease, which will necessitate the adjustment of medication dosage and additive pharmacotherapy over time

Elderly patients are at a higher risk for drug-associated hypoglycemia, due to altered metabolism and excretion rates, impaired symptom recognition, and potentially attenuated counter-regulatory responses. Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management.
For a summary of the evidence and detailed pharmacologic tables please see Appendix G3.

J-1. MONOTHERAPY

Both metformin and sulfonylureas decrease HbA_1c to a similar degree.
There is a greater weight gain associated with the use of sulfonylurea versus metformin.
Studies indicate that weight loss is an important factor in the control of HbA_1c.
In overweight patients, treatment with metformin may result in reduced diabetes endpoints for all causes of mortality and stroke.
Other oral agents, while less effective, are still appropriate first line agents if the desired increase in HbA_1c is proportionally less or if there are additional contraindications to the other first line medications.

Published studies comparing glitazone drugs with placebo show average HbA_1c reductions on the order of one percent, which is comparable to monotherapy with either sulfonylurea or metformin. The current cost of glitazones is significantly greater than either metformin or any available sulfonylurea. Weight gain and fluid retention are common side effects of glitazone therapy, and may worsen or precipitate congestive heart failure. Increases in low-density lipoprotein-cholesterol (LDL-C), averaging around 13 and 6 percent, have been observed with rosiglitazone and pioglitazone, respectively. Triglycerides decrease with pioglitazone, whereas the effect with rosiglitazone is variable. Both pioglitazone and rosiglitazone use have been associated with increased high density lipoprotein - cholesterol (HDL-C).

Metformin is as efficacious as the sulfonylureas, with a resultant 1.2 percent fall in HbA_1c for both drugs. However, as most patients with type-2 diabetes are overweight, “the net 5 percent reduction in weight reduction in favour of metformin may be of benefit in the management of the insulin resistant syndrome associated with non-insulin dependent diabetes mellitus" (Campbell, 1995).

Inzucchi (2002) reviewed the oral medications and concluded that in terms of antihyperglycemic effect alone, there was no compelling reason to favor one of the major categories of antidiabetic agents (sulfonylureas [SFUs], biguanides, and thiazolidinedione [TZDs]) over another. However, metformin's performance in the

UKPDS in obese patients, i.e., its lack of associated hypoglycemia and weight gain, make it the most attractive option for obese — if not all — patients who have type 2 DM but no contradindications to its use.

It remains unknown whether TZDs will provide for additional cardiovascular protection for patients with type 2 DM, thus their cost and adverse-effect profile make them less fitting as monotherapy or secondary treatment, unless metformin is contraindicated or poorly tolerated. The actual choice of a drug, however, must be based on a variety of clinical factors and individual patient characteristics, including predisposition to adverse effects, the degree of hyperglycemia, and cost. The paramount concern of the physician should be attainment of the negotiated glycemic target for the individual patient with whatever antiglycmic regimen is appropriate and well tolerated.

EVIDENCE

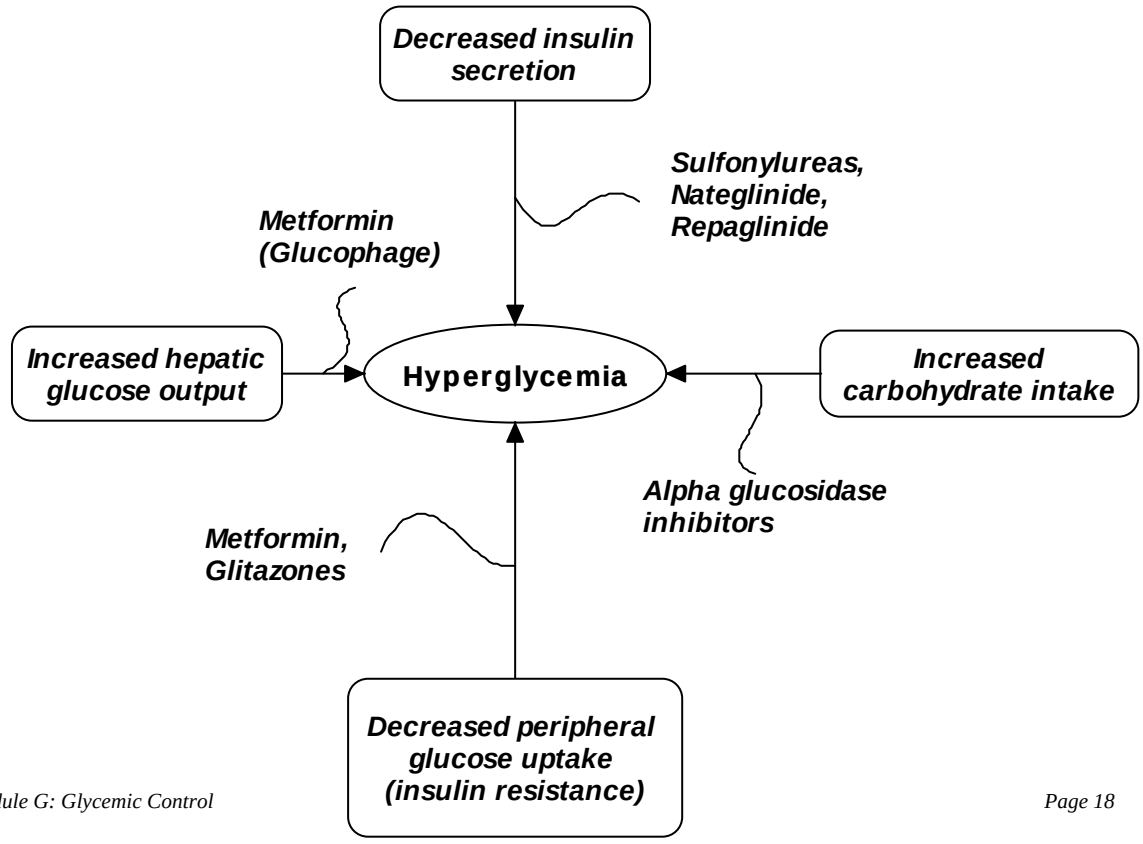
	Recommendation	Sources	QE	Overall Quality	R
1	Sulfonylurea as first line for most patients.	Inzucchi, 2002 Johansen, 1999	I	Fair	B
2	Metformin as first line for overweight patients.	Johansen, 1999 UKPDS 34, 1998	I	Good	A
3	Glitazones not preferred as monotherapy.	Chilcott et al., 2001 Ebeling et al., 2001 Malinowski & Bolesta, 2000 Nakamura et al., 2000	I II-1 I II-1	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

J-2. COMBINATION THERAPY

Combination of two hyperglycemic drugs has the benefit of reducing hyperglycemia by working on different mechanisms that cause hyperglycemia. The Diagram G2 illustrates the different mechanism of action for each class of drugs.

Diagram G2. Hyperglycemia Drugs Mechanism Of Action



Although the evidence is clear on the relative efficacy of the various medications, their usage needs to be guided by clinical practice. In reality, not all combinations of drugs used in practice are based on evidence.

Several factors should be considered when selecting combination therapy. These factors include, but are not limited to the following: how much the HbA_1c needs to be reduced, tolerability of an agent, relative or absolute contraindications a patient may have to using a particular agent, barriers to proper administration, and cost. Because of all these factors, several options for combination therapy should be available. Tables G-8 and G-9 (see Appendix G-3) are intended to assist the clinician in selecting combination therapy. Since the development of the previous guideline, recent data on combination therapy with the thiazolidinediones (TZDs) have been reported and are, therefore, presented in the annotations.

1. Glitazones In Combination With Other Agents

Several trials have each individually shown that the combination of a SFU + metformin or a SFU + glitazones result in improved HbA1c. Unfortunately there are no head-to-head trials comparing SFU + metformin versus SFU + rosiglitzone/pioglitazone in the setting of suboptimal monotherapy with SFU. However, there is one small comparative trial (n=31) which found that SFU + metformin was similar to SFU + troglitazone in terms of efficacy, side effects, and tolerability (Kirk et al., 1999). Given the lack of comparative data, factors such as safety, contraindications, and cost come into play.

Based upon a maximal efficacy of a 1.6 percent reduction (range 0.9 - 1.6 percent) with the use of metformin or glitazones, it is recommended that insulin should be a second line therapy if patients are not within 1.5 percent of their target HbA1c.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Metformin as add-on therapy to SFU for failed sulfonylurea treatment, if not contraindicated.	Kirk et al., 1999 UKPDS, 1998	I	Fair	B
2	Insulin as add-on therapy, if the patient is not within 1.5 percent of the target range.	Raskin et al., 2001 Rosenstock et al, 2002	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

Use of Metformin or Glitazones in Combination with Insulin

The primary goal of any therapy or combination therapy is to achieve glycemic control by reducing long-term microvascular complications. Glycemic control can almost always be attained with insulin monotherapy, although this may require more than one insulin injection or type of insulin. Occasionally, the risk of hypoglycemia makes intensive insulin management a less attractive choice. In addition, some patients may perceive that additional insulin either reflects badly on them or on their health status.

Clinical trials in which glitazones or metformin have been added to insulin regimens in patients with inadequately controlled HbA_1c have shown significant improvement in HbA_1c and in some cases, reduced insulin requirements. However, most of these trials did not compare the combination of glitzones with insulin to regimens of increasing insulin doses. Thus, there are limited data to suggest that this type of combination treatment is more likely to achieve the HbA_1c target when compared to intensification of an existing insulin regimen. Indeed, the average reduction in HbA_1c was approximately one percent. In some cases, onset of the effect on HbA_1c may be delayed by a few months. Most patients studied were taking 70 U insulin/day and few patients (approximately 15 percent) discontinued insulin as a result of the glitzone addition. Thus, this combination therapy regimen should be considered adjuvant, rather than as a potential substitute for insulin

treatment. While the currently available glitazones appear to be reasonably safe and do not have the potential for developing hepatoxicity, liver chemistry monitoring is still recommended. Metformin added to an insulin regimen has been similarly shown to significantly reduce HbA_1c. Since metformin carries a favorable safety profile with proven efficacy, it should be considered a preferred agent for this indication. Glitazones + insulin have shown an increase in edema and congestive heart failure (Chilcott et al., 2001).

Research has revealed several non-glycemic effects of glitazones, such as their effect on proteinuria, PAI-1, effects on vascular wall and atherosclerotic plaque, vascular reactivity, endothelial function and pancreatic B-cell function. These data are preliminary at best and do not, therefore, justify a preference for glitazones.

J-3. INSULIN THERAPY

Because type 1 DM is caused by absolute insulin deficiency, insulin replacement therapy is the only viable treatment option. Insulin therapy for patients with type 1 DM must be individualized and customized according to multiple lifestyle factors. A multidisciplinary diabetes care team most efficiently accomplishes institution and adjustment of insulin therapy. Members of such a team may include, but may not be limited to, the patient's primary care provider, an endocrinologist or other diabetes specialist, a certified diabetes educator or other instructor, or a registered dietitian or other nutrition specialist. Patients with type 1 DM are generally more sensitive to changes in insulin dose and are far more susceptible to episodes of hypoglycemia than patients with type 2 DM.

Many patients with type 2 DM can achieve their glycemic target with a single bedtime injection of long-acting insulin or split-mixed insulin, often in combination with an oral agent. Some patients will require intensified regimens to achieve their target glycemic range. Early use of insulin should be considered in any patient with extreme hyperglycemia, even if transition to therapy with oral agents is intended as hyperglycemia improves.

Insulin requirements vary widely among people with diabetes, even when other factors are similar. Types, frequency, and dosages of insulin must be individualized, considering the following factors:

- Type of diabetes
- Age
- Weight (presence or absence of obesity)
- Co-morbid conditions
- Presence of autonomic neuropathy
- Concomitant medications (specifically beta-blockers)
- Patient's ability to perform self-glucose monitoring and accurately inject insulin
- Complexity of management strategy (number of injections, variable dosing based on carbohydrate intake and pre-prandial glycemia)
- Risks and benefits of hypoglycemia, including psychosocial factors
- Magnitude and pattern of hyperglycemia

RECOMMENDATIONS

1. The patient with type 1 DM should receive insulin replacement therapy.
2. The care of patients with type 1 DM should be individualized, in consultation with a multidisciplinary diabetes care team. If expeditious consultation is not possible, the primary care provider should institute "survival" insulin therapy:
    - Calculate a total daily dose (TDD) of 0.5 units/kg body weight/day.
    - Two-thirds of the TDD administered 30 minutes prior to breakfast as two-parts human neutral protamine Hagedorn insulin (NPH) insulin and one-part human regular insulin.
    - Remaining third of the TDD can be split equally, as human regular insulin 30 minutes before supper and as human NPH insulin at bedtime
3. On at least a temporary basis, the use of intermediate- or long-acting insulin for controlling fasting plasma glucose, alone or in addition to oral agents, should be considered for patients with type 2 DM in whom:
    - Oral agents have proven ineffective, intolerable, or are contraindicated.

Rapid restoration of euglycemia is desirable, e.g., the patient with persistent symptoms of diabetes or with hyperglycemia in perioperative and/or critical care settings.

Pregnancy is desired or has already occurred.

HbA1c is >1.5 percent above target.

Relative insulin deficiency is suggested by weight loss and persistent, non-fasting ketosis.

4. Although the available intermediate- and long-acting forms of insulin include lente, ultralente, and glargine, NPH should be considered for most patients needing insulin to control fasting hyperglycemia.
5. Insulin glargine may be considered in the following settings:

   In the insulin-treated patient with frequent, severe nocturnal hypoglycemia.

   As a basal insulin for patients on multiple daily insulin injections.
6. In patients treated with insulin, regular insulin is recommended for most patients that require mealtime coverage.
7. Dietary counseling and individualized education should accompany initiation or change of mealtime insulin in response to hyperglycemia or hypoglycemia.
8. In patients treated with insulin, alternatives to regular insulin include aspart and lispro and should be considered in the following settings:

   Demonstrated requirement for pre-meal insulin coverage due to postprandial hyperglycemia AND concurrent frequent hypoglycemia

   Patients using an insulin pump (Note: aspart is FDA-approved for use in an insulin pump: satisfactory outcomes have also been reported using lispro in pumps.)

DISCUSSION

Management of type 1 and type 2 diabetes with intensive insulin therapy usually includes an intermediate- or long-acting basal component for between-meal and nocturnal glycemic control, together with preprandial bolus injections of a short-acting insulin for control of meal-stimulated increases in serum glucose levels (Gerich, 2002).

There have been few studies to address the relative merit of insulin glargine. For patients with type 1 diabetes, four RCTs have compared glargine at bedtime with NPH used once or twice daily. No consistent differences between NPH and insulin glargine were identified. *Differences in HbA_1c were small and there were no significant differences in the rate of glycemic events.* Pieber et al. (2000) did report a somewhat reduced incidence of nocturnal hypoglycemia, whereas Raskin et al. (2000) found a lower incidence with NPH. For patients with type 2 diabetes, two trials of relatively low quality (Ratner et al., 2000; and Rosenstock et al., 2000) found fewer episodes of symptomatic hypoglycemia and nocturnal hypoglycemia with glargine, at the expense of slightly higher HbA_1c.

A long-acting insulin is an essential component of a multiple injection regimen. Insulin glargine has features that make it a reasonable alternative to other intermediate to long-acting insulins in select patients. The Working Group recommends glargine for patients on multiple daily insulin injections. There are no RCTs evaluating glargine's use in this setting; rather, the pharmacokinetic/pharmacodynamic profile of glargine suggests a more steady insulin level that may benefit patients who are trying to maintain tight glycemic control.

Available evidence does not suggest that there is a clinically significant difference in effects on HbA_1c between the short-acting insulin analogs and regular insulin (Home et al., 2000; Raskin et al., 2000; Tamas et al., 2001). While pre-meal regular insulin is best-administered 30 minutes prior to a meal and the short-acting insulin analogs are administered immediately pre-meal, there is no evidence to suggest that a person's inability (e.g., active lifestyle) to take regular insulin in advance of a meal is an indication for a short-acting insulin analog.

Presently there are no data for insulin aspart in patients with type 2 diabetes, as all clinical trials have investigated its effects in type 1 DM. There is one study using the combination short-acting/intermediate-acting product (Boehm et al., 2002) in patients with type 1 and type 2; however, the results were combined for both diabetes types. In this study, there was no significant difference between the two treatments for HbA_1c, minor hypoglycemia or major hypoglycemia. Although data for patients with type 2 diabetes are lacking, there is no reason to believe that these patients would respond much differently than those with type 1 diabetes.

In studies involving aspart in type 1 diabetes, none found a difference between regular and aspart in the incidence of overall hypoglycemia. When broken down by type of hypoglycemia, one study found a difference in events/patient year for nocturnal hypoglycemia requiring parenteral glucose of 0.03 aspart vs. 0.05 regular (Home, 2000). Another study (Home, 1998) found significantly fewer major episodes of hypoglycemia with aspart.

The overall weight of the evidence does not support the use of lispro as first-line therapy with either type 1 or 2 DM, given the endpoints of severe hypoglycemia or glycemic control. One systematic review reported no differences in clinical outcomes between patients with type 1 diabetes treated with lispro and those treated with regular human insulin (Davey et al., 1997). A second review with methodological flaws (Brunelle et al., 1998) reported fewer severe hypoglycemic events for patients with diabetes treated with regular human insulin (NNT=25 to prevent one severe hypoglycemic reaction per year, p=0.024). Studies on Lispro versus regular insulin do not show substantial difference in resulting HbA_1c levels. In individual circumstances, it may be used to assist persons who are having severe hypoglycemic events on current therapy.

Insulin pump or continuous subcutaneous insulin infusion (CSII) therapy provides a treatment option that can aid in achieving glycemic control. CSII uses only rapid-acting insulin. Two recent trials have demonstrated that when used in pumps, insulin lispro provides better glycemic control than buffered regular human insulin, with a similar adverse event profile (Raskin et al., 2001; Hanaire-Broutin et al., 2000). A third trial (Bode & Strange, 2001) reported that insulin aspart and buffered regular human insulin both provided effective control of glucose levels. Patients receiving insulin aspart had fewer hypoglycemic events.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Individualized care, in consultation with a diabetes care team for patients with type 1 DM.	Working Group Consensus	III	Poor	I
2	Intermediate- or long-acting insulin to control fasting plasma glucose.	Gerich, 2002	II-2	Fair	B
3	NPH for most patients.	Pieber et al., 2000 Raskin et al., 2000 Ratner et al., 2000 Rosenstock et al., (2000) Yki-Jarvinen, et al. 2000	II-1	Good	B
4	Insulin glargine in consultation with a diabetes specialist.	Working Group Consensus	III	Poor	I
5	Insulin glargine for frequent or severe nocturnal hypoglycemia.	Ratner et al., 2000 Rosenstock et al., 2001 Yki-Jarvinen et al., 2000	II-1	Good	B
6	Insulin glargine for a multiple injection alternative.	Working Group Consensus	III	Poor	I
5	First-line regular insulin.	Home et al., 1998 & 2000 Raskin et al., 2000 Tamas et al., 2001	I	Fair	B
8	Short-acting insulin analog use for postprandial hyperglycemia with concurrent frequent hypoglycemic events on regular insulin therapy.	Home et al., 1998 & 2000 Raskin et al., 2000 Tamas et al., 2001	I	Fair	B
9	Insulin analogs for pump therapy.	Bode & Strange, 2001 Hanaire-Broutin et al., 2000 Raskin et al., 2001	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

Use of Insulin in Combination with Oral Agents in DM Type-2
(Also see – Combination with Oral Medication – Table G-9).

Efficacy may not increase beyond a single injection per day, though multiple daily doses remain a therapeutic option for some patients (Abraira et al., 1998; Chow et al., 1995; Soneru et al., 1993; Wolffenbuttel et al., 1996; Yki-Jarvinen et al., 1992 & 1999). Maximum efficacy is up to a 2 percent absolute reduction in HbA_1c.

Insulin types and species have different pharmacological properties and should not be changed inadvertently (see Table G-3, Comparison of Insulin Preparations). Patients require education on proper insulin administration, mixing if necessary, storage, and syringe disposal. Certain agents may increase or decrease the hypoglycemic effect of insulin. Dosage adjustment may be necessary in renal or hepatic impairment, during illness, increased work or exercise, or with a change in eating patterns.

Table G-3: Comparison of Insulin Preparations [a, b]

Insulin	Onset (hours)	Peak (hours)	Duration (hours)	Compatible Mixed With	Appearance
RAPID-ACTING					
Regular (Novolin R , Humulin R)	0.5-1	2-5	6-10	NPH, lente, ultralente	Clear
Lispro (Humalog)	0.25-0.5	0.5-2.5	3-6.5	Human NPH, Human ultralente [c, d]	Clear
Aspart (Novolog)	0.17-0.33	1-3	3-5	Human NPH [c, e]	Clear
INTERMEDIATE-ACTING					
NPH (Novolin N , Humulin N)	1-1.5	4-12	16-24	Regular	Cloudy
Lente (Novolin L , Humulin L)	1-2.5	7-15	16-24	Regular	Cloudy
LONG-ACTING					
Ultralente (Humulin U)	4-6	8-20	24-28	Regular	Cloudy
Insulin glargine (Lantus)	1.1	2-20	Up to 24	Not to be mixed with other insulins	Clear
PRE-MIXED PRODUCTS					
70%NPH/30% Regular (Novolin 70/30, Humulin70/30) 50%NPH/50% regular (Humulin 50/50)			Not to be mixed with other insulins		Cloudy
75% intermediate/25% lispro (Humalog mix 75/25)			Not to be mixed with other insulins		Cloudy

[a] Adapted from AHFS Drug Information, American Society of Health-System Pharmacists, Inc., 2002

[b] ..The time course of action is intended as a general guide as many factors may influence these parameters (e.g., type of preparation, dose, site of administration, and patient related variables).

[c] The effects of mixing insulin lispro or insulin aspart with insulins of animal source have not been studied. The only animal source insulin remaining on the market is purified pork as regular, NPH, and lente.

[d] The effects of mixing insulin lispro with insulins produced by manufacturers other than Eli Lilly has not been studied.

[e] The effects of mixing insulin aspart with insulins produced by manufacturers other than Novo Nordisk has not been studied.

Table G 4: Insulin Regimen Examples

Bedtime dosing of NPH or Lente insulin in addition to an oral agent	Begin with 10 to 15 units at bedtime (a dose equal to the morning glucose/18 [a]). Verify that the pre-dinner glucose remains in control.
Split mixed regimen with NPH/regular (c)	Inject 2/3 of the total insulin requirement in the morning, with a NPH/Regular ratio of 70:30. Inject 1/3 of the total insulin requirement in the evening, with a NPH/Regular ratio of 50:50 (b).
Once-daily morning NPH insulin	Good for elderly or non-compliant patients. Inject 30 to 60 minutes before breakfast. Usual dosage <40 units/day.

(a) Adapted from: Edelman et al., 1995.

(b) These are a few examples, optimal regimen depends on the individual patient

(c) Always counsel patients to mix regular insulin in syringe first, followed by NPH; mixtures of regular and Lente insulins should be injected immediately. Inject regular insulin 30 to 60 minutes before a meal; Lispro insulin should be injected within 15 minutes before a meal; mixtures of Lispro and Humulin N or Humulin U should be administered immediately. Manufacturer specific storage guidelines should be followed.

Table G 5: General Guidelines for Insulin Adjustment in the Patients with Type 2 DM on Split Regimens

If the morning fasting blood sugar is off target, adjust the evening NPH or switch evening NPH to bedtime. If the evening serum glucose is off target, adjust the morning NPH. If the evening glucose continues to be off target, have the patient check the pre-lunch glucose. If the pre-lunch glucose is off target, adjust the morning regular insulin. If the bedtime glucose is off target, adjust the evening regular insulin.

K. Determine If There Are Side Effects Or Contraindications To Current Treatment

OBJECTIVE

Modify therapy due to the side effects of drug therapy.

RECOMMENDATIONS

1. The patient with recurrent or severe hypoglycemia should be evaluated for precipitating factors that may be easily correctable (e.g., missed meals, exercise, incorrect administration of insulin—dosage or timing).

DISCUSSION

Side effects of pharmacotherapy can include drug-drug, hypoglycemia, and specific adverse drug effects. Patients may experience side effects from medications if adjustments are not made when patients undergo medical or surgical procedures, have a change in their condition, or develop an intercurrent illness.

Patients with recurrent or severe hypoglycemia should be evaluated for precipitating factors that may be easily correctable (e.g., missed meals, exercise, incorrect administration of insulin—dosage or timing). In many cases, a simple adjustment can be made in nutrition, exercise, medication and/or patient self-monitoring. In patients with near-normal glycemic control (notably patients with type 1 DM on intensive insulin treatment or patients with autonomic neuropathy), it may be necessary to relax the degree of glycemic control, at least temporarily. Complex adjustments may best be accomplished through co-management with a diabetes team.

Certain drug effects (e.g., gastrointestinal symptoms) may improve over time or with modification of the dosage regimen and thus may not necessitate discontinuance of medication. On the other hand, some drugs may have adverse effects that require vigilant monitoring, such as frequent measurement of serum liver function tests in patients treated with thiazolidinediones. Finally, patients may develop contraindications to continued use of a previously successful maintenance medication. Examples include newly recognized renal insufficiency or severe congestive heart failure in a patient treated with metformin (see detailed pharmacologic tables in Appendix G-3).

L. Are There Problems With Patient Adherence?

OBJECTIVE

Identify barriers to full adherence to the prescribed treatment regimen.

RECOMMENDATIONS

1. If the patient does not achieve his/her target range, the provider should identify barriers to patient adherence to the treatment regimen (e.g., miscommunication, lack of education or understanding, financial/social/psychological barriers, and cultural beliefs).
2. If barriers are identified referral to a case manager or behavioral/financial counselor should be considered as appropriate.

DISCUSSION

It is appropriate to briefly review adherence to the prescribed nutritional and exercise regimens, as well as to review the dosages and timing of administration of medication. If the patient does not achieve his or her target range, the practitioner should look for barriers to patient adherence to regimen. Barriers may include miscommunication, lack of education or understanding, financial, social, psychological, and cultural beliefs (e.g., learned helplessness). In addition, the patient may have treatment preferences that are not being addressed (see Module M, Appendix M-6 - Patient Self-Management and Knowledge Needs Assessment).

The patient may be considered for case management or referral to a behavioral or a financial counselor, as appropriate.

M. Should Glycemic Control Target Be Adjusted?

OBJECTIVE

Determine whether the recommended glycemic control goal remains appropriate for the patient.

RECOMMENDATIONS

1. Treatment goals should be periodically reassessed based upon patient specific factors, including changes in the patient's health status, adverse drug reactions, adherence to therapy, and preferences.

DISCUSSION

Treatment goals should be periodically reassessed based upon patient specific factors, including changes in the patient's health status, adverse drug reactions, adherence to therapy, and preferences.

Relative indications for raising the target glycemic goal include inability or unwillingness to adhere to a more intensive regimen, or an unacceptable risk of hypoglycemia relative to anticipated benefits of near-normal glycemia.

If the target range remains appropriate but has not been reached, the provider and patient should identify the reasons why the target has not been achieved and take appropriate action.

Reasons to consider lowering the target glycemic control goal include removal of barriers to improved control (e.g., substance abuse, intercurrent illnesses, and adherence issues) and resolution of relative contraindications (see Annotation D).

N. Follow-Up

OBJECTIVE

Maintain glycemic control and ensure proper patient monitoring by the healthcare team.

RECOMMENDATIONS

1. The patient should be scheduled for appropriate follow-up to evaluate response, tolerability to therapy, goal re-assessment, and management of acute and chronic problems.
2. The frequency of primary care provider visits for the patient with diabetes who is meeting treatment goals and who has no unstable chronic complications should be individualized.
3. When there is a sudden change in health status or when changes are made to the treatment regimen, follow-up within one month or sooner may be appropriate.

APPENDIX G-1
Measurements of Glycemic Control

There are three types of glycemic control tests currently in use:
1. For long-term glycemic control (past 3 to 4 months), HbA_1c is preferred.
2. For short-term glycemic control (past 10 to 20 days) fructosamine can be used, but it is not widely available.
3. Single point measurement of blood sugar can be measured on venous, plasma, or capillary samples in the lab with a glucose meter.

GLYCOSYLATED HEMOGLOBIN—HbA_1c

- The terms "glycated" and "glycosylated" hemoglobin are used interchangeably in the literature. The terms are used to describe the reaction product between sugar and a protein.
- There are four HbA_1 components: HbA_1a_1, HbA_1a_2, HbA_1b, and HbA_1c. HbA_1c is the marker of choice for the assessment of risk for the development of microvascular complications.
- Because HbA_1c can be measured by a variety of different methodologies, the normal range varies by methodology. The lab reports the percentage of hemoglobin that is glycosylated. An HbA_1c for an individual patient should be interpreted as the percent above high normal range for the facility laboratory, rather than as an absolute value. It is recommended that facilities use a method that participates in the National Glycohemoglobin Standardization Program (NGSP).
- If a patient has a hemoglobinopathy (e.g., Hb S, C, D, G, F and intermediary product) consult with the laboratory chief to determine whether or not the glycosylated hemoglobin test methodology is affected by the presence of hemoglobinopathy. Normal range varies by methodology.
- Facilities that measure total glycosylated hemoglobin (GHb) should be able to provide accurate HbA_1c equivalency values. However, there is no analytic system that measures HbA_1c and is able to report HbA_1c equivalency measures.
- Certain HbA_1c measurements may also be unreliable in the presence of the following conditions: hemolytic anemia, uremia, or pregnancy. Serum fructosamine measurement may be considered as an alternative test in these circumstances.

GLUCOSE MEASUREMENTS

- Single point measurement of blood sugar can be determined from venous samples and capillary glucose measurements. Only venous samples should be used for the diagnosis of DM. Capillary blood sugar measures can be used for home monitoring.
- The most common user error associated with self-managed blood glucose (SMBG) is inadequate sample size. Depending upon the meter used, this error can lead to a significant discrepancy between the actual and recorded blood glucose. A user's technique and maintenance procedures should be reviewed annually or as indicated.

Assuming that the mean SMBG or point of care or laboratory glucose measurements are accurate, multiple readings at various time points can be averaged to obtain approximate HbA_1c levels by using the equation shown in Table G-6, from the Diabetic Control and Complication Trial (DCCT) database.

