VA/DoD Clinical Practice Guideline

Management of Diabetes Mellitus (DM)

2010

VA/DoD Evidence Based Practice

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

With support from:

The Office of Quality and Performance, VA, Washington, DC

&

Quality Management Division, United States Army MEDCOM

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based on the best information available at the time of publication. They are designed to provide information and assist in decision-making. They are not intended to define a standard of care and should not be construed as one. Also, they should not be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in any particular clinical situation.

UPDATE - May 2010

Version 4.0

INTRODUCTION

This update of the Clinical Practice Guideline for the Management of Diabetes Mellitus was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs (VA). VHA and DoD define clinical practice guidelines as:

> *"Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes:*
>
> *Determination of appropriate criteria such as effectiveness, efficacy, population benefit, or patient satisfaction; and Literature review to determine the strength of the evidence in relation to these criteria."*

Target Audience

This guideline is designed for primary care providers, diabetes educators, and other diabetes team specialists. While the guideline is designed for 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. This guideline applies to adult patients (18 years or older) with diabetes mellitus receiving treatment in the VA or DoD health care system.

Focus of Version 4.0 of the Diabetes Mellitus Guideline

The principles of risk stratification and shared decision-making regarding glycemic control in patients with diabetes have not changed since the 2003 version of this guideline. They continue to emphasize evidence from clinical epidemiology, risk stratification and collaboration with the patient's personal preferences in developing individual target goals for glycemic control (HbA_1c).

Additionally, the VA/DoD guidelines have always emphasized the balance between benefit and harm in setting target goals. Recognizing the lack of evidence resulted in the VHA not adopting a performance measure of 'one size fits all' regarding HbA_1c target (<7%). This approach has now been validated by the results of two recently reported landmark clinical trials (ACCORD, VADT). Based on the available evidence, the current update to the guideline continues to strongly recommend that the decision for glycemic control target should be based on the individual patient's characteristics, the severity and duration of disease, and the expressed preferences of the individual patient.

Other significant updates, based on new evidence, include the following:

- Evidence based recommendations regarding Continuous Subcutaneous Insulin Infusion (CISS) and glycemic control for hospitalized patients are included in Module G.
- Self Monitoring of Blood Glucose (SMBG) recommendations are now based on recent studies that provide evidence to support previous recommendations.
- Screening and diagnosis now includes the use of the HbA_1c test. Although the guideline continues to recommend FPG as a preferred test, it suggests including HbA1c as a screening test in situations where a fasting state is not possible. However, a single HbA_1c test requires confirmation through a FPG for diagnosis of diabetes due to methodological, epidemiological and individual variations in HbA_1c test results.
- A conservative approach continues to be recommended for pharmacotherapy regarding unknown, but potential harms from recently introduced medications that do not have an extensive track record.
- The Self-Management and System Management Module (M) has been updated. New evidence addressing ways to organize and deliver diabetes care have been added. (e.g., Group visits, telemedicine, case management).
- The Eye Care Module (E) incorporates current evidence using digital imaging as a method of screening for retinopathy

- Finally, similar to the sections of the guideline addressing management dyslipidemia and hypertension, the original Module [R] - in the 2003 version -for management of renal disease has now been replaced by a summary of the recently published VA/DoD guideline for Chronic Kidney Disease (CKD).

Development Process

This VA/DoD Diabetes Mellitus guideline update builds on the 2003 version. The development process follows a systematic approach described in "Guideline-for-Guidelines," an internal working document of the VA/DoD Evidence-Based Practice Working Group that requires an ongoing review of the work in progress. Appendix A (see the full guideline) clearly describes the guideline development process followed for this guideline.

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 the Pharmacoeconomic Center (PEC) of the Department of Defense (DoD), 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 (NKF) 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 was 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.

The 2003 VA/DoD 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," just as this current version does. The Working Group updated the evidence-based action recommendations whenever possible; hence, major clinical randomized controlled trials (RCTs) and observational studies published from March 1999 through March 2002 in the areas of diabetes, hypertension, lipid management, renal disease, foot and eye care, and diabetes education were reviewed. The updated version 3.0 was reviewed and published in January 2003. Two module of the guideline (Management of Dyslipidemia and Management of Hypertension) have been replaced by a summary of two new VA/DoD full guidelines on these topics.

Development of the 2010 Diabetes Mellitus Guideline Update (Version 4.0)

The development of the 2010 Diabetes Mellitus Guideline Update (version 4.0) was initiated in January 2009 and continued through June 2010.

The Offices of Quality and Performance and Patient Care Services of the VA and the Army Medical 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 to form the Working Group (WG). For this guideline update the WG participants were drawn from the fields of primary care, endocrinology, internal medicine, nursing and diabetes education who were also from diverse geographic regions, and both VA and DoD healthcare systems.

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 2003 guideline required updating. These consultations resulted in the determinations that guided the update efforts: (1) update any recommendations from the original guideline likely to be affected 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.

After orientation to the guideline scope and to goals that had been identified, the WG developed ten (10) researchable questions within the focus area of the guideline and identified associated key terms. This ensured that the guideline development work outside of meetings focused on issues that practitioners considered important. This also produced criteria for the literature search and selection of included studies that formed the body of evidence for this guideline update.

These literature searches were conducted covering the period from January 2002 through June 2009 and focused on the topics identified by the research questions. Electronic searches were supplemented by reference lists and additional citations suggested by experts. The identified and selected studies on those issues were critically analyzed, and evidence was graded using a standardized format. The evidence rating system for this document is based on the system used by the U.S. Preventive Services Task Force (USPSTF).

If evidence exists, the discussion following the recommendations for each annotation includes an evidence table identifying the studies that have been considered, the quality of the evidence, and the rating of the strength of the recommendation which is presented in brackets following each guideline recommendation [SR] (see Table: Evidence Rating System).

Evidence Rating System

SR	
A	A strong recommendation that clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.*
B	*A recommendation that clinicians provide (the service) to eligible patients.* *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.*
C	*No recommendation for or against the routine provision of the intervention is made.* *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	*Recommendation is made against routinely providing the intervention to asymptomatic patients.* *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.*
I	*The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention.* *Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

SR = Strength of recommendation

Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations are based on the clinical experience of the Working Group. Although several of the recommendations in this guideline are based on weak evidence, some of these recommendations are strongly recommended based on the experience and consensus of the clinical experts and researchers of the Working Group. Recommendations that are based on consensus of the Working Group include a discussion of the expert opinion on the given topic. No [SR] is presented for these recommendations. A complete bibliography of the references in this guideline can be found in Appendix D to the full guideline.

This Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, and a guideline facilitator from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The draft document was discussed in two face-to-face group meetings. The content and validity of each section was thoroughly reviewed in a series of conference calls. The

final document is the product of those discussions and has been approved by all members of the Working Group.

The list of participants is included in Appendix B to the full guideline.

Implementation:

The guideline and algorithms are designed to be adapted by individual facilities in consideration of local needs and resources. The algorithms serve as a guide that providers can use to determine best interventions and timing of care for their patients in order to optimize quality of care and clinical outcomes.

Although this guideline represents the state of the art practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating of published information. New technology and more research will improve patient care in the future. The clinical practice guideline can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of clinical practice guidelines such as these may lead to the development of new practice-based evidence.

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Guideline Key Elements

Primary Prevention	• Consider **screening** all adults (age ≥45) for diabetes • Encourage **aerobic exercise and diet** to achieve weight loss and prevent the progression of prediabetes to diabetes
Secondary Prevention	• Achieve individualized **HbA_1c** target through diet, exercise, medication, and patient self-management diabetes 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 periodically for **kidney disease** • Screen for retinopathy every 12-24 months based on ophthalmic and clinical findings • 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 pneumococcal **pneumonia vaccine,** if indicated
Patient self-management & Education	• Empower patients to make informed decisions about their **self-care of diabetes**

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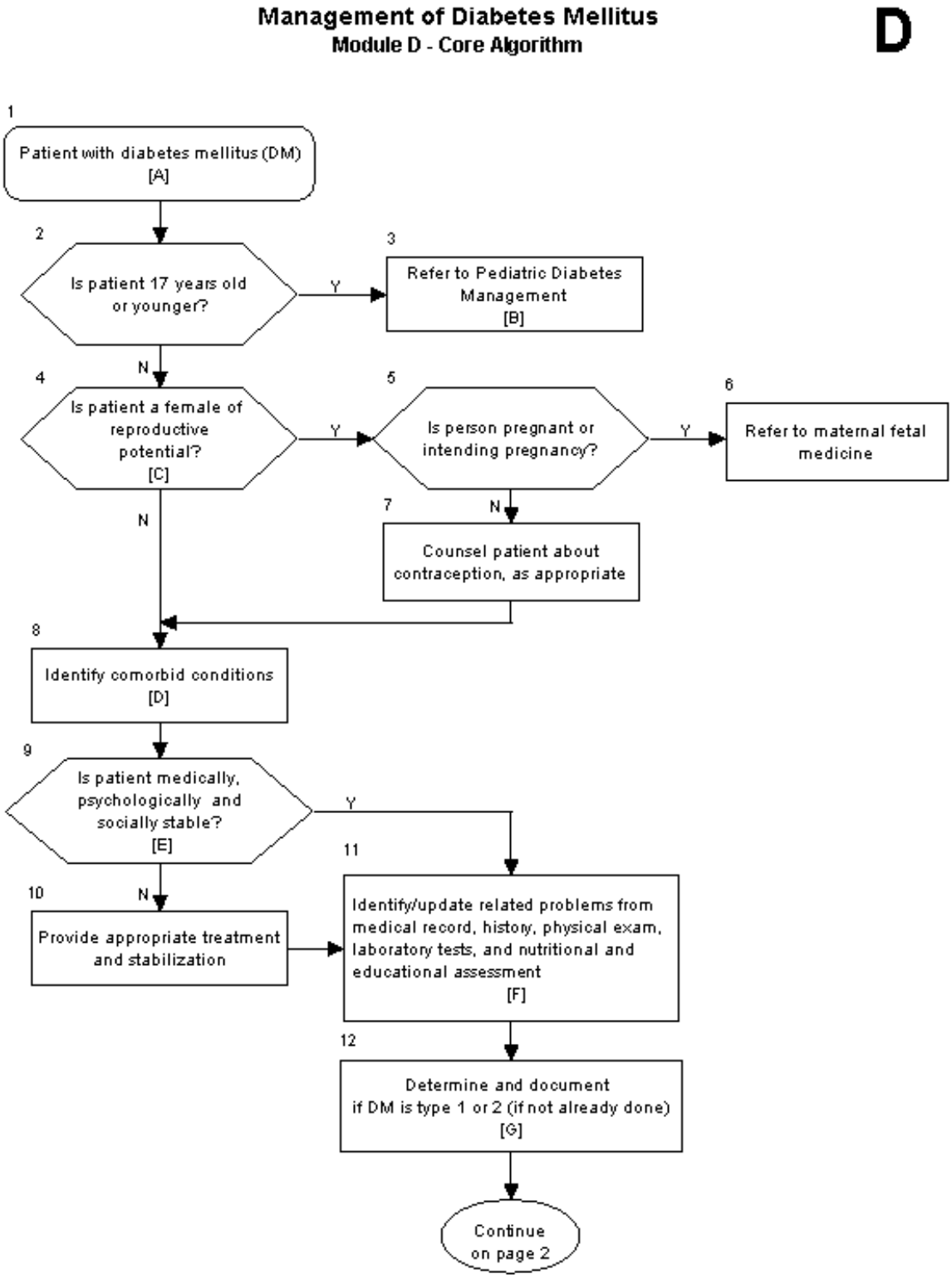
MODULE D – CORE

ALGORITHM


Management of Diabetes Mellitus
Module D - Core Algorithm
D
1
Patient with diabetes mellitus (DM) [A]
2
Is patient 17 years old or younger?
Y
3
Refer to Pediatric Diabetes Management [B]
N
4
Is patient a female of reproductive potential? [C]
Y
5
Is person pregnant or intending pregnancy?
Y
6
Refer to maternal fetal medicine
N
7
Counsel patient about contraception, as appropriate
N
8
Identify comorbid conditions [D]
9
Is patient medically, psychologically and socially stable? [E]
Y
N
10
Provide appropriate treatment and stabilization
11
Identify/update related problems from medical record, history, physical exam, laboratory tests, and nutritional and educational assessment [F]
12
Determine and document if DM is type 1 or 2 (if not already done) [G]
Continue on page 2

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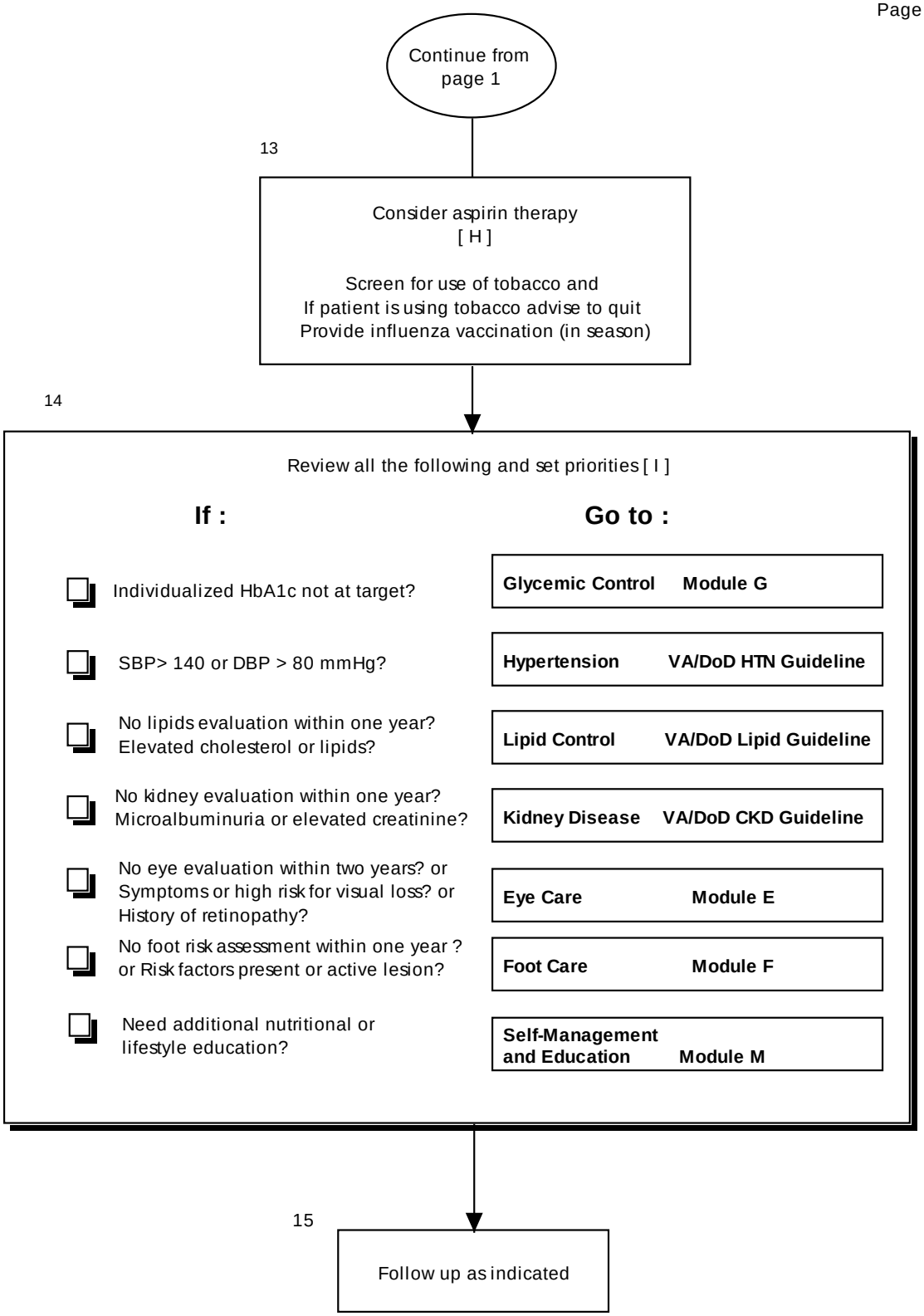
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13
Consider aspirin therapy
[H]
Screen for use of tobacco and
If patient is using tobacco advise to quit
Provide influenza vaccination (in season)
14
Review all the following and set priorities [I]
If :
Go to :
Individualized HbA1c not at target?
Glycemic 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 kidney evaluation within one year?
Microalbuminuria or elevated creatinine?
Kidney Disease VA/DoD CKD Guideline
No eye evaluation within two years? or
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MODULE D – CORE

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).

Diagnosis of Diabetes

The criteria for the diagnosis of DM include **any** of the following:

a. Fasting plasma glucose (FPG) is ≥126 mg/dL on at least two occasions; or,

b. A single HbA_1c reading of ≥ 6.5% confirmed with a FPG ≥126 mg/dL. These tests can be done on the same or different days; or,

c. HbA_1c reading of ≥ 7% on two occasions using a clinical laboratory methodology standardized to the National Glycohemoglobin Standardization Program (NGSP) not a Point of Care; or ,

d. Patient with symptoms of hyperglycemia, and a random glucose is ≥ 200 mg/dL on two occasions. However, random plasma glucose is not recommended as a routine screening test.

Oral glucose tolerance testing (OGTT) is no longer recommended in clinical practice. An individual with a casual plasma glucose level ≥200 mg/dL, but without symptoms, should have his or her fasting blood glucose measured.

The diagnostic criteria for diabetes are summarized in table D1. (See Module S: Screening for DM)

Diagnosis of Prediabetes

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes has historically been categorized as either impaired fasting glucose (IFG), or impaired glucose tolerance (IGT) depending on the methodology through which it is identified.

The criteria for diagnosis of prediabetes include **any** of the following:

a. Fasting plasma glucose (FPG) readings with result < 126 mg/dL, but ≥100mg/dL on two occasions.

b. HbA_1c readings with result ≥5.7%, with FPG ≥100 mg/dL and <126 mg/dl. The FPG can be obtained at the same time as the HbA_1c.

Additional information of the testing methodology of glycemic control can be found in Appendix G1

Table D1. Diagnosis of Diabetes Mellitus

Status	Fasting Plasma Glucose (FPG) [(a) (b)] or, Hemoglobin A_1c [(c)]	Casual Plasma Glucose [(d)]
Diabetes Mellitus	FPG ≥126 mg/dL (7.0 mmol/L) on two occasions OR HbA_1c is ≥ 6.5% **and** FPG ≥126 mg/dL (7.0 mmol/L) OR HbA_1c ≥7% on two occasions	Casual plasma glucose ≥200 mg/dL (11.1 mmol/L) plus symptoms of diabetes
Pre-diabetes	FPG ≥100 **and** <126 mg/dL on two occasions OR HbA_1c ≥ 5.7% **and** FPG ≥100 and <126 mg/dL (7.0 mmol/L)	—
Normal	FPG <100 mg/dL HbA_1c < 5.7%	—

(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 different days*

(c) *Using a clinical laboratory (not a Point of Care) methodology standardized to the National Glycohemoglobin Standardization Program (NGSP)*

(d) *Casual means any time of day without regard to time since the last meal; classic symptoms include polyuria, polydipsia, and unexplained weight loss.*

(e) *Oral glucose tolerance testing (OGTT) is no longer recommended in routine clinical practice because it is an imprecise test with poor reproducibility. 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.*

DISCUSSION

Patients with one or more of the following risk factors have a higher risk of being diagnosed with diabetes: [see also Module S: Screening, Annotation A]

Table D-2. Risk Factors for Type 2 Diabetes

- Age ≥40 years
- Family history (First-degree relative with DM)
- Member of a high-risk population (e.g. African American, Hispanic American, Native American, Asian American, and Pacific Islander)
- Prediabetes (i.e., history of impaired fasting glucose or impaired glucose tolerance tests) *
- Hypertension (blood pressure ≥140/90 mmHg)*
- 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)*
- Presence of vascular disease (coronary, cerebrovascular or peripheral)*
- Overweight or Obesity (body mass index (BMI) ≥ 25 kg/m^2)*
- Abdominal obesity*
- Women with polycystic ovarian syndrome (PCOS)*
- History of gestational diabetes mellitus (GDM)
- History of delivering babies weighing >9 pounds
- Other clinical conditions associated with insulin resistance (e.g. acanthosis nigricans, non-alcoholic steatohepatitis (NASH))
- Schizophrenia
- Patients treated with certain atypical antipsychotics or antidepressants
- Habitual physical inactivity

** Associated with insulin resistance*

B. Refer To Pediatric Diabetes Management

OBJECTIVE

Provide appropriate management for children with diabetes.

BACKGROUND

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.

RECOMMENDATIONS

1. Children with diabetes should be referred for consultative care to a pediatric diabetic team that is knowledgeable and experienced in meeting the medical, psychosocial, and developmental needs of children with diabetes.
2. The pediatric diabetic team should include a pediatric endocrinologist, if available, and/or 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.

BACKGROUND

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 before and during pregnancy.

RECOMMENDATIONS

1. All female patients with pre-existing diabetes and reproductive potential should be educated about contraceptive options, and strongly encouraged to plan and prepare for pregnancy, and to optimize their glycemic control prior to attempting to conceive.
2. Women with diabetes who are planning pregnancy should be educated about the different options of diabetes management during the pregnancy and referred to maternal fetal medicine provider before, or as early as possible, once pregnancy is confirmed.
3. Women with gestational diabetes mellitus (GDM) should be screened for diabetes 6-12 weeks postpartum and should follow-up with subsequent screening for diabetes or prediabetes (See Module S: Screening)

For management of diabetes during pregnancy – see VA/DOD clinical practice guideline for the management of pregnancy. (www.healthquality.va.gov or https://www.qmo.amedd.army.mil)

DISCUSSION

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.

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 kidney 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
- Overweight and abdominal obesity

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.

RECOMMENDATIONS

1. Urgent or semi-urgent medical conditions, including hypo- or hyperglycemia, and deficient renal function must be treated before long-term disease management principles are applied.
2. The urgency of medical treatment, including the necessity for hospitalization, will depend upon the presence of ketoacidosis, dehydration, hyperosmolarity, infections, and other life threatening conditions.
3. 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 behavioral health, social services, and case management professionals may enhance patient compliance with treatment and follow-up.
4. 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.