Table G-6: Estimate of HbA_1c

Mean Blood Glucose	Estimated HbA_1c
120 mg/dL glucose	6% HbA_1c
150 mg/dL glucose	7% HbA_1c
180 mg/dL glucose	8% HbA_1c
Every 30 mg/dL increase	1% increase

APPENDIX G-2
Estimating Benefit and Risk of Glycemic Control

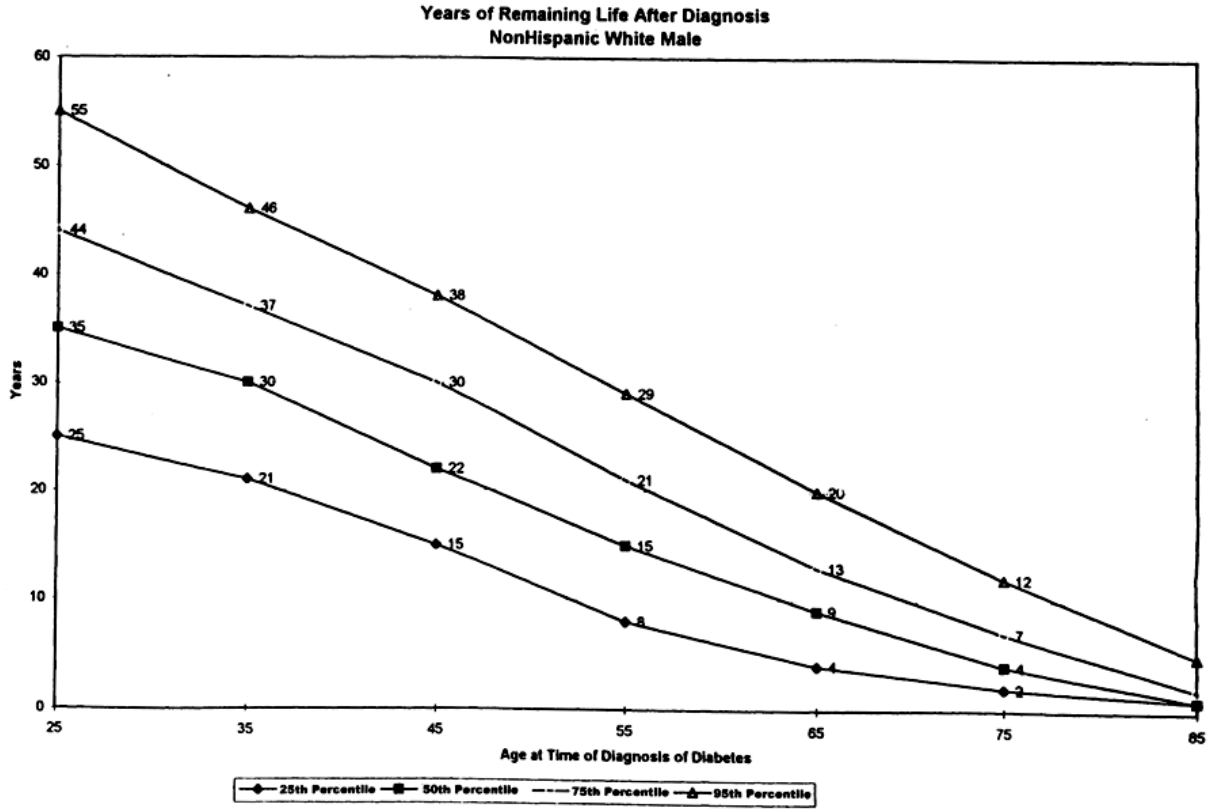
Determination of an optimal target HbA_1c level is based upon the risk for developing microvascular complications. The individual risk is dependent on life expectancy, absence or presence of pre-existing microvascular complications, and genetic factors.

DETERMINE LIFE EXPECTANCY

Statistics for the life expectancy of a population can be derived from the observed mortality rates of that population. An example commonly used in medicine is the life expectancy of patients with a particular type of end stage of cancer. The population has an average survival, with a wider range of survival into which almost all patients will fall. While it is impossible to tell a patient exactly how long he or she will live; it is possible to estimate his/her life expectancy. Based upon life expectancy and mortality rates due to the disease, the provider and patient should discuss treatment options.

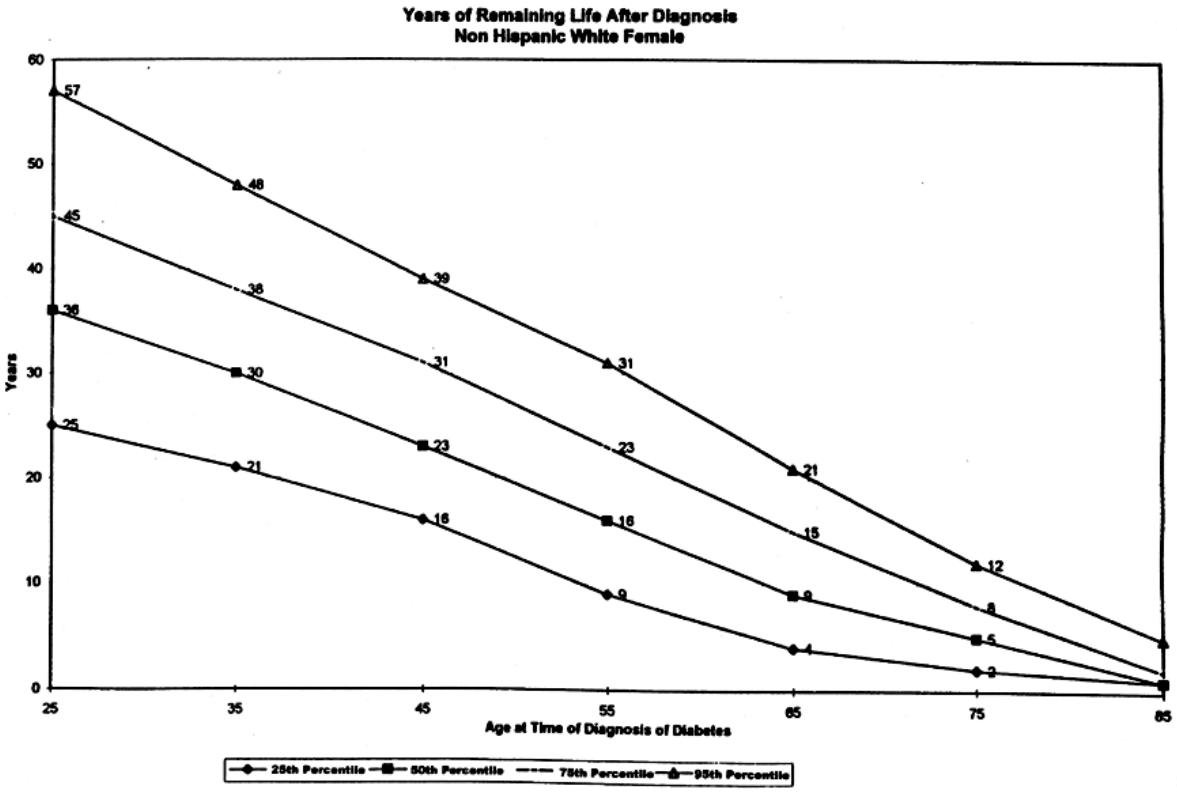
Longitudinal studies of the life expectancy of patients with DM corroborate that patients with DM have a shortened life span relative to patients without DM (Eastman, 1997; ADA, 1997b). However, the format of the data from such studies is not easily transposed. These data have been generated based upon a computer model that incorporates data from the Framingham Study. Except for end stage renal disease, the model assumes that microvascular complications do not affect survival, although they do predict progression to blindness, amputation, and dialysis.

EXHIBIT G1



For any given age at the time of diagnosis of DM, the years of life remaining after diagnosis are provided in the 25th, 50th, 75th, and 95th percentiles. It can be assumed that populations of patients with DM and other health conditions would have a survival rate less than the mean life expectancy (use 25th percentile), and that patients without co-morbid conditions and with a favorable family history would have a survival rate greater than the mean life expectancy (use 75th or 95th percentile).

EXHIBIT G2



Co-existing conditions (e.g., congestive heart failure, AIDS, chronic obstructive pulmonary disease, cirrhosis, and cancer) have a significant effect on survival. Aggressive treatment of cardiovascular risk factors, including smoking cessation, may increase life expectancy. In addition, adherence to general preventive practices (e.g., immunizations and screening for colon, prostate, and breast cancers) is also predicted to increase life expectancy in the American population. Thus, for a patient with DM, an estimate of life expectancy for a given percentile can be obtained by determining both the patient's age at the time of diagnosis of DM and the average (mean) years of life remaining and subtracting the time (in years) that has elapsed from the time of diagnosis. Providers must then use their best judgment to raise or lower it based upon coexisting medical conditions and family history. It is recommended that unless a patient has a known condition that will decrease his life expectancy, a value above the mean be used.

While a patient's age is clearly the predominant factor in estimating life expectancy, this approach ensures that the life expectancy estimate used in determining the patient's target glycemic ranges is also based upon the patient's health state and the judgment of the provider.

DETERMINE PRESENCE OF MICROVASCULAR COMPLICATIONS

The presence of microvascular complications (e.g., retinopathy and microalbuminuria; see Module E: Eye Care and Module R: Kidney Function, respectively) increases the probability that end stage microvascular complications will occur, as compared to the probability that these complications will occur in a patient without microvascular complications but with a similar life expectancy.

CONSIDER FAMILY HISTORY

The risk stratification approach can be extended by the practitioner to include family history of microvascular complications. A familial history of diabetic nephropathy or retinopathy predisposes a first generation relative to the development of microvascular complications. In patients with a given strong family history, defined as diabetic end-stage renal disease, or visual loss secondary to diabetic retinopathy in a first-degree relative, consider leaning towards a lower HbA_1c target value.

RELATIVE AND ABSOLUTE RISK REDUCTION

Until 1993, there were no RCTs to support the theory that tight glycemic control prevented complications of diabetes. Until more recently, the research trail leading to confirmation of benefits of glycemic control to the progression of microvascular disease has included studies limited in scope to a target organ or a particular patient grouping and involved relatively short timeframes. However, these studies pointed towards further definition of the benefits of glycemic control and the potential value of more comprehensive studies, such as are now reported. Analysis of the risk reduction in microvascular complications from the Diabetic Control and Complication Trial (DCCT, 1993 & 1995) concludes that the relative risk reduction of intermediate microvascular complications of DM (e.g., development of background retinopathy and microalbuminuria) can be reduced by about 40 percent for each one percent decrease in HbA_1c in patients with type 1 DM.

However, it should be noted that the conclusions of the DCCT study were based on intermediate microvascular complications. Progression to proliferative retinopathy was uncommon, and no patients progressed to renal insufficiency. Therefore, it should be recognized that maximal benefits of glycemic control in preventing the progression of microvascular disease to the endpoints of visual loss or chronic renal insufficiency accrue over a period of time longer than that of the study period of the aforementioned trial.

More recently, the issue of incidence and progression of complications in patients with type 2 diabetes over a 10 year period of observation was addressed by the UKPDS (1998). The UKPDS compared 3,867 patients with type 2 diabetes randomized into two groups: 1) intention to treat by diet alone and 2) intention to treat by intensive pharmacological intervention. These studies demonstrated a 35 percent decrease in microvascular complications for every 1 percent decrease in HbA_1c and the decrease was continuous to a HbA_1c of >6 percent. While the UKPDS intensive treatment group only achieved an 11 percent decrease in HbA_1c compared with the control group (controls 7.9, intensive 7.0) when compared to the 20 percent HbA_1c decrease achieved by the intensive group in the DCCT, the 25 percent decrease in overall microvascular complications in the UKPDS was similar to the decrease in microvascular complications achieved in the DCCT. Thus, the UKPDS study supports type 2 diabetes glycemic control in a manner similar to the DCCT in type 1 diabetes and together these studies establish that blood glucose control substantially reduces the incidence of microvascular complications in diabetes. Improved glycemic control is appropriate for all patients. However, each patient must be assessed individually, taking into account whether the patient is of advanced physiologic age, suffers from co-morbid conditions affecting his or her life expectancy, demonstrates the progression of microvascular disease or some combination of these conditions. Computer models based upon patient data from type 1 and type 2 diabetics can provide estimates of the incidence of microvascular complications, the expected decrease in microvascular complications resulting from improved glycemic control and life expectancy estimates (Eastman, 1997; Vijan et al., 1997). These models provide population risks and were used in providing an estimate of risk over time, as well as an estimate of benefit from improved glycemic control. The resulting estimates of absolute risk reduction, defined as decreases in visual loss and end stage renal disease that occur with a given decrease in percent HbA_1c reduction, indicate that in some instances the progression of co-morbid conditions factored with advanced physiological age preempt the progression of pathological processes associated with glycemic control. These are instances when aggressive efforts to achieve ideal glycemic

control are neither cost effective nor likely to result in improved outcomes. See Table G-1 and Annotation C for suggested upper limits of HbA_1c levels in categories of patients referred to above.

Taken alone or together, both computer modeling and clinical studies thus far indicate that the absolute risk reduction in end-stage microvascular disease over a patient's lifetime is the major determinant of the target range of glycemic control for a patient, and will influence the risk/benefit analysis of therapeutic options. Improvement in macrovascular diseases outcomes associated with glycemic control has not yet been proven in RCTs. Observational studies demonstrate an association between increased HbA_1c and cardiovascular disease and cardiovascular mortality risk that achieves statistical significance only for women. There are no intervention trials that conclusively demonstrate that improved glycemic control will alter cardiovascular morbidity and/or mortality. The DCCT (1993 & 1995) and the Ohkubo et al. (1995) show a nonsignificant trend towards reduced cardiovascular events with intensive insulin therapy, while the VA Cooperative trial demonstrated a nonsignificant increase in cardiovascular events and an association between decreased HbA_1c and new cardiovascular events. The UKPDS (1998) demonstrated a 16 percent reduction in the incidence of combined fatal and non-fatal myocardial infarction among intensively treated patient group, but the risk reduction was not statistically significant ($p = 0.052$) at the 10 year data collection point. This study will produce more data at 15 years and the end points (fatal and non fatal myocardial infarctions) will be determined again at that time.

APPENDIX G-3
Pharmacotherapy Tables

Table G-7. Pharmacologic Agents

Agents	Efficacy (HbA_1c) [a]	Dose	Contraindications/ Relative Contraindications	Adverse Events	Remarks
Sulfonylureas Glyburide Glipizide Glimepiride Chlorpropamide Tolazamide Tolbutamide **Stimulates insulin release from beta cells in the pancreas.*	1.0 – 2.0%	***1st generation*** Chlorpropamide 100 - 500mg once daily Tolazamide1000mg given once daily or divided into 2 doses Tolbutamide250 - 2000mg divided into 2-3 doses ***2nd generation*** Glimepiride 1 - 4mg once daily Glipizide 2.5 - 40mg given once daily or divided into 2 doses taken 30 minutes before a meal. Doses >15mg should be divided into 2 doses. Glipizide XL 5 - 10mg once daily Glyburide 1.25 - 20mg given once daily or divided into 2 doses Micronized glyburide 0.75 – 12mg given once daily or divided into 2 doses; doses >6mg when divided, may provide a better response If the response to a single daily dose does not achieve treatment goals, dividing the dose may be effective. In general, the hypoglycemic effects of glyburide and	Hypersensitivity Pregnancy	Hypoglycemia Hypersensitivity (rash, etc.) Weight gain	1st generation sulfonylureas are no longer commonly used. No difference in long term efficacy or failure rate has been demonstrated among the sulfonylureas. The preferred agents have shorter half-lives and inactive metabolites. 1st generation sulfonylureas are 100% renally eliminated. Chlorpropamide and tolazamide have active metabolites. Glipizide, glyburide, and glimepiride are renally eliminated by 80 - 85%, 50%, and 60% respectively. All but glipizide have active metabolites. Inexpensive.

Agents	Efficacy (HbA_1c) [a]	Dose	Contraindications/ Relative Contraindications	Adverse Events	Remarks
		glipizide tend to plateau at 10mg and 20mg, respectively.			
Biguanide Metformin **The major blood glucose lowering effect is through decreasing hepatic glucose production with some decrease in peripheral insulin resistance.*	1.0 – 2.0%	Starting dosage is either 500mg BID or 850mg q am: If on 500mg BID, dosage increase may be made by 500mg increments weekly up to 1000mg BID If on 850mg q am, dosage increase of 850mg may be made every other week (given as 850mg BID) The usual maintenance dose is 850 mg BID with meals. Maximum dose: 2550 mg/day (850mg TID); the dose response curve usually plateaus after 2000mg/day. Take with food to avoid possible GI symptoms. Metformin extended release: begin with 500mg daily with the evening meal. Dose may be increased by 500mg per week to a maximum of 2000mg once daily. If glycemic control is not achieved, consider dividing into 2 doses.	**Contraindications** Renal dysfunction (Scr >1.5mg/dl for males or >1.4mg/dl in females). CHF requiring pharmacologic management. Acute or chronic metabolic acidosis. Temporarily discontinue metformin use at the time of or prior to intravascular iodinated radiocontrast studies and withhold for 48 hours after the procedure. Reinstitute only after renal function has been reevaluated and found to be normal. **Not Recommended** 80 years of age unless normal creatinine clearance, and the dose should not be escalated to the maximum in elderly patients due to increased susceptibility to lactic acidosis.	Potential for lactic acidosis when used in patients for whom the drug is contraindicated Transient dose-related GI symptoms (diarrhea, nausea, vomiting, bloating, flatulence, anorexia) Decrease in vitamin B12 levels	May restore ovulation in premenopausal anovulatory females. Monitor renal function prior to drug initiation and at least annually thereafter. Inexpensive when using generic.

Agents	Efficacy (HbA_1c) [a]	Dose	Contraindications/ Relative Contraindications	Adverse Events	Remarks
			Hepatic disease or excessive ethanol intake. Withhold metformin in the presence of any condition associated with hypoxemia, dehydration or sepsis.		
Alpha-glucosidase inhibitors Acarbose Miglitol **Delays the digestion of carbohydrates, thereby decreasing postprandial hyperglycemia.*	0.4 - 1.0%	For acarbose or miglitol begin with 25 mg TID or initiate gradually: 25 mg QD x 1-2 weeks followed by 25 mg BID for 1-2 weeks followed by 25 mg TID. Once a 25mg TID dosing regimen is reached, further increases may be made at a 4-8 week interval. The usual maintenance dose is 50 mg TID. Maximum dose for acarbose is 100mg TID (50 mg TID if weight <60 kg) and 100mg tid for miglitol. Dose is to be taken with the first bite of each main meal. The patient who misses or adds a meal should omit or add the dose.	**Contraindications** Presence of intestinal complications (inflammatory bowel disease, colonic ulceration, intestinal obstructions, digestion or absorption disorders). Acarbose is contraindicated in patients with cirrhosis. Miglitol pharmacokinetics are not altered in cirrhosis and may be used. **Not Recommended** SCr > 2.0mg/dl	Transient dose-related GI symptoms (diarrhea, abdominal pain, flatulence) which can limit compliance with therapy. Acarbose, especially at doses greater than 50 mg TID, may cause serum AST/ALT elevation; monitor serum levels every 3 months during the first year of treatment.	Allows for flexible meal dosing. Moderately expensive.
Thiazolidinediones Rosiglitazone Pioglitazone **Enhances insulin sensitivity in skeletal*	1.0 - 1.5%	May be given without regard to meals Dosage adjustment is not required for renal insufficiency; however, there is insufficient data to	**Not Recommended** New York Heart Association Class III and IV. Do not initiate in patients with ALT >2.5x the	Edema Weight gain Decrease Hgb/HCT Hepatotoxicity (rare)	Liver function tests and bilirubin should be tested every 2 months for 1 year, then periodically thereafter. If ALT is >3x upper limit

Agents	Efficacy (HbA_1c) [a]	Dose	Contraindications/ Relative Contraindications	Adverse Events	Remarks
muscle, hepatic, and adipose tissue without directly stimulating insulin secretion from the pancreas. Also has a small effect on inhibiting hepatic glucose output.		recommend use in endstage renal disease. Slow onset of action. **Rosiglitazone** 4 - 8mg/day, given once daily or divided into 2 doses. **Pioglitazone** 15 - 45mg administered once daily.	upper limit of normal.		of normal, recheck another level as soon as possible. If ALT remains >3x the upper limit, discontinue use. May restore ovulation in premenopausal anovulatory females. Very expensive.
Meglitinides Repaglinide Nateglinide **Like sulfonylureas (SFU), it stimulates pancreatic secretion of insulin. It has a faster onset and shorter duration of action than SFUs, therefore postprandial glucose is affected to a greater extent than fasting blood glucose.*	0.6 - 1.9%	Take 1 – 30 minutes before a meal. The patient who misses or adds a meal should omit or add the dose. **Repaglinide** The starting dose is 0.5mg in patients with HbA_1c <8%. If the HbA_1c is ≥8%, a dose of 1 or 2mg may be initiated. Maximum dose is 4mg per meal. **Nateglinide** 120mg before each meal.	**Use With Caution** **Repaglinide** Hepatic impairment Severe renal impairment **Nateglinide** Moderate-severe hepatic impairment	Hypoglycemia Weight gain	Allows for flexible meal dosing. Do not use in patients who have failed sulfonylurea therapy. Expensive.
Insulin (see Annotation J-3 Insulin Therapy)	Dose can be adjusted to achieve a wide range of glucose lowering.	See Table G-4 for examples of insulin regimens.	Hypersensitivity to insulin	Hypoglycemia Hypersensitivity Injection site reactions Weight gain	Requires intensive patient education. Regular, neutral protamine Hagedorn insulin [NPH], and lente – inexpensive. Insulin analogs-moderately expensive.

[a] The absolute reduction in HbA_1c represents placebo-adjusted values; due to study differences, direct comparisons between classes cannot be made

Table G-8. Combination of Oral Agents [a]

Study [b]	Drug regimen	N	Duration	Efficacy (HbA_1c) [c]	Remarks
Sulfonylurea (SFU) + Biguanide					
UKPDS, 1998	Metformin titrated to 2550mg added to maximal SFUs (42% of subjects titrated to 2-2.5g)	591	3 years	Metformin + SFU – 0.47% SFU +0.44%	Higher incidence of hypoglycemia with combination than SFU alone Weight gain: SFU > metformin + SFU > metformin Variable results on lipids. In general, combination slightly decreases TC, LDL, TG, with no significant effect on HDL
DeFronzo, 1995	Metformin 2.5g added to glyburide 10mg BID (70% of subjects titrated to 2.5g)	632	29 weeks	Metformin + glyburide –1.7% Metformin –0.4% Glyburide +0.2%	
Charpentier, 2001	Glimepiride (titrated 1-6mg) added to metformin 850mg TID (41% of subjects titrated to 6mg)	372	20 weeks	Glimepiride + metformin –0.74% Glimepiride +0.27% Metformin +0.07%	
Willms, 1999	Metformin 850mg BID added to SFU (92% of subjects taking glibenclamide 10.5mg/d)	58	12 weeks	Metformin + SFU –2.5% SFU –1.3%	
Sulfonylurea (SFU) + alpha-glucosidase inhibitor					
Holman, 1999 UKPDS	Acarbose (titrated 50-100mg TID) added to SFU	378	3 years	Acarbose + SFU – 0.21% (placebo adjusted)	Hypoglycemia not mentioned in any of the trials. However, if hypoglycemia develops, oral glucose (dextrose) should be given to treat the reaction since sucrose (table sugar) or complex carbohydrates (starches) will not be readily effective May result in weight loss or be weight neutral
Chiasson, 1994	Acarbose (titrated 50-200mg TID) added to glyburide (mean dose 16.6mg)	103	1 year	Acarbose added to SFU –0.9% (placebo adjusted)	
Johnston, 1998a	Miglitol (mean dose 95mg TID at week 26 and 149mg TID at week 52) added to SFU (38% took maximum dose; mean not given) or diet (20% of study population)	340	6 months (1 endpt.) 1 year (2 endpt.)	Miglitol + SFU – 0.26%; –0.9% (1 year) SFU +0.57% (6 months); +0.22% (1 year)	

Study [b]	Drug regimen	N	Duration	Efficacy (HbA_1c) [c]	Remarks
Johnston, 1998b	Miglitol 100mg TID added to SFU (38% took maximum dose; mean not given) or diet (15% of study population)	345	6 months (1 endpt.) 1 year (2 endpt.)	Miglitol + SFU –0.53% (6 months); –0.21% (1 year) SFU +0.66% (6 months); +0.53% (1 year)	Alpha-glucosidase inhibitors seem to have no effect on the lipid profile
Costa, 1997	Acarbose 100mg TID added to glibenclamide (mean dose 14mg/d)	65	6 months	Acarbose + SFU –1.1% SFU –0.3%	
Willms, 1999	Acarbose 100mg TID added to SFU (92% of subjects taking glibenclamide 10.5mg/d)	60	12 weeks	Acarbose + SFU –2.3% SFU –1.3%	
Sulfonylurea (SFU) + TZD					
Wolffenbuttel, 2000	Rosiglitazone 1mg or 2mg BID added to SFU (mean doses GLY 12.6mg, GLIP 17mg, GLIC 185mg)	574	26 weeks	Rosiglitazone + SFU –0.52% (2mg); –0.87% (4mg) SFU +0.5%	Incidence of hypoglycemia greater with combination than with SFU alone Greater weight gain with combination than with SFU alone Significantly greater reduction in TG and increase in HDL with pioglitazone +SFU than with SFU alone The increase in LDL, HDL, TC were statistically greatest with combination rosiglitazone 4mg + SFU than with SFU alone. The increase in TG and TC with rosiglitazone 2mg + SFU was statistically greater than with SFU alone
Kipnes, 2001	Pioglitazone 15mg or 30mg added to SFU (70% taking at least half the maximum daily dose of SFU) Other oral hypoglycemic agents were discontinued in those subjects (15%) who had been on combination therapy	560	16 weeks	Pioglitazone + SFU –0.8% (15mg); –1.2% (30mg) SFU +0.1%	
Biguanide + Glitzones					

Study [b]	Drug regimen	N	Duration	Efficacy (HbA_1c) [c]	Remarks
Fonseca, 2000	Rosiglitazone 4mg or 8mg added to metformin 2.5g Other oral hypoglycemic agents were discontinued in those subjects (50%) who had been on combination therapy	348	26 weeks	Rosiglitazone + metformin –0.56% (4mg); –0.78% (8mg) Metformin +0.45%	Hypoglycemia uncommon Wt gain 0.7-1.9kg compared to wt. loss with metformin alone Pioglitazone + metformin had a statistically better effect on TG than metformin alone. Differences in other lipid parameters between the 2 treatments were not statistically different. The increase in LDL, HDL, TC were statistically greater with combination of rosiglitazone + metformin versus metformin alone Incidence of edema with metformin + glitazone > metformin
Einhorn et al., 2000	Pioglitazone 30mg added to metformin (mean dose 1555mg/d) Other oral hypoglycemic agents were discontinued in those subjects (30%) who had been on combination therapy	328	16 weeks	Pioglitazone + metformin -0.64% Metformin +0.19%	
Biguanide + alpha-glucosidase inhibitor					
Holman et al., 1999 UKPDS 44	Acarbose (titrated 50-100mg TID) added to metformin	87	3 years	Acarbose + metformin –0.32% (placebo adjusted)	Hypoglycemia uncommon with combination. However, should it occur, oral glucose (dextrose) should be given to treat the reaction since sucrose (table sugar) or complex carbohydrates (starches) will not be readily effective Weight reduction noted Only TG evaluated (Chiasson 2001, Rosenstock, Halimi) and there was no difference between metformin + AGI versus metformin alone
Chiasson, 1994	Acarbose (titrated 50-200mg TID) added to metformin (mean dose 1506mg/d)	83	1 year	Acarbose + metformin –0.8% (placebo adjusted)	
Chiasson, 2001	Miglitol (forced titration from 25mg to 100mg TID) added to metformin 500mg TID 51-66% of subjects were treatment-naive	324	36 weeks	Metformin + miglitol –1.4% Metformin –0.85% Miglitol +0.02%	
Rosenstock, 1998	Acarbose (titrated 50-100mg TID) added to metformin 2-2.5g/day	84	24 weeks	Acarbose + metformin –0.57% Metformin +0.08%	

Study [b]	Drug regimen	N	Duration	Efficacy (HbA_1c) [c]	Remarks
Halimi, 2000	Acarbose (titrated 50-200mg TID) added to metformin 850mg BID-TID	152	6 months	Acarbose + metformin –0.7% Metformin +0.2%	More adverse GI events with combination
Biguanide + meglitinide					
Horton 2000 R, DB, PC, PR	Nateglinide 120mg TID-meals + metformin 500mg TID started concurrently in patients whose baseline medications were discontinued	701	24 weeks	Nateglinide + metformin –1.4% Metformin –0.8% Nateglinide –0.5% Placebo +0.5%	Incidence of hypoglycemia greater with combination than with either agent alone Weight gain - no significant change (Horton); mean gain of 2.4 - 3kg with repaglinide and repaglinide + metformin (Moses) No significant effect on lipid parameter (Moses)
Moses 1999 R, DB, PC, DD, PR	Repaglinide added to metformin (mean dose 1.8g) in patients with inadequate glycemic control on metformin alone	82	4-5 months	Repaglinide + metformin –1.4% Metformin –0.33% Repaglinide –0.38%	
Glitazones + meglitinide[d]					
Product package insert	Titrated-dose repaglinide (median dose 6mg) + fixed-dose pioglitazone 30mg started in patients with HbA_1c > 7% on monotherapy with SFUor metformin	246	24 weeks	Repaglinide + pioglitazone –1.9% Pioglitazone –0.1% Repaglinide –0.1% *These values represent completer data only. Intent-to-treat values were not presented*	Weight gain: combination > TZD alone > repaglinide alone Peripheral edema: 5% of patients receiving repaglinide + TZD versus 4% receiving TZD monotherapy vs. 1% receiving repaglinide monotherapy CHF: 2 cases (0.8%) receiving combination therapy. Both had prior history of CAD
Product package insert	Fixed-dose repaglinide 6mg + titrated-dose rosiglitazone (median dose 4mg) started in patients with HbA_1c > 7% on monotherapy with SFUor metformin	252	24 weeks	Repaglinide + rosiglitazone –1.43 Rosiglitazone –0.56 Repaglinide –0.17	

[a] These combinations have been studied in randomized controlled trials and have a complimentary mechanism of action

[b] All trials were randomized, double-blind, placebo-controlled parallel trials except for the UKPDS 28 which was randomized, open label and the Willms study which was partially blinded

[c] Values represent change from baseline and are not placebo-adjusted unless otherwise indicated. Because of differences in study design, direct comparisons cannot be made

[d] Data were obtained from the product package insert for repaglinide and has not been published in a peer-reviewed journal

Table G-9. Combination of Insulin and Oral Agents

Study	Drug regimen	N	Duration	Efficacy (HbA_1c)	Remarks
Insulin + Sulfonylurea (SFU)					
Johnson et al., 1996 Meta-analysis	Insulin added to SFU	351	6-52 weeks	SFU + insulin –1.1% Insulin –0.25%	Addition of SFU to insulin can decrease insulin dose requirements while providing equal or better glycemic control. BIDS (bedtime insulin + daytime SFU) is a commonly used regimen. Slightly more weight gain with SFU + insulin versus insulin alone. Variable results as to whether SFU + insulin regimens versus insulin alone cause more hypoglycemia. The effect of SFU + insulin on lipid parameters is variable. In general, there are no significant changes in TC, HDL, and LDL whereas TG tends to decrease.
Wright et al., 2002 R, PR	Ultralente insulin before dinner added to SFU. Regular insulin added if preprandial glucose >126mg/dL. Insulin dose adjusted to achieve and maintain FPG <108mg/dl	584	Over 6 years	SFU + insulin –0.3% Insulin +0.2%	
Yki-Jarvinen et al., 1999 R, DB, PC, PR	Insulin added to SFU(starting insulin dose 12U NPH). Insulin doses adjusted according to FPG	46	1 year	BIDS –1.8% AM + PM NPH insulin -2.0%	
Yki-Jarvinen et al., 2000 R, OL, PR	Bedtime insulin glargine or NPH added to SFU. Insulin dose titrated to achieve FBG ≤ 120mg/dl	426	1 year	Glargine + SFU-0.76% NPH + SFU-0.66%	
Riddle et al., 1998 R, DB, PC, PR	70/30 insulin 10U before dinner added to SFU. Insulin dose adjusted according to FPG	145	24 weeks	Glimepiride + insulin –2.1% Insulin –2.1%	
Wolffenbuttel et al., 1996 R, OL, PR	Insulin added to SFU. Insulin dose adjusted to achieve FBG <126mg/dL, HbA_1c <8%	95	6 months	BIDS-2.4% SFU+ daytime NPH -2.6% 70/30 insulin twice daily -2.0%	
Landstedt-Hallin et al., 1995 R, OL, PR	Insulin at starting dose of 0.25U/kg/d added to SFU Insulin dose adjusted to achieve FBG <120mg/dL and PPG <160mg/dl	80	16 weeks	Glyburide + regular insulin TID-AC -2.1% BIDS –1.7%	
Soneru et al., 1993 R, OL, PR	Insulin added to SFU Insulin dose adjusted to achieve FPG 100-120mg/dL	29	12 weeks phase 1 6 weeks phase 2	<u>Phase 1:</u> Glyburide + AM lente insulin -1.6% Glyburide + PM lente insulin -1.4% <u>Phase 2 (discontinue glyburide):</u> To maintain glycemic control, AM insulin +39%; PM insulin +30%	
Feinglos et al., 1997 R, CO	Lispro added to maximum dose SFU. Median final daily lispro dose 24 units. Insulin dose adjusted according to premeal and HS glucose values	25	4 months (Each arm)	SFU+ lispro AC –2.6% SFUalone –0.7%	

Study	Drug regimen	N	Duration	Efficacy (HbA_1c)	Remarks
Yki-Jarvinen et al., 1992 R, OL, PR	Insulin added to SFU. Insulin dose adjusted according to FPG	153	3 months	SFU± metformin + AM NPH –1.7% SFU± metformin + HS NPH –1.9% AM NPH + PM NPH –1.8% Multiple insulin injections –1.6%	
Bastyr et al., 1999 R, OL, PR	Lispro added to max SFU HS NPH added to max SFU Lispro + HS NPH	423	2 months	Lispro + SFU–1.6% HS NPH + SFU–1.21% Lispro + HS NPH –1.4%	
Bastyr et al., 2000 R, open, PR	Lispro added to maximum dose SFU(mean final lispro dose 0.42U/kg/day) HS NPH added to max SFU(mean final NPH dose 0.29U/kg/day Metformin added to max SFU(55% of subj. required 2550mg/day)	135	3 months	SFU + lispro AC –2.4% SFU + HS NPH –1.8% SFU + metformin –1.8%	
Lindstrom et al., 1999 R, DB, PC, CO	SFU added to bedtime NPH and regular TID-AC insulin (median dose 50U/d). Insulin dose adjusted to target pre-prandial glucose 72-126mg/dl and PPG <180mg/dL	15	3 months (Each arm)	No difference between the 2 groups	
Feinglos et al., 1998 R, DB, PC, CO	SFU added to multiple daily injections of regular and/or NPH insulin (mean dose 80U/d). Insulin dose adjusted according to standard algorithms	37	3 months (Each arm)	Glipizide + insulin –2.37% Insulin -0.77	
Insulin + Metformin					
Hermann et al., 2001 R, DB, PC, PR	Metformin added to rapid acting insulin + NPH (mean dose 0.74U/kg/d). Insulin adjusted if hypoglycemic or if FBG > 216mg/dl	35	12 months	Metformin + insulin –1.1% Insulin +0.3%	Compared to insulin alone, the addition of metformin to insulin can decrease insulin dose requirements while providing equal or better glycemic control. Slight decrease in total cholesterol, triglycerides, and LDL decreased with metformin + insulin; no change in HDL. Weight decrease or small increase with metformin +
Yki-Jarvinen et al., 1999 R, DB, PC, PR	Metformin + insulin were started concurrently in patients with 2 SFUfailure (starting insulin dose 12U NPH). Insulin doses adjusted according to FPG	46	1 year	Metformin + insulin –2.5% AM + PM NPH insulin -2.0%	
Giugliano et al., 1993 R, DB, PC, PR	Metformin added to twice-daily regular and lente insulin (mean dose 90u/d). Insulin dose not adjusted unless hypoglycemic	50	6 months	Metformin+ insulin –1.84% Insulin change NS	

Study	Drug regimen	N	Duration	Efficacy (HbA_1c)	Remarks
Aviles-Santa et al., 1999 R, DB, PC, PR	Metformin added to twice daily NPH + 2-4 injections of regular insulin (mean dose 96U/d). Dose of insulin adjusted as necessary	43	24 weeks		increase with metformin + insulin compared to insulin alone. Incidence of hypoglycemia with the combination is less or equal to that of insulin alone. The effect of metformin + insulin on serum lipids is variable. Range of means. TC –8 to –28mg/dl TG –6 to –62mg/dl HDL –2 to +5mg/dl LDL –9 to –19.6mg/dl
Ponssen et al., 2000 R, DB, PC, CO	Metformin added to insulin 70/30 twice daily (mean am dose 0.39u/kg; mean pm dose 0.26u/kd). Unclear if insulin dose was adjusted	31	5 months (each arm)	Metformin + insulin –1.23% Insulin –0.7%	
Relimpio et al., 1998 R, OL, PR	Metformin added to $\geq$ 2x daily insulin regimen (mean dose 50U/d). Insulin dose not adjusted unless hypoglycemic	47	4 months	Metformin+ insulin –1.87% Insulin +0.03%	
Robinson et al., 1998 R, DB, PC, CO	Study 1 - Metformin added to usual insulin dose (mean 71U/d). Study 2 – on metformin + insulin where metformin component was stopped (mean insulin dose 41U/d). Insulin dose not adjusted unless hypoglycemic or significantly hyperglycemic	33	Study 1 and study 2 12 weeks (each arm)	Study 1: Metformin + insulin –1.1% Insulin +0.5% Study 2: HbA_1c 1.4% when metformin discontinued	
Fritsche et al., 2000 R, DB, PC, CO	Metformin added to NPH twice daily and regular TID-AC insulin (mean dose 50U/d). Insulin dose adjusted according to an algorithm	13	10 weeks (each arm)	Metformin+ insulin -1.1% Insulin –0.5%	
Golay et al., 1995 R, PC, PR	Metformin added to insulin (mean dose 43U/d)	20	2 weeks	Not assessed	
Insulin + Alpha Glucosidase Inhibitors					
Holman et al., 1999 R, DB, PC, PR	Acarbose (titrated 50-100mg TID) added to insulin	239	3 years	Acarbose+ insulin –0.28% (placebo-adjusted)	Compared to insulin alone, the addition of an AGI to insulin can decrease insulin dose requirements while providing equal or better glycemic control. In the studies assessing weight, there was no difference in weight gain between the AGI + insulin group versus insulin alone. In all but 1 study, AGI + insulin was not found to promote hypoglycemia.
Chiasson et al., 1994 R, DB, PC, PR	Acarbose added to insulin. Details on insulin dose not provided. Insulin dose by 25% if PPG < 180mg/dl	91	1 year	Acarbose + insulin –0.5% Insulin –0.1%	
Gentile et al., 2001 R, DB, PC, PR	Acarbose added to TID admin. of regular insulin NPH (mean dose 40U/d). Insulin dose adjusted based on serum glucose using an algorithm	48	28 weeks	Acarbose + insulin –1.7% Insulin +0.1%	
Kelley et al., 1998 R, DB, PC, PR	Acarbose added to stable dose of insulin (mean dose 60U/d). Insulin dose not adjusted unless hypoglycemic	195	26 weeks	Acarbose + insulin –0.6% Insulin +0.11%	

Study	Drug regimen	N	Duration	Efficacy (HbA_1c)	Remarks
Mitrakou et al., 1998 R, DB, PC, PR	Miglitol added to twice daily insulin (mean dose 40 U/d). Insulin dose if post-prandial glucose increased by >50mg/dl or decreased if pt. hypoglycemic	120	24 weeks	Miglitol + insulin –1.6% Insulin -0.3%	3 studies evaluated lipid parameters (Kelley et al., 1998, Chiasson, et al., 1994; Guvener & Gedik, 1999). TC, HDL, LDL, TG are not effected by acarbose.
Guvener & Gedik, 1999 R, DB, CC, PR	Acarbose added to regular and NPH insulin 2x daily (mean 0.56U/kg/d). Insulin adjusted to obtain adequate glycemic control	40	6 months	Acarbose+ insulin –1.2% Glibenclamide + insulin -1.1%	
Insulin + Glitazones					
Raskin et al., 2001 R, DB, PC, PR	Rosiglitazone added to twice daily insulin (mean dose 73U/d) Insulin dose not adjusted unless patient became hypoglycemic	319	26 weeks	Rosiglitazone + insulin –0.6-1.2% Insulin +0.1%	Addition of a TZD to insulin can decrease insulin dose requirements while providing equal or better glycemic

Study	Drug regimen	N	Duration	Efficacy (HbA_1c)	Remarks
Rosenstock et al., 2002 R, DB, PC, PR	Pioglitazone added to insulin (mean dose 71U/d) Insulin dose not adjusted unless patient became hypoglycemic	566	16 weeks	Pioglitazone 15mg + insulin –0.99% Pioglitazone 30mg + insulin –1.26% Insulin -0.26%	control. 15% incidence of edema. Risk of developing/exacerbation of CHF. Weight gain 2.5-5.3kg (range of mean values from the 3 studies). Weight gain with the combination is greater than with insulin alone. Greater incidence of hypoglycemia with the combination versus insulin alone. Summary of changes in lipid parameters: Rosiglitazone + insulin: TG +4.4 to +22mg/dl; TC +20 to +29mg/dL; HDL +6.5mg/dL; LDL +11 to +15mg/dL Pioglitazone + insulin: TG –27mg/dL; TC change NS; HDL +3.9mg/dL; LDL +3.4mg/dL

AC=before meals, BIDS=bedtime insulin-daytime sulfonylurea, CC=comparator controlled, CO=crossover, DB=double-blind, HDL= high density cholesterol, HS=bedtime, LDL= low density cholesterol, OL=open label, PC=placebo-controlled, PR= parallel, R=randomized, SFU= sulfonylurea, TC= total cholesterol, TG= triglycerides

[a] These combinations have been studied in randomized controlled trials.
[b] Values represent mean change from baseline and are not placebo corrected unless otherwise indicated.

Table G-10. Selected Costs for Diabetes Mellitus Drug Therapy

DRUG	USUAL DOSE [a]	COST/MONTH [b]
Sulfonylureas		
Glyburide	5mg BID	$1.54
Glipizide	10mg BID	$1.56
Glipizide XL	10mg QD	$11.20
Glimepiride	4mg QD	$10.58
Biguanides		
Metformin	850mg BID	$3.72 [c]
	1000mg BID	$4.44 [c]
Alpha-glucosidase inhibitors		
Acarbose	50mg TID	$26.22
Miglitol	50mg TID	$31.60
Thiazolidinediones		
Rosiglitazone	4mg QD	$45.57
	8mg QD	$83.33
Pioglitazone	15mg QD	$45.00
	30mg QD	$80.10
Meglitinides		
Repaglinide	1mg TID	$41.00
Nateglinide	120mg TID	$47.52
Insulin 10 ml vial		
Regular Human	Individualized	$4.49 [d]
Insulin Aspart	Individualized	$17.16
Lispro Human	Individualized	$17.16
NPH Human	Individualized	$4.49 [d]
Lente Human	Individualized	$1.00 [d]
Ultralente Human	Individualized	$11.03
Insulin glargine	Individualized	$25.38
70/30 Human - NPH/regular	Individualized	$4.49 [d]
50% / 50% Human – NPH/regular	Individualized	$11.02
75% intermediate / 25% Lispro	Individualized	$29.77

[a] commonly used doses; does not reflect equivalent dose.
[b] for updated pricing see The VA Pharmacy Benefits Management website http://www.vapbm.org/ .
[c] reflects price of generic metformin; brand name metformin is $35.00 and $33.19 per month for 850mg and 1g BID, respectively.
[d] reflects the price of contracted item by Novo Nordisk

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

MODULE E– EYE CARE

ALGORITHMS AND ANNOTATIONS

Completion Date: March, 2003
Release Date: October, 2003
Version 3.0

SUMMARY OF RECOMMENDATIONS

1. **Retinopathy screening** should be performed by a qualified professional using a dilated eye examination or a retinal image technique with proven accuracy, and interpreted by a trained reader or experienced eye care provider.
2. Routine retinopathy screening should be initiated for patients with **type 1 diabetes within 3 years** of the diagnosis and for patients with **type 2 diabetes within 3 months** of the diagnosis, at most. Patients with visual symptoms should be urgently referred.
3. Patients who have had **no retinopathy on all previous examinations** should be screened for retinopathy at least every other year (biennial screening).
4. **More frequent screening** should be considered in patients with clinical findings associated with an increased rate of progression or prevalence of retinopathy. These clinical findings include uncontrolled hypertension, chronic severe hyperglycemia, recent initiation or intensification of insulin therapy, or other known microvascular disease (e.g., albuminuria or neuropathy).
5. Patients who have **ocular risk factors**, **are on insulin**, or who have had **retinopathy detected** on a previous examination should have a **yearly fundus examination**. The eye care provider should determine the optimal screening intervals based on the patient's severity of retinopathy and risk factors associated with retinopathy progression.
6. Retinal imaging techniques cannot substitute for a comprehensive eye exam for other eye problems, when indicated. **Periodic comprehensive eye examinations** by a trained eye specialist should be scheduled by the primary care provider or eye care specialist based on the individual patient's risk factors for ocular disease, other than diabetic retinopathy.

DISCUSSION

> Optimally timed photocoagulation is very effective at preventing or delaying visual impairment caused by diabetic proliferative retinopathy or macular edema (Early Treatment Diabetic Retinopathy Study [ETDRS] Research Group, 1991). However, there is no experimental controlled research on the optimal screening interval. Therefore, if previous exams have been normal, there is no evidence to suggest that patients receive substantial clinical benefit from a repeat eye examination for diabetic retinopathy at intervals more frequent than every other year (Kohner et al., 2001 & 1999; Stratton et al., 2001; Vijan et al., 2000).

There is some evidence to suggest that progression to advanced disease within 2 to 3 years is also very rare for those with minimal retinopathy on their last examination (Kohner et al, 2001 & 1999; Stratton et al., 2001). However, the Working Group believes that it is appropriate at this time to continue to recommend annual screening for this group of patients, based on the definition of "minimal retinopathy," the reliability of determining "minimal" retinopathy in usual practice, and the amount of available evidence on this topic (Kohner et al, 1999).

The Working Group believes that caution should be exerted in extending biannual examinations to those at particularly high-risk for rapid progression or in a group with a high prevalence of retinopathy, since there may not have been an adequate sample of these high-risk individuals in available cohort data to adequately estimate their 2 to 3 year risk. Therefore, providers should strongly consider more frequent screening in these patients, especially those with very poor blood pressure or glycemic control, or recent initiation or intensification of insulin therapy.

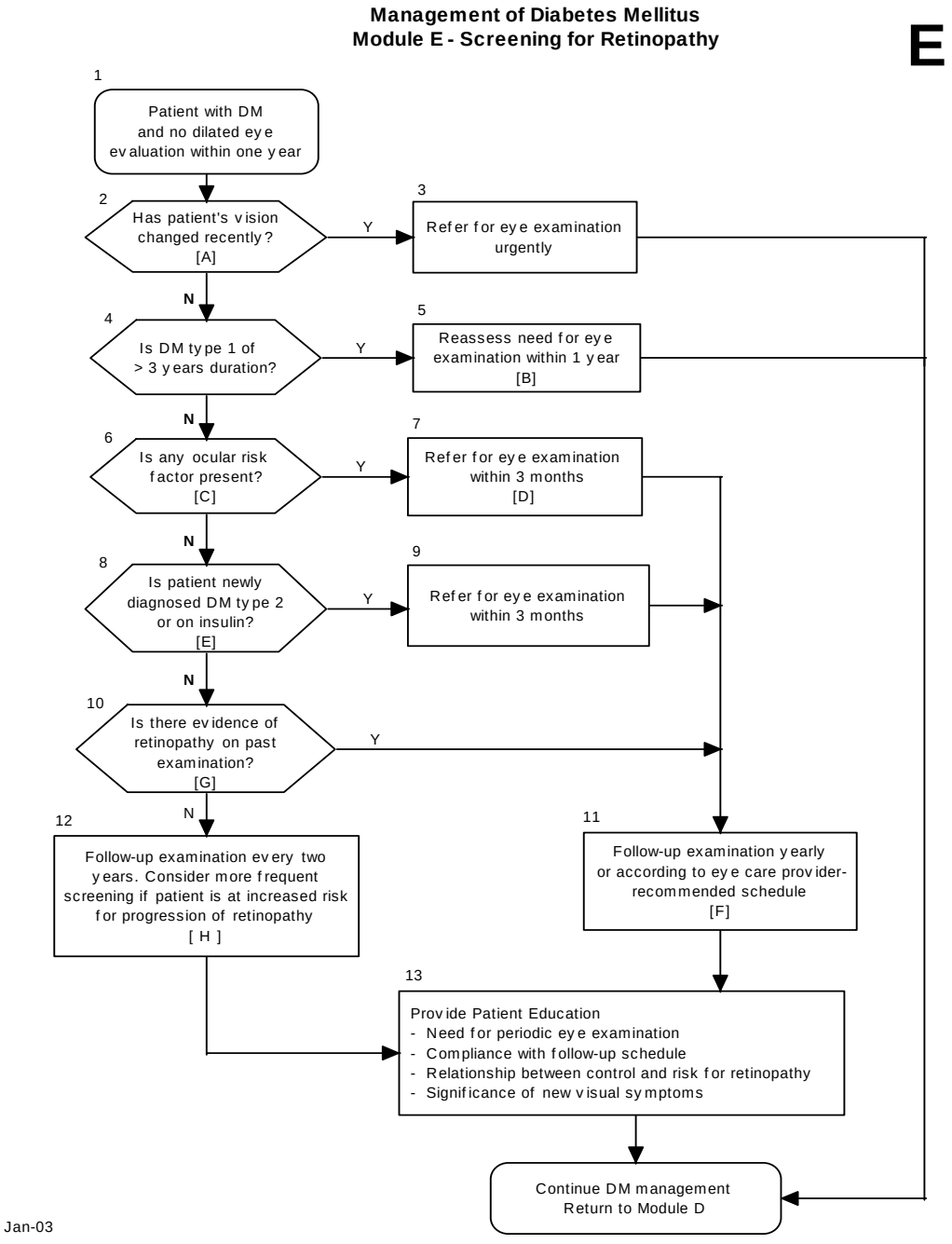
The quality of the eye examination is a critical factor in the effectiveness of this early detection and treatment strategy (Javitt et al., 1996; Singer et al., 1992; Vijan et al., 2000), therefore only fully qualified eye professionals and well-validated imaging techniques should be employed for eye screening and surveillance. Ophthalmoscopy should be performed using high magnification and stereo viewing. Digital image quality compares favorably with that of color slides, but JPEG compression will reduce sensitivity and is not encouraged. Non-mydriatic digital video-color imaging offers good sensitivity and may be useful for follow-up of early retinopathy in the posterior fundus. However, as with all non-mydriatic

imaging techniques, small pupils and/or media opacities will cause image degradation and necessitate the use of mydriasis. Portable non-mydriatic fundus imaging devices are not recommended as primary screening tools due to their lower sensitivity.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Retinopathy screening performed by a qualified professional using a dilated eye examination or a retinal image technique with proven accuracy, and interpreted by a trained reader or experienced eye care provider.	ETDRS, 1991 Javitt et al., 1996 Singer et al., 1992 Vijan et al., 2000	I	Good	B
2	Routine retinopathy screening for patients with type 1 diabetes within 3 years of the diagnosis and for patients with type 2 diabetes within 3 months of the diagnosis, at most. Patients with visual symptoms should be urgently referred.	UK Prospective Diabetes Study Group (UKPDS), 1998	II-1	Fair	C
3	Biennial screening (every other year) for retinopathy for patients with no retinopathy on all previous examinations.	Kohner et al., 2001 & 1999 Stratton et al., 2001 Vijan et al., 2000	II-1	Good	B
4	More frequent screening in patients with increased rate of progression or prevalence of retinopathy, including patients with uncontrolled hypertension, chronic severe hyperglycemia, recent initiation or intensification of insulin therapy, or other known microvascular disease (e.g., albuminuria or neuropathy).	Agardh et al, 1994 Henricsson et al., 1997 Javitt et al., 1994 & 1989 Klein et al., 1994 & 1989 Klein et al., 1989 Savage et al., 1997 Vijan et al., 2000	I	Fair	C
5	At least annual screening for patients who had retinopathy detected on previous examinations. Optimal screening intervals should be based on the patient's severity of retinopathy and risk factors associated with retinopathy progression.	Bresnick et al, 2000 ETDRS, 1991 Javitt et al., 1996 Kohner et al., 2001 & 1999 Singer et al., 1992 Stratton et al., 2001 Vijan et al., 2000	I	Fair	B
6	Periodic comprehensive eye examinations by a trained eye specialist based on the individual patient's risk factors for ocular disease, other than diabetic retinopathy.	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)


Management of Diabetes Mellitus
Module E - Screening for Retinopathy
E
1
Patient with DM and no dilated eye evaluation within one year
2
Has patient's vision changed recently? [A]
Y
3
Refer for eye examination urgently
N
4
Is DM type 1 of > 3 years duration?
Y
5
Reassess need for eye examination within 1 year [B]
N
6
Is any ocular risk factor present? [C]
Y
7
Refer for eye examination within 3 months [D]
N
8
Is patient newly diagnosed DM type 2 or on insulin? [E]
Y
9
Refer for eye examination within 3 months
N
10
Is there evidence of retinopathy on past examination? [G]
Y
N
12
Follow-up examination every two years. Consider more frequent screening if patient is at increased risk for progression of retinopathy [H]
11
Follow-up examination yearly or according to eye care provider-recommended schedule [F]
13
Provide Patient Education
- Need for periodic eye examination
- Compliance with follow-up schedule
- Relationship between control and risk for retinopathy
- Significance of new visual symptoms
Continue DM management
Return to Module D
Jan-03

ANNOTATIONS

A. Has Patient's Vision Changed Recently?

OBJECTIVE

Identify patients with diabetes mellitus (DM) in need of urgent referral to an eye care provider.

RECOMMENDATIONS

1. Patients with an acute change in vision (i.e., occurring within a 48 to 72 hours period) or a change in ocular function should be urgently referred to an eye care provider.

DISCUSSION

Acute changes in vision can be arbitrarily defined as those occurring suddenly or over a period of up to 72 hours. The rapid onset of new visual symptoms such as blurring, distortion, floaters, or light flashes should prompt an urgent referral to an eye care provider as they may indicate a serious ocular problem. Visual symptoms clearly associated with fluctuations in blood glucose level should be distinguished from those that are not, as the former are more likely to represent transient fluctuations associated with glucose control. The sudden onset of persistent pain or diplopia should likewise prompt an immediate referral.

Less acute visual disturbances may not represent an immediate threat to vision, but the primary care provider should consult with an eye care provider if he/she is uncertain about the significance of the changes in ocular status.

B. Reassess Need For Eye Examination Within One Year

OBJECTIVE

Establish the timing of the initial ocular evaluation for patients with early onset DM.

RECOMMENDATIONS

1. Diabetic patients (type 1) with early onset (age <30 years) should begin annual evaluations when the duration of the diabetes diagnosis is greater than 3 years.

DISCUSSION

For patients with type 1 diabetes, the risk for retinopathy becomes significant after 3 to 5 years of disease. These patients are unlikely to develop clinically apparent retinopathy within 3 years after the onset of the disease, but prevalence of retinopathy rises steadily after 3 years and may approach 30 percent by the fifth year (Klein et al., 1984a & 1984b). Ocular involvement is mild in the early cases, but the severity of retinopathy may progress rapidly. Patients who develop retinopathy within 3 years of diabetes onset may progress more rapidly than those who do not (Malone et al., 2001), thus it is recommended that the initial screen not be deferred beyond 3 years post diagnosis.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Annual evaluations to begin when the duration of the diabetes diagnosis is >3 years.	Klein et al., 1984a & 1984b Malone et al., 2001	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

C. Is Any Ocular Risk Factor Present?

OBJECTIVE

Identify patients at risk for advanced retinopathy or rapid progression of pre-existing diabetic eye disease.

RECOMMENDATIONS

1. All patients with diabetes should be screened for high-risk indicators for advanced retinopathy.
2. Patients are defined as high-risk if they have at least one of the following risk factors:
   - DM for 15 years or more
   - Any evidence of diabetic nephropathy (including microproteinuria)
   - Type 2 DM and cardiovascular autonomic neuropathy
   - Lower extremity amputation (LEA) related to DM
   - History of any diabetic retinopathy
   - Pregnancy and pre-existing diabetes

DISCUSSION

Patients at risk for severe retinopathy are generally those with long duration of disease and/or significant non- ocular complications.

Duration of disease is most strongly associated with advanced retinopathy in younger onset individuals (<30 years at diagnosis or type 1 DM). The prevalence of proliferative disease approaches 30 percent in these patients after 15 years of DM (Klein et al., 1992b & 1984a). The prevalence continues to rise rapidly after this point and reaches 50 percent for males and 33 percent for females after 19 or 20 years of disease. Although the risk of proliferative retinopathy is much lower for individuals with an older onset of DM ($\geq$30 years at diagnosis or type 2 DM), the prevalence of retinopathy approaches 75 percent for those on insulin and by 20 years the prevalence of proliferative disease exceeds 20 percent (Klein et al., 1984b).

Gross proteinuria and LEA are also associated with advanced stages of retinopathy (Savage et al., 1996; Klein et al., 1993; Mayfield et al., 1996). Although the relationship may not be causal, these patients typically have longstanding or advanced DM and are likely to have other evidence of micro- or macrovascular complications. Pregnancy can be associated with a dramatic and rapid progression of pre-existing retinopathy (Dibble et al., 1982; Hemachandra et al., 1995; Klein BEK et al., 1990). Pregnant patients with pre-existing diabetes require more frequent examinations as the disease may progress to sight-threatening retinopathy faster than would otherwise be expected.

The presence of cardiovascular autonomic neuropathy has been associated with a several fold increase in the risk for proliferative retinopathy in patients with type 2 DM (Schmid et al., 1995). This association appears to persist even when other risk factors are taken into account.

Patients who have undergone laser therapy for retinopathy have presumably reached the stage of vision-threatening diabetic eye disease. These patients require close long-term follow-up, and in the absence of information to the contrary, should be considered at high-risk for vision loss.

Regardless of the presence of other risk factors, glycemic control and blood pressure control are clearly related to the risk for chronic complications and the reduction in risk (Diabetes Control and Complications Trial Research Group, 1993; Ohkubo et al., 1995; UKPDS, 1998). The impact of these factors should be considered for each patient when assessing the duration of the disease as a risk factor for advanced retinopathy, and the physician should consider a lower threshold for high-risk status for patients whose disease is chronically poorly controlled.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Screening of all patients with diabetes for high-risk indicators for advanced retinopathy.	Klein et al., 1992b & 1984a Klein et al., 1993; Mayfield et al., 1996 Savage et al., 1996	II-2	Fair	B
2	Existence of at least one of the	Working Group Consensus	III	Poor	C

	listed risk factors is sufficient to define the patient as high-risk.				

QE = Quality of Evidence; R = Recommendation (see Appendix A)

D. Refer for Eye Examination Within 3 Months

OBJECTIVE

Ensure that high-risk patients are expediently referred.

RECOMMENDATIONS

1. Patients at high-risk for ocular complications should receive a comprehensive dilated eye examination within three months of diagnosis by an ophthalmologist or optometrist knowledgeable and experienced in detecting diabetic eye disease.
2. A dilated fundus examination or validated fundus imaging technique should be used to detect retinopathy, with interpretation by a qualified, experienced reader.
3. Retinal imaging techniques cannot substitute for a comprehensive eye exam for other eye problems, when indicated. Periodic comprehensive eye examinations by a trained eye specialist should be scheduled based on the individual patient's risk factors for ocular disease, other than diabetic retinopathy.

DISCUSSION

Risk stratification of patients is an appropriate strategy for prioritizing the referral of patients to specialty care (Bresnick, et al., 2000; Vijan et al., 2000). It helps maximize the effectiveness of available resources and encourages the initiation of early treatment for those most likely to need it. Timely institution of laser therapy in patients with diabetic retinopathy can reduce the risk of moderate to severe vision loss by 50 to 90 percent, but the benefits of treatment may be less dramatic for patients who are not seen until they have progressed to the most advanced stages of retinopathy.

A dilated fundus examination is the most sensitive method of detecting retinopathy (Nathan et al., 1991). The highest sensitivity and specificity are obtained by fundus photography with interpretation by an experienced reader (Singer et al., 1992). Fundus examination performed by an experienced eye care provider using stereoscopic viewing can also yield high detection rates. Nonmydriatic retinal photography can reveal disease in the posterior retina with a similar degree of sensitivity, but it may not show important findings in the peripheral retina. In addition, media opacities, such as cataracts, may lessen the sensitivity of this technique. Fundoscopy through an undilated pupil is the least sensitive method for detecting retinopathy and cannot be recommended as a standard of care. As patients with DM are at risk for other ocular disorders, neither fundoscopy nor photographic screening obviates the need of periodic comprehensive eye examinations.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Comprehensive dilated eye examination within three months of diagnosis by ophthalmologist or optometrist knowledgeable and experienced in detecting diabetic eye disease.	Klein et al., 1984a & 1984b UKPDS, 1998	II-1	Fair	C
2	Dilated fundus examination and fundus photography to detect retinopathy.	Javitt et al, 1996, 1994 & 1989 Nathan et al., 1991 Vijan et al., 2000	I	Good	B
3	Periodic comprehensive eye examinations.	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

E. Is Patient Newly Diagnosed DM Type 2 Or On Insulin?

OBJECTIVE

Screen for retinopathy in newly diagnosed patients with type 2 diabetes or those on insulin.

RECOMMENDATIONS

1. Patients who have not had a dilated eye exam within the past 12 months and are newly diagnosed with type 2 DM or on insulin for established diabetes should have a dilated fundus examination performed within 3 months.

DISCUSSION

The inability of symptoms alone to accurately predict the presence or severity of retinopathy necessitates timely referral to an eye care provider for patients who have not had a dilated eye examination within the previous 12 months and who have no established examination schedule.

The risk for retinopathy increases with duration of disease for individuals with type 1 and type 2 diabetes (Klein et al., 1992b, 1984a, 1984b). Patients who develop retinopathy may have rapid progression over the course of a year, and a small percentage with even mild retinopathy will progress to proliferative disease within this timeframe (Ginsburg & Aiello, 1993).

Patients with late onset (age 30) or type 2 DM appear to have a period of clinical latency that may last several years. Clinically apparent retinopathy can develop during this time, and nearly 20 percent of patients will have some retinopathy at the time of the diagnosis (Klein et al., 1992b & 1984b; UKPDS, 1998). Although the prevalence of vision-threatening retinopathy at the time of diagnosis is very low in asymptomatic patients (Klein et al., 1992a), a 3 to 4 percent prevalence of proliferative retinopathy within the first few years of disease makes referral of the initial retinopathy screening an inappropriate strategy for those who have not had a dilated eye examination for 12 months or more. Patients who require insulin for control are at higher risk for the development and progression of retinopathy. Timely referral for retinopathy screening for those who have not had a dilated eye exam for 12 months or more is encouraged.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Dilated eye examination performed within 3 months for newly diagnosed patients with type 2 DM.	Klein et al., 1989, 1984a, 1984b	II-1	Fair	C

QE = Quality of Evidence; R = Recommendation (see Appendix A)

F. Follow-Up Examination Yearly Or According To Eye Care Provider-Recommended Schedule

OBJECTIVE

Establish a follow-up interval for patients who may be at moderate to high-risk for retinopathy development or progression.