RECOMMENDATIONS

1. 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
2. On a follow-up visit, the evaluation should focus on updating new information and/or changes to the patient record (see Table D3 for a listing of the components of the evaluation).

Table D3. Evaluation of the Patient with Diabetes

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)	• HbA_1c • Fasting glucose
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
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
Kidney	• Known history of diabetic disease • Family history of hypertension and kidney 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

Evaluation Component	History-Patient/Family	Physical Examination	Laboratory
Coronary and Peripheral Arterial Disease/ Dyslipidemia	Atherosclerotic disease: • Myocardial infarction (MI)/angina • Stroke • 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	• Cardiac examination: • Heart • Peripheral circulation including pulses and bruits • Cutaneous or tendinous xanthomata	• Electrocardiogram (EKG) • Fasting lipid profile, if not done within the last year • Other modalities as indicated
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 patient's general knowledge and ability to adequately self-manage his or her diabetes can be assessed by asking questions such as:

- 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. (See Module M: Self-Management and Education for additional assessment tools.

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

OBJECTIVE

Determine if insulin is a necessary component of treatment for the 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.

Patients with type 1 DM may initially present with diabetic ketoacidosis (DKA). However it is not uncommon for these patients to present to primary care with hyperglycemia alone, without symptoms of ketoacidosis.

In a primary care setting, the patient's age at the time diabetes is diagnosed, plus the BMI and level of urinary ketones, and autoimmune markers are usually sufficient to classify the type of DM. In case of uncertainty a consultation with specialty care may be considered.

Table D4. 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 DM. Therefore, using age alone as a discriminator for the diagnosis of type 1 or type 2 DM may be misleading.

DISCUSSION

Because patients with type 2 or initially indeterminate DM (sometimes referred to as “atypical”, “ketosis-prone”, or “Flatbush” diabetes) can present with ketoacidosis (especially with concomitant alcohol use) they should be reevaluated after stabilization to assess continued need for insulin therapy.

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, oral agents, and/or injectable GLP-1 agonists or amylin analogs are classified as having type 2 DM.

Diagnosis of Type 1 versus Type 2 diabetes in adults presenting with ketoacidosis is challenging, especially in non-caucasian patients. Studies with good representation of Hispanics and African Americans find as many as ~50% with ketoacidosis have Type 2 DM and many can eventually be weaned of insulin. Also, patients with a history of thyroid or other autoimmune disease and patients without a family history of Type 2 diabetes are more likely to have Type 1 diabetes.

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 patients with DM 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. [A]
2. Consider beginning aspirin therapy (75 to 325 mg/day) in patients age ≥ 40 with type 2 diabetes and one or more other cardiovascular risk factors. [B]
3. Consider individual evaluation for aspirin therapy for patients age 30 to 40 with type 2 DM, with other cardiovascular risk factors, or with type 1 DM for duration of disease longer than 2 years. [I]
4. When considering the value of antiplatelet therapy, the risks of hemorrhagic stroke or gastrointestinal bleeding must be balanced against the benefits of prevention of adverse cardiovascular outcomes. [I]

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.

Five 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; Sacco et al., 2003; and Ogawa et al., 2008). 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. 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 Early Treatment Diabetic Retinopathy Study (ETDRS, 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.

Sacco et al. (2003) concluded that "low dose aspirin might be less effective in patients with DM as compared with the general population" in primary prevention of cardiovascular events. The study was suggested as inconclusive due to low statistical power. Ogawa et al. (2008) examined the efficacy of low dose aspirin for primary prevention of atherosclerotic events in Japanese patients with type 2 diabetes. There was no statistical difference in atherosclerotic events in the patients treated with low dose aspirin. However, there was a statistical difference in a prespecified subgroup analysis of atherosclerotic events in patients over age 65.

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 albumin excretion rate (AER) or monitoring of antiproteinuric treatment in such patients. They found that "treatment with 150 mg ASA daily did not have any impact on 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. Ogawa et al. (2008) found no statistically significant difference in hemorrhagic stroke or gastrointestinal bleeding between the treatment and control groups. Sacco et al. (2003) did find a statistically significant increase (1.9% in aspirin group vs. 0.2% in control group) gastrointestinal bleeding in the treatment group.

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	LE	QE	SR
1	Aspirin therapy for patients with type 2 DM and evidence of large vessel disease.	Antiplatelet Trialists' Collaboration, 1994 de Gaetano, 2001	I	Good	A
2	Aspirin therapy for patients with type 2 DM age ≥ 40 with and one or more other cardiovascular risk factors	Antiplatelets Trialists' Collaboration, 1994 de Gaetano, 2001 EDTRS, 1992 Ogawa et al., 2008 Sacco et al., 2003	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

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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. Measure blood pressure on every diabetes visit. If systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) is $\geq$90 mmHg, refer to the VA/DoD Clinical Practice Guideline for the Management of **Hypertension. (Also see Annotation J)**
3. Measure fasting lipids (TC, HDL-C, TG and calculated LDL-C) if not done within one year. If 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. Screen for proteinuria and assess kidney function if not done within one year. If the patient develops micro- or macroalbuminuria or decline in estimated glomerular filtration rate (eGFR), refer to the VA/DoD Clinical Practice Guideline for the Management of **Chronic Kidney Disease (CKD). (Also see Annotation L)**
5. Screen for retinopathy if not done within two years. If the patient has symptoms, or a previous exam showed a high-risk for visual loss or retinopathy, refer to **Module E – Eye Care**.
6. Complete a foot-risk assessment if not done within one year. If 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. (See CDC recommendations)
9. Administer pneumococcal **pneumonia vaccine,** if indicated. (See CDC recommendations)
10. If the patient is using tobacco, refer to the VA/DoD Clinical Practice Guideline for the Management of **Tobacco Use Cessation.**

J. Management of Hypertension in Diabetes Mellitus

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

Patients with Diabetes with SBP ≥140 or DBP ≥90 mm Hg

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 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.

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 DM.

RECOMMENDATIONS

1. Patients with diabetes with hypertension (systolic BP≥140 or diastolic BP ≥90 mmHg) should:
    a. Begin anti-hypertensive therapy with angiotensin converting enzyme inhibitor (ACEI) or a diuretic [A]
    b. If ACEI induced side-effects occur, consider switching to an angiotensin receptor blocker (ARB) [A]
    c. Use other preferred agents (beta blockers, long acting calcium channel blockers) as necessary, depending on other co-morbid conditions or compelling indications to achieve a blood pressure <140/80 mm Hg. [A]
2. Patients with diabetes with initial SBP <140 mmHg and DBP between 80 and 89 mmHg (within the "pre-hypertensive" category identified by JNC 7) may benefit from lowering diastolic blood pressure to < 80 mm Hg. [A]
3. Individuals with diabetes whose blood pressure is <140/80 mmHg who have clinical cardiovascular disease may benefit from ACEI therapy even without a reduction in blood pressure. [A]
4. In patients with diabetes and kidney insufficiency (i.e., eGFR < 60 mL/min/1.73m^2) and proteinuria (i.e., >1 g/24h) there are some data suggesting that further BP lowering (<125/75 mm Hg) may 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. [B]

Table D5. Target Level for HTN based on Comorbidity [JNC-7, 2004]

Condition	Target SBP/DBP (mm Hg)	Level of Evidence (LE, SR)	Resource
Hypertension	<140/90	<150/90 (I, A) <140/90 (II, B)	SBP: SHEP, Syst-Eur DPB: HDFP, HOT
Diabetes	<140/80	(I, A)	UKPDS, HOT
DM + Nephropathy	<140/80	(I, A)	IDNT RENAAL MDRD
Chronic Kidney disease	<140/90	<140/90 (I, A) <130/80 (III, C)	AASK
Proteinuria >1g/day	<125/75	(III, C)	Post analyses MDRD

LE = Level of Evidence; SR = Strength of Recommendation (see Appendix A)

The VA/DoD Hypertension Guideline recommends a **minimal** target threshold that is based on level IA evidence derived from randomized clinical trials. For persons with diabetes this is 140/80 mm/Hg, and for persons without diabetes 140/90 mm/Hg. The VA/DOD Hypertension Guideline also acknowledges that there are data from multiple observational studies, including pooled data from randomized clinical trials (level IIA evidence) demonstrating that lower blood pressure levels are associated with risk reduction for adverse outcomes; the relationship is linear without a threshold. Consequently, clinicians are encouraged to set target values for each patient **based upon their individual circumstances**, including tolerance of medications.

K. Management of Dyslipidemia in Diabetes Mellitus

For complete management of dyslipidemia see: VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Dyslipidemia at http://www.healthquality.va.gov or http://www.qmo.amedd.army.mil

Patients with Diabetes and Elevated Cholesterol or Lipids (Dyslipidemia)

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 with fasting lipid profile (triglycerides and HDL-C or LDL-C).
2. Patients with Type 2 DM are at significant increased risk of CVD compared with non-diabetic patients of similar age and should, therefore, be treated more aggressively according to secondary prevention protocols. [A]

LDL-C Target in patients with History of CHD or CVD equivalent (DM with or without other risk factors)

5. LDL should be lowered to less than 100 mg/dL for patients with previous documented CHD or CVD equivalent (DM with other major risk factors) for secondary prevention. [A]
6. LDL should be lowered to less than 130 mg/dL for patients with DM without other major risk factors for secondary prevention. [C]
7. 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.
8. 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 and addressed.

9. Statin drug therapy should be initiated for patients with previous documented CHD or CVD equivalent (diabetes with other major risk factors) if baseline LDL-C is greater than or equal to 100 mg/dL. [A]
10. Statin drug therapy should be initiated for patients with documented DM with no major risk factors if baseline LDL-C is greater than or equal to 130 mg/dL. [C]
11. Statin drug therapy should be considered for all patients with CHD or CVD equivalent (diabetes with other major risk factors) regardless of LDL-C baseline. [B]

Table D-6. Dyslipidemia Therapy Thresholds and Goals

	Risk Category	Disease Status or Risk Factors	Calculated 10-Year Risk	TLC	LDL-C Level for Considering Statin Drug Therapy	LDL Goal of Therapy
Secondary Prevention	Very high	Recent ACS	N/A	All	All	<100 mg/dL <70 optional
		CHD or DM with other risk factors	N/A	All	≥100 mg/dL	<100 mg/dL
		DM with no other risk factors	N/A	All	≥130 mg/dL 100-129 optional	<130 mg/dL
Primary Prevention	High	More than 2 RF	≥ 20%	All	≥130 (or HDL <40) 100-129 optional	<100 mg/dL
	Intermediate	More than 2 RF	15-20%	All	≥ 130 mg/dL	<130 mg/dL
			10-14 % *	All	≥ 160 mg/dL	<130 mg/dL
	Low	0 or 1 RF	N/A	All	≥190 mg/dL	<160 mg/dL
LDL-C reduction of 30-40 percent from baseline may be considered an alternative therapeutic strategy for patients who cannot meet the above goals.						

N/A = Not applicable; TLC = Therapeutic Lifestyle Changes; RF = Risk Factor; ACS = Acute Coronary Syndrome
* There is insufficient evidence at this time to recommend routine screening for other risk markers not included in the risk index (e.g., FH, hsCRP, metabolic syndrome, depression), or evidence of significant atherosclerotic burden (e.g., high coronary artery calcification scores, intima medial thickness, abnormal brachial reactivity, or abnormal ankle-brachial index). These risk markers may be useful in the intermediate risk patient for whom it is less convincing that drug therapy would have a meaningful impact on outcomes.

TREATMENT:
Appropriate lipid lowering therapy should be initiated based on LDL-C baseline level and other risk factors for CVD.

NON- PHARMACOTHERAPY

12. Therapeutic lifestyle changes (TLC) should be recommended for ALL patients with dyslipidemia, regardless of risk or baseline LDL-C level. [C]
13. For secondary prevention of recurrent CVD events, non-pharmacologic therapy is always indicated, but it should not delay appropriate pharmacotherapy.
14. Emphasis on TLC is an important component of primary prevention and is effective in reducing CVD risk by lowering LDL-C and blood pressure. [B]
15. Diet intervention should be the first step in lipid lowering therapy. [B]
16. Patients whose initial treatment is TLC should be given 3-6 months of dietary therapy prior to beginning medication and longer, if lipids are improving and nearing LDL thresholds. [B]
17. TLC is provided in a step-wise approach focused on initiating TLC components and followed by subsequent evaluation of the effect on LDL-C and moving to intensify MNT as indicated.

LIPID PHARMACOTHERAPY:

18. Statins are first line agents in primary and secondary prevention of CVD regardless of HDL-C or TG level. [A]
19. Moderate doses of formulary statins (to achieve an LDL-C reduction of 25% or greater) should be initiated unless a patient is considered to be at greater than usual risk for adverse events from statins (e.g., myopathy). [A]
20. For patients who cannot tolerate statins, niacin or resins should be considered for treatment. [A]
21. There is insufficient clinical outcome evidence to recommend ezetimibe monotherapy for reduction of CV risk. [I]
22. Ezetimibe can be considered for lowering LDL-C in patients who are unable to tolerate other lipid-lowering drugs, or in combination with other drugs. [A]
23. The dose of statin should be adjusted at 6 to 12 week intervals until individual LDL-C goals are achieved or statin doses have been maximized. [I]

Isolated Hypertriglyceridemia

24. Niacin, fibrates, or fish oil (omega-3 fatty acids) supplements may be used in treatment of isolated hypertriglyceridemia. [B]

Isolated Low HDL-C

25. For secondary prevention gemfibrozil or niacin may be used in patients with isolated low HDL-C and normal LDL-C. [A-Gemfibrozil; B-Niacin]

Table D-7. Dyslipidemia Drug Therapy

	Drug	Expected Change in Lipoprotein *	
↑ LDL-C			
		LDL-C	
Initial	Statins	-22 to -60%	
Alternate	Niacin	-15 to -25%	
	Bile acid resin	-10 to -27%	
	Ezetimibe	-18% to –20%	
↑ LDL-C and ↑ TG			
		LDL-C	**TG**
Initial	Statins	-22 to -60%	-6 to -30%
	Niacin	-15 to -25%	-20 to -50%
Alternate	Fibrates	+10 to -35%	-20 to -50%
↑ LDL-C and ↓ HDL-C			
		LDL-C	**HDL-C**
Initial	Statins	-22 to -60%	+2 to +12%
	Niacin	-15 to -25%	+15 to +30%
Alternate	Fibrates	+10 to -20%	+10 to +20%

*** Considerations:**

Statins Statins are contraindicated in active liver disease, in those persons with persistent elevation of liver transaminases, and in pregnancy.

Niacin Niacin is contraindicated in hepatic disease and relatively contraindicated in gout or history of complicated/active peptic ulcer disease (PUD). Use niacin with caution in patient with diabetes, since it may alter glucose control.

Resins Resins may increase TG and can reduce the absorption of many drugs. Therefore, other drugs should be administered 1 hour before or 4-6 hours after administration of the resin.

Fibrates Fibrates are contraindicated in severe renal or hepatic disease, including primary biliary cirrhosis and preexisting gallbladder disease.

Ezetimibe Maximum LDL-C lowering effect should be apparent within 2 weeks of initiation of treatment.

L. Management of Kidney Disease in Diabetes Mellitus

For complete management of Chronic Kidney Disease (CKD) see: VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Chronic Kidney Disease at http://www.healthquality.va.gov/ or http://www.qmo.amedd.army.mil

BACKGROUND

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 or a kidney transplant. However, progressive kidney failure can be prevented or delayed through early intervention and appropriate management. 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).

CKD is defined as the presence of decreased eGFR or proteinuria, which can occur together or independently, or the presence of microalbuminuria in patients with diabetes or structural kidney disease. The presence of proteinuria may indicate kidney disease even with a normal eGFR. Any of these patients has kidney disease that might progress to kidney failure.

Patients with diabetes who develop nephropathy are referred in this guideline as having chronic kidney disease (CKD) and should be managed according to the VA/DoD Clinical Practice Guideline for Chronic Kidney Disease.

RECOMMENDATIONS

SCREENING FOR CKD

1. Patients with, diabetes, should be screened periodically for the presence of kidney disease. [C]
2. Testing for kidney disease includes urinalysis and estimation of the glomerular filtration rate (eGFR). [B]
3. Patients with diabetes who have a negative urine protein by dipstick should be tested for the presence of microalbuminuria. [B]
4. Definitions of Chronic Kidney Disease includes any of the following:
    a. Persistent decreased eGFR < 60 ml/min/1.73m^2 on two tests at least three months apart
    b. Proteinuria (> 1+) on dipstick or urine protein-to-creatine ratio > 0.2, confirmed on two tests at least three months apart
    c. Microalbuminuria defined as albumin-to-creatine ratio > 30, confirmed on two out of three urine tests in patients with diabetes mellitus (DM)
    d. Known structural kidney disease defined by imaging or pathologic examination (e.g., polycystic kidney disease [PCKD])
    e. Estimated glomerular filtration rate (eGFR) is the preferred method to assess kidney function.
5. The severity of CKD should be classified based on the level of the glomerular filtration rate (GFR) (see Table D-9). Kidney function should be assessed by formula-based estimation of GFR (eGFR), preferably using the 4-variable Modification of Diet in Renal Disease (MDRD) equation. [A]

SCREENING for PROTEINURIA

6. Microalbuminuria – in patients with diabetes – should be assessed using a laboratory method expressed as an albumin-to-creatinine ratio. If dipsticks designed to detect urinary microalbumin are used, positive tests should be followed by laboratory confirmation.
7. The diagnosis of microalbuminuria cannot be reliably made in the presence of an acute medical condition. As far as it is practicable, the best possible metabolic control of diabetes should be achieved before evaluating for microalbuminuria. Patients should not be screened during intercurrent illness or after heavy exercise.
8. It is important to consider other causes of increased albumin excretion, especially in the case of Type 1

diabetes present for < 5 years. In addition to the previously mentioned conditions, other causes can include menstrual contamination, vaginal discharge, uncontrolled hypertension, and heart failure.

9. A 24-hour urine collection for protein and creatinine is not needed for quantitation of proteinuria, as it is more cumbersome for patients and prone to collection errors.
10. 24-hour urine collection may be considered for: pregnant women, extreme age and weight, malnutrition, skeletal muscle disease, paraplegia or quadriplegia, patients with a vegetarian diet and rapidly changing kidney function.

Table D-8. Definitions of Abnormalities in Albumin Excretion

Condition	**Random Urine for Alb/Cr Ratio** (mg/gr creatinine)
Normal	<30
Microalbuminuria	30 - 300
Macroalbuminuria	≥300

ASSESSMENT AND DIAGNOSIS

Obtain Serum Creatinine and Estimate Glomerular Filtration Rate (eGFR)

11. Serum creatinine level should be used to estimate the GFR to identify patients at risk and develop appropriate management plans.
12. 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).
13. 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.
14. 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 kidney 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 if the 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 screen for 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
    - Consider obtaining other tests and referral to specialists in nephrology or urology as indicated.

Table D-9. 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.

Referral to Nephrology

15. Nephrology consultation for help in diagnosis and treatment is indicated in:
    a. Patients with eGFR < 30 ml/min/1.73m2) to facilitate education and planning for renal replacement therapy (dialysis or kidney transplant).
    b. Patients with kidney function that is deteriorating rapidly (e.g., eGFR decline of 50 percent eGFR from previous measure over 6 months or less).
    c. Patients with metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism).
    d. Patients with CKD of unclear etiology after the initial work up, or a known or suspected kidney condition requiring specialized care (e.g., a glomerulonephritis).

TREATMENT

Strategies to Slow the Progression of the Disease

16. Treatment of high blood pressure in DM-CKD should include identification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease and development of cardiovascular disease.
17. Antihypertensive therapy should be adjusted to achieve blood pressure of < 130/80 mm Hg. [C]

NON PHARMACOLOGIC INTERVENTIONS

18. All patients with CKD with hypertension should be offered life-style advice, including maintenance of normal body weight (body mass index 18.5 to 24.9 kg/m2), reduction in dietary sodium intake (< 2 g/day), regular aerobic physical exercise, smoking cessation, and limitation of alcohol intake. [B]
19. There is insufficient evidence to recommend the routine implementation of a low protein diet (< 0.6g/kg/day) to slow the loss of GFR in patients with CKD. [D]
20. A low protein diet may delay the onset of uremic symptoms in patients close to needing dialysis but this benefit must be weighed against the risk of protein malnutrition. [B]

PHARMACOLOGIC INTERVENTIONS

21. ACEIs or ARBs are the preferred agent for patients with kidney disease and hypertension. ACEIs may be

preferred based on cost. ARBs may be substituted for patients with an ACEI induced cough. [A]

22. Many patients will require two or more medications to achieve their target blood pressure control. A diuretic should be used when a second blood pressure medication is needed, or if hyperkalemia occurs. Thiazide diuretics may be used if estimated GFR > 30 ml/min/1.73m^2, but loop diuretics are usually needed for patients with lower eGFR. Potassium-sparing diuretics should be used with caution in patients with CKD.

23. An increase of serum creatinine, as much as 30 percent above baseline, after ACEI or ARB initiation is common. ACEIs or ARBs should not be discontinued for this situation, since these medications are renoprotective.

24. Patients with refractory hypertension, defined as inability to achieve goal blood pressure despite combination therapy with three drugs from complementary classes (including a diuretic), may benefit from an evaluation by a specialist in hypertension.

USE OF AN ACEI OR ARB

25. Patients with non-DM CKD with hypertension or diabetes with macroalbuminuria should be treated with an ACEI or ARB to slow the progression of kidney disease [A] and reduce proteinuria [A].

26. Patients with diabetes and microalbuminuria should be treated with an ACEI or ARB to slow the progression from microalbuminuria to macroalbuminuria, considered a surrogate for progression to CKD. [A]

27. ACEIs and ARBs should be initiated at low doses and titrated to moderate to high doses as used in clinical trials. [A]

28. There is insufficient evidence to recommend combination therapy with an ACEI and ARB to slow the progression of kidney disease except in a limited population of non-DM CKD. [I]

29. Creatinine and potassium levels should be monitored one to two weeks after initiation or after a change in dose of ACEI or ARB therapy and periodically to maintain a normal range. [C]

30. Treatment with an ACEI or ARB should not be initiated in patients with hyperkalemia (> 5.5). [D]

31. People who develop cough on an ACEI should be switched to an ARB. Some people who develop angioedema on an ACEI may be switched to an ARB but require careful monitoring since some may also develop angioedema on an ARB. [C]

32. In most patients, an ACEI or ARB should be continued unless:

    a. There is an acute GFR decline of > 30 percent within the first two weeks after initiation. [B]
    b. Serum potassium is $\geq$ 6 mEq/L, despite appropriate treatment. [B]

FOLLOW-UP MONITORING

33. Patients with CKD should be monitored for complication of CKD: disorders of potassium balance, calcium and phosphate metabolism, acid base abnormalities, hematologic abnormalities, volume overload, and exposure to nephrotoxic drugs.

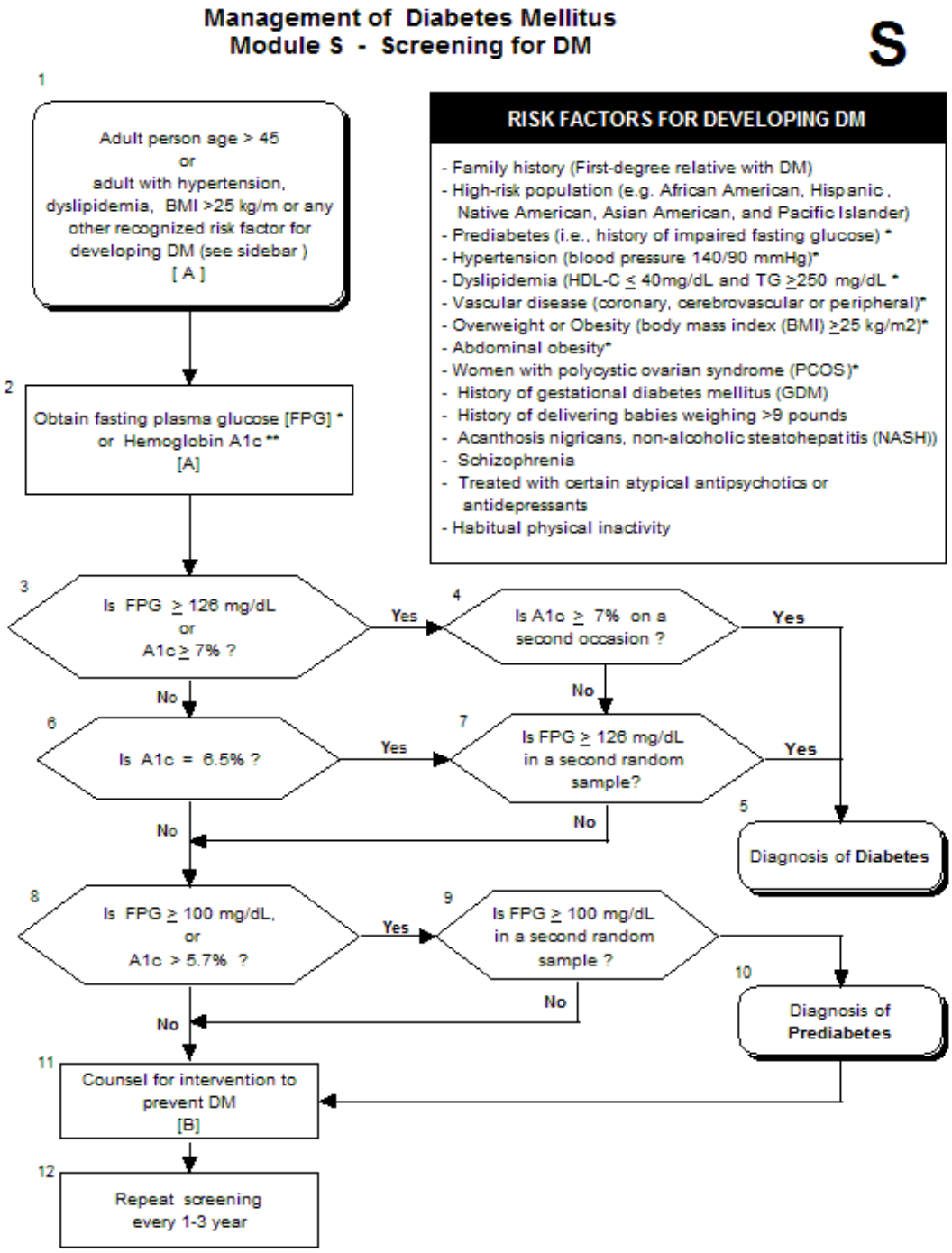
34. Patients may benefit from a dietary evaluation by a medical nutrition therapist and should be advised about a healthy diet and the preferred range of sodium, phosphate, and potassium in their diet. [C]

35. Patients with CKD and an eGFR > 30 ml/min/1.73m2 with no associated co-morbidities should be followed up every 6 to 12 months.

36. Patients with more advanced CKD should be referred to a nephrologist for consultation and/or continued follow-up.

MODULE S - SCREENING FOR DIABETES

ALGORITHM



Note:
* Fasting plasma glucose (FPG] is the preferred test. Random non-fasting plasma glucose is not recommended as first line screening. 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 FPG test.
** A1c should be measured using a clinical laboratory methodology (but NOT point of care) standardized to the National Glycohemoglobin Standardization Program [NGSP]

9/2/2010

MODULE S: SCREENING 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 pre-diabetes and diabetes mellitus can be identified on the basis of numerous, readily identifiable risk factors. It is uncertain whether early identification of pre-diabetes or early onset DM directly impacts morbidity or mortality, but awareness of glycemic status can influence the priority and/or intensity of therapies offered and the surveillance of complications.

RECOMMENDATIONS

1. Screening for pre-diabetes or diabetes should be considered for all adults age ≥45. [B]
2. Screening for pre-diabetes or diabetes should be considered in younger adults who are overweight or obese (BMI ≥ 25 kg/m^2) or are at high risk for DM based upon established risk factors (see Table S-1) at 1-3 year intervals. [B]
3. Screening for pre-diabetes or diabetes should occur at a frequency of 1-3 years. More frequent screening can be performed depending upon prior HbA_1c or FPG results, and patient or clinician preferences. [I]
4. Fasting plasma glucose (FPG) is the preferred diagnostic test for pre-diabetes and DM and is also a component of diagnostic testing.
5. HbA_1c can be used to screen for pre-diabetes or diabetes, when obtaining a blood sample in a fasting state is undesirable, but fasting plasma glucose test is required for the purpose of diagnosis. [B] The HbA1c test should be performed using clinical laboratory methodology standardized to the NSGP (not a Point of Care).
6. A diagnosis of DM is made if any of the following: [B]
    a. Fasting plasma glucose (FPG) is ≥126 mg/dL on at least two occasions, or
    b. A single HbA_1c reading of ≥ 6.5%, **confirmed** with a FPG ≥126 mg/dL. These tests can be done on the same or different days; or
    c. HbA_1c is ≥ 7% on two occasions using a clinical laboratory methodology standardized to the NSGP (not a Point of Care); or
    d. Symptoms of hyperglycemia and a casual (random) glucose ≥ 200 mg/dL on two occasions. However, casual (random) plasma glucose is not recommended as a routine screening test.
7. A diagnosis of pre-diabetes is made if any of the following: [B]
    a. Fasting plasma glucose (FPG) readings with result < 126 mg/dL, but ≥100mg/dL on two occasions.
    b. HbA_1c readings with result ≥5.7%, and **confirmed** with a FPG ≥100 mg/dL and <126 mg/dl. The FPG can be obtained at the same time as the HbA_1c.
8. Although the oral glucose tolerance test can also be used for the diagnosis of diabetes, it's is not recommended in the primary care setting. [C]
9. Random plasma glucose is not recommended as a routine screening test. [C]

Table S-1. Risk Factors for Type 2 Diabetes

- Age ≥ 40 years
- Family history (First-degree relative with DM)
- Member of a high-risk population (e.g. African American, Hispanic American, Native American, Asian American, and Pacific Islander)
- Prediabetes (i.e., history of impaired fasting glucose or impaired glucose tolerance tests) *
- Hypertension (blood pressure ≥140/90 mmHg)*
- 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)*
- Presence of vascular disease (coronary, cerebrovascular or peripheral)*
- Overweight or Obesity (body mass index (BMI) ≥ 25 kg/m^2)*
- Abdominal obesity*
- Women with polycystic ovarian syndrome (PCOS)*
- History of gestational diabetes mellitus (GDM)
- History of delivering babies weighing >9 pounds
- Other clinical conditions associated with insulin resistance (e.g. acanthosis nigricans, non-alcoholic steatohepatitis (NASH))
- Schizophrenia
- Patients treated with certain atypical antipsychotics or antidepressants
- Habitual physical inactivity

** Associated with insulin resistance*

RATIONALE

The use of HbA_1c for screening and diagnosis has been the subject of several consensus-based reports in the past year. The VA-DoD Guidelines differ from these reports by recommending that an HbA_1c test between 5.7% and 6.9% should be confirmed with a fasting blood glucose test for the purpose of diagnosis. This recommendation is based upon the following factors: (1) Even using the National Glycohemoglobin Standardization Program (NGSP) "gold standard" in a research setting, the HbA_1c is higher in older individuals and non-Caucasians patients than Caucasians for any traditional tests of glycemia. (2) In practice, even tests performed using clinical laboratory methodologies standardized to the NSGP may not be accurate enough to distinguish an absolute 0.5% difference between two HbA_1c test results. High performance Liquid Chromatography (HPLC) methods tend to have a high bias and the immunoassays tend to have a low bias. (3) Other co-morbid conditions such as, anemia, and chronic kidney disease may impact HbA_1c results. Thus, the positive and negative predictive value of HbA_1c testing may differ by methodology, age, race, and by comorbid conditions. Although an HbA_1c test has a practical advantage over FPG for screening given the fact that fasting is not necessary, reliance totally upon HbA_1c testing for diagnosis is tempered by the current lack of precision in practice.

While there is a continuous risk of developing diabetes that extends well into the normal range, i.e. a FPG below 100 mg/dl (or an HbA_1c <5.7%), the current evidence suggests that those with a FPG between 100-126 mg/dl have the highest risk for developing DM and consequently should be diagnosed as having "pre-diabetes".

DISCUSSION

Diabetes (DM) is becoming more common in the United States. From 1980 through 2006, the number of Americans with DM tripled. In 2008, DM affected nearly 24 million people in the United States, nearly 8 percent of the population. People aged 65 years or older account for approximately 37% of the population with DM. Nearly a quarter of patients with DM are unaware that they have the disease. DM is the seventh leading cause of death in the country and can cause serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations. The microvascular complications of DM can begin to appear 3 to 5 years after onset of the disease, and their incidence and prevalence increase throughout the duration of the disease.

According to the CDC (1998), 57 million people are estimated to have pre-diabetes, i.e. IFG or IGT. Progression to DM is typical. DM is present for about 10 years prior to its diagnosis in unscreened populations. At the time of diagnosis of type 2 DM, up to 20 percent of patients have retinopathy and as many as 10 percent have nephropathy. Macrovascular complications occur variably owing to individual risks, in addition to DM. There is evidence from the UK Prospective Diabetes Study (UKPDS 24, 1998) that the natural history of type 2 DM includes worsening glycemic control over time, despite intensification of drug therapy. There is evidence from the Diabetes Prevention

Program (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. Since diet and exercise are the mainstays of treatment for both pre-diabetes and diabetes, earlier efforts to improve healthy behaviors are viewed as being beneficial. However, whether or not earlier pharmacological treatment of glycemia will improve outcomes is not known (USPSTF, 2008).

HbA_1c can be used to screen for pre-diabetes or DM, but the diagnosis should be confirmed by other means. On the whole, HbA1c has a slightly lower sensitivity but higher specificity than the fasting plasma glucose (FPG) in detection of diabetes. A review of the accuracy of HbA_1c in screening for DM suggested an optimum cut off point of HbA_1c is $\geq$6.2% (Bennett et al., 2007), although population -specific factors (e.g. age, gender, ethnicity, and prevalence of diabetes) affect the test's sensitivity and specificity.

In general, there is a good correlation between HbA_1c and other measures of glycemia, and their association with complications of chronic hyperglycemia. For example, incidence of diabetic retinopathy can be predicted with HbA_1c, fasting plasma glucose (FPG), or the 2-hour plasma glucose during an oral glucose tolerance test (OGTT) (Engelgau et al., 1997; Rushforth et al., 1975). However, HbA_1c may overestimate glycemic burden, based upon traditional measures of glycemia, in certain populations. An analysis of participants in the DPP concluded that HbA_1c levels were higher in non-white participants, compared to whites, limiting the ability to compare glycemic control across these groups (Herman et al. 2007). Evidence from the Framingham Offspring Study (FOS) and the National Health and Nutrition Examination Survey (NHANES) 2001–2004 demonstrated that HbA_1c levels are positively associated with age in non-diabetic populations even after exclusion of subjects with IFG and/or IGT (Pani et al., 2008).

Methods used to measure HbA1c include electrophoresis, boronate-affinity chromatography, immunoassay, and cation-exchange high performance liquid chromotography (HPLC). HbA_1c values are influenced by red cell survival and, in some assays, abnormal hemoglobins (such as HbF and HbS). Falsely high values may be seen in iron, vitamin B12, or folate deficiency anemias. Rapid red cell turnover leads to falsely low HbA_1c values, e.g. patients with hemolysis, or those treated for nutritional deficiencies or with erythropoeitin. HbA_1c values may be falsely elevated or decreased in those with chronic kidney disease. The presence of increased amounts of HbF causes an underestimation of HbA1c by immunoassay. The National Glycohemoglobin Standardization Program (NGSP) website (www.ngsp.org) contains current information about substances that interfere with HbA_1c test results. Note that in order for a 0.5% change in HbA_1c to be considered significant the assay's coefficient of variation (CV) must be <3%, ideally <2%. Many, but not all, individual laboratory assay methods can meet this criterion. However, there are some methods that could lead to over diagnosis of diabetes. For example, high performance liquid chromatography (HPLC) methods tend to have a high bias and the immunoassays tend to have a low bias. The performance characteristics of CLIA-waived HbA_1c tests (i.e., Point of Care testing) may have more substantial assay CV, and for that reason are not permitted for screening or diagnosis.

There are no published studies demonstrating a negative impact on patients from a false-positive diagnosis of diabetes. While patients who exceed the threshold levels used in diagnosing DM are at greater risk for complications, the health risks associated with hyperglycemia are continuous. Nonetheless, appropriate diligence should be applied when translating results from screening tests to a diagnosis of DM as certain populations may be affected by emotional distress and /or effects on employability, for example the veteran with an underlying anxiety disorder or the active duty member pending deployment or career advancement. The unintended consequences of systematic misdiagnosis (higher false positive rates) of DM for population health are not known at this time. Regardless, intensifying lifestyle therapy, considering metformin for first line therapy, and treatment of associated risk factors would still be recommended.

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	Determine glycemic status based on risks	USPSTF, 2008 ADA, 2009 CDA, 2008 Waugh et al., 2007 Feig et al., 2005	I III III I I	Fair	B
2	Screening of asymptomatic persons age ≥45 for DM.	Centers for Disease Control and Prevention (CDC), 1998 Rao, 1999 Tuomilehto et al., 2001	II-2	Good	B
3	Screening of persons with DM risk factors.	American Diabetes Association (ADA), 2002 Working Group Consensus	III III	Fair Poor	C
4	FPG - preferred for screening test and diagnose DM or pre-diabetes	ADA, 2009 Engelgau et al., 2000	III II-3	Good	B
5	HbA_1c for screening	Bennett et al., 2007 Herman et al., 2007	I I	Fair	B
6	HbA_1c predicts retinopathy	Engelgau et al., 1997 Rushforth et al., 1975	II-2 II-2	Good	B
7	HbA_1c disparities based on race	Herman et al., 2007	II-2	Good	B
8	HbA_1c affected by age	Pani et al., 2008	II-2	Good	B
9	HbA_1c variation	www.ngsp.org	II-3	Fair	C

LE= Level of Evidence; QE = Quality of Evidence; SR =Strength of Recommendation (see Appendix A)

B. Prevention of Diabetes

OBJECTIVE

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

BACKGROUND

Individuals with pre-diabetes 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 pre-diabetes. In addition, numerous studies have shown that a variety of pharmacologic interventions can prevent progression to diabetes.

RECOMMENDATIONS

1. Patients with pre-diabetes should be counseled about the risks of progression to diabetes and the rationale for implementing preventive strategies. [A] Individuals with risk factors for diabetes who are not diagnosed with pre-diabetes should also be counseled and educated about how to reduce risks.
2. Lifestyle modifications to prevent diabetes, including regular aerobic exercise and a calorie-restricted diet to promote and maintain weight loss, should be instituted in patients with pre-diabetes. [A]
3. An individualized goal to achieve and sustain weight loss of ≥ 5 percent of body weight should be set for patients with risk factor for diabetes and a BMI ≥ 25. [A]
4. When lifestyle modifications have been ineffective at preventing a sustained rise in glucose, the patient may be offered pharmacologic therapy with a metformin or an alpha-glucosidase inhibitor (e.g., acarbose) to delay progression from pre-diabetes to a diagnosis of diabetes. [A]

DISCUSSION

There is evidence in patients with diabetes that both duration and severity of hyperglycemia increase risk for microvascular and perhaps macrovascular complications (UKPDS 1998, DCCT, 1993). Up to 20-50% of patients with newly diagnosed with DM have microvascular disease (UKPDS, 1998). Treatment of hyperglycemia reduces the increased risk of complications (DCCT, 1993; UKPDS-33, DCCT/EDIC). However, treatment of pre-diabetes, which may delay the diagnosis of diabetes, has not been shown to affect microvascular or macrovascular disease. The diagnosis of pre-diabetes and DM are, by convention, dichotomous but risks associated with hyperglycemia are continuous.

There is evidence from the DPP (Knowler et al., 2002) that persons with pre-diabetes who participate in intensive lifestyle modification including regular aerobic exercise and calorie-restricted diet and achieve a sustained weight loss, develop DM at a lower rate than untreated individuals. In addition, a meta-analysis (Yamaoka & Tango, 2005) showed that in patients with pre-diabetes, education in lifestyle modifications reduces progression to diabetes by 50%. Collectively, these observations suggest that treatment of pre-diabetes may prevent the complications of diabetes.

Two high quality RCTs addressed the impact of weight loss/exercise on the development of type 2 DM 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).

While lifestyle modifications are preferred, many patients will either not respond or have only initial success. In these patients, the use of pharmacologic agents could be considered. A series of agents have been studied – alpha-glucosidase inhibitors, metformin, thiazolidinediones; and in hypertensive patients, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Each has been shown to delay progression from pre-diabetes to diabetes. There are no data that suggest that the selection of one agent is preferred over another. None have been shown to reduce long-term complications of diabetes and none have FDA indications for this use. While the thiazolidinediones have been shown to delay diabetes, they are not recommended because of concerns over their long-term safety data and side effects associated with their use.