BACKGROUND

The inability of symptoms alone to accurately predict the presence or severity of retinopathy necessitates regularly scheduled fundus examinations for patients with diabetes. While some patients will remain retinopathy free for several years, the course of the disease cannot be reliably predicted for any individual. Patients who require insulin for control are at higher risk for the development and progression of

retinopathy. Similarly, patients whose disease is poorly controlled or who are hypertensive have a higher prevalence of retinopathy and are more likely to show progression. In light of these associations, as well as the relationship of disease duration and the presence of other microvascular complications to the risk for retinopathy, it would be prudent to perform yearly fundus examinations on selected patients.

RECOMMENDATIONS

1. Patients who have ocular risk factors, are on insulin, or who have had retinopathy detected on a previous examination should have a fundus examination at least yearly with the precise examination interval determined by the eye care specialist.

DISCUSSION

Patients who have no evidence of retinopathy on dilated fundus examination are unlikely to develop vision-threatening disease within a 2 to 3 year period.

There is clear and convincing evidence that previous retinopathy can progress rapidly and unpredictably once present (Dasbach et al., 1991; Javitt et al., 1994 & 1989; Klein et al., 1994 & 1989; Kohner et al, 2001; Savage et al., 1997; Stratton et al., 2001; Vijan et al., 2000). Many patients will require follow-up at intervals much less than one year. The precise follow-up intervals are not clearly established by research and should be individualized for the patient and determined by a qualified eye care professional. Although there is some evidence that minimal disease may have a very low 3 year progression rate, the Working Group believes that this evidence is too preliminary to warrant recommending longer follow-up intervals for this group.

Other components of the eye examination do not need to be repeated on a yearly basis, except where indicated by coexisting ocular conditions, patient symptoms, or the presence of risk factors for other disorders requiring yearly screening.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	At least annual evaluation for patients who had retinopathy detected on previous examinations, have ocular risk factors, or are on insulin.	Chen et al., 1995 Dasbach et al., 1991 Javitt et al., 1994 & 1989 Klein et al., 1994 & 1989 Kohner et al., 2001 Morisaki et al., 1994 Savage et al., 1997 Stratton et al, 2001 Vijan et al., 2000	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

G. Is There Evidence Of Retinopathy On Past Examination?

OBJECTIVE

Establish a follow-up interval for patients who have had retinopathy detected on a previous examination.

RECOMMENDATIONS

1. Patients who have had retinopathy detected on previous examinations should be seen at least annually. The eye care provider should determine the optimal screening intervals based on the patient's severity of retinopathy and risk factors associated with retinopathy progression.

DISCUSSION

Patients who develop retinopathy may have rapid progression over the course of a year and a small percentage with even mild retinopathy will progress to proliferative disease within this period. These

patients often require follow-up at frequent intervals (much less than every 12 months) and should be referred for an examination at least yearly if they have no scheduled follow-up with an eye care provider (see Annotation F, discussion section)

H. Follow-Up Examination Every Two Years; Consider More Frequent Screening If Patient Is At Increased Risk For Progression Of Retinopathy

OBJECTIVE

Establish a follow-up interval for patients who have had no retinopathy detected on previous examinations and who do not require insulin for control.

RECOMMENDATIONS

1. Patients who have had no retinopathy on all previous examinations should be screened for retinopathy at least every other year (biennial screening).
2. More frequent screening should be considered in patients with clinical findings associated with an increased rate of progression or prevalence of retinopathy. These clinical findings include poorly controlled hypertension, chronic severe hyperglycemia, recent initiation or intensification of insulin therapy, or other known microvascular disease (albuminuria or neuropathy).

DISCUSSION

There is no experimental controlled research on the optimal screening interval; however, if previous exams have been normal, there is no evidence to suggest that patients receive substantial clinical benefit from a repeat eye examination for diabetic retinopathy at intervals more frequent than every other year. Vijan et al. (2000) used information from previous epidemiological studies and a validated simulation model to examine the benefits of different retinopathy screening intervals. The investigators found that for most patients with no retinopathy at baseline, screening every 2 to 3 years was probably more than adequate. In addition, close follow-up for those with known retinopathy seemed to be the most important factor in preventing visual loss, even for those in high-risk groups. These findings were subsequently confirmed by analyses conducted on the UKPDS cohort (Kohner et al., 2001; Stratton et al., 2001). The authors confirmed that early retinopathy on previous examinations was the main risk factor for requiring photocoagulation within the next 3 to 6 years. Of 2,316 patients with no retinopathy at baseline, only 0.2 percent required any photocoagulation within 3 years and only 1.1 percent needed treatment within 6 years, despite this cohort having many patients with poor glycemic and blood pressure control. The Working Group made further inquiries to experts in the field, which uncovered two other unpublished cohort studies that appear to add further support to this finding. There is no additional epidemiological evidence (published or unpublished) to suggest that screening intervals more frequent than every other year provide clinical benefit for those whose previous examinations have been normal.

There is some evidence to suggest that progression to advanced disease within 2 to 3 years is also very rare for those with minimal retinopathy (Kohner et al., 2001). However, the Working Group believes that continuing to recommend annual screening for this group is appropriate at this time, based on the definition of "minimal retinopathy," the reliability of determining "minimal" retinopathy in usual practice, and the amount of available evidence on this topic.

In addition, the Working Group recommends that clinicians exert caution in extending biennial (every other year) examinations to those patients at high-risk for retinopathy and retinopathy progression. Although the UKPDS results suggest that every 2 year screening intervals are adequate, even when the patient population includes many with poor glycemic and blood pressure control, there may still be high-risk patients in whom every 12 to 18 month screening is preferable. Risk factors for rapid progression of retinopathy include poor glycemic or blood pressure control, pregnancy with pre-existing diabetes, and recent initiation or intensification of insulin therapy (Agardh et al., 1994; Henricsson et al., 1997; Klein, 1994 & 1989; Savage et al., 1997). Risk factors for a high prevalence of retinopathy include the following: evidence of other glycemic related complications (nephropathy and neuropathy), need for insulin treatment, and long duration of disease (Agardh et al., 1994; Henricsson et al., 1997; Klein, 1994 & 1989; Savage et al., 1997).

There is some evidence to suggest that ethnicity may be an additional risk factor for some Native and Mexican Americans, independent of the control. The Working Group cautions providers that this recommendation only applies to patients who have had no retinopathy on all previous retinal examinations (screening examinations). Much closer follow-up (i.e., surveillance examinations) is important for patients with known retinopathy.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	At least biennial screening exams (every other year) for retinopathy for patients who had no retinopathy on all previous examinations.	Kohner et al., 2001 & 1999 Stratton et al., 2001 Vijan et al., 2000	II-1	Good	B
2	Consideration of more frequent screening in patients with risk factors associated with an increased rate of progression or prevalence of retinopathy.	Agardh et al., 1994 Henricsson et al., 1997 Javitt et al., 1994 & 1989 Klein et al., 1994 & 1989 Savage et al., 1997 Vijan et al., 2000	I	Fair	C

QE = Quality of Evidence; R = Recommendation (see Appendix A)

APPENDIX E-1
Notes on Diabetic Ocular Disease

Diabetic retinopathy is a microangiopathy characterized by a combination of retinal vascular incompetence and capillary closure. It is usually divided into non proliferative and proliferative forms, in large part dependent upon whether the complications of vascular leakage or closure predominate.

Non proliferative retinopathy is manifest clinically by the presence of microaneurysms, hemorrhages, lipid exudates, and retinal edema. Patients develop microinfarcts, or cotton wool spots, in areas of capillary constriction. As the non proliferative disease advances, the veins may take on a beaded appearance or show small kinks or loops. The appearance of fine intraretinal microvascular anomalies (IRMAs) may be confused with preretinal neovascularization and often precedes its development.

Proliferative retinopathy occurs when widespread retinal ischemia leads to the proliferation of newly formed vessels over the surface of the retina or optic nerve. Vessels involving the optic nerve or immediately adjacent retina are termed neovascularization at the disc (NVD); vessels involving the remainder of the fundus are called neovascularizaton elsewhere (NVE). Vitreous hemorrhage occurs when fibrous tissue accompanying the new vessels contracts and causes traction on the retinal surface. The hemorrhage obscures fundus details and causes a corresponding loss of vision in the involved eye.

Laser therapy has been shown to be highly effective in treating diabetic retinopathy and preventing vision loss (Ferris, 1993). It is applied focally to areas of vascular leakage to treat macular edema and in "scatter" fashion to large areas of the retina to treat proliferative retinopathy. It may take several weeks to months for a therapeutic response to occur and it is not unusual for patients to require multiple treatment sessions.

The effects of DM on the eye are not limited to diabetic retinopathy. Glaucoma and cataract occur with increased frequency in individuals with DM and can cause significant visual impairment if not treated (Ederer et al., 1981; Klein & Klein, 1995; Klein et al., 1994; Klein et al., 1995).

Cataract formation, or opacification of the lens, is a normal aging phenomenon. Cataracts degrade the quality of vision due to irregular refraction of light and reduction in the optical clarity of the lens. These changes produce symptoms of glare, loss of contrast, and blurred vision. If symptoms become incapacitating or limit normal activity, the lens is removed and replaced with a prosthetic one. Occasionally, cataracts require removal due to their obscuration of the fundus view, thus limiting one's ability to appropriately follow and treat co-existing disorders.

Glaucoma is a progressive optic neuropathy that is associated with loss of the neural rim of the optic nerve head and a gradual reduction in peripheral vision. Central vision may also be lost with advanced disease. Although glaucoma is typically associated with increased intraocular pressure, a significant minority of patients have no documented ocular hypertension (Bonomi et al., 1998; Sommer et al., 1991). The overwhelming majority of patients with glaucoma have no specific symptoms attributable to their disease until it is far advanced, making periodic screening for glaucoma by an eye care provider an important management strategy.

Race, age, and family history are important risk factors for glaucoma (Mason et al., 1989; Tielsch et al., 1991 & 1994). It is four to five times more prevalent among blacks than among whites and is the leading cause of blindness in African Americans. The risk for glaucoma increases with age and is significant for black people age 40 and over and for all individuals age 60 and over. A history of glaucoma in first-degree relatives further increases the risk, and siblings of individuals with glaucoma are at very high-risk. An association with diabetes has not been found by all investigators (Tielsch et al., 1995), but glaucoma is found with increased frequency in the age groups most often affected by older-onset diabetes.

Glaucoma can be treated with a variety of topical medications that lower the intraocular pressure. Beta-blockers are used most frequently, but while generally safe, they can be associated with the same complications as systemic beta-blockers. The treatment goal is to lower the intraocular pressure to a level

at which further damage will not occur. This "target pressure" is established based on several criteria but is generally 30 to 50 percent of the baseline level, or untreated value. Laser surgery is most often used to supplement medical therapy, while surgery is usually reserved for patients who require a very low pressure or who have not responded sufficiently to other therapies.

Diabetes is also a risk factor for retinal venous occlusive disease (Sperduto et al., 1998). Clinically, this condition may simulate diabetic retinopathy, but the predominance of hemorrhage and the typical distribution of the hemorrhagic retinopathy help establish the correct diagnosis. In addition, venous occlusions rarely present bilaterally, whereas diabetic retinopathy is typically a bilateral disorder. Macular edema and neovascularization can complicate venous occlusions but in most cases can be treated successfully with laser therapy.

Arterial occlusive disease, optic neuropathy, and acute mononeuropathies are additional ocular abnormalities that are frequently seen in individuals with diabetes. Diabetes is found in approximately 25 percent of patients with central retinal artery occlusion (Brown & Margargal, 1982). The existence of occlusive carotid disease and hypertension in persons with diabetes may contribute to this association.

Sudden swelling of the optic nerve head can occur in young patients with type 1 diabetes. It is associated with mild-to-moderate loss of vision and may involve one or both eyes. The loss of vision helps to distinguish this entity from papilledema, when bilateral. It may represent a mild form of anterior ischemic optic neuropathy and is associated with good visual recovery. Classic anterior ischemic optic neuropathy associated with pallid disk edema and moderate-to-severe vision loss is not uncommon in older adults, but its occurrence in individuals under age 45 suggests diabetes (Beri et al., 1987).

Acute mononeuropathies involving the III, IV, or VI nerve are also associated with diabetes. The III nerve is involved most frequently, but the pupil is spared 80 percent of the time. The palsy is generally self-limiting, but other causes for oculomotor nerve weakness should be considered at the time of initial presentation.

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

MODULE F – FOOT CARE

ALGORITHMS AND ANNOTATIONS

Completion Date: March, 2003
Release Date: October, 2003
Version 3.0

SUMMARY OF RECOMMENDATIONS

The goal of Module F – Foot Care is to identify patients who are at high-risk for the development of foot ulcers and lower extremity amputations (LEA). Patients are identified through a foot risk assessment that stratifies them into either high-risk or low-risk for lower extremity (LE) complications. Once the patient is identified as high-risk, he/she is referred to a foot care specialist for a more intensive follow-up plan that includes patient education, appropriate footwear, and other specialty referrals, as needed.

Screening and Assessment

1. **Visual inspection** should be performed in high-risk patients at each routine primary care visit. Inspection includes screening for breaks in the skin, erythema, trauma, pallor on elevation, dependent rubor, changes in foot size/shape, nail deformities, extensive callus, tinea pedis, and pitting edema.
2. A **foot risk assessment** should be performed and documented annually to evaluate for skin breakdown, LE arterial disease, and foot deformity; assess protective sensation; determine prior history of ulcers or amputations; and evaluate footwear.

   High-risk patients are defined as having at least one of the following characteristics:

   Lack of sensation to Semmes-Weinstein 5.07 monofilament at one or more noncallused plantar sites

   Evidence of LE arterial disease (absence of both dorsalis pedis and tibialis posterior pulses, dependent rubor with pallor on elevation, history of rest pain or claudication, and prior history of LE bypass surgery)

   Foot deformities (specifically hammer toes, claw toe, Charcot's arthropathy, bunions, and metatarsal head deformities)

   History of foot ulcer or non-traumatic LEA

Treatment/Referral

1. Patients with **life threatening conditions** should be referred to the appropriate level of care for evaluation and treatment.
2. **High-risk patients or those with limb-threatening conditions** (e.g., systemic infection, acute ischemia/rest pain, foot ulceration, puncture wound, ingrown toenail, and hemorragic callus with or without cellulites) should be referred to a foot care specialist for a more intensive treatment program of in-depth patient education concerning foot care practices, hygiene, and footwear.
3. Patients with circulatory **symptoms that limit their lifestyle** should be referred to a vascular specialist to determine the appropriateness of surgical intervention on a patient-specific basis. Vascular procedures should be justified based on outcomes of vascular interventions.
4. Patients with **minor foot wounds or lesions** should be referred to a foot care specialist (i.e., podiatrist, vascular surgeon, orthopedic surgeon, and other healthcare providers) with demonstrated training, competence, and licensure in foot care for evaluation and treatment.
5. Patients with **uncomplicated minor lesions** (e.g., onychomycosis, painful corns, dry skin, athlete's foot, minor calluses, uncomplicated nail trimming and improper foot hygiene) may be provided with local wound care and offload pressure, as indicated, with follow-up on a specified schedule.
6. **Footwear prescriptions** should be determined based upon the individual structural and clinical findings. Patients and families should be educated on preventive foot care and footwear including daily foot inspection and preventive care; skin, nail, and callus care; what to report and whom to call regarding any foot injury or abnormality; and footwear.

Management of Diabetes Mellitus
Module F - Foot Care

F

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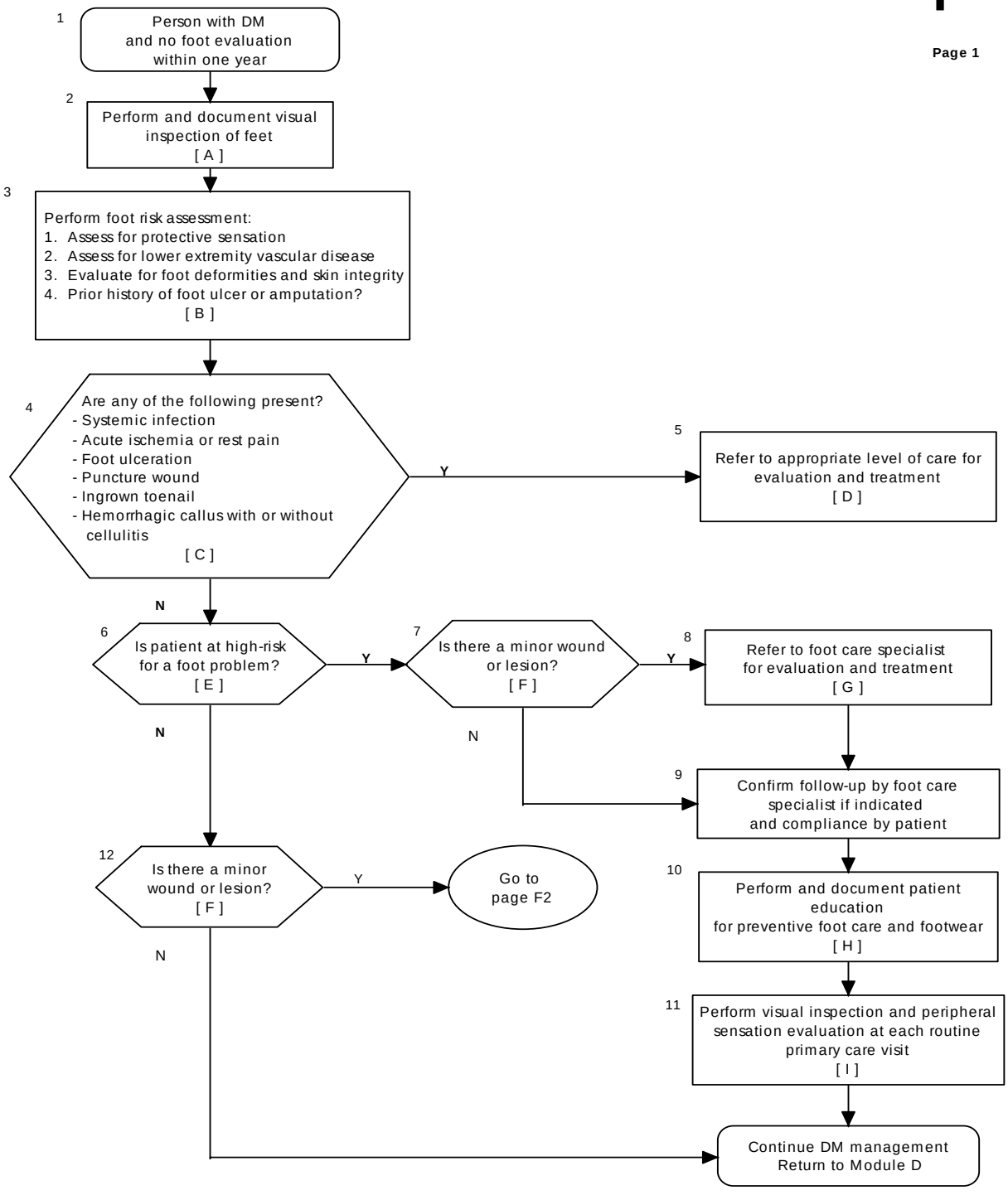
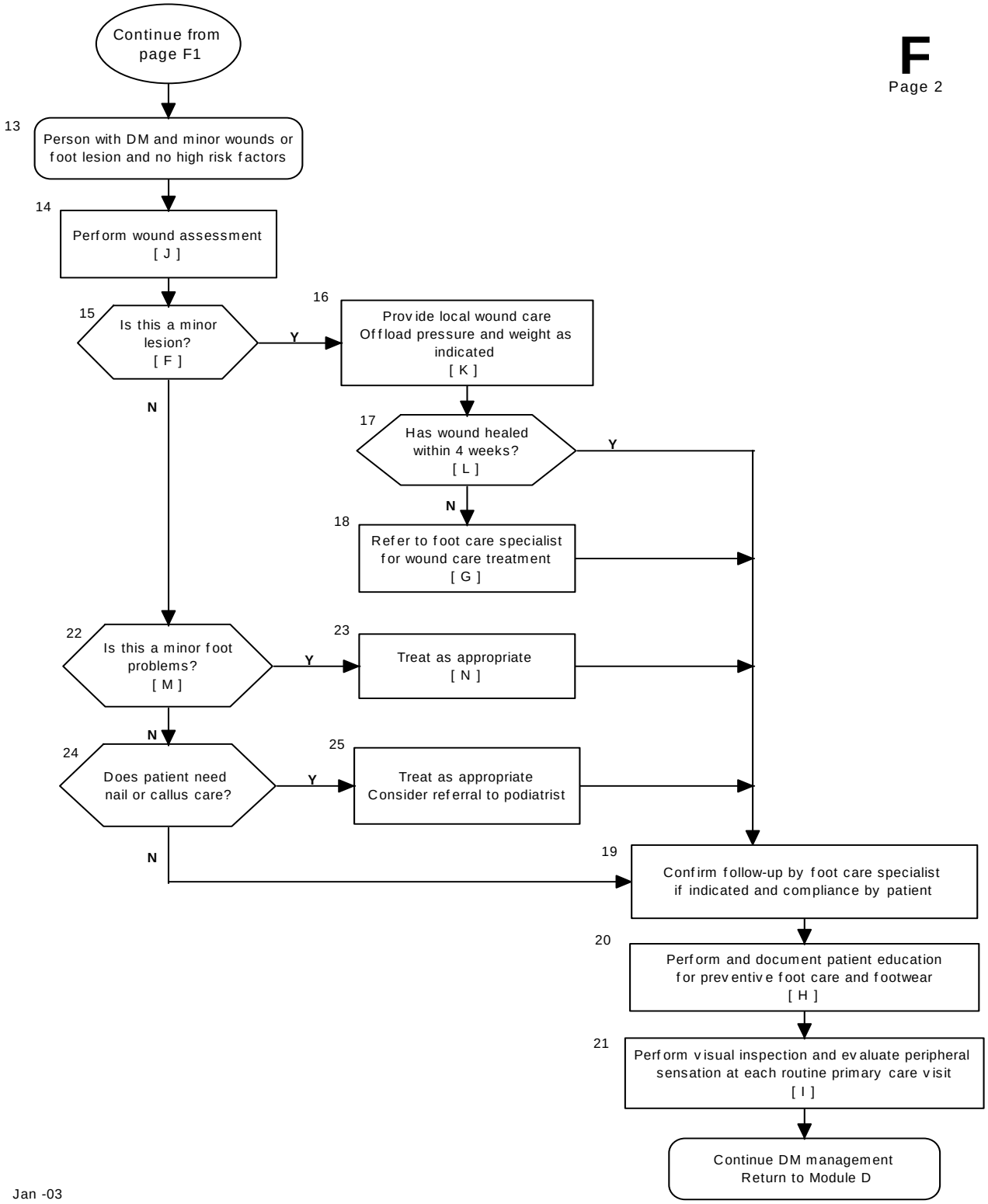


Jan-03


Continue from page F1
F
Page 2
13
Person with DM and minor wounds or foot lesion and no high risk factors
14
Perform wound assessment [J]
15
Is this a minor lesion? [F]
Y
16
Provide local wound care Offload pressure and weight as indicated [K]
N
17
Has wound healed within 4 weeks? [L]
Y
N
18
Refer to foot care specialist for wound care treatment [G]
22
Is this a minor foot problems? [M]
Y
23
Treat as appropriate [N]
N
24
Does patient need nail or callus care?
Y
25
Treat as appropriate Consider referral to podiatrist
N
19
Confirm follow-up by foot care specialist if indicated and compliance by patient
20
Perform and document patient education for preventive foot care and footwear [H]
21
Perform visual inspection and evaluate peripheral sensation at each routine primary care visit [I]
Continue DM management Return to Module D
Jan -03

ANNOTATIONS

A. Perform And Document Visual Inspection Of Feet

OBJECTIVE

Examine the patient's feet for any abnormal findings.

RECOMMENDATIONS

1. The patient's feet should be visually inspected for:
   - Breaks in the skin
   - Erythema
   - Trauma
   - Pallor on elevation
   - Dependent rubor
   - Changes in the size or shape of the foot
   - Nail deformities
   - Extensive callus
   - Tinea pedis
   - Pitting edema

DISCUSSION

Despite limited information, there is consensus in the diabetes professional community that visual inspection combined with peripheral sensation testing may identify some unsuspected lesions in patients with diabetes. This practice also demonstrates to the patient the importance of foot assessment.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Visual inspection of the feet at every routine primary care visit.	ADA, 2002 Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

B. Perform Foot Risk Assessment

OBJECTIVE

Identify the patient at risk for LE ulcers and amputations.

RECOMMENDATIONS

1. A foot risk assessment must be performed and documented at least once a year. A complete foot risk assessment includes:
   - Evaluation of the skin for breakdown
   - Assessment of protective sensation using the Semmes-Weinstein 5.07 monofilament
   - Evaluation for LE arterial disease
   - Evaluation for foot deformity
   - Prior history of ulcers or amputations

   In addition, the patient's footwear should be evaluated.

DISCUSSION

Patients with diabetes are at risk for developing peripheral neuropathy with loss of sensation. Patients who develop peripheral vascular disease or end stage renal disease, are considered high-risk for developing a foot ulcer. Protective and prophylactic foot care and early detection of any deformity or skin breakdown may prevent the development of ulcers and risk of amputation. The tensile strength of mature scar tissue is

about 80 percent of original tissue strength, thus increasing the chance of developing further ulceration. The patient should therefore be questioned about foot ulcer history. A person who has had a foot ulcer is at life-long risk of further ulceration.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Foot risk assessment.	**ADA, 2002** Mayfield et al., 1998 [SR] Mayfield et al., 2000	III II II	Fair	B

QE = Quality of Evidence; R = Recommendation; SR = Systematic Review (see Appendix A).

C. Are Any Limb-Threatening Conditions Present?

OBJECTIVE

Identify a limb-threatening condition that may require immediate attention, referral, or hospitalization.

RECOMMENDATIONS

1. Evaluation should be performed for limb-threatening conditions, such as systemic infection, acute ischemia/rest pain, foot ulceration, puncture wound, ingrown toenail, and hemorragic callus with or without cellulitis.

DISCUSSION

Systemic or Ascending (Worsening) Infection

Limb-threatening conditions could include signs and symptoms of systemic infection including gas gangrene, ascending cellulitis and lymphangitis, or gangrene.

Although infection is not always clinically apparent, common signs and symptoms include perilesional warmth, erythema, purulent drainage, odor, and involvement of bone. Pain may or may not be present. There may or may not be lymphangitis and lymphadenopathy, and fever and white blood cell count may or may not be present. Sudden loss of glycemic control often heralds serious infections (Orchard & Strandness, 1993).

Acute Ischemia or Rest Pain

Absence of palpable pedal pulses - Examine the patient to determine presence of dorsalis pedis and posterior tibial pulses. Absent pulses and signs of acute ischemia, e.g., rest pain associated with dependent rubor with pallor or palpably cold extremities, warrant urgent referral to a vascular surgeon.

Acute ischemia or rest pain – Evidence of arterial insufficiency*:* lower limb pain at rest, dusky/blue or purple/black color, gangrene, or cold extremity. Pain in the toes or forefoot may be relieved by dependency of the limb. Assessment is needed for prompt vascular/surgical intervention. Patient with acute arterial occlusion will present with pain, pallor, pulseless, paresthesia, and/or paralysis (Orchard & Strandness, 1993).

Claudication - Severe claudication is determined as pain in the thigh or calf that occurs when walking less than one block and is relieved by rest.

Peripheral vascular diseases are associated with diabetic bilateral amputation. Preventative foot care programs should focus on peripheral vascular assessment to identify patients at risk and on the development of timely intervention strategies (Carrington et al., 2001).

Foot Ulceration

Active foot ulcer - A cutaneous erosion with a loss of epithelium that extends to or through the dermis can involve deeper tissue and is characterized by an inability to self-repair in a timely and orderly manner (ADA, 2002; Brodsky & Schneidler, 1991; Caputo et al., 1994; Eckman et al., 1995; Reiber et al., 1995).

Puncture Wound

Puncture wound - A lesion through the epidermis, dermis, and other tissues caused by a piercing or penetrating object. Patients with diabetes with puncture wounds can quickly develop severe limb-threatening complications.

Ingrown Toenail

Ingrown toenail - Presents as a nail plate that has pierced the surrounding periungual tissue with associated erythema and drainage or an area of thick or discolored callus. The primary care provider should consider referral to a podiatrist for excision of infected ingrown nails, especially in the case of high-risk patients (Giacalone, 1997).

Hemorrhagic Callus With or Without Cellulitis

The provider must determine if the cellulitis may be associated with callus tissue or necrotic tissue that may obscure an underlying ulceration or deeper infection.

The callus tissue must be debrided to properly assess the extent of an underlying ulceration and possible deeper more serious infection. Necrotic tissue must also be debrided to help eradicate the infection and determine the full extent of the infection. The patient should be promptly referred to a foot care specialist for complete evaluation and treatment.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Assessment of peripheral vascular disease.	Carrington et al., 2001 Orchard & Strandness, 1993	II-1 III	Fair	B
2	Evaluation for acute ischemia or rest pain.	Orchard & Strandness, 1993	III	Poor	I
3	Evaluation for foot ulceration.	ADA, 2002 Brodsky & Schneidler, 1991 Caputo et al., 1994 Eckman et al., 1995 Reiber et al., 1995	III	Poor	I
4	Evaluation for ingrown toenail.	Giacalone, 1997	II-1	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A).

D. Refer To Appropriate Level Of Care For Evaluation And Treatment

OBJECTIVE

Determine the appropriate intervention.

RECOMMENDATIONS

1. Patients with limb-threatening conditions should be referred to the appropriate level of care for evaluation and treatment.
2. If the patient's symptoms limit his/her lifestyle, a vascular specialist should determine the appropriateness of surgical intervention on a patient-specific basis. Justification of vascular procedures should be based on the outcomes of the vascular interventions.

A foot care specialist is defined as a podiatrist, vascular surgeon, orthopedic surgeon, or other healthcare provider with demonstrated training, competence, and licensure in foot care.

DISCUSSION

The patient with cellulites, that is not complicated by hemorrhagic callus or necrotic tissue, and without systemic signs of infection, should be treated with appropriate antibiotics, off-loading weight from the affected limb, and aggressive follow-up to ensure that the condition does not become severe.

The patient should be alert to signs and symptoms of systemic infection to include fever, chills, nausea and vomiting, and elevation in blood sugars. If the patient manifests any of these symptoms, he/she should notify the provider immediately. If the infection has not resolved within 7 days of oral therapy or there is a worsening of the symptoms, the patient should be admitted to a hospital for appropriate IV antibiotic therapy. Once the cellulitis has resolved, the patient should be referred to a foot care specialist for intensive secondary prevention (Conte et al., 1995; Currie et al., 1995).

Initial therapy could include antibiotics, wound cleansing, tetanus prophylaxis (if indicated), and/or same-day referral to a foot care specialist.

Patients with diabetes, especially neuropathic patients, often present late for treatment with mixed aerobic and anaerobic infections that require prompt referral and evaluation by a qualified provider who is experienced in the management of this condition (Lavery et al., 1995).

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Referral for life-threatening conditions.	Working Group Consensus	III	Poor	I
2	Referral to a vascular specialist for symptoms that limit lifestyle.	Conte et al., 1995 Currie et al., 1995 Lavery et al., 1995	III II III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A).