EVIDENCE

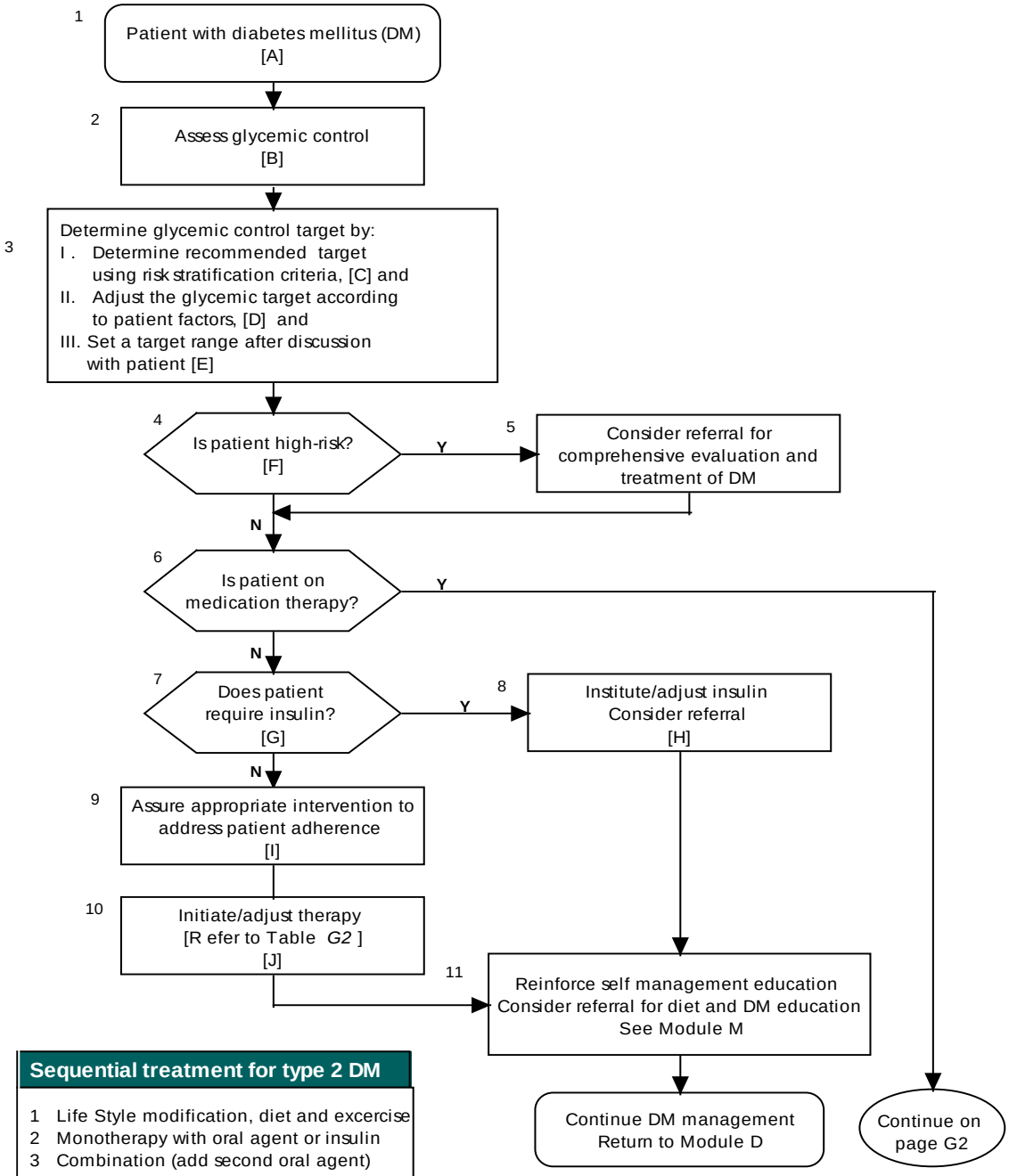
	Recommendation	Sources	LE	QE	SR
1	Weight loss and exercise counseling of patients with FPG $\geq$100.	Yamaoka and Tango, 2005	I	Good	A
2	Diet and exercise leading to weight loss may slow progression to diabetes.	Knowler et al., 2002 Tuomilehto et al., 2001 Pan et al., 1997 Gillies et al., 2007	I	Good	A
3	Weight loss for patients with a BMI >25 or those with other risk factors for diabetes	Knowler et al., 2002 Swinburn et al., 2001 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
5	Pharmacologic therapy delays progression to the diagnosis of diabetes	Chiasson et al., 2006 Gillespie et al., 2005 Scheen et al., 2004 Padwal et al., 2005 Van de Laar et al., 2006 Salpeter et al., 2008	I	Good	A

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

MODULE G - GLYCEMIC CONTROL

MANAGEMENT OF DIABETES MELLITUS
Module G - Glycemic Control

G1



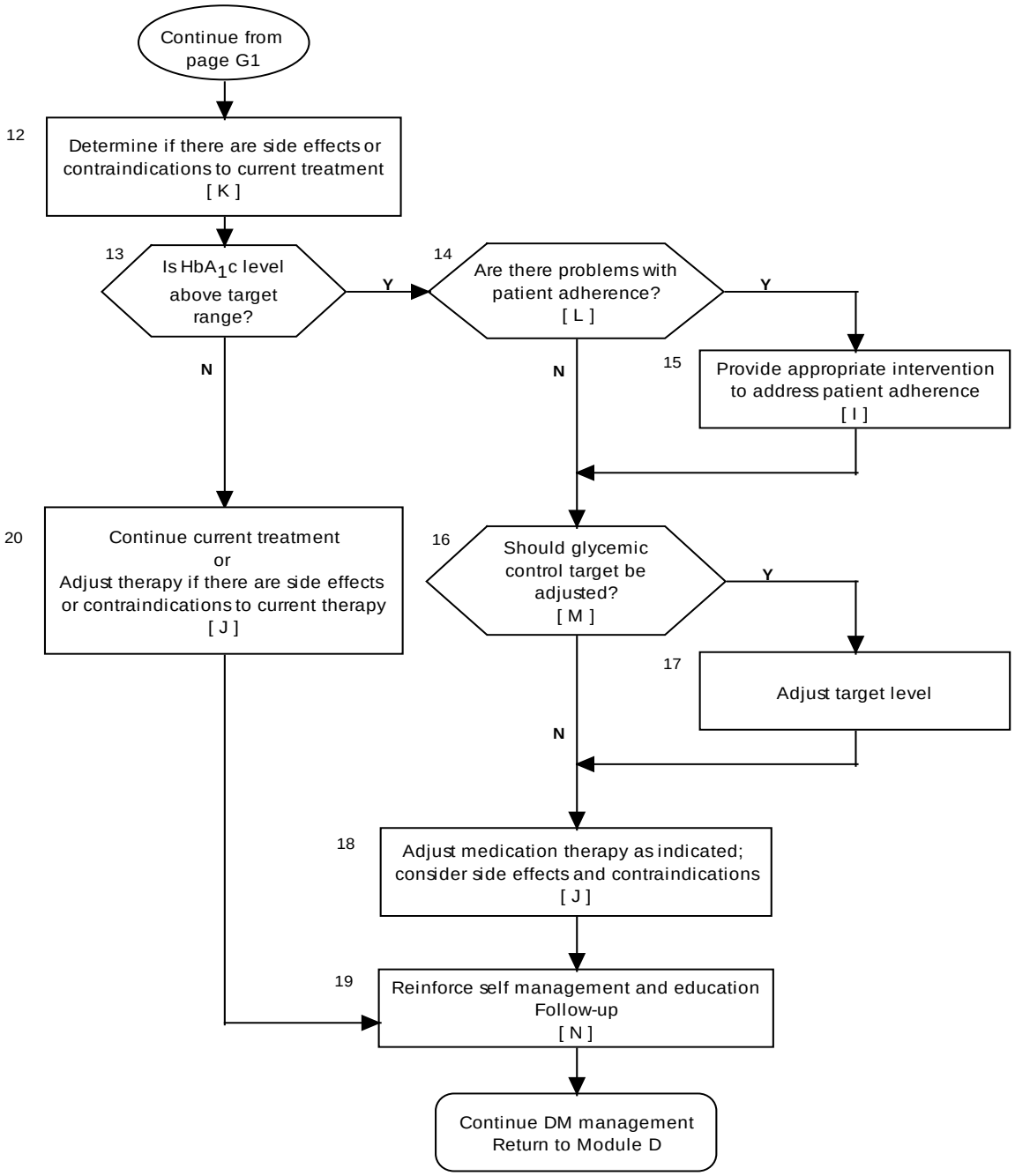
Sequential treatment for type 2 DM

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

MODULE G – GLYCEMIC CONTROL 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 HbA_1c, is the only laboratory test measure validated in randomized controlled trials as a predictor of risk for microvascular complications. Hence, periodic measurement of HbA_1c is recommended to assess glycemic control over time.

Self-monitoring of blood glucose (SMBG) is the process by which patients use a home blood glucose monitor to gain timely knowledge regarding their diabetes control. SMBG may enable patients to make self-care decisions as directed by their provider. Monitoring devices vary in features, readability, portability, and cost. The choice of meter is based on personal preference, cost, features, and ease of use, as well as by the core formulary in the patient's institution.

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. Scheduled (i.e. before breakfast, post prandial, bedtime) SMBG may be beneficial if followed by feedback. This means that the healthcare team should obtain the results, provide feedback to the patient, and document the interaction in the record. Documenting and discussing the readings results with the patients will help patients maximize the use of their meters and foster optimal health status.

SMBG is indicated for persons on insulin. Although the evidence does not support the routine use of SMBG for patients not on insulin, SMBG might be beneficial for individual patients meeting the above criteria.

The Working Group recommends a risk stratified approach to the use of SMBG to enable stable patients to determine if they are hyperglycemic in the face of symptoms or intercurrent illness; evaluate symptoms of hypoglycemia if on sulfonylurea therapy, and to manage active titration of medications.

RECOMMENDATIONS

1. HbA_1c should be measured in patients with diabetes at least annually, and more frequently (up to 4 times per year) if clinically indicated, to assess glycemic control over time.
2. Self Monitoring of Blood Glucose (SMBG) may be used to monitor glycemic control and adjust treatment [B]
3. Patients, for whom SMBG is appropriate, should receive instruction on the proper procedure, the importance of documenting results, and basic interpretation and application of results to maximize glycemic control.
4. SMBG results should be discussed with the patient to promote understanding, adjust treatment regimens, and facilitate treatment adherence. [B]
5. Remote electronic transmission of SMBG data should be considered as a tool to assess glycemic patterns. [C]
6. The frequency of SMBG in patients using insulin 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. [C]

7. A combination of pre-and postprandial tests may be performed, up to 4 times per day. [C]
8. The schedule of SMBG in patients on oral agents (not taking insulin) should be individualized, and continuation justified based upon individual clinical outcomes. Consider more frequent SMBG for the following indications:
    - Initiation of therapy and/or active adjustment of oral agents
    - Acute or ongoing illness
    - Detection and prevention of hypoglycemia when symptoms are suggestive of such, or if there is documented hypoglycemia unawareness
    - Detection of hyperglycemia when fasting and/or post-prandial blood glucose (PPG) levels are not consistent with HbA_1c.

DISCUSSION

Assessment of glycemic control requires an understanding of the assessment methods, as well as their accuracy.

The HbA_1c reflects average blood glucose over a period of time. The relationship between HbA_1c and mean plasma glucose is now based upon the HbA_1c Derived Average Glucose (ADAG, 2008) study. This demonstrated a linear relationship between HbA_1c and mean plasma glucose (MPG) measures in patients with stable type 1 and type 2 diabetes; for an HbA_1c of 7% the mean MPG was 154 mg/dl, with a 95% confidence interval of 123 mg/dl-185 mg/dl.

Subsequently, Herman et al., (2009) reported that although the estimated MPG (~200 mg/dl) at the time of entry into a study of insulin analogs did not differ between Caucasian and non-Caucasian groups, HbA1c was up to 0.8% higher in minority patients.

The measurement of HbA_1c is subject to inter-laboratory variability, red cell survival, and the composition of red cell hemoglobin.

(See Appendix G-1, Measurements of Glycemic Control)

Assessment of Postprandial Plasma Glucose

Glycemia can be assessed through the measurement of postprandial blood glucose (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, decreasing variability in glycemic excursions throughout the day has not been shown to reduce complications in outcome studies in patients with either type 1 or type 2 diabetes. (ADA, 2002)

Self-Monitoring of Blood Glucose

The literature on the efficacy of self monitoring of blood glucose in stable type 2 diabetes, not on insulin, does not support a consistent benefit for this intervention in improving glycemic control. Scheduled monitoring is therefore not recommended in stable patients. There is some evidence to support the use of SMBG by non-insulin treated patients who attended a self-management education program and know what to do with the results. SMBG has

modest effects in non-insulin users, but may be useful in insulin users or clearly in those seeking tight control (e.g. gestational diabetes). Electronic data transfer methods may help patients manage the data better, but with uncertain therapeutic benefits.

Efficacy of SMBG in Patients with Type-2 diabetes, not Requiring Insulin

- Balk et al. (2007) suggested a small but clinically nonsignificant reduction in HbA_1c with SMBG but the studies were inconclusive for patients with non insulin requiring type 2 diabetes.
- Jansen (2006) found a small reduction (0.21-0.83%) in HbA_1c in non-insulin using patients with type 2 diabetes using SMBG and the reduction was larger if the patients were given regular medical feedback.
- McGeoch et al. (2007) concluded that SMBG was most beneficial in patients with type 2 diabetes and HbA_1c of greater than 8% and the patient understood what to do with the results. McGeoch suggested benefit of SMBG in persons with newly diagnosed non-insulin requiring type 2 diabetes, those undergoing initiation of, or a change in medication as well as those with gestational diabetes, hypoglycemia unawareness, or who were ill.
- Poolsup et al. (2008) found that SMBG was beneficial (decrease in HbA1c of 0.27%) in patients with non-insulin requiring type 2 diabetes as long as the information was used to adjust treatment regimens. If the patient had well-controlled diabetes, SMBG was not as efficacious.
- Sarol et al. (2005) concluded that patients with non insulin requiring type 2 diabetes using SMBG and integrating the results with educational advice achieved greater HbA_1c reduction (0.39%). The recommendation for frequency of testing SMBG was 5 to 7 times per week.
- Towfigh et al. (2008), in a meta-analysis of 9 RCTs of SMBG use among patients with non-insulin requiring type 2 diabetes demonstrated a clinically modest, but statistically significant decrease in HbA_1c (0.21%) outcomes at 6 months. Results at 3 months or 12 months were not significant. Their overall conclusion was that SMBG is an intervention of modest efficacy in patients with DM not taking insulin, although their analysis of "quality studies" indicated no benefit.
- Welschen et al. (2005) found that patients with non-insulin requiring type 2 diabetes using SMBG had a statistically significant but clinically small (0.39%) decrease in HbA_1c.
- Farmer et al. (2007) showed no difference in glycemic control in SMBG utilizing patients versus controls. The conclusion was that SMBG was not effective.
- Simon et al. (2008) showed that SMBG with training was not cost effective.
- O'Kane et al. (2008) showed that patients newly diagnosed with diabetes showed no difference in drop in HbA_1c in SMBG versus non SMBG patients. Patients in both groups were aggressively treated and had 1.6 drop in HbA_1c in 3 months.

Remote Monitoring of Blood Glucose

- Farmer et al. (2005) showed that remote monitoring was feasible but not efficacious.
- Balas et al. (2004) evaluated the effectiveness of computerized analysis and reporting for insulin dose and therapy adjustments in 25 studies with1286 adults and 197 children. Results suggested small, but significant improvement in diabetes outcomes, but additional educational and or technical interventions were included in several of the studies and findings did not differentiate among the impact of the various interventions.
- Bergenstal et al. (2005) randomized patients to modem transfer of SMBG data or telephone transfer of the SMBG. Patients in both groups were contacted weekly. Although the modem transmission was more accurate, there was no significant difference in HbA_1c reduction.
- Montori et al. (2004) compared the impact of receiving immediate feedback and asking for feedback in type 1 diabetics who were asked to test four times a day, 7 days per week. SMBG data was transmitted every 2 weeks. The immediacy of feedback improved results (0.4% difference in HbA_1c at 6 months) but the overall lowering effect was clinically small.

- Kruger et al. (2003) determined that there was no significant difference in glycemic control among women with gestational diabetes who transmitted SMBG data telephonically versus electronically. However, the electronic transfer was shown to be more convenient and efficient for both patients and providers.
- An RCT by Kwon et al. (2004) studied the effects of Internet recording of SMBG with feedback and no outpatient visits versus patients without Internet recordings but with monthly outpatient visits. There was a small decrease in SMBG with the Internet recordings group and a small increase in SMBG with the non-Internet recordings group.
- An RCT by Laffel et al. (2007) compared the effectiveness of using an integrated glucose meter and electronic logbook and conventional meters and paper logbooks in a group of insulin treated patients. The use of the integrated meter and electronic logbook resulted in small but significant improvement in HbA_1c up to one year
- In a meta-analysis by St. John et al. (2010), the results of five RCTs in patients with non–insulin-treated type 2 diabetes were combined with two earlier RCTs which yielded a significant pooled SMBG-related decrease in HbA_1c of −0.22 (95% CI −0.34% to −0.11%).

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	Instruction in interpretation and use of SBGM data may improve glycemic control.	Balk et al., 2007 Jansen et al., 2006 Sarol et al., 2005 McGeoch et al., 2007	I	Fair	C
2	Periodic HbA_1c is sufficient to ascertain diabetic control.	Coster et al., 2000 Faas et al., 1997 Harris et al., 2001 Meier et al., 2002 Oki et al., 1997 Piette & Glasgow, 2001 Wieland et al., 1997	II	Fair	B
3	Consider SMBG in non-insulin requiring type 2 diabetics undergoing initiation or change of therapy, illness, or hypoglycemia unawareness and the **SMBG data is used to adjust treatment regimens**	Balk et al., 2007 Farmer et al., 2007 Jansen et al., 2006 McGeoch et al., 2007 O'Kane et al., 2008 Poolsup et al., 2008 Sarol et al., 2005 Simon et al., 2008 Towfigh et al., 2008 Welschen et al., 2005	I	Fair (small benefit)	B
4	Utilizing SMBG data remotely is more convenient for many patients without adding an excess burden on providers	Balas et al., 2004 Bergenstal et al., 2005 Farmer et al., 2005 Kruger et al., 2003 Kwon et al., 2004 Laffel et al., 2007 Montori et al., 2004	I	Fair (small benefit)	C

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

C. Determine Recommended Glycemic Control Target Using Risk Stratification Criteria

OBJECTIVE

Determine an appropriate target for glycemic control (HbA_1c) based upon the patient's risk for developing microvascular complications of diabetes mellitus (retinopathy, nephropathy, and neuropathy) in the context of his or her co-morbidities, life expectancy, risk of causing hypoglycemia, presence or absence of pre-existing microvascular complications, and the patient's preferences.

BACKGROUND

The HbA_1c level remains the best measure of the severity of hyperglycemia over time. Lowering HbA_1c has been associated with a reduction of microvascular complications in patients with both type 1 and type 2 diabetes mellitus (DM). The duration of glycemic exposure is analogous to smoking duration for cancer risk; the level of hyperglycemia is similar to the number of packs of cigarettes smoked daily. Setting the HbA_1c target should take into consideration the limitations (accuracy and bias) of the local laboratory methodology used to assess glycemic control, the benefit and risk of intensification of treatment, and the patient's capabilities and preferences in adhering to a lower target.

RECOMMENDATIONS

1. Treat diabetes more aggressively early in its course. [B]
2. The target range for glycemic control should be individualized, based on the provider's appraisal of the risk-benefit ratio and discussion of the target with the individual patient. [C]
3. Providers should recognize the limitations of the HbA_1c measurement methodology reconciling the differences between HbA_1c readings and self-monitoring results on a case-by-case basis.
4. Setting the initial target range should consider the following: (see Table G-1)
    a. The patient with either none or very mild microvascular complications of diabetes, who is free of major concurrent illnesses, and who has a life expectancy of at least 10-15 years, should have an HbA_1c target of <7 percent, if it can be achieved without risk. [A]
    b. Any patient with diabetes should have a HbA_1c target of <9 percent to reduce symptoms of hyperglycemia. [C]
    c. The patient with longer duration diabetes (more than10 years) or with comorbid conditions, and who require combination medication regimen including insulin, should have an HbA_1c target of < 8 percent. [A]
    d. The patient with advanced microvascular complications and/or major comorbid illness, and or a life expectancy of less than 5 years is unlikely to benefit from aggressive glucose lowering management and should have a HbA_1c target of 8-9 percent. [A]
    e. Risk of hypoglycemia should be considered in recommending a target goal. [B]

DISCUSSION

Observational studies demonstrate a dose response for increases in HbA_1c values and increased risk of both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications of DM over a 7-20 year period. (DCCT.1993, UKPDS 35, 2000). However, the relationship is complex, and the absolute benefit—as opposed to relative benefit—is clearly related to the underlying patient characteristics (duration of diabetes, comorbid conditions, therapy).

Microvascular Complications

Prospective trials have consistently shown that improved glycemic control reduces the risk of microvascular complications in both type 1 and type 2 DM (DCCT; Ohkubo 1995, UKPDS33; ADVANCE). The relationship between HbA_1c and the risk of microvascular complications is continuous, with no apparent threshold of benefit. In the DCCT, a 10% reduction in HbA_1c (e.g. from 8.0 to 7.2%) was associated with a 40 to 50% reduction in the incidence and progression of microalbuminuria and retinopathy, although the absolute reduction in risk was substantially less at lower HbA_1c levels (DCCT, 1995). In the UKPDS, this relationship between HbA_1c and

microvascular complications was directly linear, with each 1.0% (absolute) reduction in mean HbA_1c associated with a 37% decline in microvascular complications, as measured by reduced rates of laser therapy and cataract surgery. Long-term follow-up (for about 10 years) of the DCCT (aka EDIC) and UKPDS cohorts demonstrated that tight control early in the course of type 1 DM and type 2 DM, respectively, was strongly associated with a reduction in complications. This was true even though the HbA_1c level of the original intensive and control treatment groups became indistinguishable (about 8%) after the termination of the original randomized trial.

Macrovascular Complications

The relationship between improved glycemic control and macrovascular complications is less clear-cut. Early studies, such as that by Gaede et al. (2003), demonstrated a relationship between improved glycemic control and reduced cardiovascular disease (CVD) events. A relationship between glycemic control and CVD risk was also supported by the UKPDS; each 1% reduction in HbA_1c resulted in a 14% lower rate of myocardial infarction (MI) and fewer deaths from diabetes or any cause (UKPDS 33). However, such studies were criticized because they employed multiple pharmacologic agents that simultaneously targeted multiple risk factors (hyperglycemia, hypertension, dyslipidemia, and microalbuminuria) and were therefore not able to isolate the impact of strict glycemic control on macrovascular complications.

More recently, Nathan et al. (2005) published evidence that improved glycemic control reduced the risk of CVD in patients with type 1 DM. Over 11 years, the risk of CVD morbidity and mortality was reduced by 42 to 57% in the intensive insulin therapy group). Unfortunately, large randomized controlled trials have failed to show similar benefit for people with type 2 DM (ADVANCE,2008; ACCORD,2008; VADT,2009).

Risks of Intensive Management

In some circumstances, aggressive management of glycemic control may cause frank harm. This is particularly true for patients with type 2 DM treated with insulin.

- Data from the DCCT showed that the risk of severe hypoglycemia in patients with type 1 DM was three times higher in the intensive treatment arm (DCCT, 1993).
- Aggressive management of patients with type 2 DM enrolled in the ACCORD trial was halted after a mean 3.5 years of follow-up because of safety concerns. The incidence of death was 11 per 1000 per year in the conventional treatment group (median achieved A1C of 7.5%) vs. 14 per 1000 per year in the intensive treatment group (median achieved HbA_1c of 6.4%). Furthermore, intensive treatment was also associated with a significantly higher risk of severe hypoglycemia requiring medical assistance (3.1% in the intensive treatment group vs. 1.4% in the conventional treatment group) and weight gain.
- Post hoc analyses of the ACCORD study (Bonds et al., 2010) reported an association of serious hypoglycemia with mortality that was weaker in the intensive group than in the standard group (HR 1.28 versus 2.87).
- In the ADVANCE trial (2008), although intensive treatment (median achieved HbA_1c of 6.5%) decreased nephropathy by 21%, weight gain and severe hypoglycemia occurred more frequently than in the conventionally treated group (median achieved HbA_1c of 6.5%). At least one large RCT (Gerstein et al., 2008), has produced higher mortality rates.
- Identification of the clinical characteristics that are associated with hypoglycemia, cardiovascular events and death are currently under investigation by ACCORD, VADT, and ADVANCE investigators.

Risk Stratification

Given these considerations, the Working Group advocates an individualized approach based on the patient's absolute risk for developing microvascular complications balanced against known co-morbidities, projected life expectancy, presence or absence of pre-existing microvascular complications, the risk of polypharmacy with attendant drug-drug interactions, exposure to medications with limited post-marketing experience, the risk of and ability to perceive hypoglycemia, and patient preference. Recommendations for determining HbA1c target range are summarized in the Table G-1:

Table G-1. Determination of Target HbA_1c Level [(1) (2)]

Major Comorbidity [(d)] or Physiologic Age	Microvascular Complications		
	Absent or Mild [(a)]	Moderate [(b)]	Advanced [(c)]
Absent >10 years of life expectancy	<7%	<8%	8-9% *
Present [(e)] 5 to 10 years of life expectancy	<8 %	<8%	8-9% *
Marked [(f)] <5 years of life expectancy	8-9% *	8-9% *	8-9% *

(1) Based upon the DCCT referent standard. Clinicians need to evaluate the methodology used at their site.

(2) Reflects a "goal" over time. Intensification of therapy should be undertaken based upon individual clinical circumstances and treatment option.

(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 active conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent stroke, and life-threatening malignancy.

(e) Major co-morbidity is present, but is not end-stage and management achievable.

(f) Major co-morbidity is present and is either end-stage or management is significantly challenging.

* Further reductions may be appropriate, balancing safety and tolerability of therapy.

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	**Type 1 DM (short duration)**				
	Microvascular Outcomes: Progression to non-proliferative retinopathy, microalbuminuria, neuropathy	DCCT Research Group, 1993	I	Good	A
	Macrovascular: Myocardial infarction, stroke, cardiovascular death	Nathan et al., 2005	I-2	Fair	B
3	**Type 2 DM (longer duration)**				
	Microvascular: Progression to proteinuria.	Duckworth et al., 2009 (VADT) Gerstein et al., 2007 ADVANCE 2008 Gaede et al., 2003 Gaede et al., 2008 Gerstein et al., 2008	I	Good	A
2	**Type 2 DM (new diagnosis)**				
	Microvascular: Progression to microalbuminuria.	UKPDS 33	I	Good	A
	Macrovascular	Holman et al., 2008	I-2	Fair	B

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

D. Adjust the Glycemic Target According To Patient Factors

OBJECTIVE

Determine a target range for HbA_1c that can be safely achieved taking into consideration individual risk, benefit, and patient's 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. Patients should be invited to participate in decision-making regarding glycemic targets, therapies, and goals of treatment.

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 the Patient

OBJECTIVE

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

RECOMMENDATIONS

1. The patient and provider should agree on a specific target range of glycemic control after discussing the risks and benefits of therapy.
2. The patient should be assessed for knowledge, performance skills, and barriers (e.g., psychosocial, personal, or financial), and if necessary referred to a primary care case manager or endocrine/diabetes clinic to address barriers for achieving treatment goals.

DISCUSSION

A target range of HbA_1c based upon life expectancy, microvascular complications, and family history, is a starting point for shared decision making 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 discuss a lower one. Rather, it implies that there are reduced benefits 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 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 might 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 patient for whom consultation with, or referral to a subspecialty multi-disciplinary team would be appropriate to assist in the development of a treatment plan and/or supervise ongoing care.

RECOMMENDATIONS

1. The indications to consider a consultation or referral to specialty include patients who:
    - Have type 1 DM; especially patients with history of hospitalizations for metabolic complications and/or patients who are receiving intensive insulin therapy
    - Have new-onset insulin-requiring DM
    - Have marked insulin resistance
    - Have contraindications or intolerances to medications typically used in managing diabetes
    - 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 visual and/or renal impairment

- Have psychosocial problems (including alcohol or substance abuse) that complicate management
- Have HbA_1c > 9.0 percent and are considered for aggressive management on an expedited basis.
- Are not achieving glycemic control despite comprehensive treatment with complex regimen of combination pharmacotherapy including insulin
- Require evaluation or management beyond the level of expertise and resource level of the primary team.

G. Does Patient Require Insulin?

OBJECTIVE

Identify the patient for whom insulin treatment is necessary.

RECOMMENDATIONS

1. The patient with type 1 diabetes mellitus (DM) must receive insulin replacement therapy.
2. 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.

DISCUSSION

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. Some patients with ketosis prone diabetes can eventually be weaned from insulin.

H. Institute/Adjust Insulin; Consider Referral

OBJECTIVE

Achieve glycemic control using insulin.

RECOMMENDATIONS

1. All patients with type 1 DM should be managed by a provider experienced in managing type 1 DM in a multidisciplinary approach or by a clinic team with multidisciplinary resources (e.g., diabetologist, diabetes nurse, educator/manager, and registered dietitian) for institution and adjustment of insulin therapy.
2. When expeditious referral is not possible, the primary care provider should institute “survival” insulin therapy comprised of total daily insulin (TDI) 0.5 units/kg/day; half as basal insulin and half as meal time insulin.

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 Diabetes clinic with multidisciplinary resources including diabetologists, diabetes nurses, educator/managers, and registered dietitians. If expedient referral cannot be accomplished, the healthcare provider should institute "survival" insulin therapy. This can be initiated at a calculated TDI of 0.5 Units/kg body weight/day. (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 regularly assessed for knowledge, performance skills, and barriers to self-management.
2. 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).
3. 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 self-management. 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 dietary modification and exercise alone is usually the appropriate initial management in patients with new onset type 2 diabetes, depending upon severity of symptoms, psychosocial evaluation, patient motivation, and overall health status. Encourage diet and exercise and lifestyle modifications.
3. Use various approaches (e.g., individual or group, counseling, coaching, motivational interviewing) to promote healthful behaviors, such as healthful diet, adequate physical activity, and smoking cessation.
4. If treatment goals are not achieved with diet and exercise alone, drug therapy should be initiated while encouraging lifestyle modifications.

The concept of sequential treatment is commonly employed in clinical management of chronic diseases. The sequential steps for glycemic control therapy are summarized in Figure G1.

DISCUSSION

Non-Pharmacologic Therapy

Each patient with newly diagnosed type 2 DM without markedly elevated HbA_1c or symptomatic hyperglycemia should be offered trial of non-pharamcological therapy 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). Dietary modicficaion 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.

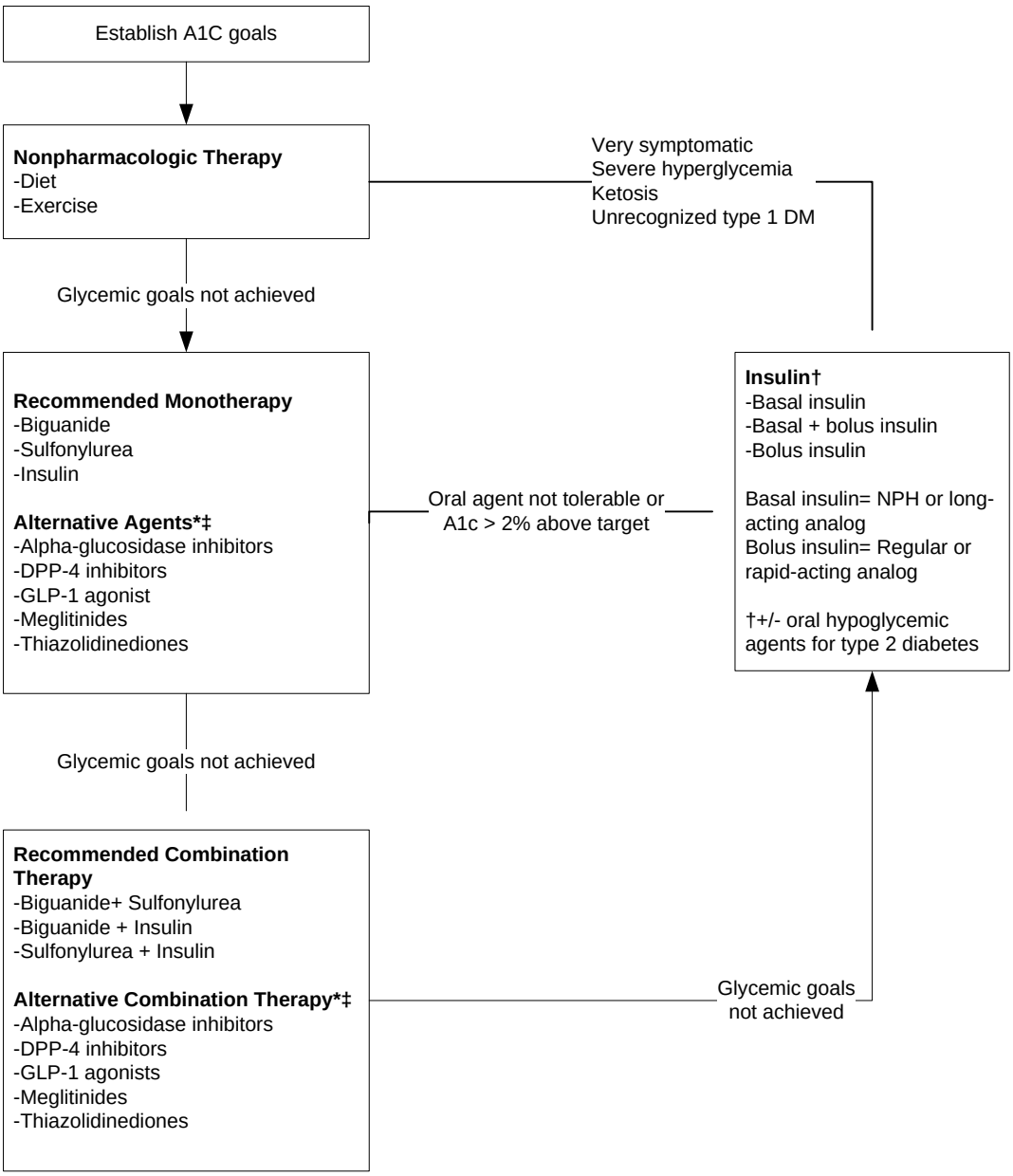
Pharmacotherapy

When glycemic goals are not achieved with nonpharmacologic therapy such as diet and exercise, adjunctive therapy with medications is indicated. When initiating treatment, monotherapy with an oral agent is appropriate for most patients. For those who have severe hyperglycemia or symptoms, initiating insulin is often necessary.

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.

Most trials evaluated the impact of drug therapy on surrogate endpoints such as HbA_1c. More trials evaluating relevant endpoints such as mortality and morbidity are needed.

Figure G1. Sequential Treatment of Type 2 Diabetes



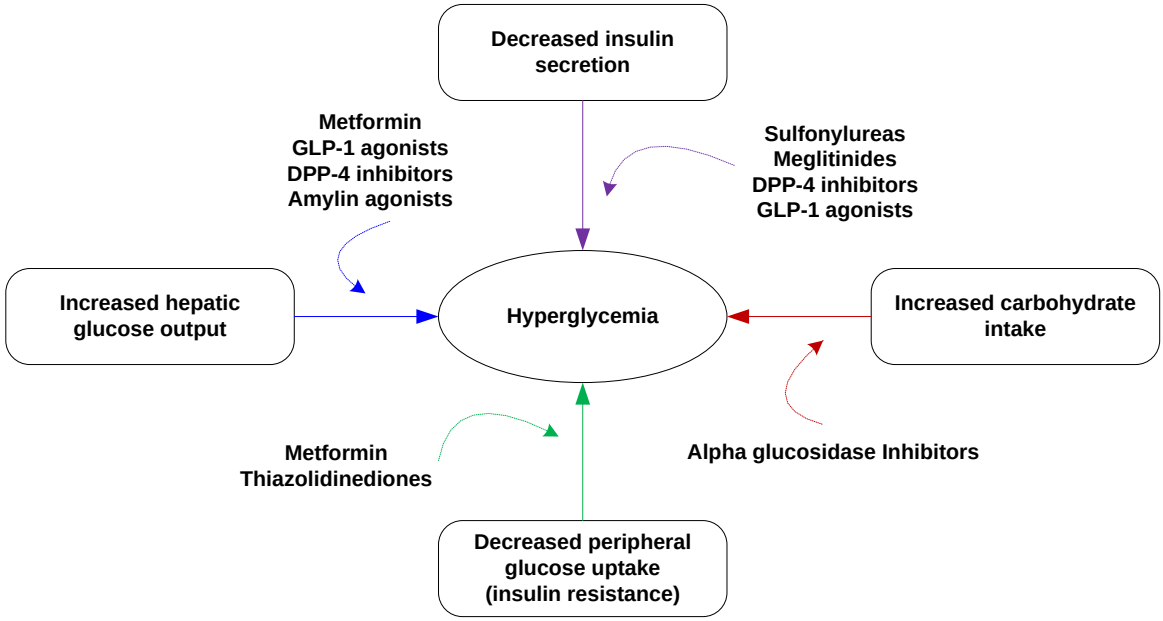
***Listed alphabetically; not in order of preference**
‡If applicable, refer to VA www.pbm.va.gov or http://vaww.pbm.va.gov or DoD guidance/ criteria for further recommendations on use of these agents

J-1. MONOTHERAPY (Initial therapy)

BACKGROUND

Several mechanisms contribute to the hyperglycemia that is seen in individuals with diabetes. Figure G-2 illustrates the site(s) at which oral agents used to treat hyperglycemia exert their primary effect(s).

Figure G-2. Primary Sites of Action of Agents Used to Treat hyperglycemia



RECOMMENDATIONS

1. When selecting an agent, consideration must be given to efficacy, contraindications, drug interactions, and side effects. Educate patient about treatment options and arrive at a shared treatment plan with consideration for patient preferences. [I]
2. Insulin should be considered in any patient with extreme hyperglycemia or significant symptoms; even if transition to therapy with oral agents is intended as hyperglycemia improves. (See section on insulin for further details.) [B]
3. Metformin (preferred) or sulfonylureas (SU) should be given as first line agents unless there are contraindications. [A]
4. Alternative monotherapy agents such as thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1(GLP-1) agonists should be reserved for patients who have contraindications to or are unable to tolerate metformin or SU. [B]
5. Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management. [I]

RATIONALE

Several reviews of the oral medications concluded that in terms of antihyperglycemic effect alone, there was no compelling reason to favor one of the major categories of antidiabetic agents (sulfonylureas, biguanides, and TZDs) over another. However, metformin's performance in the UKPDS in obese patients, and its lack of associated hypoglycemia and weight gain, make it the most attractive option for patients who have type 2 DM but no contraindications to its use.

EVIDENCE STATEMENTS

A systematic review by the Agency for Healthcare Research and Quality found that older agents such as metformin and second-generation SU have similar or superior effects on glycemic control, lipids, and other intermediate endpoints compared with TZDs, alpha-glucosidase inhibitors, and meglitinides. Trials through January 2006 were included in the analysis. Each agent is associated with adverse events; however, metformin appears to have the best benefit to risk profile. (Bolen et al., 2007)

- Metformin, SU, TZDs, and repaglinide produced a similar reduction in HbA_1c of about 1%. The alpha-glucosidase inhibitors and nateglinide reduced HbA_1c to a lesser extent (approximately 0.5%).
- Metformin, SU, TZDs had a minimal effect (decrease <5mmHg) on systolic and diastolic blood pressure.
- The TZDs consistently increased LDL (mean of 10mg/dL), metformin decreased LDL cholesterol, SU, acarbose, and repaglinide had little effect on LDL cholesterol. TZDs increased HDL cholesterol (mean 1-5mg/dL) whereas the other agents had little impact on HDL cholesterol. Only rosiglitazone was shown to slightly increase triglycerides.
- Sulfonyureas, TZDs, and repaglinide can cause weight gain of about 1-5kg. Metformin and acarbose are considered to be weight neutral.
- Hypoglycemia occurs more frequently with SU (esp. glyburide) and repaglinide than metformin or TZDs
- Metformin and acarbose cause more GI symptoms than SU, TZDs or repaglinide
- Metformin, SU, and TZDs had similarly low rates of elevated aminotransferase level > 1.5-2 x ULN. The few data that were available for the meglitinides show the effects on aminotransferases are similar to the other agents.
- Peripheral edema was more common with TZDs (0-26%) than SU (0-8%) or metformin (0-4%). Risk for heart failure is increased with TZDs.
- Metformin was associated with a slightly lower risk of all-cause mortality and cardiovascular mortality compared to SU, but results had a moderate risk of bias. There were insufficient data to compare the other agents.
- Metformin was associated with a slightly lower risk of cardiovascular morbidity compared to SU and was similar to TZDs; however, results were very imprecise.
- Compared to metformin, pioglitazone had a more favorable effect in reducing the urinary albumin-to-creatinine ratio.

A forthcoming update to the 2007 AHRQ review includes trials up to March 31, 2010. This review was expanded to include newer agents such as the DPP-4 inhibitors and the GLP-1 agonists. The 2010 AHRQ review states there were insufficient data comparing monotherapy with DPP-4 inhibitors or GLP-1 agonists with other agents. There are no long-term outcome studies with these agents at this time.

DPP-4 inhibitors or GLP-1 agonists compared to placebo

As monotherapy, the DPP-4 inhibitors reduce HbA_1c by an average of 0.5-0.7%. The incidence of hypoglycemia with monotherapy is not significantly different than placebo. These agents are considered to be weight and lipid neutral (Raz et al., 2006; Aschner et al., 2006; Rosenstock et al., 2009).

The mean reduction in HbA_1c with monotherapy with GLP-agonists ranged from 0.7-1.1%. On average, the change in weight ranged between -2 to -3kg. Adverse GI effects were reported more commonly in patients receiving GLP-agonists versus comparator/placebo. Hypoglycemia was uncommon. Liraglutide is not recommended as first-line therapy for patients inadequately controlled on diet and exercise but may be used as monotherapy in those in whom other medications are either not tolerated or contraindicated (Moretto et al., 2008, Garber et al., 2009).

EVIDENCE TABLE

	Recommendation	Sources	LE	QE	SR
1	Choice of drug must be based on a variety of clinical factors and individual patient characteristics, including predisposition to adverse effects, the degree of hyperglycemia	Work Group consensus	III	Poor	I
2	Metformin (preferred) or sulfonylurea as first line for most patients	Bolen et al., 2007	I	Good	A
3	TZDs, alpha-glucosidase inhibitors, meglitinides, DPP-4 inhibitors, and GLP-1 agonists as alternative agents for patients unable to use metformin or sulfonylureas due to contraindications, adverse effects, or other reasons	Work Group Consensus	II-1	Fair	B
4	Insulin should be considered in any patient with extreme hyperglycemia or significant symptoms; even if transition to therapy with oral agents is intended as hyperglycemia improves	Work Group Consensus	II-1	Fair	B
5	Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management	Work Group Consensus	III	Poor	~~I~~

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

J-2. COMBINATION THERAPY (Add-on)

BACKGROUND

When initial therapy no longer provides adequate glycemic control, addition of a drug from another class rather than substitution (reserve substitution for intolerance/adverse effect to a drug) is usually necessary. Combination of two anti-hyperglycemic drugs has the benefit of reducing hyperglycemia by working on different mechanisms that cause hyperglycemia (refer to Figure G-2). 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 have evidence. Additionally, the data are limited on comparison of different combination regimens that assess which combination is preferred.

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. Because of all these factors, several options for combination therapy should be available.

RECOMMENDATIONS

1. Metformin + sulfonylurea is the preferred oral combination for patients who no longer have adequate glycemic control on monotherapy with either drug. [A]
2. Other combinations (TZDs, AGIs, meglitinides, DPP-4 inhibitors, and GLP-1 agonists) can be considered for patients unable to use metformin or a sulfonylurea due to contraindications, adverse events, or risk for adverse events (see Appendices G-2 and G-3). [B]
3. Addition of bedtime NPH or daily long-acting insulin analog to metformin or sulfonylurea should be considered, particularly if the desired decrease in HbA_1c is not likely to be achieved by use of combination oral therapy. [A]
4. Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management. [I]

DISCUSSION

The systematic review by the Agency for Healthcare Research and Quality found that combination therapy with TZDs, SU, metformin and repaglinide were additive and provided an additional 1% decrease in HbA_1c over

monotherapy (Bolen et al., 2007). For patients with inadequate glycemic control on metformin, addition of an alpha-glucosidase inhibitor, the treatment effect for HbA_1c was -0.61% in studies of 24-32 weeks duration (Monami et al., 2008).

DPP-4 Inhibitors

Addition of a DPP-4 inhibitor to metformin, SU, or TZD resulted in mean decreases in HbA_1c ranging from 0.3-0.9%. (Chacra et al., 2009; Charbonnel et al., 2006; DeFronzo et al., 2009; Hermansen et al., 2007; Hollander et al., 2009; Nauck et al., 2007b; Rosenstock et al., 2006a; Scott et al., 2008).

The addition of a DPP-4 inhibitor to metformin or TZD did not significantly increase the incidence of hypoglycemia compared to monotherapy with metformin or TZD. However, when a DPP-4 inhibitor is combined with a SU, the incidence of hypoglycemia with the combination was greater than SU alone.

Mean weight loss is similar with combination metformin and DPP-4 inhibitor compared to metformin alone. Mean weight gain with combination DPP-4 inhibitor and SU or TZD is slightly greater than with the SU or TZD alone.

Decrease in HbA_1c, weight, and incidence of hypoglycemia are similar between sitagliptin and saxagliptin when added to ongoing metformin therapy. (Study D1680C00002)

Addition of sitagliptin or glipizide (mean dose 10mg) resulted in a similar decrease of HbA_1c of 0.6%. There was a higher incidence of hypoglycemia and weight gain with SU (Nauck et al., 2007b)

Addition of sitagliptin 100mg or rosiglitazone 8mg daily resulted in a similar decrease in HbA_1c (-0.73 and -0.79 respectively). Rosiglitazone resulted in lower fasting and 2-h post-prandial glucose levels and increased weight and lipid levels. There was no increased risk of hypoglycemia. (Scott et al., 2008)

GLP-1 Agonists

Adding a GLP-1 agonist to metformin or SU resulted in mean decrease in HbA_1c ranging from 0.8-1.0%. (Buse et al., 2004; Defronzo et al., 2005; Kendall et al., 2005; Marre et al., 2009; Nauck et al., 2009; Zinman et al., 2007)

Hypoglycemia was relatively infrequent, but occurs slightly more often in triple therapy regimens or regimens including a SU.

GLP-1 agonists generally result in weight loss. The weight loss is mitigated when combined with SU or TZDs.