E. Is Patient At High-Risk For A Foot Problem?

OBJECTIVE

Identify the patient at high-risk for LE foot ulcers and amputations.

RECOMMENDATIONS

1. Patients without limb-threatening conditions should be evaluated for their level of risk for LE foot ulcers and amputations.
2. The existence of one of the following characteristics is sufficient to define the patient as high-risk for foot problem.

   Lack of sensation to Semmes-Weinstein 5.07 monofilament at one or more noncallused plantar sites

   Evidence of LE arterial disease (absence of both dorsalis pedis and tibialis posterior pulses, dependent rubor with pallor on elevation, history of rest pain or claudication, and prior history of LE bypass surgery)

Foot deformities (specifically hammer toes, claw toe, Charcot's arthropathy, bunions, and metatarsal head deformities)
History of foot ulcer or non-traumatic LEA at any level.

3. The patient at high-risk should be referred to a foot care specialist for a more comprehensive evaluation and intensive treatment plan including patient education concerning foot care practices, hygiene, and footwear.

EVIDENCE

	1. **Recommendation**	**Sources**	**QE**	**Overall Quality**	**R**
1	Identification of risk factors in the diabetic foot.	ADA, 2002 Bailey et al., 1985 Birke et al., 1988 Bloomgarden, 2001 Boyko et al., 1996 Carrington et al., 2001 Holewski et al., 1988 Mayfield et al., 1996 Pecoraro et al., 1990 Rith-Najarian et al., 1992 Sims et al., 1988	III III III III II-2 II III II II III II	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A).

F. Is There A Minor Wound Or Lesion?

OBJECTIVE

Determine the extent of the injury.

RECOMMENDATIONS

1. Minor lesions or wounds that could possibly be treated by the primary care provider are blisters, erosions, and/or minor cuts that do not extend beyond subcutaneous tissue. Pulses are present, there are no signs of acute infection, and there is no severe lower limb pain and no sign of a worsening lesion.
2. Patients with an ingrown toenail should be referred to a foot specialist for evaluation and treatment (see Annotation C, Ingrown Toenail).

G. Refer To Foot Care Specialist For Complete Evaluation And Treatment

OBJECTIVE

Ensure a more intensive follow-up treatment plan.

RECOMMENDATIONS

1. High-risk patients with a minor foot wound or lesion should be promptly referred to a foot care specialist (i.e., podiatrist, vascular surgeon, orthopedic surgeon, and other healthcare providers with demonstrated training, competence, and licensure in foot care) for evaluation and treatment.
2. Footwear prescriptions should be based upon individual characteristics of foot structure and function.

DISCUSSION

Mechanical modalities may include footwear recommendations, and consideration of a footwear prescription will be based upon the individual structural and clinical findings. Depth shoes should be prescribed for a patient with foot deformities and peripheral neuropathy as they can accept pressure-reducing insoles and accommodate foot deformities. In-depth shoes usually have soft leather uppers paired

with a crepe or Vibram outsole. Custom-molded shoes are reserved for patients with foot deformities that cannot be accommodated in a depth shoe (Bloomgarden, 2001).

Running shoes have been shown to reduce plantar pressures in individuals with diabetes; however, they may not accommodate foot deformities.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Referral to a foot care specialist for high-risk patients with minor foot wounds.	Working Group Consensus	III	Poor	I
2	Consideration of a footwear prescription.	Bloomgarden, 2001	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A).

H. Perform And Document Patient Education For Preventive Foot Care And Footwear

OBJECTIVE

Empower the patient to perform proper foot care practices.

RECOMMENDATIONS

1. All patients and their families should receive self-management education for preventive foot care and selection of footwear. Instruction should include recommendations for daily foot inspection and preventive foot care, skin care, and use of emollients, nail care, and treatment for callus.

DISCUSSION

Begin with nonjudgmental assessment of the patient's current self-care practices including asking, "Do you do anything special to protect your feet?"

Patient and family foot education should include the following components and considerations:

Keep it simple and appropriate for the patient's educational level.

Make it interactive, including demonstrations in washing, drying, and inspecting feet; nail cutting; and suitable footwear selection, including footwear for temperature extremes.

Provide opportunities for the patient to state the need for what are basics of daily skin and foot care and preventive measures.

Include practice time during the educational session to demonstrate and have the patient, in return, demonstrate safe toenail trimming.

Provide repetitive examples of and messages about how care of the feet can prevent complications. Include recommendations that distinguish minor foot problems from more serious problems that require early or immediate professional treatment, together with a name and telephone number for prompt assistance.

Make realistic recommendations (appropriate to the patient's physical and visual capabilities) while personalizing information and highlighting key points. This may include a referral to home healthcare.

Provide written guidelines in large print and/or graphics that the patient can hang in the bathroom as a reference and reprints of lay articles. Patients should be alerted that elevation in blood sugar might be a sign of an active or impending infection. Use of a night-light or turning on lights when getting up at night may prevent foot injuries. Patients should be made aware of potential dangers in the home.

For patients with high-risk feet, twice-daily inspection in good light is recommended, looking for any redness or drainage and running the hands over the foot to detect any swelling or increased

local warmth. Patients with neuropathic fingers may need to enlist help or use a mirror to inspect their feet.

Before putting on shoes, inspect for torn linings, rough spots, and foreign objects (e.g., gravel, stones, glass, and children's toys).

Alternating between pairs of shoes during the day is recommended. A minimum of two serviceable pairs of shoes, insoles, and orthoses are required.

Educators can utilize numerous publications on patient foot care instruction that are free of charge and have no copyright restrictions. The following publications are available through the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), and American Association of Diabetes Education (AADE):

- Take Charge of Your Diabetes: Prevent Foot Problems
- Taking Care of Your Feet
- Tips on Good Foot Care: from Feet Can Last a Lifetime

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Patient education on specific aspects of care.	ADA, 2002 Litzelman et al., 1993 Young et al., 1992	III I III	Fair	B
2	Patient instruction on self-foot care.	Ahroni, 1993 Barth et al., 1991 Fain & Melkus, 1994 Feste, 1991 Mayfield et al., 1998 [SR] Weir et al., 1994	III II II III II III	Fair	B

QE = Quality of Evidence; R = Recommendation; SR = Systematic Review (see Appendix A).

I. Perform Visual Inspection And Peripheral Sensation Evaluation At Each Routine Primary Care Visit

OBJECTIVE

Ensure ongoing screening to identify patients at risk for LE ulcers and amputation.

RECOMMENDATIONS

1. Visual inspection and peripheral sensation testing should be performed at each routine primary care visit for all patients (see Annotation A).

J. Perform Wound Assessment

OBJECTIVE

Determine the character and nature of the wound.

RECOMMENDATIONS

1. Patients with diabetes with minor wounds or foot lesions should have a wound assessment.
2. The wound assessment includes:

   A review of anatomic, physical, and lesion characteristics including determination or circumference, depth, and involvement of deep structures.

   Assessment for signs of infection including necrosis, sinus tracts, exudate, odor, presence of fibrin, and healthy granulation tissue.

   Assessment of surrounding areas for signs of edema, cellulitis, or abscess.

K. Provide Local Wound Care; Offload Pressure And Weight, As Indicated

OBJECTIVE

Provide care of an uncomplicated minor lesion.

RECOMMENDATIONS

1. Patients with diabetes with uncomplicated minor lesions should receive local wound care. Primary care providers should attempt to offload weight-bearing on the affected extremity.
2. Patients with diabetes with uncomplicated minor lesions must be followed at least monthly.

DISCUSSION

The following are simple guidelines for the care of uncomplicated minor lesions:

Provide local wound care: cleanse wound with saline, remove necrotic and callus tissue, apply appropriate dressing, and other indicated treatments.

*Offload pressure and weight, as indicated: c*onsider lesion site and then provide pressure relief (e.g., special shoes and insoles and bed rest). To avoid further trauma to the lesion site, use a post-operative shoe, offloading, or depressurization footwear based on the lesion site(s).

Follow-up on a specified schedule: VA facility specific patients with active lesions need to be followed at least monthly.

Review the Self-Management and Education Module (Module S): reinforce nutrition, exercise and diabetes self-management. Avoid initiation of a calorie restriction diet for weight loss in patients with foot lesions.

Provide patient and family education.

Refer for foot care assistance, as needed, for patients unable to carry-out local wound care. Educate a family member on local wound care or refer the patient to a home health service.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Local wound care.	ADA, 2000 Brodsky & Schneidler, 1991 Caputo et al., 1994 Eckman et al., 1995	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A).

L. Has Wound Healed Within 4 Weeks?

OBJECTIVE

Determine appropriateness of the treatment outcome.

RECOMMENDATIONS

1. Patients with diabetes treated for an uncomplicated wound should be assessed within four weeks from the initial wound assessment for appropriate reduction in lesion size and depth and appearance of healthy granulating tissue with no evidence of infection.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Assessment of wound healing progress within 4 weeks.	ADA, 2000	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A).

M. Is This A Minor Foot Problem?

OBJECTIVE

Identify minor conditions that could be attended to by the patient and/or family member.

RECOMMENDATIONS

1. Patients with diabetes with minor foot problems (e.g., onychomycosis, painful corn, dry skin, athlete's foot, minor calluses, uncomplicated nail trimming and improper foot hygiene) may be treated by a primary care provider in the office or by the patient or family members at home (see Annotation F).

N. Treat As Appropriate

OBJECTIVE

Determine the feasibility of treating the patient at home or in the office of the primary care provider.

RECOMMENDATIONS

1. Assure that patient and family members have received appropriate education regarding preventive foot care.
2. Treat minor foot problems, as appropriate.

DISCUSSION

Many minor foot problems can be treated by the patient, family members, or primary healthcare providers without referral to a foot care specialist. If this approach is chosen, it is necessary that the patient and family members have received appropriate education regarding preventive foot care.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Treatment of minor foot problems, as appropriate.	Ahroni, 1993 Barth et al., 1991 Fain & Melkus, 1994 Feste, 1991 Weir et al., 1994	III II III III III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A).

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

MODULE R – KIDNEY FUNCTION

ALGORITHMS AND ANNOTATIONS

Completion Date: March, 2003
Release Date: October, 2003
Version 3.0

SUMMARY OF RECOMMENDATIONS

Screening

1. Patients with type 1 diabetes mellitus (DM) should be screened for kidney disease after puberty and at a minimum of every five years. Patients with type 2 DM should be screened for kidney disease at the time of DM diagnosis, since the onset of type 2 DM occurs on average 10 years before a clinical diagnosis is made.
2. Patients with diabetes who have a probable life expectancy of >5 years should be screened for elevated urinary albumin or protein excretion using the cut-points adopted [Table R-1] from the American Diabetes Association.
3. Patients with diabetes should be monitored annually for kidney function (estimated glomerular filtration rate [eGFR]), and protein-to-creatinine ratio.
4. The preferred method for nephropathy screening is a random spot urine sample to measure the albumin-to-creatinine ratio. A 24-hour urine collection for protein and creatinine may also be used, but is more cumbersome for patients and prone to collection errors.
    - The use of urine "strips" are not the recommended screening method, because they do not take into account possible errors resulting from alterations in urine concentration.
    - Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-months period should be abnormal before diagnosing microalbuminuria.
    - Results of urine albumin/creatinine test of ≥30 µg/mg in a random specimen should be repeated to ensure that the level was not transiently elevated (by heavy exercise, urinary tract infection, acute febrile illness, or heart failure).

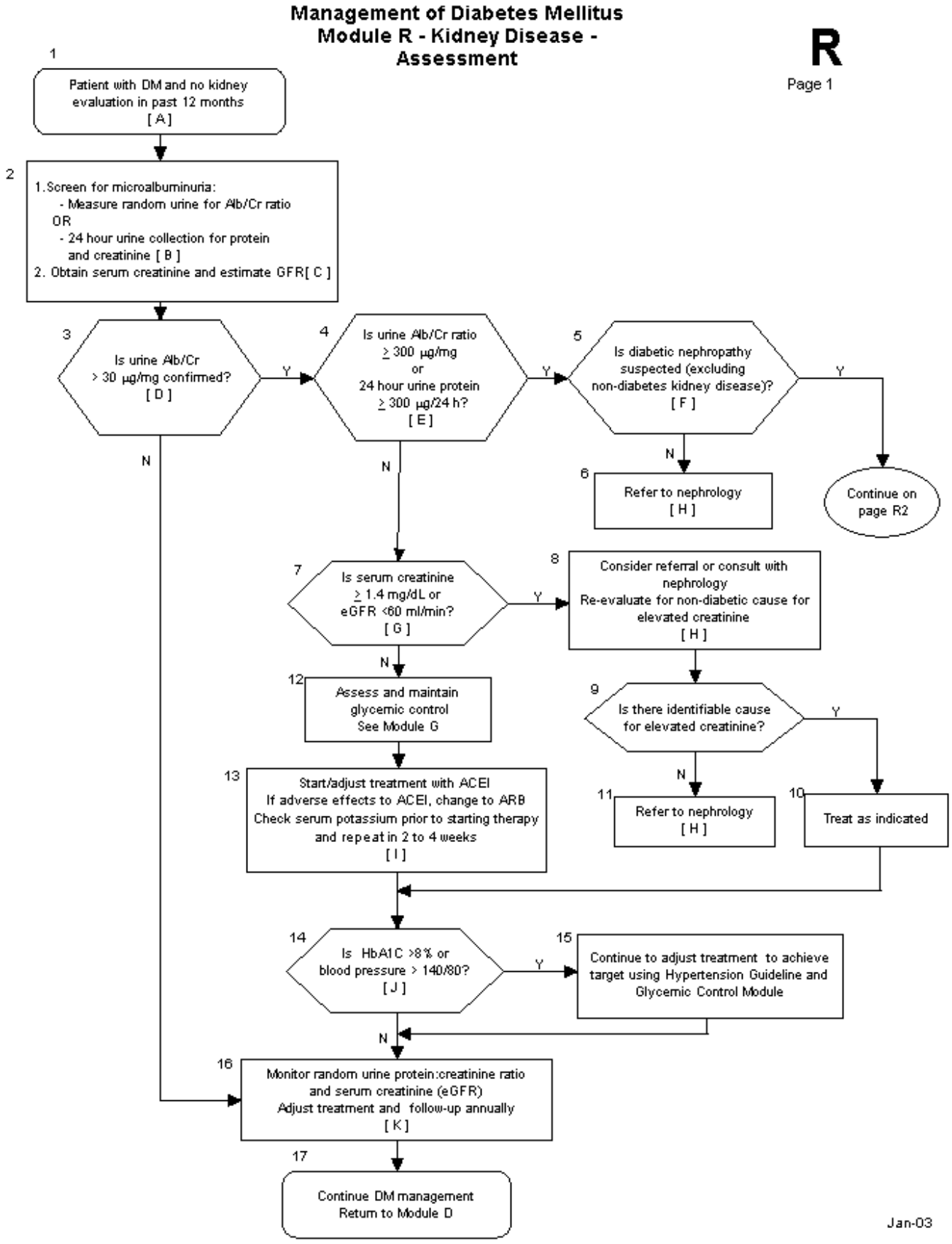
Assessment and Diagnosis

1. Serum creatinine level should be used to estimate the GFR to identify patients at risk and develop appropriate management plans.
2. Persons with diabetes and macroalbuminuria (i.e., urine Alb/creatinine ratio ≥300 µg/mg or 24-hour urine protein ≥300 mg/dL) should be assessed for level of kidney function as these levels of albuminuria indicate established to advanced diabetic renal disease.
    - Document the course of the albuminuria. It would be unusual to go from having normal urine to macroalbuminuria in less than one year in diabetic kidney disease.
    - Document that blood pressure has been rising. As diabetic kidney disease progresses from micro- to macroalbuminuria, the blood pressure usually rises.
    - Document the presence of other diabetic complications, such as retinopathy. All patients with diabetes with macroalbuminuria should undergo an eye exam to confirm the diagnosis of retinopathy (findings include microaneurysm, flame hemorrhage, and soft/hard exudates) (see Module E, Eye Care) because >90 percent of patients with macroalbuminuria from diabetes will also have at least mild retinopathy.
    - If the course has been atypical (i.e., rapidly progressive or no evidence of retinopathy), refer or consult with nephrology for further work-up.
    - Consider alternative explanations for reduced kidney function including pre-renal, renal, and post-renal causes.
    - Obtain renal ultrasound in all patients with reduced kidney function except those whose reduced kidney function is easily resolved.
    - Consider obtaining other tests and referral to specialists in nephrology or urology as indicated.

Treatment

1. Primary care providers should consult with or refer to a nephrologist when a patient has macroalbuminuria with normal creatinine but other features inconsistent with the sole diagnosis of diabetic nephropathy. These atypical features include absence of diabetic retinopathy on dilated eye exam, rapidly progressive course, short duration of diabetes, small kidneys on ultrasound, red blood cell casts in the urine, and/or lack of increase in blood pressure concurrent with increasing albuminuria.

2. Patients with diabetes with reduced kidney function may have electrolyte disturbances, anemia, or bone disease. Also, these patients' kidney failure may progress and they may need dialysis or evaluation for renal transplantation. For these reasons, an initial evaluation by nephrology for confirmation of diagnosis, optimal management of kidney disease, and appropriate timing of dialysis access is recommended for patients with chronic kidney disease or for acute kidney disease that does not rapidly resolve (see the VA/DoD Clinical Practice Guideline on Pre-ESRD).
3. Persons with diabetes should be assessed for contraindications to angiotensin converting enzyme inhibitor (ACEI) use.
4. Start/adjust treatment with ACEIs.
5. Change ACEI to angiotensin receptor blocker (ARB) if patient has an ACEI-induced cough. Angioedema risk may be lower with ARB vs. ACEI, but providers should use great caution if ARB is prescribed to a patient with a history of angioedema associated with ACEI use.
6. ACEI and ARB may cause similar rates of hyperkalemia and abrupt reduction of kidney function.
7. If the patient's macroalbuminuria is not improving, or diabetes and/or blood pressure is not controlled, consider a change in treatment.
8. Reevaluate the current treatment regimen (i.e., ACEIs, blood pressure control, and glycemic control) for patients with diabetes with progressing kidney disease.
9. Consider counseling patients with diabetes with macroalbuminuria (diabetic nephropathy) to reduce daily dietary protein allowance to 0.8 g-1/kg body wt-1/day-1 (~10 percent of calories).
10. If albuminuria is progressing or the estimated GFR is continuing to decline, consider increasing the ACEI to the maximum recommended dose, while reinforcing glycemic control and a low-protein diet.
11. Patients with diabetes on ACEIs should have a spot urine for Alb/Cr ratio at 6 months from initiation of ACEI.


Management of Diabetes Mellitus
Module R - Kidney Disease - Assessment
R
Page 1
1
Patient with DM and no kidney evaluation in past 12 months [A]
2
1. Screen for microalbuminuria:
- Measure random urine for Alb/Cr ratio
OR
- 24 hour urine collection for protein and creatinine [B]
2. Obtain serum creatinine and estimate GFR [C]
3
Is urine Alb/Cr > 30 µg/mg confirmed? [D]
Y
4
Is urine Alb/Cr ratio ≥ 300 µg/mg or 24 hour urine protein ≥ 300 µg/24 h? [E]
Y
5
Is diabetic nephropathy suspected (excluding non-diabetes kidney disease)? [F]
Y
Continue on page R2
N
6
Refer to nephrology [H]
N
N
7
Is serum creatinine ≥ 1.4 mg/dL or eGFR <60 ml/min? [G]
Y
8
Consider referral or consult with nephrology
Re-evaluate for non-diabetic cause for elevated creatinine [H]
N
12
Assess and maintain glycemic control
See Module G
9
Is there identifiable cause for elevated creatinine?
Y
N
11
Refer to nephrology [H]
10
Treat as indicated
13
Start/adjust treatment with ACEI
If adverse effects to ACEI, change to ARB
Check serum potassium prior to starting therapy and repeat in 2 to 4 weeks [I]
14
Is HbA1C >8% or blood pressure > 140/80? [J]
Y
15
Continue to adjust treatment to achieve target using Hypertension Guideline and Glycemic Control Module
N
16
Monitor random urine protein:creatinine ratio and serum creatinine (eGFR)
Adjust treatment and follow-up annually [K]
17
Continue DM management
Return to Module D
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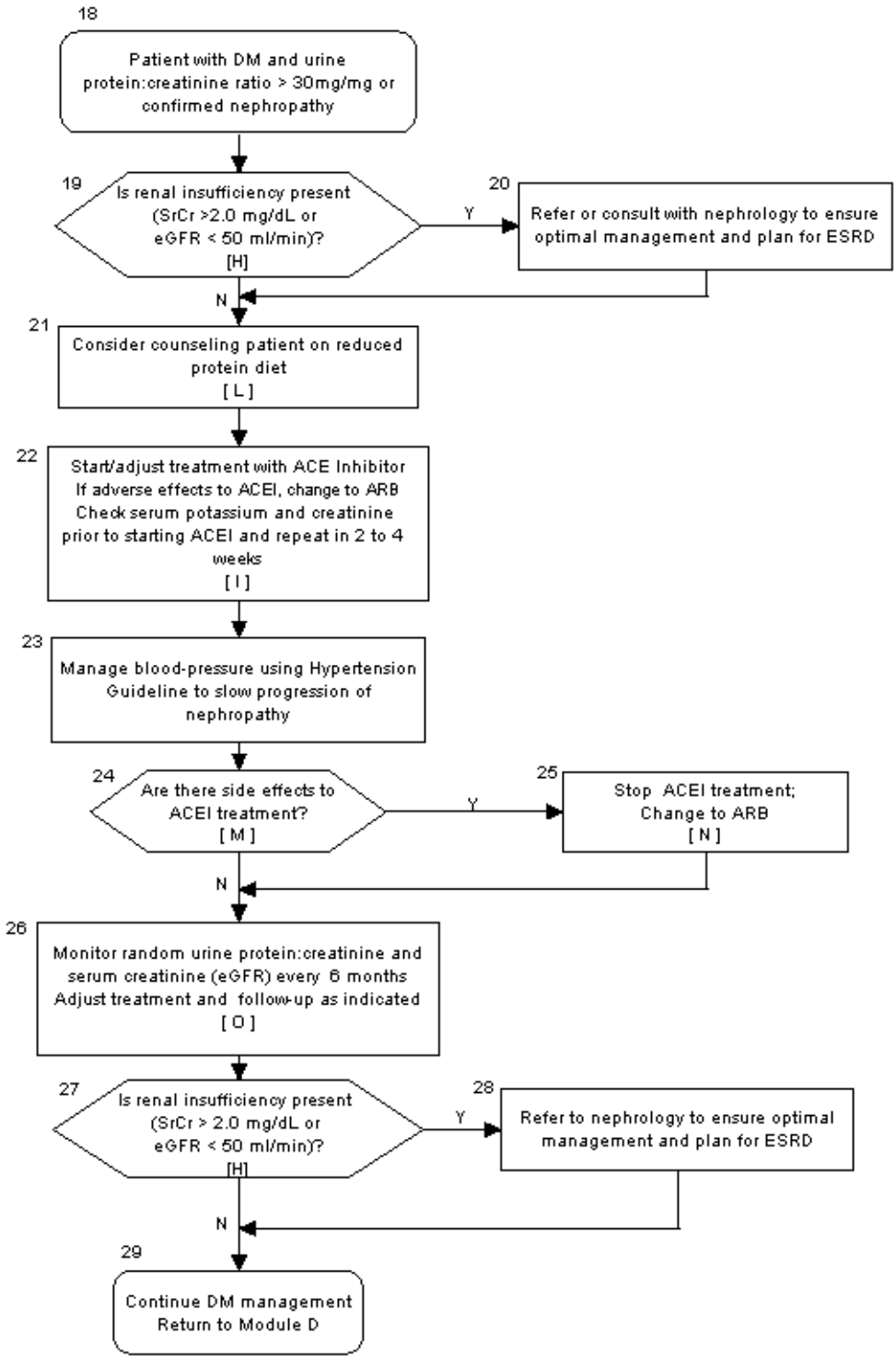
Management of Diabetes Mellitus
Module R - Kidney Disease - Treatment

R

Page 2



Jan-03

ANNOTATIONS

A. Patient With Diabetes Mellitus And No Kidney Evaluation In Past 12 Months

Patients with type 1 diabetes mellitus (DM) should be screened for kidney disease after puberty and at a minimum of every five years. Patients with type 2 DM should be screened for kidney disease at the time of DM diagnosis, since the onset of type 2 DM occurs on average 10 years before a clinical diagnosis is made (Harris, 1995a).

Patients being treated with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), because of either a prior diagnosis of microalbuminuria (or other medical problems such as CHF or hypertension), may still require an annual assessment of their kidney function to monitor onset or progression of their nephropathy and adjust treatment accordingly. For example, the new onset of nephropathy in a patient with diabetes and hypertension on ACEI might prompt a lower blood pressure control goal for that individual patient.

DISCUSSION

Twenty-five to 45 percent of patients with type 1 and type 2 DM will develop diabetic nephropathy. Clinical evidence for nephropathy, manifested by microalbuminuria, proteinuria, and reduced kidney function, can be seen 5 to 20 years after the development of DM. Generally, nephropathy steadily progresses until the patient requires dialysis, a kidney transplant, or dies of uremia. However, progressive kidney failure can be prevented or delayed through early intervention and appropriate management. Even when end stage renal disease (ESRD) is inevitable, appropriate steps should be taken to prepare for ESRD (see the VA/DoD Clinical Practice Guideline on Pre-ESRD). Finally, patients with nephropathy have a very high cardiovascular risk and should undergo appropriate screening and prevention if life expectancy is not already limited by co-morbid conditions (e.g., metastatic cancer and severe Chronic Obstructive Pulmonary Disease).

The National Kidney Foundation has developed guidelines that include useful information including epidemiology of kidney disease, definition of kidney disease stages, evaluation, and management http://www.kidney.org/professionals/doqi/kdoqi/toc.htm.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Annual reevaluations of life expectancy.	Working Group Consensus	III	Poor	I
2	If probable life expectancy has increased significantly from the previous year (due to improvements in comorbidities), consider the appropriateness of screening for nephropathy.	Bennet et al., 1995 Gall et al., 1991 Mogensen, 1987 Ordonez & Hiatt, 1989	II-1	Poor	C

QE = Quality of Evidence; R = Recommendation (see Appendix A)

B. Screen For Microalbuminuria: Measure Albumin-To-Creatinine Ratio In A Random Spot Urine OR 24-Hour Urine Collection For Protein And Creatinine

OBJECTIVE

Quantify the amount of proteinuria.

RECOMMENDATIONS

1. Patients with diabetes who have a probable life expectancy of >5 years should be screened for elevated urinary albumin or protein excretion using the cut-points adopted [Table R-1] from the American Diabetes Association.
2. The use of urine "strips" is not the recommended screening method, because they do not take into account possible errors resulting from alterations in urine concentration.
3. The preferred method for nephropathy screening is a random spot urine sample to measure the albumin-to-creatinine ratio. A 24-hour urine collection for protein and creatinine may also be used, but is more cumbersome for patients and prone to collection errors.
4. Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-months period should be abnormal before diagnosing microalbuminuria.
5. Heavy exercise (within 24 hours of urine collection), urinary tract infection, acute febrile illnesses, and heart failure may transiently increase urinary albumin excretion and thus, screening should be postponed in these situations to avoid false positive determination. Patients should be instructed not to exercise the day before providing a urine specimen,
6. The Working Group does not recommend stopping an ACEI or ARB prior to screening, even though these drugs may decrease urinary albumin excretion.

Table R-1. Definitions of abnormalities in albumin excretion.

Condition	24-Hour Urine Collection (mg/24h)	Random Urine for Alb/Cr Ratio (μg/mg creatinine)	Timed Urine Collection (μg/min)
Normal	≤30	<30	≤20
Microalbuminuria	30 - 300	30 - 300	20 - 200
Macroalbuminuria	≥300	≥300	≥200

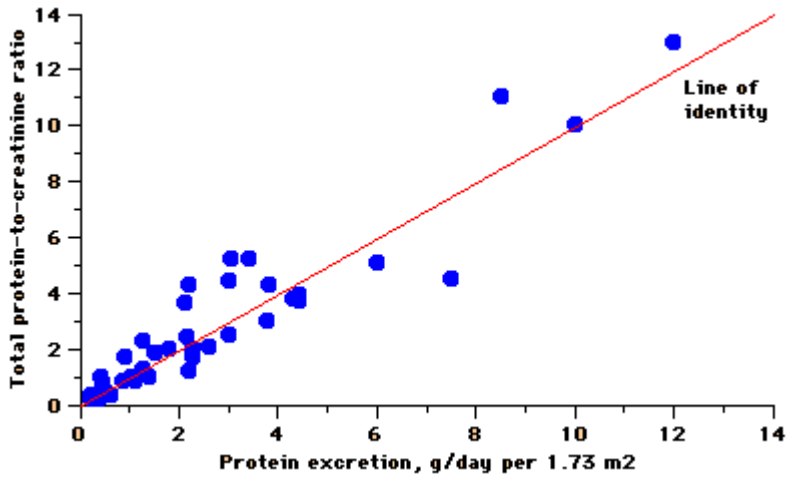
Ref: ADA, Diabetes Care 2002;25:222-224.

DISCUSSION

A complete 24-hour urine collection can be difficult for patients to complete. Several studies have demonstrated close correlation between the ratio of urine albumin to creatinine (urine albumin/creatinine) calculated from random urine collections.

This correlation is near unity with a relatively narrow standard deviation until daily albumin excretion exceeds 3.5 g/dL in patients with diabetes, and even then it distinguishes between patients with and without nephrotic syndrome (Rodby et al., 1995). A urine albumin/creatinine ratio of 1000 μg/mg creatinine is equivalent to a 24-hour urine albumin excretion rate of 1.0 g/24 hours; a ratio of 300 μg/mg creatinine would be the equivalent of 300 mg/24hours).

Exhibit R1. Protein-Creatinine Ratio to Estimated Protein (Albumin) Excretion



Close relation between total daily protein excretion and the total protein-to-creatinine ratio (mg/mg) determined on a random urine specimen (Data from Ginsberg et al., 1983; Exhibit R1 reproduced from Up To Date in Medicine: Rose, 1999).

Table R-2. Factors that Transiently Interfere with Urinary Screening for Albuminuria

Increases in Albuminuria	Decreases in Albuminuria
Blood in urine CHF Exercise Excessive protein intake Fever Uncontrolled diabetes Uncontrolled hypertension Urinary tract infection Vaginal fluid contamination of specimen Nonsteroidal anti-inflammatory drugs (NSAID)	ACEI/ARB Malnutrition NSAID

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Strip testing (not recommended).	Kouri et al., 1991	II	Fair	B
2	A random urine for protein/Cr ratio or Alb/Cr ratio.	Ginsberg et al., 1983 Rodby et al., 1995 Toto et al., 1997	II	Fair	B
3	Postponement of urinary screening for albuminuria if patient has done heavy exercise or has a UTI, acute febrile illness, or heart failure.	ADA, 1997 Bennett et al., 1995	III	Poor	I
4	Stopping an ACE inhibitor prior to urinary screening (not	Working Group Consensus	III	Poor	I

	recommended).				

QE = Quality of Evidence; R = Recommendation. See Appendix A.

C. Obtain Serum Creatinine And Estimate Glomerular Filtration Rate (eGFR)

OBJECTIVE

Detect presence of reduced kidney function, and identify patients at risk for progressive kidney failure, uremic complications, and high risk for cardiovascular disease.

RECOMMENDATIONS

1. Serum creatinine level should be used to estimate the GFR to identify patients at risk and develop appropriate management plans.

DISCUSSION

Abnormalities of urinalysis or reduced renal function identify patients with kidney disease (see Table R-2). Patients with chronic kidney disease are at risk for progressive loss of kidney function. Most clinicians first identify patients with abnormal kidney function when serum creatinine (Scr) is elevated on routine laboratory testing. However, as Exhibit R2 demonstrates, significant reduction in kidney function is required before the Scr rises significantly. Also, patients with baseline Scr in the lower range of normal may lose significant amounts of kidney function before the Scr increases above the normal range (typically >1.2 mg/dL in females and > 1.5 mg/dL in males). Therefore, Scr alone is not a good test.

Table R-3. Definition of Chronic Kidney Disease Criteria

Chronic Kidney Disease Criteria
1. Kidney damage for $\geq$3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*: • Pathological abnormalities; OR • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60mL/min1.73m^2 for $\geq$3 months, with or without kidney damage

Exhibit R2. Creatinine Clearance Plotted Against Serum Creatinine Concentration Graph (Schrier, 1976)

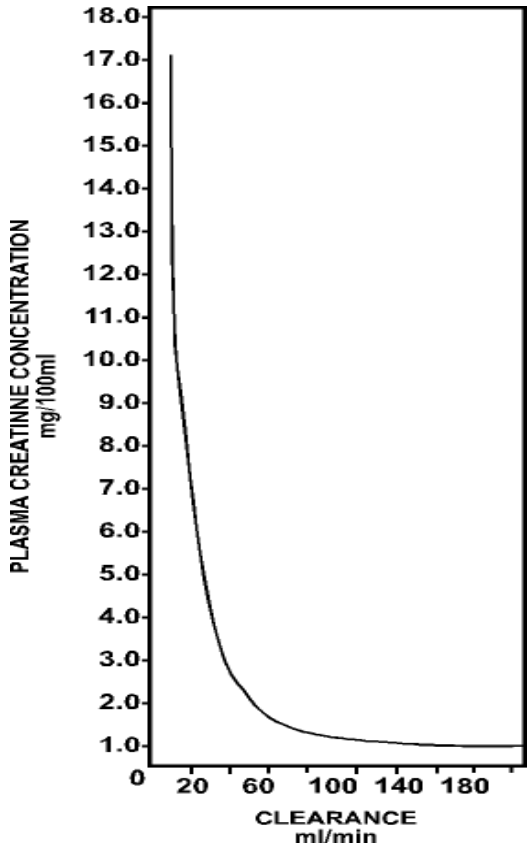


Exhibit R2 plots the creatinine clearance against serum creatinine concentration. It illustrates the lack of sensitivity of the serum creatinine level as a test for loss of renal function. For every 50 percent reduction in GFR (approximated by the creatinine clearance rate), the serum creatinine concentration approximately doubles. Waiting to aggressively treat the condition until the serum creatinine level rises is not likely to prevent end-stage renal disease, but rather just delay the need for dialysis a few more months (Bennett et al., 1995).

Measuring creatinine clearance (Clcr) or estimating Clcr or GFR by calculation formulas can be used to monitor abnormal kidney function. Measuring Clcr by 24-hour urine collection has been the traditional method for estimating GFR. However, collection inaccuracies and patient difficulties make this test unsatisfactory. Estimation of Clcr or GFR using routine clinical information is now recommended for estimating and monitoring kidney function. Cockroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulas are acceptable tools for estimating Clcr and GFR, respectively. CG is a simple formula that has been in use for over 2 decades. The MDRD formula is more precise, and online calculators are available.

Kidney Function Estimation Formulas:

- CG formula (estimated Clcr in cc/min): [(140 - age)/Scr (mg/dL)] x [wt (kg) /72] x 0.85 (if female)

- MDRD formula (estimated GFR in cc/min per 1.73 m^2): http://www.hdcn.com/calcf/gfr.htm

Estimated GFR (ml/min/1.73m^2): = 186 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if African - American)

("four-variable" (abbreviated) equation in Levey et al. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130(6):461-70.

The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI Clinical Practice Guidelines for Kidney Diseases) has developed a staging system for grading kidney disease (see table below). These stages can be used to monitor and educate patients, assess impact of management, and assist the primary provider in coordinating care with specialists and making plans for ESRD care.

Table R-4. Chronic Kidney Disease (CKD): A Clinical Action Plan

Stage	Description	GFR ($mL/min/1.73m^2$)	Action*
	At increased risk	≥90 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with Normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, Cardiovascular disease risk reduction
2	Kidney damage with Mild ↓ GFR	60 – 89	Estimating progression
3	Moderate	30 – 59	Evaluating and treating complications
4	Severe ↓ GFR	15 - 29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Shaded area identifies patients who have chronic kidney disease; unshaded area designates individuals who are at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR, <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
*Includes actions from preceding stages.

D. Is Urine Alb/Cr ≥30 µg/mg Confirmed?

OBJECTIVE

Establish a diagnosis of early diabetic nephropathy and ensure that albuminuria is persistent, not transient, before committing the patient to treatment.

RECOMMENDATIONS

1. Patients with diabetes with urine albumin/creatinine levels of ≥30 µg/mg in the random specimen should repeat the test to ensure that the level was not transiently elevated (by heavy exercise, urinary tract infection, acute febrile illness, or heart failure).
2. If a second test is ≥30 µg/mg, the patient has persistent microalbuminuria; if the second test is <30µg/mg, repeat the test a third time.

DISCUSSION

Urine albumin/creatinine ratios of ≥30 µg/mg represent microalbuminuria. If the first specimen is ≥30µg/mg, repeat the test and be sure to have addressed the factors that may have transiently elevated the urine's albumin (see Annotation B). If the second specimen is also ≥30 µg/mg, the patient has persistent microalbuminuria. If the second test is <30 µg/mg, repeat the test a third time. Multiple urinary measurements are necessary because as much as 30 to 50 percent variability in day-to-day urine microalbumin measurements may occur (Murray, 1996).

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Multiple urinary measurements.	Murray, 1996	I	Fair	B
2	Urine Alb/Cr ratio ≥30µg/mg–screening criteria for microalbuminuria.	ADA, 2002 Bennett et al., 1995	II	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

Evidence for the cutpoints come from epidemiological and laboratory diagnostic studies. Ninety-five percent of individuals with no diagnosis of diabetes, hypertension, or intrinsic renal disease (i.e., normal adult population) have urinary albumin to creatinine ratios of < 30 µg/mg. Epidemiologic studies document that patients with diabetes with albumin excretion in the upper normal range (10 to 20 µg/min; 15 to 30 mg/24 h) have a higher risk for the subsequent development of diabetic microalbuminuria. This suggests that albumin excretion in type 1 DM may increase in a continuous manner in patients at risk for nephropathy, rather than an abrupt transition to this marker for nephropathy. Microalbuminuria is a harbinger of renal failure and cardiovascular complications in type 1 and 2 DM. Persistent albuminuria (>200µg/min >300 mg/d) is often accompanied by a gradual decline in the GFR. If left untreated, kidney disease eventually leads to uremia and death after approximately 7 to 10 years (Bennett et al., 1995).

E. Is Urine Alb/Cr Ratio ≥300 µg/mg, Or 24-Hour Urine Protein ≥300 mg/24h?

OBJECTIVE

Help distinguish established from incipient nephropathy.

RECOMMENDATIONS

1. Persons with diabetes and macroalbuminuria (i.e., urine Alb/creatinine ratio ≥300 µg/mg or 24-hour urine protein ≥300 mg/d) should be assessed for level of kidney function as these levels of albuminuria indicate established to advanced diabetic renal disease.

DISCUSSION

Macroalbuminuria is the stage prior to progressive loss of kidney function in diabetic nephropathy (Nelson et al., 1995).

F. Is Diabetic Nephropathy Suspected? (Can Non-Diabetic Kidney Disease Be Excluded?)

OBJECTIVE

Collect additional evidence confirming the diagnosis of diabetic nephropathy. Clinicians should assess whether the patient has had the typical course and features of diabetic kidney disease.

RECOMMENDATIONS

1. Document the course of the albuminuria. It would be unusual to go from having normal urine to macroalbuminuria in less than one year in diabetic kidney disease.
2. Document that blood pressure has been rising. As diabetic kidney disease progresses from micro- to macroalbuminuria, the blood pressure usually rises.
3. Document the presence of other diabetic complications such as retinopathy. All patients with diabetes with macroalbuminuria should undergo an eye exam to confirm the diagnosis of retinopathy (findings include microaneurysm, flame hemorrhage, and soft/hard exudates) (see Module E, Eye Care) because >90 percent of patients with macroalbuminuria from diabetes will also have at least mild retinopathy.
4. If the course has been atypical (i.e., rapidly progressive or no evidence of retinopathy), refer or consult with nephrology for further work-up.

DISCUSSION

If the primary care provider finds retinopathy on an undilated eye exam, then it is likely that the patient has diabetic nephropathy. Findings such as microaneurysm, flame hemorrhage, soft or hard exudates, all indicate the presence of retinopathy and the patient should be referred to ophthalmology. However, if no retinopathy is seen on undilated exam, a dilated exam by an optometrist or opthamologists is necessary to confirm the presence of retinopathy. Because 90 percent of patients affected by significant diabetic nephropathy have background or proliferative diabetic retinopathy, the diagnosis of diabetic nephropathy is generally presumed if a patient with heavy proteinuria is found to have diabetic retinopathy.

G. Is Serum Creatinine >1.4 mg/dL Or eGFR <60 ml/min (Kidney Function Abnormal)?

OBJECTIVE

Evaluate individuals with reduced kidney function to identify potential etiologies for kidney disease other than diabetes.

RECOMMENDATIONS

1. Consider alternative explanations for reduced kidney function including pre-renal, renal, and post-renal causes.
2. Obtain renal ultrasound in all patients with reduced kidney function except those whose reduced kidney function is easily resolved.
3. Consider obtaining other tests and referral to specialists in nephrology or urology as indicated.

DISCUSSION

All patients with reduced kidney function identified by formula or elevated Scr should have a basic evaluation to identify potential causes other than diabetes (see kidney disease stages and estimation formula in Annotation C). Potential etiologies can be classified into pre-renal (e.g., dehydration and CHF), renal (e.g., glomerulonephritis, diabetes, hypertension, polycystic kidney disease, tubular necrosis, and interstitial

nephritis), or post-renal (e.g., obstruction from any cause). A baseline renal ultrasound (to assess for renal size, echogenicity, and hydronephrosis) should be done for all patients whose reduced kidney function is not quickly resolved. In addition to obstruction, the renal ultrasound can indicate the presence of other causes of kidney disease such as polycystic kidney disease, ischemic renal disease, cysts, and renal cancer. Measuring post-void residual by direct catheterization or bladder ultrasound may also be helpful for detecting obstruction. Referral to a specialist may aid in further differentiating the potential cause of kidney disease. Refer patients with obstruction, hematuria without medical cause, and kidney mass to a urologist. Most other patients should be referred to a nephrologist. Suspected renovascular disease can be referred to vascular surgery, cardiology, nephrology, or interventional radiology for further diagnosis and treatment.

H. Refer To Nephrology

OBJECTIVE

Obtain consultation from a nephrologist regarding the need for further work-up for non-diabetic causes of kidney disease, potentially including renal biopsy.

RECOMMENDATIONS

1. Primary care providers should consult with or refer to a nephrologist when a patient has macroalbuminuria with normal creatinine but other features inconsistent with the sole diagnosis of diabetic nephropathy. These atypical features include absence of diabetic retinopathy on dilated eye exam, rapidly progressive course, short duration of diabetes, small kidneys on ultrasound, red blood cell casts in the urine, and/or lack of increase in blood pressure concurrent with increasing albuminuria.
2. Patients with diabetes with reduced kidney function may have electrolyte disturbances, anemia, or bone disease. Also, these patients' kidney failure may progress and they may need dialysis or evaluation for renal transplantation. For these reasons, an initial evaluation by nephrology for confirmation of diagnosis, optimal management of kidney disease, and appropriate timing of dialysis access is recommended for patients with chronic kidney disease or for acute kidney disease that does not rapidly resolve (see the VA/DoD Clinical Practice Guideline on Pre-ESRD).

DISCUSSION

Patients with stage 3-5 kidney disease have substantial loss of kidney function and are at risk for further progression of kidney failure. These patients may already be developing secondary complications and need a nephrology assessment or co-management. Early intervention may prevent or delay ESRD. A kidney disease specialist may help the primary care physician jointly manage the patient with:

- Complex or difficult hypertension
- Electrolyte disorders (e.g., hyperkalemia and acidosis)
- Secondary hyperparathyroidism
- Anemia secondary to erythropoietin deficiency
- Fluid overload
- Preparation for dialysis access, including development of forearm muscle mass and preservation of vascular access site (no needle sticks)
- Immunizations, including Heptovax

Aggressive treatment of high blood pressure and lower dietary potassium and protein intake may delay the need for dialysis.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Referral to or consultation with a nephrologist for stage 3-5 kidney disease.	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

I. Start/Adjust Treatment With ACEI; If Adverse Effects To ACEI, Change To ARB; Check Serum Potassium Prior To Starting ACEI and Repeat In 2 To 4 Weeks

OBJECTIVE

Reduce albuminuria and ensure that ACEIs or ARBS do not induce or aggravate hyperkalemia.

RECOMMENDATIONS

1. Start/adjust treatment with ACEIs.

DISCUSSION

Use of ACEIs or ARBs in normotensive patients with diabetes (both type 1 and 2) with micro- or macroalbuminuria has been shown to reduce albuminuria. Longer term studies are needed to confirm that such early ACEI does indeed prevent progression of renal disease (Lovell, 2002). The open-label extension of Ravid and Ravid's (1996) trial in type 2 DM concluded that treatment with enalapril resulted in an absolute risk reduction of 42 percent for nephropathy over a seven year period (95% CI: 15-69%, $p<0.001$). Direct comparisons of ACEI vs. ARB in diabetic nephropathy have not been reported.

Frequency of monitoring post initiation of therapy

After initiation of therapy with ACEI, the efficacy of this intervention should be monitored by assessing the albumin/creatinine ratio every 3 to 6 months. Because the urine albumin-excretion rate would be expected to increase by approximately 10 percent to 30 percent per year, stabilization of the albumin/creatinine ratio or a reduction in this ratio by up to 50 percent would be a favorable outcome. Serum potassium and creatinine should be checked one week after initiation of therapy (Bennett et al., 1995).

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Begin ACEI treatment with onset of persistent microalbuminuria in both Type 1 and 2 diabetic patients, even in the absence of hypertension.	Lovell, 2002	I	Good	A
2	Check serum potassium and creatinine prior to starting ACEI and in 2 to 4 weeks.	Bennett et al, 1995	II-2	Fair	C

QE = Quality of Evidence; R = Recommendation (see Appendix A)

J. Is HbA1c >8% Or Blood Pressure >140/80?

OBJECTIVE

Identify persons who may benefit from intensified blood pressure management.

RECOMMENDATIONS

1. If the patient's macroalbuminuria is not improving, or diabetes and/or blood pressure is not controlled, consider a change in treatment.

DISCUSSION

The goal of controlling the blood pressure (BP) in these patients is to slow decline in renal function and reduce cardiovascular risk with the fewest side effects. However, there may be different optimal blood pressures to: a) protect the kidneys; and b) prevent cardiovascular events. Aggressive treatment of hypertension can slow the progression of renal disease. If the patient's proteinuria is not improving, a change in treatment should be considered. Patients with nephropathy often require multiple medications to achieve target blood pressure. If the patient is already on ACEI or ARB, diuretics, then calcium channel blockers, beta-blockers (UKPDS, 1998) and direct vasodilators may also be used. Although combination ACEI and ARB may reduce proteinuria more than either class of medication alone, long-term kidney and cardiovascular benefits have not been reported. Use of alpha-adrenergic blockers should be considered cautiously due to their possible association with increased risk of heart failure.

The Joint National Committee for Hypertension VI Persons with diabetes with elevated serum creatinine and/or urinary protein excretion above 1 gm/d recommends lower BP targets (<125/75 mm Hg) to slow the progression of renal disease. However, a more recent study indicated there is no benefit for lowering BP to 128/78, but there is definite benefit with the use of ACEIs (Lazarus et al., 1997). Consequently, BP targets should be made on an individual basis taking into account patient preferences and medication tolerability/adherence issues.

For recommendations about glycemic control please refer to Module G- Glycemic Control.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
	Patients with diabetes with elevated serum creatinine and/or urinary protein excretion above 1 gm/d may benefit from lower BP targets (<125/75 mm Hg) to slow the progression of renal disease.	Lazarus et al., 1997	II-2	Fair	B
GENERAL THERAPEUTIC RECOMMENDATIONS					
	Antihypertensive therapy for patients with diabetes with BP >140/80 mm Hg should start with ACEI. Switch to ARB if ACEI-induced side-effects occur, then use other agents to achieve BP target <140/80 mm Hg.	Anderson et al., 2000 Hansson et al, 1998 HOPE Study Investigators, 2000 Lacourciere et al., 2000 Lindholm et al., 2002 Mogensen et al., 2000	I	Good	A

		Muirhead et al., 1999 Nielsen et al., 1997			
SPECIFIC THERAPEUTIC RECOMMENDATIONS					
	ACEI should be used in normotensive patients with type 1 DM and proteinuria, and in patients with type 2 DM and microalbuminuria or a high-risk for cardiovascular disease.	HOPE Study Investigators, 2000 Lewis et al., 1993	I	Good	A
	Consider ACEI for normotensive patients with type 1 DM.	Laffel et al., 1995 Viberti et al., 1994	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

K. Monitor Urine Protein-To-Creatinine Ratio And Estimated GFR; Adjust Treatment And Follow-Up Annually

OBJECTIVE

Decide if kidney disease is progressing on the current regimen that includes ACEI, blood pressure control, and glycemic control.

RECOMMENDATIONS

1. Persons with diabetes should be monitored annually for kidney function (estimated GFR) and protein-to-creatinine ratio.
2. Reevaluate the current treatment regimen (i.e., ACEIs, blood pressure control, and glycemic control) for patients with diabetes with progressing kidney disease.

DISCUSSION

If kidney disease is progressing, as evidenced by declining kidney function or an increase in proteinuria, the treatment regimen should be reevaluated, including BP and glycemic goals (ADA, 1994, 1995b, 1997a, 2002; Bennett et al., 1995; Gall et al., 1991; Ordonez & Hiatt, 1989; Ravid et al., 1993).

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Reevaluation of the current treatment regimen of patients with progressive kidney disease.	ADA, 1994, 1995b, 1997a, 2002 Bennett et al., 1995 Gall et al., 1991 Ordonez & Hiatt, 1989 Ravid et al., 1993	II-1 III II-2 II-2 II-1	Fair	B
2	Monitor at one year.	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

L. Consider Counseling Patient On Reduced Protein Diet

OBJECTIVE

Advise the patient that lowering protein intake may have a positive effect on the progression of his/her kidney disease.

RECOMMENDATIONS

1. Consider counseling patients with diabetes with macroalbuminuria (diabetic nephropathy) to reduce daily dietary protein allowance to 0.8 g^{-1}/kg body wt^{-1}/day^{-1} (~10 percent of calories).

DISCUSSION

In people with type 1 DM and overt diabetic nephropathy, restriction of dietary protein has been shown to retard the progression toward kidney failure. There is some evidence that this may also be true in type 2 DM. Therefore, a protein intake of approximately the adult recommended dietary allowance—0.8 g^{-1}/kg body wt^{-1}/day^{-1} (~10 percent of calories)—is recommended for individuals with evidence of macroalbuminuria" (ADA, 1997a).

A number of studies have demonstrated a slowing of the rate of progression of type 1 diabetic nephropathy with a low-protein diet (0.6 to 0.7 g/kg/day). However most of these studies were relatively small, 11 to 35 patients (Ciavarella et al., 1987; Evanoff et al., 1989; Walker et al., 1989; Zeller et al., 1991). The Modification of Diet in Renal Disease study (Coggins et al., 1994), the largest study of the effect of low-protein diet on all kidney disease, did not show this effect to be significant. Only approximately 50 patients with diabetes were enrolled and insulin-using patients were specifically excluded. None of the studies cited above have lasted long enough to look at the effect of a low protein diet on progression to ESRD.

Although the value of a low-protein diet has not been adequately established, the Working Group recommends offering it as an option in the treatment of diabetic nephropathy.

Table R-5. Clinical Trials of the Effect of Dietary Protein Reduction on the Course of Diabetic Nephropathy in Patients with Type 1 DM with Clinical Proteinuria (adopted from Nelson et al., 1995)

Reference	Number of Patients	Treatment Duration	Protein Restriction	Outcome in Treatment Group
Ciavarella et al., 1987	16	4.5 months	0.7 g/kg/day	Decreased urinary albumin excretion
Evanoff et al., 1989	11	24 months	0.6 g/kg/day	Decreased urinary protein excretion
Walker et al., 1989	19	33 months	0.7 g/kg/day	Decreased rate of GFR decline; decreased urinary albumin excretion
Zeller et al., 1991	35	34.7 months	0.6 g/kg/day	Decreased rate of GFR decline; decreased urinary albumin excretion

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Reduction of daily dietary protein allowance to 0.8 g^{-1}/kg body wt^{-1}/day^{-1} (~10 percent of calories) in	ADA, 2002 Ciavarella et al., 1987 Evanoff et al., 1989	II-1 II-1 II	Fair	C

	Type 1 DM with macroalbuminuria	Walker et al., 1989 Waugh & Addlesee , 1997 Zeller et al., 1991	II III II-1		

QE = Quality of Evidence; R = Recommendation (see Appendix A)

M. Are There Side Effects To ACEI Treatment?

OBJECTIVE

Screen the patient for contraindications to ACEI use.

RECOMMENDATIONS

1. Persons with diabetes should be assessed for contraindications to ACEI use.

DISCUSSION

Absolute contraindications include:
- Pregnancy
- Hyperkalemia (advanced renal insufficiency or hyporeninemic hypoaldosteronism)
- Known allergy to ACEI
- Angioedema with prior ACEI use

Relative contraindications include:
- Known bilateral renal artery stenosis

N. Stop ACEI Treatment; Change To ARB

OBJECTIVE

Ascertain if there are side effects that warrant discontinuation of the ACEI.

RECOMMENDATIONS

1. Change ACEI to ARB if patient has an ACEI-induced cough. Angioedema risk may be lower with ARB vs. ACEI, but providers should use great caution if ARB is prescribed to a patient with a history of angioedema associated with ACEI use.
2. ACEI and ARB may cause similar rates of hyperkalemia and abrupt reduction of kidney function.

DISCUSSION

Many patients present with a dry, nonproductive cough from ACEI use. The etiology of the cough should be evaluated (e.g., upper respiratory infection, exacerbation chronic obstructive pulmonary disease ,and

dry heat). If the cough is felt to be due to ACEI but is not clinically significant (e.g,. does not affect the patient's quality of life), continue ACEI. If the cough is significant, discontinue ACEI and one of the ARBs (e.g., losarten) may be used. ARBs appear to have similar short-term effects as ACEI (Anderson et al., 2000; Lacourciere et al., 2000; Muirhead et al., 1999; Nielsen et al., 1997) in patients with diabetes and nephropathy. ARBs are effective in patients with type 2 DM with nephropathy (Brenner et al., 2001; Lewis et al., 2001) or microalbuminuria (Morgensen et al., 2000: Parving et al., 2001). Treating patients with type 2 DM and nephropathy with an ARB resulted in a reduction in the composite endpoint of doubling of serum creatinine, progression to end-stage renal disease, and all-cause mortality when compared to placebo (Brenner et al., 2001; Lewis et al., 2001). However, there are no long-term outcome trials comparing an ACEI to an ARB to determine if these agents provide similar long-term benefits in patients with DM.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
	Switch to an ARB if an ACEI-induced cough occurs.	Anderson et al., 2000 Hansson et al, 1998 Lacourciere et al., 2000 Lindholm et al., 2002 Mogensen et al., 2000 Muirhead et al., 1999 Nielsen et al., 1997	I	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix A)

O. Monitor Random Urine Protein-To-Creatinine Ratio And Serum Creatinine (eGFR) Every 6 Months; Adjust Treatment And Follow-Up, As Indicated

OBJECTIVE

Decide whether the kidney disease is progressing on the current dose of ACEI.

RECOMMENDATIONS

1. Patients with diabetes on ACEIs should have a spot urine for Alb/Cr ratio at 6 months from initiation of ACEI.
2. If albuminuria is progressing or the estimated GFR is continuing to decline, consider increasing the ACEI to the maximum recommended dose, while reinforcing glycemic control and a low-protein diet.

DISCUSSION

If albuminuria is progressing or the estimated GFR is continuing to decline, a more aggressive treatment should be considered. The ACEI could be increased to the maximum recommended dose. If BP is rising, an additional agent could be added (see Annotation C for kidney function monitoring and Annotation J for BP medications). Low-protein diet and glycemic control should be reinforced.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Increase ACEI to maximal dose as long as nephropathy is progressing.	Lovell et al., 2001	1	Good	A
2	Add other anti-hypertensives to maximal ACEI dose if nephropathy is still progressing.	ADA, 2002 Parving et al., 2001 UKPDS, 1998	1	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix A)

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

MODULE M – SELF-MANAGEMENT AND EDUCATION

ALGORITHMS AND ANNOTATIONS

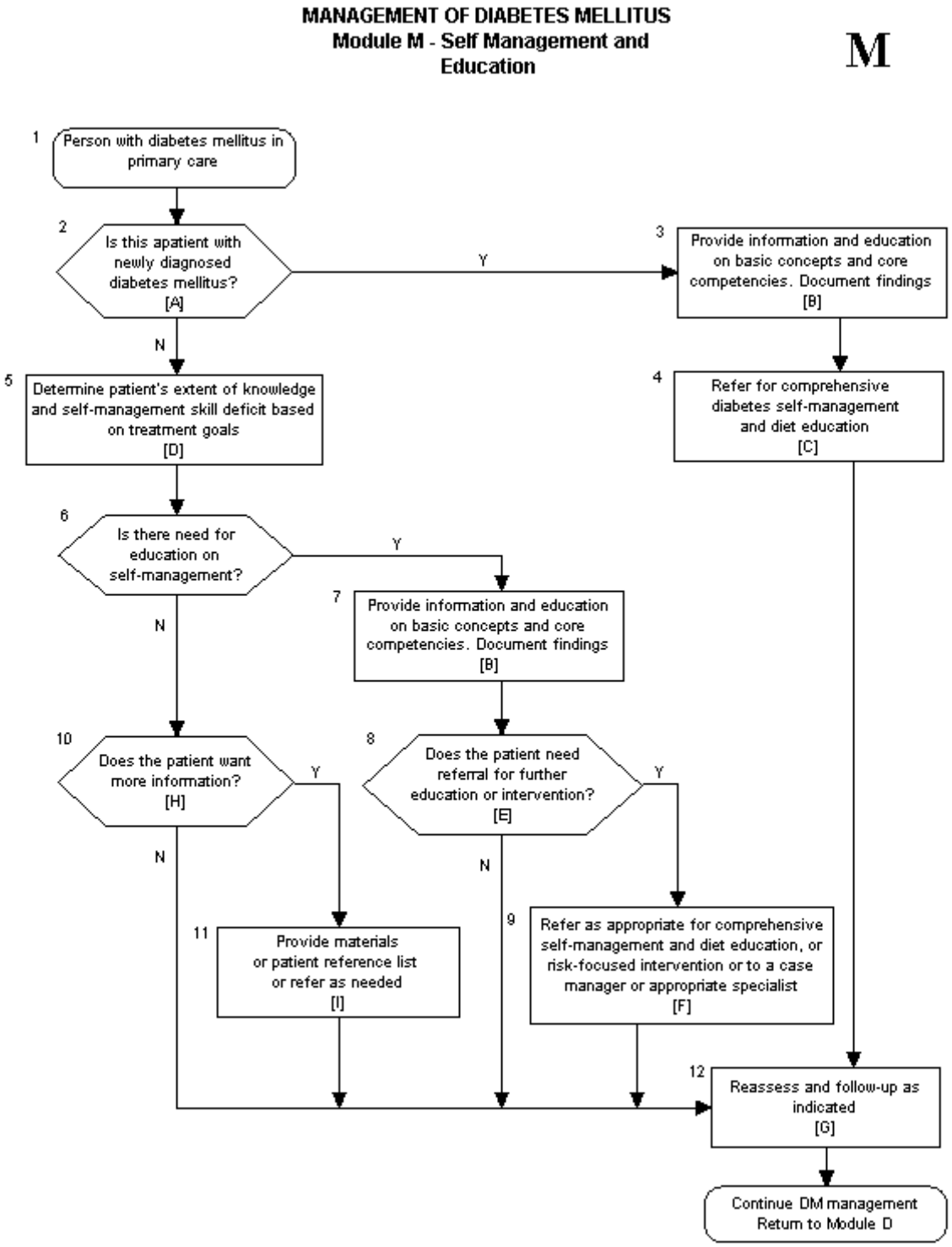
Completion Date: March, 2003
Release Date: October, 2003
Version 3.0

SUMMARY OF RECOMMENDATIONS

Diabetes self-management education (DSME) is considered necessary by most healthcare organizations to assist persons with diabetes in their day-to-day self-management and with making informed self-care choices. DSME includes providing the patient with behavioral strategies to help him/her establish and maintain a healthy lifestyle. Comprehensive education programs should address the patient's fluctuating diabetes clinical state over a lifetime and provide clinically relevant knowledge and skills to facilitate implementation of ever-changing treatment plans.

RECOMMENDATIONS

1. Education in core competencies, also known as "survival skills," should be provided to all patients newly diagnosed with diabetes. Core competency education includes: response to acute complications (hyperglycemia and hypoglycemia); how and when to take medication(s); self-monitoring of blood glucose, basic diet guidelines; sick day management; and guidance on when and how to seek further treatment or medical advice.
2. Comprehensive education on self-management and diet should be provided to all patients newly diagnosed with diabetes. Education should be individualized and tailored to the patient's needs. Education can be provided through an in-house comprehensive diet consultation for Medical Nutrition Therapy (MNT), a comprehensive DSME program recognized by the American Diabetes Association (ADA); if neither of these options is available, comprehensive DSME should be provided at the provider's facility.
3. Upon completion of the initial DSME/MNT education, behavioral goals should be set and a follow-up visit schedule determined by the provider and patient.
4. Information sources (e.g., books, pamphlets and web sites) and points of contact for organizations and other relevant resources should be provided to all patients.
5. Assessment of the following factors should be completed to determine the extent of the patient's educational and skills deficit and his/her ability for self-management: knowledge of the diabetes disease process, treatment goals, management skills, cultural influences, health beliefs/behavior, attitudes, and socioeconomic factors and barriers.
6. At follow-up, the patient's understanding of, and knowledge about, DM should be reviewed. The provider should consider referring the patient to case management or other specialized care, if the patient exhibits poor glycemic control, has high-risk factors, or fails to demonstrate good knowledge of self-care. The provider should coordinate the patient's care with caregivers to whom the patient has been referred and obtain updates on the patient's condition and needs.
7. The provider should always be ready to respond to the patient's *ad hoc* inquiries about new treatments, problems, or concerns.
8. As the patient's DM control and status improves or declines, the provider should readjust the follow-up schedule for less- or more-frequent visits. Continuing education may be necessary, based on the patient's needs.