Adverse GI effects, particularly nausea, are the most commonly reported adverse effects

Reduction in mean HbA_1c was greater with liraglutide combined with glimepiride (-1.1%) compared to rosiglitazone combined with glimepiride (-0.44%). There was a lower rate of hypoglycemia, but greater weight gain in the later group. (Marre et al., 2009)

The reduction in HbA_1c is similar between liraglutide + metformin versus glimepiride + metformin. The liraglutide groups experienced weight loss with means ranging from 1.8-2.8kg compared to mean weight gain of 1kg in the later group. The rate of minor hypoglycemia was higher with glimepiride + metformin (0.87 vs. 0.05 events/patient-year). (Nauck et al., 2009)

Reduction in mean HbA_1c was greater with liraglutide + metformin (1.2-1.5%) compared to sitagliptin + metformin (0.9%). There was greater weight loss and more adverse GI events in the liraglutide groups. The rate of hypoglycemia was similar between groups. (Pratley et al., 2010)

When added to metformin, SU, or both, liraglutide reduced mean HbA_1c by 1.12% compared to 0.79% with exenatide. Minor hypoglycemia was less frequent with liraglutide than with exenatide (1.93 vs. 2.60 events per patient per year). Weight loss was similar with both agents (liraglutide -3.24 kg vs. exenatide -2.87 kg). (Buse et al., 2009)

Addition of GLP-1 agonist vs. insulin to oral agents

Liraglutide versus insulin glargine (mean dose 24 units daily) in combination with metformin and sulfonylurea therapy decreased mean HbA_1c by 1.3% and 1.1% respectively. Rates of minor hypoglycemia were similar in the 2 groups; however, there were 5 cases of major hypoglycemia with liraglutide and none in the glargine group. Mean change in weight was -1.8kg and +1.6kg in the liraglutide and glargine groups respectively. (Russell-Jones et al., 2009)

Two RCTs showed that adding exenatide versus insulin glargine (mean doses 25-29U/day) to metformin, SU or both metformin +SU resulted in a similar reduction in HbA_1c; however, reduction in fasting glucose was greater with insulin glargine. Exenatide use resulted in mean weight loss (2-3kg) whereas insulin glargine use resulted in mean weight gain (1.0-2.3kg). The results for overall hypoglycemia were inconsistent, where 1 study showed no difference between glargine and exenatide and the other showed significantly fewer episodes with exenatide. The rate of nocturnal hypoglycemia was lower with exenatide in both studies. In a subgroup of patients receiving SU as background therapy, the rate of hypoglycemia was similar with exenatide and glargine. The exenatide group reported a greater incidence of adverse GI effects and had more patients dropping out of the studies (Heine et al., 2005; Barnett et al., 2007).

In patients with inadequate glycemic control on combination metformin + SU, the addition of exenatide versus biphasic insulin aspart was compared in a 52-week and 24-week trial. The 52-week study showed no significant difference in reduction in HbA_1c between the 2 agents (mean insulin dose 24.4U) and in overall incidence of hypoglycemia; however, exenatide was associated with less nocturnal hypoglycemia (0.6 vs.1.1 events/patient-year). On the contrary, the 24-week treat-to-target study found that reduction in HbA1c with biphasic insulin aspart was superior compared to exenatide and had significantly greater rate of hypoglycemia. Both studies showed exenatide use resulted in mean weight loss (2-2.5kg) whereas biphasic aspart insulin use resulted in mean weight gain (2.9-4kg). The exenatide group reported a greater incidence of adverse GI effects and had more patients dropping out of the studies (Bergenstal et al., 2009; Nauck et al., 2007a)

Triple oral therapy

The long-term safety and efficacy of three oral hypoglycemic agents is unknown. For patients who have not achieved their glycemic goal on a 2-drug oral regimen, addition of once daily or bedtime insulin is preferred. However, addition of a third oral agent could be considered for those who are not good candidates for insulin or decline insulin use and the target HbA1c is within the efficacy range of the oral agent. (Dailey et al., 2004; Hermansen et al., 2007; Roberts et al., 2005; Rosenstock et al., 2006b).

Four drug oral therapy

The efficacy and safety of such a combination is not known and should be strongly discouraged. Such a trial might rarely be considered in patients with inadequate glycemic control on 3-drug therapy and are not good candidates for the addition of insulin.

Combination with Insulin

The data seems to suggest that patients receiving combination treatment with oral hypoglycemic agents (OHAs) plus insulin have significantly lower HbA1c levels when compared to those treated with insulin monotherapy. However, studies in this area have several limitations: 1.Fasting plasma glucose values were not consistently assessed by most of the studies; 2. Many of the studies had small sample sizes and/or were of low quality, and several were open-labeled; and 3. Direct comparison between studies is hampered by the number of different drug combinations and comparisons, and dosing and titration regimens.

A Cochrane review (Goudswaard et al., 2004) of randomized controlled trials assessing the effects of insulin monotherapy versus insulin-OHA combinations therapy found that bedtime NPH insulin combined with oral hypoglycemic agents provided comparable glycemic control to insulin monotherapy and was associated with less weight gain if metformin is used.

- Insulin-OHA combination therapy had statistically significant benefits on glycemic control (mean difference 0.3% (95% CI 0.0 to 0.6, p=0.03)) over insulin monotherapy only when the latter was applied as a once-daily injection of NPH insulin
- Conversely, twice-daily insulin monotherapy (NPH or mixed insulin) provided superior glycemic control (mean difference 0.4% (95% CI 0.1 to 0.8, p=0.03)) to insulin-OHA combination therapy regimens where insulin was administered as a single morning injection.
- Regimens utilizing OHAs with bedtime NPH insulin provided comparable glycemic control to insulin monotherapy (administered as twice or more daily injections).
- Overall, insulin-OHA combination therapy was associated with a 43% reduction in total daily insulin requirement compared to insulin monotherapy.

- Combination therapy with bedtime NPH insulin resulted in statistically significantly less weight gain compared to insulin monotherapy, provided metformin was used with or without SU.

Janka et al., (2005) demonstrated that the combination of insulin glargine once-daily plus OHA (metformin or sulfonylurea) produced significantly lower HbA1c (-1.64% vs. -1.31%, p=0.0003) compared to twice-daily NPH insulin 70/30. Other studies of similar design have reported comparable results with various insulin-OHA combinations.

Riddle and colleagues (2003) demonstrated that the addition of bedtime insulin glargine or NPH once daily to oral medications achieved an HbA1c ≤7% in 60% of patients in the study. Fewer patients receiving insulin glargine developed nocturnal hypoglycemia (26.7% vs. 33.2%, p <.05).

Hermansen et al. (2006) compared insulin detemir versus NPH insulin added to oral therapy and found a similar percentage of patients reached fasting and pre-dinner blood glucose targets of <108 mg/dL for both regimens. A greater proportion on insulin detemir achieved this goal without developing hypoglycemia and risk of nocturnal hypoglycemia reduced by 55%.

Other trials have compared pre-mixed insulin plus OHA to pre-mixed insulin alone and demonstrated that the combination significantly lowered HbA1c versus monotherapy. (Douek et al., 2005; Malone et al., 2004, 2005)

Several RCTs demonstrated that biphasic insulin aspart (BIAsp) added to OHA significantly lowered HbA1c versus monotherapy. (Kvapil et al., 2006; Raz et al., 2005)

Insulin Adjunctive Therapy

Pramlintide is a synthetic analog of the neuroendocrine hormone amylin. Amylin works in concert with insulin in maintaining glucose homeostasis. This drug is administered with insulin, not in place of insulin. Pramlintide has been studied in patients with type 1 and type 2 diabetes. In these trials patients were maintained on their usual insulin regimes and received various doses of pramlintide prior to meals. In type 1 diabetes, the mean change in HbA1c ranged from -0.1 to -0.39% with pramlintide compared to -0.12 to +0.09% in the placebo group. In type 2 diabetes, the mean change in HbA1c ranged from -0.3 to -0.62% with pramlintide versus -0.15 to -0.25% with placebo. (Ratner et al., 2002 and 2005; Whitehouse et al., 2002)

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	Metformin + sulfonylurea are the preferred oral combination for patients who no longer have adequate glycemic control on either drug.	Bolen et al., 2007	I	Good	A
2	For patients unable to use metformin or a sulfonylurea due to contraindications, adverse events, or risk for adverse events, other combinations can be considered.	Work Group Consensus	II-1	Fair	B
3	Addition of bedtime NPH or daily long-acting insulin analog to metformin or sulfonylurea should be considered, particularly if the desired decrease in HbA1c is not likely to be achieved by use of combination oral agents.	Goudswaard et al., 2004 Riddle et al., 2003 Hermansen et al., 2006 Janka et al., 2005 Kvapil et al., 2006 Raz et al., 2005 Douek et al., 2005 Malone et al., 2004, 2005	I	Good	A
4	Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management.	Work Group Consensus	III	Poor	I

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

J-3. INSULIN THERAPY

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

Many patients with type 2 DM can achieve their glycemic target with a single bedtime injection of long-acting insulin or pre-meal 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. Other insulin options include: Adding basal insulin (NPH or long-acting analog) and continuing therapy with one or two oral agents, adding a premixed insulin while continuing insulin sensitizers (e.g., metformin), and discontinuing secretagogues, or adding rapid-acting insulin at mealtimes and continuing therapy with one or two oral agents. (Adapted from: White, 2007)

The care of patients with type 1 or type 2 DM (needing insulin) 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. The degree of insulin resistance determines the starting dosing; for example:

- Newly diagnosed, lean, T1DM; total daily insulin (TDI) 0.5 units/kg/d; half as basal insulin
- Long standing, obese, T2DM; TDI 0.8. to 1 units/kg/d; half as basal insulin

RECOMMENDATIONS

1. Use of insulin therapy should be individualized, and managed by a healthcare team experienced in managing complex insulin therapy for patients with type 1 DM. [I]
2. Use intermediate- or long-acting insulin to provide basal insulin coverage. [B]
3. Insulin glargine or detemir may be considered in the NPH insulin-treated patient with frequent or severe nocturnal hypoglycemia. [B]
4. Use regular insulin or short-acting insulin analogues for patients who require mealtime coverage.
5. Alternatives to regular insulin (aspart, lispro, or glulisine) should be considered in the following settings: [B]
    - Demonstrated requirement for pre-meal insulin coverage due to postprandial hyperglycemia AND concurrent frequent hypoglycemia
    - Patients using insulin pump.

RATIONALE

Patients with type 1 DM have an absolute insulin deficiency and require lifelong insulin replacement. In most patients with type 2 DM, blood glucose control deteriorates over a period of years, due to declining insulin production. In these circumstances oral therapies can no longer maintain blood glucose control to targets and insulin replacement therapy becomes inevitable.

DISCUSSION

Singh et al. (2009) conducted a meta-analysis to compare the outcomes of insulin analogues with conventional insulins in the treatment of type 1, type 2 (adult and pediatric) and gestational diabetes. Authors concluded that rapid-and long-acting insulin analogues offer little benefit relative to conventional insulins in terms of glycemic control or reduced hypoglycemia.

- In terms of hemoglobin HbA_1c, there were minimal differences between rapid-acting insulin analogues and regular human insulin in adults with type 1 diabetes (weighted mean difference (WMD) for insulin lispro: -0.09%, 95% confidence interval [CI] -0.16% to -0.02%; for insulin aspart: -0.13%, 95% CI -0.20% to -0.07%). Similar outcomes were found among patients with type 2 diabetes (WMD for insulin lispro: -0.03%, 95% CI -0.12% to -0.06%; for insulin aspart: -0.09%, 95% CI -0.21% to 0.04%).
- Differences between long-acting insulin analogues and NPH insulin in terms of HbA_1c were also minimal among adults with type 1 diabetes (WMD for insulin glargine: -0.11%, 95% CI -0.21% to -0.02%; for insulin detemir: -0.06%, 95% CI -0.13% to 0.02%) and among adults with type 2 diabetes (WMD for insulin glargine: -0.05%, 95% CI -0.13% to 0.04%; for insulin detemir: 0.13%, 95% CI 0.03% to 0.22%). Benefits in terms of reduced hypoglycemia were inconsistent.

Rapid (short)-acting insulin analogues vs. regular human insulin (RHI)

A Cochrane review (Siebenhofer, et al., 2006) assessed the effects of short-acting insulin analogues versus regular human insulin. Authors concluded that there was only a minor benefit of short-acting insulin analogues in the majority of patients with diabetes over those treated with RHI.

Mannucci et al. (2009) conducted a meta-analysis of RCTs and found that short-acting insulin analogues provided better control of HbA1c and postprandial glucose than RHI, without any significant reduction of the risk of severe hypoglycemia.

- Short-acting analogues reduced HbA_1c by 0.4% (0.1-0.6%) ($p = 0.027$) in comparison with RHI. A significant improvement was observed also in self-monitored 2 h post-breakfast and dinner blood glucose.
- The overall rate of severe hypoglycemia was not significantly different between short-acting analogues and RHI.

All of the short-acting insulins (analogues and RHI) are FDA approved for use in insulin pumps and may be used in continuous subcutaneous insulin infusion (CSII) therapy.

Long acting insulin analogues vs. NPH.

A Cochrane review (Vardi et al., 2008) assessed the effects of intermediate acting versus long acting insulin analogues for basal insulin replacement in patients with type 1 diabetes, and concluded that long acting insulin analogues seem to exert a beneficial effect on nocturnal glucose levels, but their effect on the overall diabetes control is clinically unremarkable.

A Cochrane review (Horvath et al., 2007) assessed the effects of long-term treatment with long-acting insulin analogues (insulin glargine and insulin detemir) compared to NPH insulin in patients with type 2 diabetes mellitus. Authors concluded that, only a minor clinical benefit of treatment with long-acting insulin analogues for those patients treated with "basal" insulin regarding symptomatic nocturnal hypoglycemic events.

Note: There are dosing differences between the long-acting analogues. Detemir is indicated for once daily or twice daily (BID) dosing and glargine is only indicated for once daily dosing. Glargine once daily dosing may be given at any time of the day, at the same time each day. However, detemir once daily dosing should be given with the evening meal or at bedtime. Twice daily dosing should be given with the evening meal, at bedtime, or 12 hours before the morning dose. Insulin requirements vary widely among people with diabetes, even when other factors are similar. Types, frequency, and dosages of insulin must be individualized, considering multiple factors. Below are recommendations from the manufactures on dosing in certain patients types. (Sources: Package inserts)

Insulin Dosing Examples (Sources: Package inserts)

Type of patient	Insulin detemir	Insulin glargine
Type- 1 or type- 2 DM on basal-bolus treatment	Changing basal insulin to detemir can be done on a unit-to-unit basis Dose of detemir should then be adjusted to achieve glycemic targets In some patients with type- 2 DM more detemir may be required than NPH insulin (0.77 Units/kg for detemir and 0.52 Units/kg for NPH human insulin)	Changing once daily NPH to once daily glargine can be done on a unit-to-unit basis Changing twice daily NPH to once daily glargine: glargine dose is 80% of total NPH requirement
Patients currently receiving only basal insulin	Changing the basal insulin to detemir can be done on a unit-to-unit basis	--
Insulin-naïve patients with type-2 DM who are inadequately controlled on oral antidiabetic drugs	0.1 to 0.2 Units/kg once-daily in the evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemic targets	10 units (or 0.2 Units/kg) once daily, which should subsequently be adjusted to the patient's needs
Patients with type- 1 DM, newly diagnosed	--	Glargine should account for one-third to one-half of the total daily insulin requirement. Short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirement.

Long-acting insulin analogues vs. Biphasic aspart (BIAsp) insulin

Raskin et al., (2005) compared biphasic insulin aspart before breakfast and before supper to insulin glargine at bedtime (insulin naïve patients) and found more patients achieved HbA1c <7% on BIAsp (66%) then those on insulin glargine (40%); p .001). Patients with baseline HbA1c >8.5% had the greatest improvement. However, the BIAsp group had greater incidence of minor hypoglycemia and weight gain.

EVIDENCE TABLE

	Recommendation	Sources	LE	QE	SR
1	Use of insulin therapy should be individualized; providers should be experienced in managing complex insulin therapy and for patients with type 1 DM and have access to an interdisciplinary team.	Workgroup consensus	III	Poor	I
2	Intermediate- or long-acting insulin to control fasting plasma glucose, for patients with type 1 DM.	Vardi et al., 2008	I	Fair	B
3	Insulin glargine or detemir for patients with type 2 DM with frequent or severe nocturnal hypoglycemia.	Horvath et al., 2007	I	Fair	B
4	Use regular insulin or short-acting insulin analogues for patients who require mealtime coverage.	Mannucci et al., 2009 Siebenhofer et al., 2006	I	Fair	B
5	Rapid-acting insulin analogues (aspart, lispro, or glulisine) as an alternative to regular insulin for postprandial hyperglycemia with concurrent frequent hypoglycemic events and patients on CSII.	Mannucci et al., 2009	I	Fair	B

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

J-4. CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII)

BACKGROUND

Continuous subcutaneous insulin infusion (CSII) was introduced in the 1970s as a way of achieving glycemic control in patients with type 1 diabetes. With the recognition of the benefits of tight glycemic control, insulin regimens mimicking physiologic insulin secretion have become more commonly used in patients not meeting glycemic goals with less intensive insulin regimens. This can be achieved through use of insulin regimens that use a basal-bolus approach with multiple daily injections (MDI) and with CSII. More recently, the same approach has been used to varying degrees in patients with type 2 diabetes. As both approaches are effective at achieving tight glycemic control and are in widespread use, recent literature has concentrated on comparison of MDI and CSII with respect to efficacy and safety.

RECOMMENDATIONS

1. CSII therapy should only be initiated and managed by an endocrinologist/diabetes team with expertise in insulin pump therapy
2. CSII therapy should only be considered in patients who have either documented type 1 diabetes [history of DKA, low c-peptide or evidence of pancreatic autoimmunity] or be insulin deficient with a need for intensive insulin therapy to maintain glycemic control and are not able to maintain it using multiple daily injections (MDI) therapy. This may include patients with:
    a. Poor glycemic control (including wide glucose excursions with hyperglycemia and serious hypoglycemia and those not meeting HbA_1c goal) despite an optimized regimen using MDI in conjunction with lifestyle modification. [A]
    b. Marked dawn phenomenon (fasting AM hyperglycemia) not controlled using NPH at bedtime, glargine or detemir. [B]
    c. Recurrent nocturnal hypoglycemia despite optimized regimen using glargine or detemir. [B]
    d. Circumstances of employment or physical activity, for example shift work, in which MDI regimens have been unable to maintain glycemic control. [I]
3. Patients using CSII should have:
    a. Demonstrated willingness and ability to play an active role in diabetes self-management to include frequent self-monitoring of blood glucose (SMBG), and to have frequent contact with their healthcare team.
    b. Completed a comprehensive diabetes education program.
4. The use of CSII over MDI regimens is not recommended in most patients with type 2 diabetes. [D]

DISCUSSION

The use of long- and rapid-acting insulin analogs for MDI appears to be superior to older regimens using NPH for basal insulin and Regular for bolus insulin. CSII safety and efficacy has also improved over the past decade owing to significant technologic advances in insulin pumps and the shift from use of Regular insulin to rapid-acting analogs. As greater experience was gained with use of CSII, the incidence of hypoglycemia declined significantly, and in fact some earlier studies (e.g., Bode, 1996) indicated that CSII was associated with a significant decrease in severe hypoglycemia in patients switched from MDI therapy. Modern insulin pumps offer the ability to set varying basal rates throughout the day, improving the ability to overcome the dawn phenomenon and to decrease nocturnal hypoglycemia. These advances over the past decade bring into question the relevance to older literature comparing CSII and MDI.

In patients with type 1 diabetes, CSII has been shown in randomized controlled trials to result in improved glycemic control as measured by HbA1c or fructosamine compared to MDI. (Hirsch et al., 2005, Hoogma et al., 2006) While the difference in HbA1c between groups was statistically significant in these two randomized controlled trials as well as three meta-analyses looking at adult patients (Fatourechi et al., 2009; Jeitler et al., 2008; Retnakaran et al., 2004), the absolute difference in HbA1c was in the range of 0.2 – 0.4%. The clinical significance of this degree of a reduction in HbA1c is uncertain.

Older studies comparing CSII to MDI regimens using NPH for basal control showed significant reduction in severe hypoglycemia in patients with type 1 diabetes. Newer long-acting analogs are also successful in reducing the incidence of nocturnal hypoglycemia observed in many patients using NPH-based regimens. This has brought into question whether newer MDI regimens using long-acting analogs are comparable to CSII with regard to incidence of severe hypoglycemia, fasting hyperglycemia due to the dawn phenomenon, and nocturnal hypoglycemia. One short-term randomized controlled trial showed that, compared to MDI using glargine as basal insulin, CSII was associated with less hyperglycemic and hypoglycemic excursions, less nocturnal hypoglycemia, and generally lower glucose values during the evening, nighttime and morning during monitoring with continuous glucose monitoring systems (CGMS) (Hirsch et al., 2005). Two meta-analyses that included studies using NPH-based MDI regimens showed no overall difference in the incidence of nocturnal, minor or severe hypoglycemia (Fatourechi et al., 2009; Jeitler et al., 2008), while another that included adults and children did show a significant reduction in severe hypoglycemia that was most apparent in adult patients. (Pickup et al., 2008) There are no randomized controlled trials comparing CSII to MDI using newer insulin analogs looking at the primary outcomes of reduction of glucose variability, severe hypoglycemia, dawn phenomenon, or nocturnal hypoglycemia. For patients who are experiencing these complications using MDI with newer insulin analogs, the ability to set variable basal rates on CSII could reasonably be expected to be beneficial.

There are some potential adverse effects associated with use of CSII which include increased cost, need for expert healthcare team to implement, potential malfunction (which could lead to DKA in patients with type 1 diabetes), and local skin complications at the insertion site such as infection.