MANAGEMENT OF DIABETES MELLITUS
Module M - Self Management and Education
M
1
Person with diabetes mellitus in primary care
2
Is this apatient with newly diagnosed diabetes mellitus? [A]
Y
3
Provide information and education on basic concepts and core competencies. Document findings [B]
N
4
Refer for comprehensive diabetes self-management and diet education [C]
5
Determine patient's extent of knowledge and self-management skill deficit based on treatment goals [D]
6
Is there need for education on self-management?
Y
7
Provide information and education on basic concepts and core competencies. Document findings [B]
N
8
Does the patient need referral for further education or intervention? [E]
Y
9
Refer as appropriate for comprehensive self-management and diet education, or risk-focused intervention or to a case manager or appropriate specialist [F]
N
10
Does the patient want more information? [H]
Y
11
Provide materials or patient reference list or refer as needed [I]
N
12
Reassess and follow-up as indicated [G]
Continue DM management
Return to Module D

ANNOTATIONS

A. Is This A Patient With Newly Diagnosed Diabetes Mellitus?

Module M applies to patients who have been diagnosed with diabetes mellitus (DM) and require diabetes self-management education (DSME) and knowledge and skills to facilitate implementation of their treatment plan.

B. Provide Information and Education On Basic Concepts And Core Competencies. Document Findings

OBJECTIVE

Ensure that patients with diabetes understand the core competencies (survival skills) and other basic information so that they may safely self-manage their diabetes.

RECOMMENDATIONS

1. Ensure that patients newly diagnosed with DM are provided with core competency education (see Appendix M-1: Core Competencies [Survival Skills] for Patients with Diabetes).

DISCUSSION

Primary care staff has limited time to provide in-depth education to patients newly diagnosed with diabetes; however, it is critical to provide basic concepts and information based on core competencies and identify knowledge/skills deficits addressed in other modules in this guideline.

Core competency education (survival skills) is directed at providing immediate education that will help ensure the patient's safety until in-depth self-management education can be obtained. The core competencies are not substitutes for an in-depth DSME program.

The core competencies include (see Appendix M-1: Core Competencies (Survival Skills) for Patients with Diabetes):

Acute complications (hyperglycemia and hypoglycemia)
Medication education
Self-monitoring of blood glucose
Basic diet principles
Sick day management
When to seek further assistance

Appendices M-3, Suggested Points of Contact for Patient Education/Nutrition/Self-Management Programs; M-4, Primary Care Staff Office Diabetes Education Resources and Tools; and M-7, List of Patient References: Diabetes Resources. Patient education materials from these resources, as well as other patient education materials, can be made available to the patient in the office setting to assist the provider in addressing additional concepts and information not included in the core competencies.

Self Monitoring of Blood Glucose (SMBG)

Self monitoring of blood glucose is the process by which patients use a home blood glucose monitor to gain timely knowledge regarding their diabetes control. SMBG enables patients to make self-care decisions. Monitoring gives patients information on effects of meal pattern, food intake, medication, activity, and stress. The test schedule is based on treatment and blood glucose goals. Readings outside the blood glucose goals and illness are indications for more frequent testing. Monitoring devices vary in features, readability, portability, and cost. The choice of meter is based on personal preference, cost, features, and ease of use. Record keeping will help all patients to collaborate with their diabetes health care team, and foster optimal health status.

Table M-1: Recommendations for SMBG

Recommendations for SMBG	
Patients on Oral Agents	For stable type 2 DM: no more than 50 strips per 150 days. This allows for twice-weekly testing. An increased numbers of strips may be needed for a limited time period for the following indications: Initiation of therapy and/or active adjustment of oral agents, meal plan, or exercise/activity Detection and prevention of hypoglycemia when symptoms are suggestive of such, or if there is documented hypoglycemia unawareness Detection of hyperglycemia when symptoms or urine glycosuria (for the occasional patient using urine test strips) are suggestive of such
Patients on Insulin	The frequency of monitoring should be individualized based on the frequency of insulin injections, hypoglycemic reactions, level of glycemic control, and patient/provider use of the data to adjust therapy. A combination of pre-and postprandial tests should be performed, up to 4 times per day.

Patients on stable doses of medications do not need frequent SMBG unless the information is being used to alter self-management or the provider is considering altering medications. In most cases, periodic HbA_1c is sufficient to ascertain diabetic control (Faas et al., 1997; Oki et al., 1997; Wieland et al., 1997).

Patients who demonstrate good glycemic control while on stable oral regimens (stable patients) may require fewer or no strips. When metabolic control worsens or changes (e.g., illness or change in exercise/activity or diet), testing requirements may increase. Each provider must ascertain that the patient has proficiency in SMBG technique. Initial and ongoing justification for SMBG use must be provided and should be linked to health outcomes.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Periodic HbA_1c is sufficient to ascertain diabetic control.	Coster et al., 2000 Faas et al., 1997 Harris , 2001 Meier et al., 2002 Oki et al., 1997 Piette & Glasgow, 2001 Wieland et al., 1997	II	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

A. Refer For Comprehensive Diabetes Self-Management And Diet Education

OBJECTIVE

Provide or refer for comprehensive DSME and MNT.

BACKGROUND

Diabetes self-management is considered necessary by most healthcare organizations to assist persons with diabetes (a) in their day-to-day self-management demands and (b) with making informed self-care choices. This includes providing behavioral strategies that establish and maintain a healthy lifestyle. Since the diabetes

clinical state fluctuates within individuals over their life span, education programs need to be comprehensive enough to provide clinical knowledge and skills to facilitate implementation of the changing treatment plans.

RECOMMENDATIONS

1. Patients newly diagnosed with diabetes should receive comprehensive DSME and education for MNT. The education component should be tailored to the patient's needs and should be provided through one of the following ways:
   - Refer to a diabetes self-management education program. This referral can be to either an in-house comprehensive diet consultation—MNT—or a comprehensive DSME program.
   - An ADA recognized program is recommended, if available (see Appendix M-3: Suggested Points of Contact for Patient Education/Nutrition/Self-Management Programs).
   - Conduct education in your clinical setting in the absence of an available comprehensive self-management program. Topics should be covered by the most qualified healthcare professionals, knowledgeable in the topic area. A team approach is highly desirable and could include, but is not limited to, a referral to a dietitian, certified diabetes educator, registered nurse, pharmacist, psychologist, exercise physiologist, physical therapist, social worker, endocrinologist, behaviorist, ophthalmologist, optometrist, physician, podiatrist, other health care professionals and paraprofessionals, or other specialized physicians based on the individual patient's needs. See Appendix M-4: Primary Care Staff Office Diabetes Education Resources and Tools, for resource materials.
   - Education may take place in either individual or group settings.
2. DSME, including MNT, should be an interactive, collaborative, ongoing process involving patients with diabetes and educators and include the following four-step process:
   - Assessment of the patient's educational needs
   - Identification of the patient's specific self-management goals
   - Education and behavioral interventions aimed at meeting the patient's goals
   - Evaluation of the patient's progress towards the goals

DISCUSSION

Leading experts in diabetes care and education revised the original National Diabetes Advisory Board (NDAB) Standards (Mensing et al., 2000). The revised standards identify the following as essential curricula components for DSME:

- Describing the diabetes disease process and treatment options
- Incorporating appropriate nutritional management
- Incorporating physical activity into lifestyle
- Using medications (if applicable) for therapeutic effectiveness
- Monitoring blood glucose, monitoring blood or urine ketones (when appropriate), and using the results to improve control
- Preventing, detecting, and treating acute complications
- Preventing (through risk-reduction behavior), detecting, and treating chronic complications
- Goal setting to promote health; problem-solving for daily living
- Integrating psychosocial adjustment into daily life
- Promoting preconception care, management during pregnancy, and gestational diabetes management (if applicable)

Primary care staff members have limited time to provide in-depth education. It is critical, however, to provide immediate education that will help ensure the patient's safety until in-depth DSME can be obtained. Appendix M-1: Core Competencies (Survival Skills) for Patients with Diabetes, details the core competency content.

Several studies have demonstrated the benefits and the limits of self-management training in type 2 diabetes. Norris et al. (2001) reviewed a total of 72 studies and reported a positive effect on knowledge, frequency and accuracy of self-monitoring, self-reported dietary habits, and glycemic control for studies with short follow-up. Effects on lipids, physical activity, weight, and blood pressure were variable. With longer follow-up,

interventions that used regular reinforcement were sometimes effective in improving glycemic control. No studies demonstrated the effectiveness of self-management training on cardiovascular morbidity or mortality. The American College of Physicians (ACP) Journal Club review of the Norris 2001 systematic review noted that DSME is a broad term that includes both effective interventions (collaborative sessions that are repeated) and ineffective interventions (single didactic sessions). A referral for in-depth DSME and diet consultation (if separate from the diabetes self-management program) is recommended for all patients diagnosed with DM.

The inclusion of these program components is recommended based on expert opinion and research, although not all of the program components are evidence-based. Because research on educational interventions is complex, expensive, and time consuming, few studies have addressed the effectiveness of such programs (Jacobson et al., 1983; Merritt et al., 1983; Miller and Goldstein, 1972; Rubin et al., 1998).

In a randomized trial, Rickheim et al. (2002) found that diabetes education delivered in a group setting, when compared with an individual setting, was equally effective at delivering education and providing equivalent improvements in glycemic control.

Norris et al. (2002a) performed a systematic review, finding 31 randomized controlled trials (RCTs) that tested the effect of self-management education on adults with type 2 diabetes and reported extractable data on the effect of treatment on HbA_1c. Self-management education improved HbA_1c levels at immediate follow-up and increased contact time increased the effect. The benefit declined 1 to 3 months after the intervention ceased, however, suggesting that learned behaviors change over time, or that continued follow-up and reinforcement is needed.

There is some evidence-based work on the effectiveness of MNT. In a RCT, Franz et al., (1995) reported that patients in the intervention group (n = 94), receiving ongoing MNT (3 visits) from registered dietitians, had a mean 10.5 percent lower fasting plasma glucose (FPG) level; while an intervention group (n = 85) with a single registered dietitian intervention, showed a 5.3 percent lower FPG level; the control group (n = 62), not receiving any MNT from a registered dietitian, showed no improvement in glycemic control at the end of a 6-month period.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Provision of comprehensive DSME and MNT education.	Corabian & Harstall, 2001 Davidson et al., 1979 Franz et al., 1995 Funnel & Haas, 1995 Jacobson et al., 1983 Merritt et al., 1983 Miller et al., 2002 Miller and Goldstein, 1972 Norris et al., 2002a Norris et al., 2001 Rickheim et al., 2002 Rubin et al., 1998	I II-2 II-2 III III III I III I I I III	Good Fair Fair Poor Poor Poor Fair Poor Poor Fair Fair Poor	B
2	Individualized and tailored sessions to meet participants' needs.	Arseneau et al., 1994 Conget et al., 1995 Ellison & Rayman, 1998 Miller et al., 2002 Monk et al., 1995 Rachman et al., 2002 Raji et al., 2002 Schlundt et al., 1994 Travis, 1997	I III III I III I I III III	Good Poor Poor Fair Poor Good Fair Poor Poor	B
3	Setting behavioral goals and determining a follow-up schedule	Conget et al., 1995 Garcia and Suarez, 1996	III II-3	Poor Fair	B

	with patient.	Glasgow et al., 1992 Pascale et al., 1995	I I	Good Good	
4	Assessment of patient's knowledge of DM and understanding about self-care.	DCCT, 1997 UKPDS, 1998	I	Good	A
5	Provision of specialized referrals when necessary.	Aubert et al., 1998 Franz et al., 1995 Norris et al., 2002b Sikka et al., 1999	II-1 II-2 I II-2	Fair Fair Good Fair	B
6	Education provided in either individual or group settings.	Rickheim et al., 2002	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

B. Determine Patient's Extent of Knowledge And Self-Management Skill Deficit Based On Treatment Goals

OBJECTIVE

Determine the education and skills enhancement needed to enable the patient to self-manage.

RECOMMENDATIONS

1. Assessment of the following factors should be completed to determine the extent of the patient's educational and skills deficit and his/her ability for self-management: knowledge of the diabetes disease process, treatment goals, management skills, cultural influences, health beliefs/behavior, attitudes, socioeconomic factors and barriers.
2. Results from the assessment of the patient's learning needs, abilities, preferences, and readiness to learn should be documented.

DISCUSSION

Choose the questions that relate to the clinical treatment goals/issues pertinent to the individual patient grouped according to treatment goals:

Nutrition and meal planning
Goal setting
Home monitoring
Foot care
Exercise/Activity
Medications
Acute complications
Psychosocial
Preventive screening
Treatment adherence
Lifestyle

A panel of certified diabetes educators compiled a list of initial questions to assist the provider (see Appendix M-5: Questionnaire on Patient's Knowledge and Adherence). This list of questions is not a validated instrument and may need to be adjusted to fit the patient's level of education and/or comprehension.

Appendix M-6: Patient Self-Management and Knowledge Needs Assessment, includes patient responses to the questions in Appendix M-5 and suggested actions to take when the patient is unable to demonstrate knowledge/skills.

Results from the assessment of the patient's learning needs, abilities, preferences, and readiness to learn should be documented. Cultural and religious practices should be included as well as emotional barriers, desire and

motivation to learn, physical and cognitive limitations, language barriers, and the financial implications of care choices. The patient's understanding of the newly acquired education should also be assessed.

C. Does The Patient Need Referral For Further Education Or Intervention?

OBJECTIVE

Identify patients who are at high-risk for diabetes complications or in need of further educational intervention.

ANNOTATION

After explaining the basic concepts, if the provider determines that the patient does not yet understand the concepts or would benefit from a more in-depth, risk-focused education or intervention, a consultation should be requested. Because primary care appointments frequently do not provide adequate time to address background and educational issues, a referral or separate visit(s) to address the patient's needs may be required. Referral may involve sending the patient to the comprehensive DSME program, possibly for a second time. However, it may be necessary to send the patient to another provider/specialist for individual visit(s) to evaluate and address an often complex combination of educational issues, treatment issues, coordination of care issues, psychosocial issues or financial issues. High-risk patients may benefit from these types of referrals. Decisions for referral are based on level-of-risk and extent of educational deficits.

Examples of conditions that may warrant risk-focused intervention include:

- Elevated HbA_1c (3 percent above the upper limit of normal or >9.5 percent)
- Uncontrolled hypertension (>140/90)
- Serum creatinine level >2 mg/dL
- High-risk feet
- Pregnancy; or planned pregnancy; or woman of child bearing age
- Poor eyesight
- Severe psychosocial or economic barriers
- Advanced age
- Intensive insulin therapy
- Recurrent hypoglycemia or hypoglycemia unawareness
- Recent hospitalization for diabetic ketoacidosis (DKA) or severe hyperglycemia
- Disease complexity

The need for risk-focused education interventions may also have been identified through other modules of this guideline.

Any deficiencies in the critical areas reviewed in the medical history (see Module D) may indicate patient knowledge needs in multiple areas and should trigger a referral for comprehensive DSME.

D. Refer As Appropriate For Comprehensive Self-Management And Diet Education Or Risk-Focused Intervention Or To A Case Manager Or Appropriate Specialist

OBJECTIVE

Determine which referrals are appropriate, based on the patient's needs and availability of providers, programs, and benefit coverage.

RECOMMENDATIONS

1. Patients at high-risk may have needs beyond educational deficits and should be referred for focused attention by other services. Possible referrals could include, but are not limited to, the following: dietitian,

medical nutrition therapist, certified diabetes educator or comprehensive DSME Program, case manager, registered nurse, pharmacist, psychologist, exercise physiologist, physical therapist, social worker, endocrinologist, ophthalmologist, optometrist, physician, podiatrist, behaviorist, other health care professionals, or paraprofessionals.

2. A case manager is a valuable resource for providing ongoing, detailed coordination of care for high-risk patients.

DISCUSSION

Aubert et al. (1998) reported that patients in one health maintenance organization (HMO) who were case managed had improved glycemic control, increased quantitative protein, and more frequent microalbuminuria testing and follow-up testing when compared to patients who were not case managed.

Franz (1995) reported that patients with type 2 diabetes who were randomized to receive MNT from dietitians had significant lower HbA_1c levels than those who were randomized to no MNT intervention during the 6 month trial.

Norris et al. (2002b) performed a systematic review of the effectiveness and economic efficiency of disease management and case management for people with diabetes. They found that evidence supports the effectiveness of disease management on glycemic control; on screening for diabetic retinopathy, foot lesions and peripheral neuropathy, and proteinuria; and on the monitoring of lipid concentrations. This evidence is applicable to adults with diabetes in managed care organizations and community clinics in the United States and Europe. Case management is effective in improving both glycemic control and provider monitoring of glycemic control. This evidence is applicable primarily in the United States managed care setting for adults with type 2 diabetes. Case management is effective both when delivered in conjunction with disease management, and when delivered with one or more additional educational, reminder, or support interventions.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Provision of specialized referrals when necessary.	Aubert et al., 1998 Franz et al., 1995 Norris et al., 2002b [SR] Sikka et al., 1999	II-1 II-2 I II-2	Fair Fair Good Fair	B

QE = Quality of Evidence; R = Recommendation; [SR] = Systematic Review (see Appendix A)

E. Reassess And Follow-Up As Indicated

OBJECTIVE

Identify the frequency of patient appointments needed to evaluate educational effectiveness or reinforce education/self-management skills.

RECOMMENDATIONS

1. When knowledge deficits continue to exist or a large number of lifestyle changes are necessary, frequent follow-up may be indicated.
2. Recently learned diabetes skills or information should be re-evaluated no longer than 3 months after initial instruction. One possible method involves follow-up at earlier time points, e.g., 1 month.
3. When appropriate, single behavioral goals should be identified and prioritized to increase the likelihood of the patient adopting lifestyle changes necessary to achieve treatment goals.

DISCUSSION

Definitive evidence is not available to support specific frequencies of follow-up. Frequency of appointments has been reported from weekly to annually (Conget et al., 1995; Pascale et al., 1995). Garcia and Suarez (1996) documented the benefit of interactive and ongoing education and the need to provide individualized follow-up.

Glasgow et al. (1992) compared the immediate and delayed intervention and concluded that both could achieve positive results. The importance of individualization and tailoring sessions to participants' needs has been amply documented (Arseneau et al., 1994; Conget et al., 1995; Ellison & Rayman, 1998; Monk et al., 1995; Schlundt et al., 1994; Travis, 1997). Therefore, frequency of re-assessment should be individualized based on the patient's and provider's perception of need. Panel experts recommend that recently learned diabetes skills or information should be reassessed within 3 months of the initial instruction. When appropriate, single behavioral goals should be identified and prioritized to increase the likelihood of the patient adopting lifestyle changes that are necessary to achieve the treatment goals.

F. Does The Patient Want More Information?

OBJECTIVE

Address the patient's desire (motivation) for additional information.

ANNOTATION

Patients often hear of developments in diabetes or have specific questions regarding newer treatment modalities. They may also decide they want to improve their glycemic control or their life style.

G. Provide Materials Or Patient Reference List Or Refer As Needed

OBJECTIVE

Provide additional information in response to the patient's questions about new treatments or advanced self-management skills that have been communicated from other persons with diabetes or the media.

ANNOTATION

If the patient requests additional information it may not be essential for the caregiver to intervene professionally or refer to a specialist. Appendix M-7, List of Patient References: Diabetes Resources, may provide the patient with adequate information.

APPENDIX M-1
Core Competencies (Survival Skills) for Patients with Diabetes

The following core competencies are not substitutes for diabetes self-management education (DSME) or medical nutrition therapy. It is preferable for patients to participate in a comprehensive interdisciplinary DSME program. If such a program is not available or if the patient is unwilling to attend or is newly diagnosed and awaiting enrollment in such a program, core competency (survival skills) education should be given. Core competency education should cover at least the following topics:

Hyperglycemia
Hypoglycemia (if applicable)
Medication education (including insulin administration, if applicable)
Self-monitoring of blood glucose
Basic dietary guidelines
Sick day management
When to seek further treatment and/or medical advice.

HYPERGLYCEMIA	
Definition	**Blood glucose 250 mg/dL**
Causes	Forgetting to take diabetes medication Overeating Infection/Illness Stress Not exercising Not taking enough diabetes medication
Symptoms	Fatigue Polydipsia Polyuria, especially nocturnal Blurry vision
Intervention/ Treatment	Drink plenty of non-caloric fluids Increase self-monitoring of blood glucose (SMBG) before meals and bedtime while awake until blood glucose is 200 mg/dL. If DM is type 1, urine ketones should also be tested Continue to take prescribed diabetes medication Follow meal plan.

HYPOGLYCEMIA	
Definition	**Blood glucose <70 mg/dL**
Causes	Delaying meals Not eating enough food Too much diabetes medication Unplanned, strenuous activity
Symptoms	Weakness Rapid heart beat Sweating Shakiness Light-headedness or confusion
Intervention/ Treatment	If patient is unconscious, a spouse or friend should call 911 If conscious, treat immediately by eating a food or glucose replacement with 15-20 g of fast-acting carbohydrates (CHO) (see Appendix M-2) If on acarbose, treat with a glucose product (tabs or gel equal to 15-20 g CHO) Check blood glucose in 15 minutes. If <70 mg/dL or symptoms have not subsided, take an additional 15g CHO Eat a meal with CHO within 30 minutes

	If blood glucose is <70 mg/dL and does not increase after eating, seek further medical help.

MEDICATION EDUCATION (IF APPROPRIATE)

Education regarding diabetes medications should include:

- Names of medications
- Action & duration of medications
- Times & mode of administration
- Possible side effects
- Drug/food interactions

Education for patients receiving insulin should also include the following:

- Preparation of equipment
- Filling of the syringe
- Administration
- Insulin action(s), e.g., onset(s), peak(s), and duration(s)
- Insulin storage
- Needle/syringe disposal
- Rotation within selected anatomical sites
- Demonstration with return demonstration by the patient

SELF-MONITORING OF BLOOD GLUCOSE

Education regarding self-monitoring of blood glucose should include:

- Indications and frequency of routine monitoring, including target glycemic range
- Indications for more frequent monitoring
- Preparation and use of monitoring devices, including puncture devices
- Recording and analysis of results
- Collaborating with providers in applying results
- Actions to take, whom to call when results are out of target range

BASIC DIET GUIDELINES

Meal plans can be initiated with use of the "FIRST STEP in Diabetes Meal Planning." This basic, self-contained nutrition pamphlet can be reviewed and provided to clients to use until an individualized meal plan can be developed. General principles to be reviewed are:

- Eat at regular times—distribute CHO food intake throughout the day.
- Define CHO, protein, and fat.
- Describe which foods affect blood sugar the most (e.g., CHO).
- Emphasize the importance of eating a variety of foods, increasing fiber, and a hypocaloric diet—if overweight, e.g., decreasing fat intake and controlling portion sizes.

SICK DAY MANAGEMENT

The main sick day management rules are:

- Take diabetes medication.
- Self-monitor blood glucose more frequently.
- Test urine ketones if DM type 1.
- Eat the usual amount of CHO divided into smaller meals and snacks if necessary—if blood glucose is >250 mg/dL, the usual CHO may be unnecessary.
- Drink fluids frequently, 8 oz per hour while awake.
- Refer to example of sick day guide (see Appendix M-2).

WHEN TO SEEK FURTHER MEDICAL ASSISTANCE

Blood glucose >250 mg/dL or double the range set with the primary care provider
If blood sugar is less than 70 mg/dL and does not get better after food
Urine test shows moderate to high ketones
Fever of 101 degrees Fahrenheit or greater
Nausea and vomiting, especially if no food or fluid intake for more than 5 hours
Symptoms of shakiness or nervous feeling, lightheadedness, sweating, rapid heart rate or confusion that do not improve after eating CHO foods
Any of the following problems on the feet: burns, splinters, stubbed toe, foot trauma, blister, swelling, black or blue discoloration, bleeding, or oozing of fluid

APPENDIX M-2
Food for Sick Days and Hypoglycemia

HYPOGLYCEMIA TREATMENT

Items in this table can be used for immediate treatment of hypoglycemia/low blood sugar. The items in the fruit and other carbohydrate list will relieve the symptoms of hypoglycemia the fastest. In addition to the food items listed, commercial glucose products containing 15g to 20g fast acting carbohydrates (CHO) may be used (glucose tablets or gels).

Fruit List	Other Carbohydrates	Milk	Starches
1/2 cup orange juice 1/2 cup grapefruit, pineapple, or apple juice 1/3 cup cranberry, grape or prune juice	4 oz regular cola (1/2 cup) 6 oz regular ginger ale 1 tablespoon honey, brown sugar, or corn syrup 1/2 cup sherbet	1 cup *skim* milk 1/2 cup pudding	3 Graham crackers 8 animal crackers 6 Saltine crackers

FOODS FOR SICK DAYS

1. Take your pills or insulin. You may need to take more insulin than normal.
2. Check your blood sugar every 4 hours. If it is above 250 mg/dL, and you have type 1 diabetes, also check your urine for ketones.
3. If you are sick and your blood sugar is above 250 mg/dL and urine ketones are positive on 2 consecutive checks, call your provider or clinic nurse.
4. If blood sugar is consistently very high (above 300 mg/dL) after 2 to 3 checks, call your provider.
5. Drink at least 1/2 to 1 cup of fluids every hour while awake.
6. Eat frequent small meals of whatever foods you can tolerate and replace carbohydrate containing foods that would have normally been in your daily plan.
   1 Starch = 15g CHO
   1 Fruit = 15g CHO
   1 Milk = 12g CHO

If a person with diabetes is nauseated and can not keep down solid food, replace food items on the meal plan with other items from the same food group, if possible (e.g., replace a slice of bread with saltine crackers or cream soup/vegetables with tomato juice).

Each portion on the following table contains 15g of carbohydrates:

Solid Foods Containing 15g CHO		Beverages Containing 15g CHO	
Food	Amount	Food	Amount
Milk List			
Yogurt (artificially sweetened)	1 cup	Skim or low fat milk	1 1/4 cup
Yogurt (with fruit)	1/3 cup	—	—
Vanilla pudding	1/4 cup	—	—
Ice cream (no sugar added)	1/2 cup	—	—
Ice milk (no sugar added)	1/2 cup	—	—
Starch List			
Cooked cereal	1/2 cup	Chicken noodle soup	1 cup
Toast (bread)	1 slice	Cream soup	1 cup
Graham crackers (2 ½ inch)	3	—	—
Animal crackers	8	—	—

Solid Foods Containing 15g CHO		Beverages Containing 15g CHO	
Saltine crackers (2 inch)	6	—	—
Fruit List			
—	—	Grapefruit, orange, or pineapple juice	1/2 cup
Raisins	2 T	Grape or cranberry juice	1/3 cup
Vegetable List			
—	—	Tomato juice	1 1/2 cup
Other			
Regular gelatin	1/3 cup	Ginger ale, regular	6 oz
Twin popsicle	3/4 popsicle	Cola, regular	4 oz
Sherbet	1/4 cup	Corn syrup	1 T
Honey	1 T	—	—
Brown Sugar	1 T	—	—

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APPENDIX M-3
Suggested Points of Contact for Patient Education/Nutrition/Self-Management Programs

The American Diabetes Association maintains lists of local programs that have received recognition that they meet the national Standards for Diabetes Self-Management Education Program. The phone number for the national office is: 1-800-diabetes (342-2383). The web site address is http://www.diabetes.org .

The national office of The Center for Disease Control and Prevention (CDC) can also provide the name of each State Diabetes Control Program and identify any Diabetes Self-Management Education (DSME) programs endorsed through the state programs. State certification is usually based on the national standards for Diabetes Self-Management Education. The telephone number for the CDC is (1-877-232-3422); the web site address is http://www.cdc.gov/diabetes/ .

Lists of registered dietitians who provide nutrition counseling are available from The American Dietetic Association by calling 1-800-877-1600 or checking the web site: http://www.eatright.org/journal/ .

The American Dietetic Association's Nationwide Nutrition Network is a national referral service that links consumers, physicians, food manufacturers, distributors or restaurant owners or managers with registered dietitians. All participants in The American Dietetic Association's Nationwide Nutrition Network (dietitian referral service) are registered dietitians—professionals who provide reliable, objective nutrition information, separate facts from fads and translate the latest scientific findings into easy-to-understand nutrition information. The web site address is http://www.eatright.org/find.html or go to the http://www.eatright.org and select *Find a Dietitian* from the bottom menu.

The National Certification Board for Diabetes Educators (NCBDE) maintains a listing of certified diabetes educators (CDEs). These health professionals have passed the certification examination administered by the NCBDE. Requests should be in writing. Contact information is as follows:

National Certification Board for Diabetes Educators
330 East Algonquin Road, Suite 4
Arlington Heights, IL 60005
Phone: 847-228-9795
Fax: 847-228-8469
Email: info@ncbde.org
Web Address: http://www.ncbde.org

APPENDIX M-4
Primary Care Staff Office Diabetes Education Resources and Tools

SUGGESTED REFERENCES FOR OFFICE

Life with Diabetes. A Series of Teaching Outlines, (2nd edition) The American Diabetes Association, University of Michigan. Diabetes Research and Training Center. 2000 (Includes teaching plans). Can be ordered at http://merchant.diabetes.org/adabooks .

Take Charge Of Your Diabetes. Third edition. Can be downloaded from the CDC web site: http://www.cdc.gov/diabetes/pubs/tcyd/index.htm .

What I Need To Know About Eating And Diabetes. Can be obtained free from the National Diabetes Clearing House (301) 654-3327 or at http://www.ndic@info.niddk.nih.gov/ .

APPENDIX M-5
Questionnaire on Patient's Knowledge and Adherence

Treatment Goals		Questions	Response Accurate?
Nutrition & Meal Planning	1	What times of the day do you eat your meals and snacks? What is the relationship of your meals to when you take your medication?	
	2	When should you eat in relationship to the time you take insulin/medication?	
	3	Which food affects your blood sugar the most—chicken breast, salad, or a potato?	
Goal Setting	4	Do you remember your target goals (BP, LDL, blood sugar, HbA1c, weight, activity)?	
	5	What are your target goals? (BP, LDL, blood sugar, HbA1c, weight, activity)?	
Home Monitoring	6	When do you test your blood sugar?	
	7	What are your blood sugar results and how do you use them to manage your diabetes?	
Foot Care	8	How often do you look at your feet?	
	9	When would you contact a health care provider if you have a foot problem?	
	10	What are the symptoms of foot disease and when would you contact your provider?	
Activity	11	What effect does activity have on your blood sugar?	
Medication	12	What diabetes medicine do you take and how often?	
	13	Do you take your diabetes medication when you are sick and unable to keep food down?	
Acute Complications	14	Do you know what to do when your sugars are too low, too high, and when to call your provider?	
Psychosocial	15	Are there any problems in your life that make it difficult for you to take care of your diabetes?	
	16	Are you overwhelmed by your diabetes?	
	17	Do you worry about developing complications of diabetes?	
Preventive Screening	18	Do you know why you have to have periodic eye examinations?	
	19	Have you scheduled your annual eye and foot examinations?	
Treatment Adherence	20	Is there anything that has been recommended that you do for your diabetes that you think you will have difficulty with, or will be unable to do?	
	21	What part of diabetes treatment do you have difficulty with?	
Lifestyle	22	How do alcohol and cigarettes affect your diabetes?	
	23	Do you want to get pregnant—either now or in the near future?	
	24	If you are sexually active, what contraception methods are you using?	
	25	Have there been any major changes in your life (family crisis, job loss)?	