In patients with type 2 diabetes, two randomized controlled trials comparing CSII to MDI (one using NPH, the other using glargine) showed similar improvement in glycemic controls, with no superiority of CSII over MDI (Herman et al., 2005; Raskin et al., 2003). Neither study showed any significant difference in hypoglycemia. A meta-analysis of these two studies was consistent with these findings. (Jeitler et al., 2008) While one study showed higher patient satisfaction in patients with type 2 diabetes on CSII compared to MDI, another showed no difference in QoL measures. Given the difference in cost and complexity of implementation of CSII over MDI with no clear benefit of CSII over MDI, there is no evidence to support the use of CSII in most patients with type 2 diabetes.

EVIDENCE STATEMENTS

Type 1 Diabetes

- In a 10 week randomized open label crossover study (each treatment 5 weeks) of 100 adults with type 1 diabetes comparing CSII and glargine-based MDI, CSII resulted in a lower fructosamine level and better CGMS profiles (last week of each period) but no difference in 8-point SMBG profiles. Subjects treated with CSII spent more time in the glucose range between 80 and 140, spending less time above and below that range as measured by area under the curve (AUC) based on CGMS monitoring during the last week of each treatment period. The major contributor to these outcomes was improved glycemic control during the nighttime and morning hours. CSII resulted in a higher rate of daytime hypoglycemia but reduced nocturnal hypoglycemia. Neither treatment resulted in “major” hypoglycemia. The authors concluded that because of the ability to fine tune basal rates with CSII, it may offer an advantage over MDI in controlling the dawn phenomenon and possibly curtailing the exacerbation of postprandial hyperglycemia at breakfast (Hirsch et al., 2005).
- In the 5-Nations trial, which was a 16 month randomized controlled multicenter crossover study of 272 adults with type 1 diabetes, compared to NPH-based MDI regimens CSII showed a 60% reduction in frequency of severe hypoglycemic episodes, though the absolute frequency of such events was rare (0.5 events per patient year vs. 0.2 events per patient year). There was also a reduction in episodes of mild hypoglycemia, better glycemic control as measured by HbA1c, less fluctuation of glucose levels, and a better overall score of the diabetes quality of life (QoL) questionnaire (Hoogma et al., 2005).
- There are no head-to-head comparisons of CSII and MDI regimens using glargine or detemir showing an improvement in the rate of severe hypoglycemia in patients with type 1 diabetes.
- A small meta-analysis of three studies with a total of 139 patients with type 1 diabetes showed that CSII was associated with better glycemic control (using fixed effects model; random effects model showed a 95% CI that crossed zero) as measured by HbA1c compared with MDI using insulin analogs. They found a larger effect on HbA1c associated with a higher baseline HbA1c, suggesting that patients with a higher baseline HbA1c benefit more from CSII than those already closer to goal (Retnakaran et al., 2004).

- In another systematic review and meta-analysis, CSII resulted in better glycemic control as measured by HbA1c than MDI in patients with type 1 diabetes, and no statistically significant difference for patients with type 2 diabetes, with no difference in incidence of hypoglycemic events. (Jeitler et al., 2007)
- A recent systematic review addressed the question of whether CSII benefits patients at high risk for hypoglycemia (whether CSII can help reduce incidence of hypoglycemia in such patients). For patients with type 1 diabetes CSII seemed to result in better glycemic control as measured by HbA1c than does MDI. Although trends favored CSII (less hypoglycemia), there was no significant difference in severe or nocturnal hypoglycemia between CSII and MDI. This review reported that pooled weighted mean difference in minor hypoglycemia favored MDI, but two of the three trials were in pediatric patients. The single study of adults with type 1 diabetes showed no significant difference (though trend was toward favoring MDI) (Fatourechi et al., 2009).
- A meta-analysis of 22 studies in adults and children with type 1 diabetes published between 1996 and 2006 showed a significant reduction in severe hypoglycemia compared with MDI. Although this analysis did not separate studies on adults from studies on children, there was a significantly greater reduction in severe hypoglycemia in older patients. Of note, there were no trials comparing CSII to MDI using newer long-acting analogs where severe hypoglycemia could be analyzed (Pickup et al., 2008).
- One systematic review studied quality of life issues in patients with type 1 diabetes on CSII (Barnard et al., 2007) One study (Tsui et al., 2001) of type 1 diabetes showed no differences between CSII and MDI with regard to QoL (glycemic outcomes not mentioned in the systematic review), while another (DeVries et al., 2002) showed improved glycemic control, general health status and health related QoL in patients with a long history of poor glycemic control.

Type 2 Diabetes

- A 24 week multicenter randomized parallel group study of 132 adults over age 35 with type 2 diabetes compared CSII with MDI therapy using NPH and aspart. Both groups achieved improvement in HbA1c, though there was no significantly significant difference between the two groups. Hypoglycemia was similar between the two groups. Patients using CSII were more satisfied with their diabetes management (convenience, flexibility, ease of use, overall preference) (Raskin et al., 2003).
- In a 12 month randomized controlled trial of 107 adults over age 60 with type 2 diabetes, there was no advantage in the use of CSII over MDI, though both approaches achieved excellent glycemic control and were associated with high patient satisfaction (Herman et al., 2005).
- A randomized crossover study (18 weeks for each treatment period) of 40 obese patients with type 2 diabetes showed improved glycemic control by HbA1c with CSII compared to MDI as well as reduced mealtime glycemic excursions based on CGMS, but this study compared CSII using lispro with an MDI regimen using NPH and regular insulin (Wainstein et al., 2005).
- Two reviews that included studies on type 2 diabetes showed no statistically significant difference between CSII and MDI with respect to glycemic control as measured by HbA1c and no difference in incidence of hypoglycemia. With respect to incidence of severe hypoglycemia, one review discussed that whether CSII can help reduce the incidence in patients at high risk for severe hypoglycemia has not been addressed since patients with prior severe hypoglycemia were excluded from the two trials that enrolled patients with type 2 diabetes (Fatourechi et al., 2009, Jeitler et al., 2007).
- There are no head-to-head comparisons of CSII and MDI regimens using glargine or detemir showing an improvement in the rate of severe hypoglycemia in patients with type 2 diabetes.

EVIDENCE TABLE

	Recommendation	Sources	LE	QE	SR
1	CSII for patients with poor glycemic control (including wide glucose excursions with hyperglycemia and hypoglycemia and those not meeting HbA1c goal)	Hirsch et al., 2005 Hoogma et al., 2006 Retnakaran et al., 2004 Jeitler et al., 2008 Fatourechi et al., 2009 Pickup et al., 2008	I	Fair to Good	A
2	CSII for patients with marked dawn phenomenon (fasting AM hyperglycemia)	Hirsch et al., 2005	I	Fair	B
3	CSII for patients with recurrent nocturnal hypoglycemia	Hirsch et al., 2005	I	Fair	B
4	CSII for patients with circumstances of employment, for example shift work, in which MDI regimens have been unable to maintain glycemic control	Working Group Consensus	III	Poor	I
5	Patients using CSII should have type 1 diabetes	Retnakaran et al., 2004 Hirsch et al., 2005 Hoogma et al., 2006 Barnard et al., 2007 Jeitler et al., 2008 Pickup et al., 2008 Fatourechi et al., 2009	I	Good	A
6	Patients using CSII should have demonstrated willingness and ability to play an active role in diabetes self-management to include frequent self-monitoring of blood glucose (SMBG)	Working Group Consensus	III	Poor	I
7	Patients using CSII should have completed a comprehensive diabetes education program	Working Group Consensus	III	Poor	I
8	Patients using CSII should have demonstrated willingness and ability to have frequent contact with their healthcare team.	Working Group Consensus	III	Poor	I
9	No evidence to support use of CSII over MDI regimens in most patients with type 2 diabetes	Raskin et al., 2003 Herman et al., 2005 Wainstein et al., 2005 Jeitler et al., 2008 Fatourechi et al., 2009	I	Good	D

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

J-5. Glycemic Control for Hospitalized Patients

BACKGROUND

Hyperglycemia during hospitalization is associated with adverse outcomes independent of diabetes. Importantly, glucose lowering interventions have been shown to reduce morbidity and mortality in some critically ill populations. However, establishing evidence-based guidelines for inpatient glycemic control is challenging due to the fact that trials have produced discrepant findings and in many cases have had methodologic problems limiting the conclusions that can be made. Overall, the evidence supports the treatment of hyperglycemia during hospitalization, in both patients with and without a diagnosis of diabetes. Evidence to support "tight" glycemic control (80-110 mg/dl) remains insufficient. Although there are few studies examining the benefits of more moderate glucose lowering, the overall body of literature supports treating hyperglycemia to glucose levels < 180 mg/dl. Most of the controversies have centered on the ideal and exact glucose target for hospitalized patients, as well as which populations would derive benefit from glucose lowering interventions. However, a growing body of evidence from hospitals throughout the country indicates that more basic aspects of diabetes and glucose management during hospitalization are often not addressed. The following recommendations are intended for hospitalized patients with hyperglycemia and/or diabetes mellitus (DM) but are not intended for those with diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic nonketotic syndrome (HHNS) or pregnancy.

RECOMMENDATIONS

1. In patients with known DM, it is reasonable to document the DM diagnosis in the medical record. Because of the potential harm from omission of insulin in patients with type 1 DM, it is suggested that the type of DM also be documented. [I]
2. In order to identify potentially harmful hyperglycemia and hypoglycemia, blood glucose monitoring may be ordered in hospitalized patients with diagnosed DM and/or hyperglycemia (BG > 180 mg/dl) on admission. There is no evidence to support a given frequency of monitoring. Therefore, the frequency of monitoring should be based upon clinical judgment taking into account the management of diabetes, the reason for admission, and the stability of the patient. [I]
3. Due to safety concerns related to potential adverse events with oral anti-hyperglycemic medications, it is prudent to thoughtfully review these agents in the majority of hospitalized patients. It may be reasonable to continue oral agents in patients who are medically stable and have good glycemic control on oral agents at home. [I]
4. For patients with DM and/or hyperglycemia who are not medically stable or who are poorly controlled with oral anti-hyperglycemic medications at home, initiating insulin therapy should be considered. It is appropriate to continue pre-hospitalization insulin regimens, but reasonable to reduce the dose in order to minimize the risk of hypoglycemia. In the ICU, continuous intravenous insulin infusion is recommended. Scheduled subcutaneous insulin is appropriate in the non-ICU setting and may include a long-acting basal insulin as well as a nutritional insulin for those eating discrete meals or receiving enteral nutrition. A supplementary correction (sliding) scale is also recommended but correction scale insulin regimens as sole therapy are discouraged. [B]
5. Insulin should be adjusted to maintain a BG < 180 mg/dl with the goal of achieving a mean glucose around 140 mg/dl. Evidence is lacking to support a lower limit of target blood glucose but based on a recent trial suggesting that blood glucose < 110 mg/dl may be harmful, we do not recommend blood glucose levels < 110 mg/dl. [A]
6. Insulin therapy should be guided by local protocols and preferably "dynamic" protocols that account for varied and changing insulin requirements. A nurse-driven protocol for the treatment of hypoglycemia is highly recommended to ensure prompt and effective correction of hypoglycemia. [I]
7. To minimize the risk of hypoglycemia and severe hyperglycemia after discharge it is reasonable to provide hospitalized patients who have DM and knowledge deficits, or patients with newly discovered hyperglycemia, basic education in "survival skills". [I]
8. Patients who experienced hyperglycemia during hospitalization but who are not known to have DM should be re-evaluated for DM after recovery and discharge. [B]

RATIONALE

Numerous controlled studies (randomized trials and meta-analyses)have examined either glucose lowering or insulin infusion in patients with critical illness and acute myocardial infarction. The questions addressed in these studies and the findings produced vary greatly. Controlled trials are lacking in patients admitted to general medical/surgical wards and with acute stroke, although high quality observational studies do exist for these populations. While there is little direct evidence specifically evaluating a blood glucose of < 180 mg/dl versus higher levels, the totality of evidence and the importance of avoiding abnormalities in fluid status from glucosuria, make this a prudent and safe upper limit for blood glucose level.

DISCUSSION

Glycemic control

Randomized trials examining glycemic control and/or insulin therapy are limited to the study of hospitalized patients with severe illness (ICU, acute myocardial infarction, acute stroke). There have been no controlled trials conducted in other settings. However, numerous observational studies, some of which are well controlled, have demonstrated a strong relationship between hyperglycemia and mortality or morbidity (Baker et al., 2006; Bruno et al., 2008; Falciglia et al., 2009; Kosiborod et al., 2005; McAlisyter et al., 2005; Pomposelli et al., 1998; Umpierrez et al., 2002).

Tight glycemic control

The term "tight" glycemic control is not uniformly defined in the literature, and this has led to confusion in discussions of published evidence on this topic. Although some studies have described even targets of glucose < 180 mg/dl as "tight", the most recognized concept of tight control was introduced by Van den Berghe et al. in a randomized trial of surgical ICU (SICU) patients that examined the effects of continuous insulin infusion to achieve a target glucose of 80-110 mg/dl (Van den Berghe et al., 2001). The investigators demonstrated that establishing normoglycemia resulted in substantial reductions in hospital and ICU mortality, bloodstream infections, renal insufficiency, and the need for mechanical ventilation and blood transfusions. Despite the enthusiasm for adopting tight glycemic control following publication of this study, subsequent trials have been unable to reproduce these results. The same investigators conducted a similar study in patients admitted to the medical ICU (MICU) (Van den Berghe et al., 2006a). Because the greatest benefit in the SICU study was observed in patients who remained in intensive care for over 5 days, the investigators powered the MICU study to demonstrate improved outcomes in those staying over 3 days. In this group, a significant decrease in mortality was observed, with absolute reductions comparable to their study of SICU patients. However, no significant mortality difference was demonstrated in the intent-to-treat or short-stay groups, although improvements for other important outcomes such as decreased incidence of renal insufficiency, accelerated weaning of mechanical ventilation, and shortened length of stay were demonstrated in the intent–to-treat group. Given the lack of mortality benefit in the short-stay group and the inability to predict how long a patient would require care, these results raised some debate about the overall benefits of tight glycemic control and whether it should be initiated on admission. Van den Berghe et al. performed a subsequent analysis in which they pooled data from their two previously published SICU and MICU studies, demonstrating that tight glycemic control not only reduced mortality in the long-stay group but also in the entire (intent-to-treat) cohort (Van den Berghe et al., 2006b). Mortality rates in the first 3 days of ICU care were similar.

The VISEP trial was a four-arm study examining both fluid resuscitation and tight glycemic control (80-110 mg/dl) in ICU patients with severe sepsis (Brunkhorst et al., 2008). The trial was stopped early due to high rates of hypoglycemia (17% vs. 4%). Although it did not demonstrate a mortality benefit from tight glycemic control, the trial was underpowered with only 537 subjects included in the final analysis. The recently published NICE-SUGAR trial has been able to shed some light on tight glycemic control as it included over 6000 patients at surgical and medical ICUs throughout Australia, New Zealand and Canada (Finfer et al., 2009). The investigators found no reduction in 90-day mortality (primary outcome) in the study group receiving tight control (mean glucose 115 mg/dl) versus the control group (mean glucose 144 mg/dl). It was also noted that although there was no significant difference in hospital or 28-day mortality between the 2 groups, there were significantly more deaths at 90 days in the intensively treated group, raising many questions about the possible causative factors of death at 90 days after 4 days of intensive glucose control.

There is little evidence from controlled trials that specifically addresses glycemic control in patients with acute stroke. The largest published trial examining tight glycemic control after acute stroke is the UK Glucose in Stroke Trial (GIST) that examined the effects of a 24-hour intervention with GIK infusion to keep blood glucose 72-126

mg/dl (Gray et al., 2007). Although no mortality benefit was observed, the mean glycemic difference between study and control groups was only 10 mg/dl with no difference in glucose levels at 24 hours. Furthermore, the trial was underpowered due to poor enrollment with only complete glucose data on 440 patients. Another small randomized trial of individuals suffering from subarachnoid hemorrhage demonstrated a reduction in post-operative infections in those receiving tight glycemic control (80-120 mg/dl) who had undergone aneurysm clipping (Bilotta et al., 2007). A systematic review of observational studies demonstrated increased mortality and poor functional recovery in those admitted with acute stroke and hyperglycemia (Capes et al., 2001).

There have been various small randomized trials also examining tight glycemic control, some of which demonstrated a benefit from normalizing blood glucose (Grey et al., 2004; Bilotta et al., 2007), but because most of these small studies lack statistical power, their findings are most appropriately considered within a cumulative meta-analysis. The most comprehensive meta-analysis to date, that includes data from the NICE-SUGAR trial is particularly informative because unlike most other systematic reviews in this field it includes only trials where glucose control was the goal and also distinguishes between trials of "very tight" (< 110 mg/dl) and "tight" glycemic control (< 149 mg/dl)) (Griesdale et al., 2009). This meta-analysis found that there was no mortality benefit for tight glucose control overall, but in the SICU a significant reduction in mortality was observed (RR 0.63; CI 0.44-0.91).

"Moderate" glycemic control

Moderate levels of glycemic control have not been well studied. The NICE-SUGAR trial demonstrated that achieving a blood glucose of 140-180 mg/dl resulted in lower 90 day mortality than tight glycemic control (80-108 mg/dl). However, there are few studies examining moderate control versus a lack of glycemic control, in part due to changes in clinical practice that challenge the ethics of allowing patients to become hyperglycemic without treatment. One of the earliest randomized trials of insulin therapy after acute myocardial infarction that predates more rigorous standards, the Diabetes and Insulin–Glucose Infusion in Acute MI (DIGAMI) trial, was able to demonstrate reduced mortality rates with glucose lowering < 180 mg/dl (Malmberg et al., 1997). Among the patients with admission blood glucose levels ≥ 200 mg/dl who received the intervention, mortality at one year decreased by 29%. A 58% relative reduction in hospital mortality in the intervention group was observed for the pre-defined sub-group of patients who were insulin naïve and low cardiovascular risk, but not for the intent-to-treat group. Nevertheless, since the intervention arm of DIGAMI included 3 months of intensive insulin therapy after discharge, it was not possible to discern whether the reduction in long-term morbidity and mortality was due to inpatient treatment, outpatient treatment, or the combination. DIGAMI-2 was designed to resolve this issue (Malmberg et al., 2005), but due to insufficient power, and again, the inability to reach treatment goals, was not successful in achieving this primary goal. Two subsequent studies of individuals with acute myocardial infarction that have been commonly interpreted as "negative" trials in respects to the benefits of glycemic control are the CREATE-ECLA (Mehta et al., 2005)and HI-5 studies (Cheung et al., 2006). However, because both trials failed to establish glycemic differences between intervention and control groups, they do not provide an adequate basis for examining the potential benefits of glucose lowering with insulin.

Lastly, two intervention studies examined more moderate glucose lowering with insulin therapy compared to historical controls. The "Portland Diabetic Project", a study of over 5,000 patients undergoing cardiac surgery, demonstrated that treating hyperglycemia with continuous insulin infusion reduced the risk of deep sternal wound infection and hospital mortality when compared to historical controls (Furnary et al., 2003; Furnary et al., 1999). Krinsley demonstrated reductions in mortality by lowering glucose to < 140 mg/dl in MICU and SICU patients (Krinsley 2004). However, like the Portland Project, this "before and after" design is less rigorous than a randomized study since many other changes taking place after the implementation of the intervention could have contributed to improved outcomes.

Limitations of trials and systematic reviews of insulin therapy in hospitalized patients

Randomized trials of insulin and glucose-lowering interventions have varied in the questions they have addressed, glucose levels studied and in the quality of methodology. As such, the discordant findings and interpretations of these trials and how they have informed the clinical practice of inpatient diabetes care and glycemic control have generated much controversy. Accordingly, this variation among trials has resulted in difficulty interpreting the systematic reviews that include these studies in their analyses. Therefore, it is important to understand and consider the differences among these intervention studies when assessing the evidence.

First, many of the trials examining insulin therapy in the hospital have specifically studied glucose-insulin-potassium (GIK) infusions with little or no regard to the glucose level or treatment of hyperglycemia. This is particularly evident in studies of patients with acute myocardial infarction (AMI). Systematic reviews that have

conducted separate analyses of studies using GIK (as opposed to insulin only infusions) have generally found that GIK interventions do not improve outcomes especially if glucose lowering is not a goal (Pittas et al., 2004; Pittas et al., 2006; Gandhi et al., 2008; Kansagara et al., 2008). Similarly, trials examining the effects of isolated insulin infusion where glucose control is not a goal also have failed to show benefit. In sum, the evidence suggests that insulin treatment in hospitalized patients without the correction of hyperglycemia fails to improve outcomes. This is an important point because in several randomized trials where no benefit was observed from intervention with insulin infusion the glucose levels in the intervention group were similar (Malmberg et al., 2005; Cheung et al., 2006; Gray et al., 2007) and in some cases *higher* than the control groups (Mehta et al., 2005).Therefore, these trials do not address the effects of glycemic control and should be used cautiously in making decisions on glycemic control. Systematic reviews that include such trials also warrant careful interpretation (Pittas et al., 2004; Pittas et al., 2006; Gandhi et al., 2008; Wiener et al., 2008; Kansagara 2008).

Another related difference among trials to note is the ability to establish glycemic differences between study and control groups and if present, the size of difference between glucose levels. As standards of care have improved over the years, it has become increasingly difficult to design a study where the control group is sufficiently more hyperglycemic than the intervention group to demonstrate a difference in outcome. The mean glucose at 24 hours of the control group in the DIGAMI-1 study (Malmberg 1997) was 211 mg/dl. In contrast the mean glucose of the control group in the recent NICE-SUGAR trial was 144 mg/dl. This has several implications: First, trials such as NICE-SUGAR are examining the effects of "tight" glycemic control versus "good" glycemic control, not poor glycemic control and therefore the absence of treatment benefit observed cannot be used to justify hyperglycemia in the hospital setting. Second, a narrower gap between glucose levels in both groups requires a larger sample size , such as that of NICE-SUGAR to have sufficient power to observe a significant benefit. The requirement of such large samples has limited the power of several randomized trials unable to demonstrate a benefit from glucose lowering (Brunkhorst 2008; Malmberg et al., 2005). Lastly, the improved standards of care over time makes it more likely that the trial will fail to establish any significant glycemic difference between study and control groups at all as was observed in the DIGAMI-2 trial (Malmberg et al., 2005).