APPENDIX M-6
Patient Self-Management and Knowledge Needs Assessment

Treatment Plan & Goals	Questions to Ask	Patient Response	Suggested Actions To Be Taken
Nutrition & Meal Planning	1. What times of the day do you eat your meals and snacks and what is the relationship of taking your medication to your meals?	If patient indicates an irregular eating schedule, consider it a problem with nutrition/diet behavior.	· Take complete nutrition history to determine extent to which self-management skills have been incorporated into lifestyle, identify barriers, and create self management plan—or refer for nutrition counseling or comprehensive diabetes self management program. · Refer to dietitian or take nutrition history, determine calorie needs, identify normal eating habits, identify foods and meal planning principles that will match patient's needs, identify goals for diet changes to be made, and establish follow-up appointment.
	2. When should you eat in relationship to the time you take insulin?	If patient is unable to explain relationship between time of eating and medication, consider it a nutrition knowledge deficit.	
	3. Which food affects your blood sugar the most, chicken breast, salad, or a potato?	If patient can't answer that potatoes will have most effect, consider it a nutrition knowledge deficit.	
Goal Setting	4. Do you remember your target goals (BP, LDL, blood sugar, HbA_1c, weight, activity)? *or* 5. What are your target goals (BP, LDL, blood sugar, HbA_1c, weight, activity)?	If patient can not verbalize target goals, consider it a knowledge deficit.	· Explain target goals and assess if patient knows what behaviors are linked to those goals. Explore to see if other knowledge deficits exist.
Home Monitoring	6. When do you test your blood sugar?	If patient is unable to verbalize that self-monitoring of blood glucose (SMBG) schedules is based on the individual's needs, desires and use of the results (e.g., more frequent monitoring during insulin adjustment), consider it a knowledge deficit.	· Educate the patient on the importance of SMBG to their diabetes self-management and recommend schedule for SMBG. Timing of SMBG is variable depending on the medication and glucose goals.

Treatment Plan & Goals	Questions to Ask	Patient Response	Suggested Actions To Be Taken
	7. What are your blood sugar results and how do you use them to manage your diabetes?	If patient is unable to verbalize that SMBG may be used for: identifying and treating low blood sugar; making decisions about food choices, medication adjustment and activity; determining effect of certain foods/portions on blood sugars; pattern management; managing illness; and managing hypoglycemia unawareness, consider it a knowledge deficit. If SMBG results are not within the goals, consider that it could be a knowledge deficit or behavior issue.	· Recommend referral to CDE on SMBG when individual is deficient in testing skills and/or utilizing results of SMBG to manage diabetes. · Recommend referral to CDE if individual having frequent low/high blood sugar results. · Base treatment recommendations (meal plan/activity/medication) on individual's SMBG results.
Foot care	8. How often do you look at your feet?	If patient cannot verbalize appropriate behavior , consider it a knowledge deficit: · Examine feet daily including between the toes · Washing feet daily; and · Proper selection of footwear Then determine if knowledge or behavior is the issue.	· Instruct in importance of foot care and shoe selection. Then ask several more unrelated questions to determine if general knowledge of diabetes self-management is missing.
	9. When do you contact a health care provider about a foot problem? *or* 10. What are the symptoms of foot disease and when would you contact your provider?	If patient does not indicate that any time there is heat, redness, swelling, or infection, the provider should be contacted, consider it a knowledge deficit. If patient can not verbalize signs and symptoms of foot disease, and to contact the provider if there are burns, splinters, blisters, stubbed toe, trauma, black & blue discoloration, bleeding or oozing of fluid, heat, redness, swelling, or infection, consider it a knowledge deficit.	· If more areas are deficient begin scheduling a series of appointments for education and provide written material to review prior to discussion (see Appendix M-3) or refer for an educational needs assessment from CDE, podiatrist, or diabetes program manager.
Activity	11. What effect does activity have on your blood sugar?	If patient cannot verbalize that activity in most situations will lower blood sugars, consider it a knowledge deficit.	· Instruct on planning for activity, including adjustments of medication and food, and contraindications for activity. · Instruct patient to have a glucose source readily available during activity.

Treatment Plan & Goals	Questions to Ask	Patient Response	Suggested Actions To Be Taken
Medications	12. What diabetes medicine do you take and how often?	If the patient does not recall what medication(s) he/she is taking, it is unlikely that he or she knows its potential side effects and how to take it appropriately (e.g., acarbose needs to be taken at the time of the meal). Consider it a knowledge deficit.	Educate patient on: · Importance of knowing his/her medications for the treatment of diabetes; · Its potential side effects; and · When they should be taken to obtain the best results.
	13. Do you take your diabetes medication when you are sick and unable to keep food down?	If patient is unable to identify what to do in this situation (see Appendix M-2 for desired responses), consider it a knowledge deficit. If patient verbalizes what is supposed to happen, but indicates inability to follow regimen, consider it a knowledge deficit. If patient is unable to verbalize the importance of frequent home monitoring and to increase medication dosage (if applicable) if BS is high and that he/she should call provider if food or fluids cannot be keep down, consider it a knowledge deficit.	· Sick-day guidelines keeping in mind the particular medications he/she is taking (see Appendix M-2). · Address barriers limiting treatment adherence. · Deficiency in either one of these questions in addition to another major category or if this is not the first time the patient has had difficulty with this category warrants a referral for either comprehensive diabetes self management education program or individual appointment with appropriate provider--dietitian, CDE pharmacist, or nurse educator.
Acute Complications	14. Do you know what to do when your sugars are low or high, and when to call your health care provider?	If the patient is unable to verbalize the following, consider it a knowledge deficit: · When the blood sugar is low he/she should eat or drink 15-20 g of fast acting carbohydrate (CHO) food or fluid. · If blood sugar is high he or she should know when or if to increase medication, to increase the frequency of SMG, to call primary care provider with results, and to drink large amounts of sugar free fluids.	Educate patient on: · Signs and symptoms of hyper/ hypoglycemia; · Calling their healthcare provider when they have repeated episodes of unexplainable hyper/hypoglycemia.
Psychosocial	15. Are there any problems in your life that make it difficult for you to take care of your diabetes?	If patient responds with symptoms of depression, denial, or anger that interfere with self-management, consider those indicative of psychosocial	· Address this issue in primary care setting and educate, if appropriate.

Treatment Plan & Goals	Questions to Ask	Patient Response	Suggested Actions To Be Taken
	16. Are you overwhelmed with your diabetes?	issues.	· Otherwise, refer to Behavioral Medicine for evaluation and counseling.
	17. Do you worry about developing complications of diabetes?		
Preventive Screening	18. Do you know why you have to have a periodic eye exam?	If patient is unable to verbalize importance of eye examinations to prevent blindness and identify changes in vision, consider it a knowledge deficit.	Educate on importance of annual eye exam to identify changes early so treatment can be initiated before irreversible damage occurs.
	19. Have you scheduled your annual eye and foot examinations?	If patient does not verbalize need and/or intent to schedule visit, consider it a knowledge deficit.	Facilitate scheduling of appropriate exams.
Treatment Adherence	20. Is there anything that has been recommended that you do for your diabetes that you think you will have difficulty with, or are unable to do? *or* 21. What part of diabetes treatment do you have difficulty with?	If patient identifies a specific area of concern (e.g., diet, blood sugar testing), select appropriate questions to determine if patient has knowledge of how to self-manage diabetes. Consider the possibility of knowledge deficit or psychosocial of issues.	· If primary care staff has adequate time to address areas of concern then identify barriers, potential solutions, and develop plan. · Assess for barriers to care/ self management: financial, social, psychiatric, nutritional, health beliefs, cultural differences, language difficulties. Refer if: · Specific need/ barrier to learning has been identified which does not allow the patient to perform self-management. This need may be addressed with an individual consultation; · If a specific barrier has not been identified or more than one need/barrier is identified, referral to a comprehensive diabetes education program is recommended. · Evaluate barriers and engage patient in identifying potential self-management goals to overcome barriers. · If time does not permit, schedule another appointment, refer to CDE or specialist in area of concern to address barriers or refer to comprehensive DSME program (see Appendix M-1).

Treatment Plan & Goals	Questions to Ask	Patient Response	Suggested Actions To Be Taken
Lifestyle	22. How do alcohol and cigarettes affect your diabetes?	If patient is unable to verbalize that alcohol increases weight, can cause severe hypoglycemia; and smoking cigarettes causes poor circulation and contributes to HTN and macrovascular disease, consider it a knowledge deficit.	Address areas of concern, and provide prevention education. Refer if indicated. If time does not permit, schedule another appointment, refer to CDE, or specialist in area of concern.
	23. Do you want to get pregnant- either now or in the near future?	If patient response is "yes" then additional knowledge is required—refer.	Refer to Ob-Gyn or appropriate provider that specializes in reproductive counseling for women with diabetes.
	24. If you are sexually active, what contraception methods are you using?	If patient is unable to verbalize adequate contraceptive methods, consider it an indication for additional interventions/ counseling.	(See above)
	25. Have there been any major changes in your life?	If patient response is "yes", consider it an indication that psychosocial issues are of concern.	Refer to appropriate provider to address these issues or determine effect of changes on ability to meet diabetes treatment goals (e.g., shift changes and medication/diet adjustments, spouse no longer doing cooking and patient has not done this in the past).

Resource: A Core Curriculum for Diabetes Education, fourth edition, American Association of Diabetes Educators (Franz, 2001).

APPENDIX M-7
List of Patient References: Diabetes Resources

ORGANIZATIONS

American Diabetes Association
1701 N. Beauregard Street
Alexandria, VA 22311
(703) 549-1500 National Center
(800) 232-6733 Publications
(800) DIABETES (342-2383) for information about diabetes

The American Dietetic Association
216 West Jackson Blvd., Suite 800
Chicago, IL 60606-6995
Call (800) 366-1655 to speak with a dietitian, find a dietitian, or order free information.

American Association of Diabetes Educators
100 West Monroe, Suite 400
Chicago, IL 60603
(800) 338-3633 Association number
Call (800) TEAM-UP4 for a 24-hour opportunity to speak with a diabetes educator.

EDUCATIONAL MATERIAL

National Diabetes Information Clearinghouse (NDIC)
1 Information Way
Bethesda, MD 20892
(301) 654-3327
(301) 907-8906 (fax)

PRINTED INFORMATION

American Diabetes Association
Publication Orders
(800) 232-6733

JOURNALS FOR PEOPLE WITH DIABETES

Diabetes Forecast (monthly magazine)
(800) 806-7801
[Subscription included with American Diabetes Association membership]

Diabetes Self-Management (monthly subscription magazine)
(800) 234-0923

DIABETES NEWSLETTERS

Diabetes Wellness Letter
P.O. Box 3837
Merrifield, VA 22116

INTERNET RESOURCES

American Diabetes Association (ADA): http://www.diabetes.org
[Lists association events, daily menu, publication ordering, and selected articles from ADA publications]

National Institute of Diabetes and Digestive and Kidney Disease (NIDDK): http://www.niddk.nih.gov/
[Information includes: research, statistics, questions to ask your doctor, and a directory of diabetes organizations]

Juvenile Diabetes Research Foundation International (JDRF): http://www.jdrf.org/index.php **.**

Division of Diabetes Translation at Centers for Disease Control and Prevention (CDC)
National Diabetes Education Program at http://www.cdc.gov/nccdphp/ddt/ddthome.htm .

Department of Veterans Health Affairs (VHA): http://www.va.gov/

Innovations College National Eye Institute: http://www.nei.nih.gov//tools/search.htm **.**

APPENDIX M-8
Diabetes Self-Management Education (DSME)

Diabetes self-management education (DSME), including medical nutrition therapy, is an interactive, collaborative, ongoing process involving people with diabetes and educators. As opposed to didactic education, DSME is skill-based learning. The four-step process comprises:

- Assessment of the individual's educational needs
- Identification of individual's specific self-management goals
- Education and behavioral interventions aimed at meeting individual's goals
- Evaluation of the individual's progress towards goals

The revised standards identify the following as essential curricula components for DSME:

- Describing the diabetes disease process and treatment options
- Incorporating appropriate nutritional management
- Incorporating physical activity into lifestyle
- Using medications (if applicable) for therapeutic effectiveness
- Monitoring blood glucose, monitoring blood or urine ketones (when appropriate), and using the results to improve control
- Preventing, detecting, and treating acute complications
- Preventing (through risk-reduction behavior), detecting, and treating chronic complications
- Goal setting to promote health; problem-solving for daily living
- Integrating psychosocial adjustment into daily life
- Promoting preconception care, management during pregnancy, and gestational diabetes management (if applicable)
- Diabetes overview
- Stress and psychological adjustment
- Family involvement and social support
- Nutrition
- Exercise and activity
- Medication
- Monitoring and use of results
- Relationships among nutrition, exercise/activity, medication, and blood glucose level
- Prevention, detection, and treatment of acute complications
- Prevention, detection, and treatment of chronic complications
- Foot, skin, and dental care
- Behavioral strategies, goal setting, and problem solving
- Benefits, risks, and management options for improving glucose control
- Preconception, pregnancy, and gestational diabetes
- Use of health care systems and community resources

Patient's knowledge and skills can be assessed by questions that relate to the clinical treatment goals/issues identified pertinent to the individual patient grouped according to treatment goals (for a list of questions, see Appendix M-5: Questionnaire on Patient's Knowledge and Adherence):

- Nutrition and meal planning
- Goal setting
- Home monitoring
- Foot care
- Exercise/activity
- Medication
- Acute complications
- Psychosocial
- Preventive screening

Treatment adherence
Lifestyle

A panel of certified diabetes educators has compiled a list of initial questions to assist the provider (see Appendix M-5: Questionnaire on Patient's Knowledge and Adherence). This list of questions is not a validated instrument and may need to be adjusted to fit the patient's level of education and/or comprehension. Appendix M-6: Patient Self-Management and Knowledge Needs Assessment, includes patient responses to the questions in Appendix M-5 and suggests actions to take if the patient is unable to demonstrate sufficient DM knowledge or self-care skills.

Results from the assessment of the patient's learning needs, abilities, preferences, and readiness to learn should be documented. Cultural and religious practices should be included as well as emotional barriers, desire and motivation to learn, physical and cognitive limitations, language barriers, and the financial implications of care choices. The patient's understanding of the newly acquired education should also be assessed.

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DIABETES MELLITUS** IN PRIMARY CARE

APPENDICES

APPENDIX A
GUIDELINE DEVELOPMENT PROCESS

DEVELOPMENT OF THE 1997 AND 1999 DIABETES MELLITUS GUIDELINES (VERSIONS 1.0 AND 2.0)

The initial Veterans Health Administration (VHA) Diabetes guideline development process was undertaken from August 1996 through March 1997. The list of more than 70 developers/contributors included VHA professionals, senior representatives from key federal health-related agencies (Diabetes Division of the National Institutes for Diabetes [DDNID]; Digestive and Kidney Diseases [DKD]; Division of Diabetes Translation; Centers for Disease Control and Prevention [CDC]; Office of Managed Care; Health Care Financing Administration [HCFA]; and Pharmacoeconomic Center [PEC] of the Department of Defense), as well as private sector experts provided by the VHA External Peer Review Program contractor. Many participants held senior leadership positions in the American Diabetes Association (ADA), the National Institutes of Health (NIH)/Center for Disease Control and Prevention (CDC), and the National Diabetes Education Program (NDEP).

The 1997 VHA Diabetes Mellitus Guideline and algorithm (version 1.0) drew heavily from existing ADA, National Cholesterol Education Program (NCEP), and National Kidney Foundation practice guidelines for diabetes mellitus. The 1997 Guideline integrated the recommendations developed by VHA's Medical Advisory Panel (MAP) to the Pharmacy Benefits Management Strategic Health Group examining the pharmacological management of persons with diabetes, hypertension, and hyperlipidemia. Consumer input was also included in the guideline revision. The perspective of beneficiaries and their family members sensitized panelists to patient needs.

The 1997 VHA Diabetes Mellitus Guideline represented the first comprehensive guideline for this disease by a federal agency or national healthcare system in which risk stratification was both explicit and evidence-based. The 1997 VHA Guideline was reviewed at a joint meeting of the NDEP Steering Committee and the Diabetes Mellitus Federal Interagency Coordinating Committee (DMICC) on October 21, 1997. The DMICC report acknowledged the flexibility of the VHA guideline in that they explicitly indicated the need for individual provider assessments and patient preferences, and authorized the use of the NDEP logo to reflect the collaboration with the NDEP executive steering committee members.

The 1997 VHA Diabetes Mellitus Guideline represented a "seed document" that was updated and adapted by the joint VHA/DoD Diabetes Guideline Development Group over a six-month period from January to June 1999. As with the original Working Group, the charge of the VHA/DoD group was to provide evidence-based action recommendations whenever possible; hence, major clinical randomized controlled trials (RCTs) and observational studies published from March 1997 through March 1999 in the areas of diabetes, hypertension, lipid management, renal disease, foot and eye care, and diabetes education were reviewed. The updated version 2.0 was reviewed and published in December 1999.

DEVELOPMENT OF THE 2003 DIABETES MELLITUS GUIDELINE UPDATE (VERSION 3.0)

The development of the 2003 Diabetes Mellitus Guideline Update (version 3.0) was initiated in March 2002 and continued through January 2003. The development process followed the steps described in "Guideline for Guideline," an internal working document of VHA's National Clinical Practice Guideline Council, which requires an ongoing review of the work in progress.

Target Audience

This guideline is designed for primary care providers, diabetes educators, and other diabetes team specialists. While each module is designed for use by primary care providers in an ambulatory care setting, the modules can also be used to coordinate and standardize care within subspecialty teams and as a teaching tool for students and house staff.

Guideline Development Process

The Offices of Quality and Performance and Patient Care Service, in collaboration with the network Clinical Managers, the Deputy Assistant Under Secretary for Health, and the Medical Center Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD that formed the Guideline Development Working Group.

At the start of the update process, the clinical leaders, guideline panel members, outside experts, and experts in the field of guideline and algorithm development were consulted to determine which aspects of the 1999 guideline required updating. These consultations resulted in the following recommendations that guided the update efforts: (1) update any recommendations from the original guideline likely to be effected by new research findings; (2) provide information and recommendations on health systems changes relevant to diabetes care; (3) address content areas and models of treatment for which little data existed during the development of the original guideline; and (4) review the performance and lessons learned since the implementation of the original guideline.

The Working Group participated in a face-to-face session to reach a consensus about the guideline recommendations and to prepare a draft document. The draft was revised by the experts through numerous conference calls and individual contributions to the document.

Experts from the VA and DoD internal medicine, endocrinology and primary care reviewed the final draft. The draft was also reviewed by diabetes educators and other professionals involved in diabetes education teams. Their feedback was integrated into the final draft. Nonetheless, this document is a work in progress. It will be updated every two years, or when significant new evidence is published.

This 2003 Guideline Update is the product of many months of diligent effort and consensus building among knowledgeable individuals from the Veterans Administration (VA), Department of Defense (DoD), academia, and guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The list of participants is included in the introduction to the guideline update.

Formulating of Questions

The Working Group developed eighteen researchable questions and associated key terms after orientation to the seed guidelines and to goals that had been identified by the Working Group. The questions specified: (adapted from the Evidence-Based Medicine (EBM) toolbox, Centre for Evidence-Based Medicine, (http://minerva.minervation.com/cebm/)

Population – characteristics of the target patient population
Intervention – exposure, diagnostic, or prognosis
Comparison – intervention, exposure, or control used for comparison
Outcome –outcomes of interest

These specifications served as the preliminary criteria for selecting studies.

Selection of Evidence

Published, peer-reviewed, RCTs were considered to constitute the strongest level of *evidence* in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, scientifically sound basis for judging comparative efficacy. The Working Group made this decision recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. Meta-analyses that included randomized controlled studies were also considered to be the strongest level of evidence, as well as reports of evidence-based systematic reviews.

A systematic search of the literature was conducted. It focused on the best available evidence to address each key question and ensured maximum coverage of studies at the top of the hierarchy of study types: evidence-based guidelines, meta analyses, and systematic reviews. When available, the search sought out critical appraisals already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and EPC reports.

The search continued using well-known and widely available databases that were appropriate for the clinical subject. In addition to Medline/PubMed, the following databases were searched: Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials (CCTR). For Medline/PubMed, limits were set for language (English), date of publication (1999 through May 2002) and type of research (RCT and meta-analysis). For the CCTR, limits were set for date of publication (1990 through 2002).

Once definitive reviews or clinical studies that provided valid relevant answers to the question were identified, the search ended. The search was extended to studies/reports of lower quality (observational studies) only if there were no high quality studies.

Exclusion criteria included reviews that omitted clinical course or treatment. Some retrieved studies were rejected on the basis of published abstracts, and a few were rejected after the researchers scanned the retrieved citation for inclusion criteria. Typical exclusions included studies with physiological endpoints or studies of populations that were not comparable to the population of interest (e.g., studies of diabetes in children or pregnancy).

The results of the search were organized and reported using reference manager software. At this point, additional exclusion criteria were applied. The bibliographies of the retrieved articles were hand-searched for articles that may have been missed by the computer search. Additional experts were consulted for articles that may also have been missed.

Literature Review and Inclusion Criteria

As a result of the original and updated literature reviews, more than 180 articles were identified for possible inclusion. These articles formed the basis for formulating the guideline recommendations. The literature search for the guideline update was validated by: (1) comparing the results to a search conducted by the independent research and appraisal team; (2) a review of the database by the expert panel; and (3) requesting articles pertaining to special topics from the experts in the working group.

It is important to note that due to application of article screening criteria in the updated guideline, some of the studies that were included in the original guideline were not included in the updated analyses.

Preparation of Evidence Tables (reports)

A group of clinician reviewers and other researchers in health care, with experience in evidence-based appraisal, independently read and coded each article that met inclusion criteria. Each article was turned into a one-page summary of the critical appraisal by the research team and added to a central electronic database. Clinicians from the Center for Evidence-Based Practice at the State University of New York, Upstate Medical

University, Department of Family Medicine [SUNY] contributed several of the appraisal reports. Each of the evidence reports covered:

Summary of findings
Methodology
Search terms
Resources searched
Summary table of findings
Critical appraisal of each study

Quality ratings were made for each evidence using the grading scale presented in Table 4 [USTFP, 2001). The quality rating procedure used in this update was different from the rating scale used in the development of the original guideline in 1999. Where adjustments to the update process were made, articles from the original process were re-graded to reflect the changed rating scale (e.g., the level of recommendation [R] was assigned for each evidence, based on study design and significance of the quality of the evidence)

Recommendation and Overall Quality Rating

Evidence Grading System used in 1999 (version 2.0)

1a. Strength of Recommendation

Level I	Usually indicated, always acceptable and considered useful and effective.
Level IIa	Acceptable, of uncertain efficacy and may be controversial. Weight of evidence in favor of usefulness/efficacy.
Level IIb	Acceptable, of uncertain efficacy and may be controversial. May be helpful, not likely to be harmful.
Level III	Not acceptable, of uncertain efficacy and may be harmful. Does not appear in guidelines.

1b. Level of Evidence

	A	B	C
Primary Evidence	Randomized	Well designed clinical studies	Panel consensus
Secondary Evidence	Other Clinical studies	Clinical studies related to topic but not in a population with diabetes	Clinical studies Unrelated to topic

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group reviewed the evidence and graded it using the rating scheme developed by the USPSTF (2001). The experts themselves, after an orientation and tutorial on the evidence grading process, formulated Quality of Evidence ratings (see Table 1), a rating of Overall Quality (see Table 2), a rating of the Net Effect of the Intervention (see Table 3), and an overall Recommendation (see Table 4).

Evidence Grading System used in 2003 (version 3.0)

TABLE 1: Quality of Evidence (QE)

I	At least one properly done RCT
II-1	Well designed controlled trial without randomization
II-2	Well designed cohort or case-control analytic study
II-3	Multiple time series, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, case reports, and expert committees

TABLE 2: Overall Quality

Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; *or* Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

TABLE 3: Net Effect of the Intervention

Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; *or* A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *or* A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering; *or* An infrequent condition with a significant impact on the individual patient level.

TABLE 4: Final Grade of Recommendation

	The net benefit of the intervention			
Quality of Evidence	**Substantial**	**Moderate**	**Small**	**Zero or Negative**
Good	*A*	*B*	*C*	*D*
Fair	*B*	*B*	*C*	*D*
Poor	*I*	*I*	*I*	*I*

A A strong recommendation that the intervention is always indicated and acceptable
B A recommendation that the intervention may be useful/effective
C A recommendation that the intervention may be considered
D A recommendation that a procedure may be considered not useful/effective, or may be harmful.
I Insufficient evidence to recommend for or against – the clinician will use clinical judgment

Abstract of the USPSTF:

> Once assembled, admissible evidence is reviewed at three strata: (1) the individual study, (2) the body of evidence concerning a single linkage in the analytic framework, and (3) the body of evidence concerning the entire preventive service. For each stratum, the Task Force uses explicit criteria as general guidelines to assign one of three grades of evidence: good, fair, or poor.

Good or fair quality evidence for the entire preventive service must include studies of sufficient design and quality to provide an unbroken chain of evidence-supported linkages that generalize to the general primary care population and connect the preventive service with health outcomes. Poor evidence contains a formidable break in the evidence chain, such that the connection between the preventive service and health outcomes is uncertain.

For services supported by overall good or fair evidence, the Task Force uses outcomes tables to help categorize the magnitude of benefits, harms, and net benefit from implementation of the preventive service into one of four categories: substantial, moderate, small, or zero/negative.

The Task Force uses its assessment of the evidence and magnitude of net benefit to make a recommendation, coded as a letter: from A (strongly recommended) to D (recommend against). It gives an "I" recommendation in situations in which the evidence is insufficient to determine net benefit (Harris et al., 2001).

Lack of Evidence – Consensus of Experts

The majority of the literature supporting the science for these guidelines is referenced throughout the document and is based upon key RCTs and longitudinal studies published from 1992 through May 2002. Following the independent review of the evidence, a consensus meeting was held to discuss discrepancies in ratings and formulate recommendations. Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on "Working Group Consensus".

Algorithm Format

The goal in developing the guideline for diabetes mellitus was not to repeat the guideline development process, but rather, to incorporate the information from several existing, national consensus, evidence-based guidelines into a format which would maximally facilitate clinical decision-making. The use of the algorithm format was chosen because of the evidence that such a format improves data collection, diagnostic and therapeutic decision-making and changes patterns of resource use. However, few guidelines are published in such a format. To enhance continuity of care, the Diabetes Guidelines (version 1.0 and 2.0 and 3.0) were designed to encompass a broad spectrum of outpatient care of persons with diabetes. This required incorporating multiple published guidelines into a single, unified document.

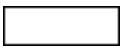
The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process, and includes:

An ordered sequence of steps of care
Recommended observations
Decisions to be considered
Actions to be taken.

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (SMDMC, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.

Rounded rectangles represent a clinical state or condition.

Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.



Rectangles represent an action in the process of care.

Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

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APPENDIX B
ACRONYM LIST

ACEI	angiotensin converting enzyme inhibitor
ACP	American Association of Diabetes Education
ADA	American Diabetes Association
AER	albumin excretion rate
AGI	alpha glucosidase inhibitor
Alb/Cr	urine albumin/creatinine ratio
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AST/ALT	aspartate amino transferase/amino alanine transferase ratio
AUDIT	Alcohol Use Disorders Identification Test
BCF	basic care formulary
BIDS	bedtime insulin daytime sulfonylurea
BMI	body mass index
BP	blood pressure
BPH	benign prostatic hyperplasia
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAGE	alcohol abuse screening test mnemonic
CCB	Calcium channel blocker
CG	Cockroft-Gault
CSII	continuous subcutaneous insulin infusion
CDC/CDCP	Centers for Disease Control and Prevention
CDE	certified diabetes educator
CHD	coronary heart disease
CHF	congestive heart failure
CHO	fast-acting carbohydrates
Clcr	creatinine clearance
COPD	chronic obstructive pulmonary disease
CVA	cerebrovascular accident
CVD	cardiovascular disease
DBP	diastolic blood pressure
DCCT	Diabetic Control and Complication Trial
DHCCB	dihydropyridine calcium channel blockers
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DN	diabetic nephropathy
DoD	Department of Defense
DPP	NIH-funded Diabetes Prevention Program
DQIP	Diabetes Quality Indicator Project
DSME	diabetes self-management education
DTR	deep tendon reflex
eGFR	estimated glomerular filtration rate
EKG	electrocardiogram
EPRP	External Peer Review Program
ESRD	end stage renal disease
ETDRS	Early Treatment Diabetic Retinopathy Study
ETOH	ethanol
FBS	fasting blood glucose
FPG	fasting plasma glucose
FY	fiscal year

g	gram
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GHb	glycosylated hemoglobin
GI	gastrointestinal
GU	genitourinary
HbA_1c	hemoglobin marker (A_1c)
HCFA	Health Care Financing Administration
HCTZ	hydrochlorthiazide
HDL	high density lipoproteins
HDL-C	high density lipoproteins - cholesterol
HMG CoA	Hydromethylglutaryl coenzyme A
HMO	health maintenance organization
HOT	Hypertension Optimal Treatment study
HPLC	high pressure liquid chromatography
HTN	hypertension
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IRMA	intraretinal microvascular anomalies
ISH	isolated systolic hypertension
JDRF	Juvenile Diabetes Research Foundation International
JNC VI	Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure
K/DOQI	National Kidney Foundation's Kidney Disease Outcome Quality Initiative
LDL	low density lipoproteins
LDL-C	low density lipoproteins-cholesterol
LE (Foot Care)	lower extremity
LE (Evidence Table)	level of evidence
LEA	lower extremity amputation
MAST	Michigan Alcohol Screening Test
MDRD	Modification of Diet in Renal Disease
mg/dL	milligrams per deciliter
MI	myocardial infarction
mmols/dL	millimoles per deciliter
MNT	medical nutrition therapy
MTF	medical treatment facility
NCBDE	National Certification Board for Diabetes Educators
NCCB	nondihydropyridine calcium channel blocker
NCEP	National Cholesterol Education Program
NCQA	National Committee for Quality Assurance
NDAB	National Diabetes Advisory Board
NGSP	National Glycohemoglobin Standardization Program
NIDDK	National Institute of Diabetes and Digestive and Kidney Disease
NIDDM	non-insulin dependent diabetes mellitus
NIH	National Institutes of Health
NNT	number needed to treat
NPH	neutral protamine Hagedorn insulin
NSAID	nonsteroidal anti-inflammatory drugs
NVD	neovascularization at the disc (eye)
NVE	neovascularization elsewhere (eye)
OGTT	oral glucose tolerance test
OQP	Office of Quality and Performance

PDR	proliferative diabetic retinopathy
PG	postload glucose
PPG	postprandial plasma glucose
PTH	parathyroid hormone
PUD	peptic ulcer disease
PVD	peripheral vascular disease
RCT	randomized controlled trial
RD	registered dietitian
SBP	systolic blood pressure
Scr	serum creatinine
SFU	sulfonylurea
SLE	Systemic Lupus Erythematosis
SMBG	self-monitoring of blood glucose
SME	self-management education
SR	strength of recommendation
SUD	substance use disorder
TC	total cholesterol
TDD	total daily dose
TG	triglycerides
TIA	transient ischemic attack
TNT	treating to new targets
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
UTI	urinary tract infection
VISN	Veterans Integrated Services Network
WESDR	Wisconsin Epidemiological Study of Diabetic Retinopathy
VA	Veterans Affairs
VHA	Veterans Health Administration

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