Other important differences among inpatient insulin therapy trials include variable glucose targets and unknown glycemic variability; for instance, a mean glucose of 140 mg/dl in one trial may represent an average of many hypoglycemic and hyperglycemic episodes which may have markedly different effects on outcome than what is observed in another trial where mean glucose is 140 mg/dl with little standard deviation. Such information is not provided by most trials and this lack of information also limits the interpretation of systematic reviews that cannot account for these differences. Similarly, there are differences in protocols among trials. This includes frequency and method of glucose measurement. Trials where glucose is measured infrequently may underestimate the rate of hypoglycemia which could significantly impact outcomes. Furthermore, it has been demonstrated that POC testing, although the most practical method, is often inaccurate in critically ill patients and thus, a trial that uses a glucose analyzer (e.g., YSI) may more accurately capture and treat hypoglycemia than one which simply uses capillary measurements – these differences may also influence outcomes.

There are significant differences among trials in case-mix related to diabetes, admission diagnosis and severity of illness. A large observational study (Falciglia et al., 2009) demonstrated that the relationship between hyperglycemia and mortality varies by admission diagnosis. Therefore, the disparate findings observed in trials may be related to differences in the case-mix of the units studied. Whether or not individuals have diabetes has been found to modify the relationship between hyperglycemia and mortality and importantly, a combined analysis by Van den Berghe of both SICU and MICU studies (Van den Berghe et al., 2006b) demonstrates that normalization of blood glucose improved outcomes for those without a diagnosed diabetes but not for those with diabetes. Therefore, the balance of individuals with and without diabetes in these trials may impact their ability to demonstrate treatment benefits with glucose lowering (Arabi et al., 2008). The differences in illness severity may influence the potential benefits of insulin treatment. The mean APACHE score of the largest randomized trials have been variable and this might explain some disparity in findings. It is important to note that systematic reviews are unable to adequately account for these differences in case-mix among the trials included in their analyses.

Lastly, it is important to note that while much of the controversy and attention has focused on the ideal glucose target, there are many ways in which the care of hospitalized individuals with diabetes and hyperglycemia can be improved. Many recent investigations of hospitals throughout the country have revealed that there is a high prevalence of severe hyperglycemia (BG > 200 mg/dl), infrequent documentation of diabetes and hyperglycemia, and a lack of orders for blood glucose monitoring (Boord et al., 2009; Cook et al., 2007a; Knecht et al., 2006; Matheny et al., 2008; Schnipper et al., 2006; Umpierrez et al., 2007; Wexler et al., 2007a; Wexler et al., 2007b;).

These studies also reveal that oral agents are often used rather than insulin, and when insulin is ordered, sliding scale monotherapy is common. Lastly, insulin is infrequently adjusted after the initial order.

Hypoglycemia

Hypoglycemia is the most common complication associated with inpatient glycemic control, and is one of the leading adverse outcomes limiting the quality of trials addressing the benefits of intensive glycemic control (Brunkhorst et al., 2008; Gandhi et al., 2008; Finfer et al., 2009). In a recent meta-analysis by Griesdale et al., among the trials that reported hypoglycemia, the pooled relative risk with intensive insulin therapy was 6.0 (95% CI 4.5-8.0)(Griesdale et al., 2009). As such, the fear of hypoglycemia remains one of the most common barriers to the implementation of inpatient diabetes care strategies. Studies of hypoglycemia during hospitalization have identified factors that increase the risk for hypoglycemia; some of these include heart failure, renal or liver disease, malignancy, infection, or sepsis. Additional precipitating factors which can further increase the likelihood of inducing hypoglycemia include changing clinical condition, reduction of corticosteroid dose, reduction in the amount of nutrition (e.g. interruption of enteral feeding or intravenous dextrose, NPO status), vomiting, and inappropriate timing of short- or rapid-acting insulin in relation to meals (Smith et al., 2005; Krinsley et al., 2007; Fischer et al., 1986). Therefore, in order to prevent and promptly manage hypoglycemia, standardized protocols to treat hypoglycemia should be in place for nurses to implement immediately without an additional order from the physician. As with other adverse events in the hospital, instances of severe hypoglycemia should be documented and a root-cause analysis can be helpful. Monitoring such episodes and analyzing their cause can be used to eliminate future occurrences of these episodes.

Some studies have demonstrated a relationship between hypoglycemia and increased mortality, however it is unclear if hypoglycemia is a marker of severe illness that is frequently observed in individuals with serious comorbidities such as sepsis, hepatic and renal failure, or if it is a direct cause of adverse outcomes. Several recent studies that control for these comorbidities or segregate the analysis based on spontaneous versus iatrogenic hypoglycemia are reassuring in that they have demonstrated no association between iatrogenic hypoglycemia and mortality (Kagansky et al., 2003; Vriesendorp et al., 2006; Kosiborod et al., 2009). Nevertheless it remains unclear what the consequences of hypoglycemia are during severe illness and how these sequelae may vary based on acute vs. chronic complications or susceptibility in different disease states.

Oral anti-hyperglycemic agents

Various circumstances and conditions related to hospitalization increase the likelihood of adverse effects typically associated with the use of oral agents. These include derangements in renal, cardiovascular, and hepatic function; changes in hemodynamic and fluid status; frequent changes in nutritional status; a rapidly changing clinical condition; and imaging studies requiring contrast. Because of the safety concerns, the use of oral agents should be discouraged for most hospitalized patients. However, in some hospitalized patients who are medically stable and have been controlled prior to admission with oral agents, the continuation of these medications may be of less risk than the initiation of insulin.

Insulin

Insulin is encouraged as an anti-hyperglycemic agent for hospitalized patients because it is able to address both basal and nutritional needs separately and is the only anti-hyperglycemic agent that allows intravenous infusion for critically ill patients with poor subcutaneous absorption (e.g. edema, hypotension, vasopressors). Furthermore, the rapidity of onset of action as well as flexibility in a variety of conditions makes insulin an ideal medication for glycemic management in inpatient setting (Inzucchi, 2006).

When given subcutaneously, insulin should be prescribed with specifications for a basal, nutritional, and correction dose. The basal insulin dose, which is meant to suppress hepatic gluconeogenesis in the non-fed state can be calculated based on body weight for the insulin–naïve patient or based on previously known total daily dose of insulin at home for patients who have been on insulin. A recent study suggests that decreasing the total daily insulin dose of the patient's home regimen by 20-25% is prudent given the observation that initiating the total home insulin dose is associated with higher rates of hypoglycemia during hospitalization (Umpierrez et al., 2009). The nutritional insulin, meant to correct glycemic excursions related to meals, should be tailored to the nutritional regimen, which could be discrete meals, enteral or total parenteral nutrition. Basal insulin is an important component of an effective insulin regimen. It should not be withheld in those individuals with "NPO" status, and is critical for an individual with type 1 diabetes in whom withholding basal insulin can precipitate diabetic ketoacidosis (Clement et al., 2004; Inzucchi 2006). The "sliding scale" method of insulin delivery is an algorithm for insulin orders to treat

hyperglycemia in reaction to hyperglycemia after it has already occurred. When administered as the only insulin regimen, sliding scale often results in both recurrent hyperglycemia and hypoglycemia. There are several studies which have shown that "sliding scale" as a sole treatment regimen for hyperglycemia is not effective (Queale et al., 1997; Golightly et al., 2006; Schnipper et al., 2006; Umpierrez et al., 2007). This "reactive" method has been largely replaced by a more "proactive" strategy that instead anticipates a patient's insulin requirements. A regimen of basal and/or meal time insulin in conjunction with "correction dose" insulin offers the most physiologic method of insulin administration in the hospital setting (Inzucchi 2006).

Models of implementation and basic principles of an inpatient glycemic control program

Despite evidence to support the treatment of inpatient hyperglycemia and also published strategies for how to manage hyperglycemia effectively in the hospital setting, the challenge lies in the implementation of this evidence-based practice and dissemination of relevant knowledge to the front line providers directly involved with patient care (Moghissi et al., 2005). Several models for the hospital-wide implementation of glycemic management practices are available. For instance, a consultant model utilizes the expertise of an endocrinologist or diabetes specialist providing recommendations and guidance as requested by the primary physician or team. An advantage of this approach is that it requires less specialized knowledge among hospital staff about glycemic control practices since the consultation team assumes primary responsibility. However, a disadvantage of this approach is that one consultation team can only evaluate a limited number of the many patients who develop hyperglycemia throughout the hospital at any given time, and furthermore many facilities do not have specialists available to provide such consultative services. A model that has the advantage of more widespread implementation is a "system –wide" strategy. In this approach, a team, ideally multidisciplinary, of hospital staff develops nurse-driven protocols for the entire institution and provides support and education to all hospital staff on the use of these protocols. While this model may have the most far-reaching impact on an institution's adaptation of glycemic management practices, it requires continuous education of hospital staff and willingness to learn about and accept new clinical practices.

Irrespective of the type of model chosen, the successful implementation of an inpatient glycemic control initiative requires a team of providers who are committed to the common goal of improving glycemic control at the institution (Moghissi et al., 2005). Including the front line providers who are directly involved with and affected by the process of glycemic improvement at the institution is key. Involving representatives from different disciplines who can contribute their expertise, (e.g. medical house staff, nurses, pharmacists, nutritionists and dietary services) facilitates the development of policies and algorithms which are both applicable and acceptable to hospital staff. Support from the hospital administration is important, not only in terms of drafting and enacting policy but also to mobilize necessary resources, to engage ancillary departments such as information system groups, and to promote the initiative as an important priority. Strong leadership from those who have the commitment, knowledge and capacity to generate enthusiasm among staff and foster collaboration between different disciplines and sections of the hospital is important and should be encouraged (Moghissi & Hirsch, 2005; Wexler et al., 2007a; Wexler et al., 2007b).

Standardization of care facilitates the widespread, safe and effective implementation of glycemic control practices. Among the numerous aspects of inpatient diabetes management that can be incorporated into standardized order sets are scheduled blood glucose monitoring, algorithms for intravenous and subcutaneous insulin administration, protocols for the treatment of hypoglycemia, and dietary orders that are tailored for individuals with diabetes or hyperglycemia (e.g. consistent carbohydrate). There are several published protocols currently available for intravenous insulin, both manual as well as computerized, which have been reviewed and compared in a recent review (Wilson et al., 2007). Most of them are effective in reducing hyperglycemia and the choice of infusion protocol can be based upon the institution's needs and resources. An ideal intravenous insulin infusion protocol is dynamic and accounts for variation in insulin sensitivity and requirement. With dynamic protocols the dose of insulin per hour is easily titrated based on not only the blood glucose level but the rate of change. The ideal protocol should also be nurse-driven without the need to obtain additional orders from the physician after its initiation

Education is a key component that should be provided on a continuing basis. This becomes especially important at institutions with graduate medical education programs in which there is a constant influx of new hospital staff. Lack of knowledge and familiarity with specific requirements of in-house glycemic management is one of the more common reasons underlying lack of adherence to evidence-based-practices or "clinical inertia" among prescribing physicians (Cook et al., 2007a; Cook et al., 2007b; Rubin et al., 2007). Frequent and ongoing in-service training is useful to ensure competency among healthcare providers in caring for hospitalized individuals with diabetes and hyperglycemia (Donaldson et al., 2006; Schnipper et al., 2006). The training should include a review of insulin action depending on different types and routes of administration. Special emphasis should be placed on the

importance of not withholding insulin in those with type 1 DM as well as how to prevent, identify and treat hypoglycemia. Practitioners should be made aware of how to dose insulin with the various modes of nutrition and based on other factors that contribute to hyper or hypoglycemia such as changes in clinical condition and feeding status, and glucocorticoid use. Educational programs should emphasize that blood glucose data need to be analyzed daily and the treatment regimen adjusted to match changing insulin requirements.

Nurses play a key role in every step involved with glycemic management and need to be regarded as leaders in inpatient diabetes initiatives. Early recognition of hyperglycemia, accurate performance of bedside blood glucose measurement, properly timed administration of insulin that is appropriately coordinated with meals, attention to changing nutrition or clinical condition, and prompt identification and treatment of hypoglycemia are just a few examples where nurses can play a critical role. Because nurses are front line providers of care, they must be included in the development and implementation of diabetes management programs and protocols; such collaboration is critical if these initiatives are to be successful.

Medical nutrition therapy is an integral part of glycemic management and it is important to involve dietary experts in the planning of inpatient diabetes care. Insulin orders should be able to meet the specifications of dietary orders and often, physiologic insulin regimens such as basal-bolus approaches must be modified to address the complex nutritional status during hospitalization. For instance, regular insulin given every 6 hours may provide better coverage for patients receiving continuous enteral nutrition, and regular insulin might be added to total parenteral nutrition so that if the infusion is interrupted for any reason hypoglycemia can be prevented (Moghissi & Hircsh, 2005).

EVIDENCE TABLE

	Evidence	Sources	LE	QE	SR
1	Documentation of known diabetes or hyperglycemia in the medical record	The Joint Commission, Working group consensus	III	Poor	I
2	Blood glucose monitoring may facilitate identification of hyperglycemia and hypoglycemia	Meijering et al., 2006 The Joint Commission	III	Poor	I
3	Hospitalization and acute illness may increase the likelihood of adverse events	Working group consensus	III	Poor	I
4	Continuous IV insulin infusion is safe and most effective treating hyperglycemia in the ICU. Scheduled subcutaneous insulin regimens appear to be preferable to correction (sliding) scale insulin monotherapy. Hypoglycemia may be more common when total pre-hospitalization insulin dose is continued in the hospital.	Meijering et al., 2006 Umpierrez et al., 2009 Umpierrez et al., 2007 Observational: Queale et al., 1997 Golightly et al., 2006 Schnipper et al., 2006 Umpierrez et al., 2002	I II-1	Fair	B

5	Treating hyperglycemia to glucose < 180 mg/dl is effective in improving outcomes in the surgical and medical ICU, appears to be effective in those with AMI, and may be effective in those with acute stroke. Hyperglycemia is independently associated with increased morbidity and mortality in patients with acute stroke and in general medical/surgical wards. Blood glucose < 110 mg/dl may be harmful.	**ICU** Griesdale et al., 2009 Wiener et al., 2008 Pittas et al., 2006 Van den Berghe 2001, 2006a, 2006b Finfer et al., 2009 Grey et al., 2004 Krinsley et al., 2004 Furnary et al., 1999, 2003 **AMI**: Malmberg et al., 1997, Cheung 2006, Observational: Capes et al., 2001, Kosiborod et al., 2005, 2009, Falciglia et al., 2009 **Stroke:** RCT: Bilotta et al., 2007 Observational: Capes et al., 2001 Falciglia et al., 2009	I I II-2	Good	A
6	Insulin treatment protocols, particularly those that are dynamic, are effective in treating hyperglycemia and avoiding hypoglycemia. Hypoglycemia treatment protocols may expedite treatment of hypoglycemia.	Meijering et al., 2006 DeSantis et al., 2006, Wilson et al., 2007	I III	Good	A
7	Patient education of "survival skills" at discharge may minimize hypoglycemia and severe hyperglycemia after discharge.	The Joint Commission	III	Poor	I
8	Hyperglycemia in hospitalized patients without known DM may represent unrecognized DM.	Norhammer et al., 2002 Ishihara et al., 2006	II-3	Fair	B

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

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 may 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.

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. 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 follow-up visits for the patient with diabetes who is meeting treatment goals and who has 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.

APPENDIX G-1

Measurements of Glycemic Control

The correlation between tests of glycemic control and HbA_1c, even using the National Glycosylated Standardization Program reference standard, may differ by methodology, age, race, and by comorbid conditions.

- Certain HbA_1c measurements may also be unreliable in the presence of the following conditions: hemolytic anemia, uremia, chronic kidney disease or pregnancy.
- HbA_1c is higher for a given level of glycemic control in older individuals and minority patients than in Caucasians.
- The measurement of HbA_1c is subject to red cell survival, and the composition of red cell hemoglobin

Measurements of Glycemic Control

1. For long-term glycemic control (past 3 months), HbA_1c is the preferred method unless the patient has a clinical condition (acute blood loss, iron deficiency anemia, significant chronic renal insufficiency, severe anemia.)
2. Clinical laboratories should use methodologies that are certified to the National Glycosylated Standardization Program (NGSP; ngsp.org). However, even use of certified assays does not mean that a laboratory result is directly comparable to the NGSP reference standard, or that there is no interference from hemoglobinopathies.
3. Relative to the DCCT standard, some methods (such as HPLC) tend to overestimate, while immunoassays tend to underestimate true A1c values ("bias").
4. Clinicians should recognize that any HbA_1c value from any laboratory has measurement error associated with it (the intra-assay coefficient of variation). In order to achieve National Glycosylated Standardization Program certification an HbA_1c value must be within ±8% of the referent standard in 2010, and ±6% in 2011. This has implications for the way HbA_1c levels are interpreted as to whether a patient has or has not achieved their glycemic control target. As an example, an HbA_1c value of 7% could vary by up to 0.5% within the same assay. The National Glycosylated Standardardization Program web site should be accessed for the most up-to-date information (ngsp.org).
5. Target values for glycemic control do not have to be a whole number since HbA_1c is a continuous risk factor. It should be understood that achieving the goals must not occur at the expense of safety; that small differences from goal may not have significant impact upon absolute risk reduction of complications. Also, goals can and should be modified (upward or downward) as clinical circumstances or patient preferences warrant.
6. Point of Care (POC) HbA_1c methodologies are available. However, in June 2009 the National Glycosylation Standardization Program noted the following: "There was much concern regarding the lack of data on POC methods, the fact that these methods are CLIA-waived means that users of the methods are not required to participate in the CAP survey. Nonetheless these methods are widely used, especially in the developing world, and therefore it is important to know how well they are performing in the field." Local facilities should develop their own policies for supervision of POC in practice and inform clinicians of the likely variance between these test results and those obtained in the clinical laboratory. This information needs to be communicated to clinicians using the tests.

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.

APPENDIX G-2

FDA Approved Combination Therapy

	Metformin	**Sulfonylurea SU**	**Acarbose**	**Miglitol**	**Repaglinide/ nateglinide**	**Pioglitazone/ rosiglitazone**	**Sitagliptin/ Saxagliptin**	**Exenatide Liraglutide**	**Pramlintide**	**Insulin**
Metformin		X	X		X	X	X	X		X
Sulfonylurea (SU)	X		X	X		X	X	X		X
Acarbose	X	X								X
Miglitol		X								
Repaglinide/ nateglinide	X					X				
Pioglitazone/ rosiglitazone	X	X			X		X	X		X**
Sitagliptin/ Saxagliptin	X	X				X				X†
Exenatide Liraglutide	X	X				X				
Pramlintide										X‡
Insulin	X	X	X			X**	X†		X‡	

** *Rosiglitazone + insulin not recommended*

† *Sitagliptin is approved for use with insulin*

‡ *In Type 2 diabetes, insulin + pramlintide may be used with or without a concurrent sulfonylurea agent and/or metformin.*

APPENDIX G-3

Pharmacotherapy Table*

Drug Class‡	Average § HbA_1c Reduction	Potential for Hypoglycemia	Clinical Considerations	Adverse Events
Insulin (prandial) *Short-acting* Regular *Rapid-acting analog* Aspart Glulisine Lispro Insulin (basal) *Intermediate-acting* NPH *Long-acting analog* Detemir Glargine **Premixed** NPH/Regular (70/30, 50/50) Biphasic insulin aspart (70/30) Insulin lispro protamine/lispro (75/25, 50/50)	Variable	Moderate - significant risk	• Use well established • Most effective at lowering elevated glucose • Dosing can be individualized • Beneficial effect on triglycerides and HDL-C • Contraindicated in those with hypersensitivity to insulin • Precaution in concomitant use with potassium-lowering drugs or drugs sensitive to serum potassium level • Dose adjustment needed for renal and hepatic impairment • Inexpensive (human insulin); moderately expensive (analogs)	• Hypoglycemia • Hypersensitivity reactions • Weight gain • Injection site reactions • Anaphylaxis

Sulfonylureas *2nd generation* Glipizide Glipizide XL Glyburide Glyburide miconized Glimepiride *1st generation* sulfonylureas (chlorpropamide, tolbutamide, tolazamide) seldom used	1.0-2.0%	Minimal-significant risk (glipizide is associated with the least risk and glyburide with the most risk)	• Use well-established • No difference in long-term efficacy or failure rate has been demonstrated among the sulfonylureas • Contraindicated in those with hypersensitivity • Use in patients with sulfonamide allergy is not specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. • Concomitant use of glyburide and bosentan is contraindicated • Glyburide not recommended if Clcr <50mL/min • The majority of the glycemic benefits are realized at half-maximal dose. Higher doses should generally be avoided. • Inexpensive	• Hypoglycemia • Hypersensitivity (urticaria, pruritus, morbilliform or maculopapular eruption, etc.). Angioedema, arthralgia, myalgia, and vasculitis have been reported. • Weight gain • GI (nausea, epigastric fullness, heartburn) • May cause hypoglycemia or disulfuram reaction (rare) if used with alcohol

Biguanides Metformin Metformin XR	1.0-2.0%	Negligible risk as monotherapy	• Use well-established • May restore ovulation in premenopausal anovulatory females • Monitor renal function prior to and at least annually thereafter • Weight neutral or slight weight loss • Decrease LDL-C • Contraindicated in: o Renal dysfunction (serum creatinine ≥ 1.5mg/dL [males]; ≥ 1.4mg/dL [females] or abnormal creatinine clearance , 30ml/min) o Acute or chronic metabolic acidosis • Temporarily discontinue metformin at the time of or prior to intravascular iodinated radio contrast studies and withhold for 48 hours after the procedure. Reinstitute only after renal function has been reevaluated and found to be normal. • Temporarily discontinue for surgical procedures (except minor procedures not associated with restricted intake of food or fluids). Do not restart until oral intake has resumed and renal function has been evaluated as normal. • Do not use if patient is ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced; do not titrate to maximum dose. • In general, avoid metformin in patients with clinical or laboratory evidence of hepatic disease • Patients should be warned against excessive acute or chronic alcohol use. • Discontinue metformin in the presence of cardiovascular collapse • Patients with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia are at increased risk of lactic acidosis • Inexpensive	• Potential for lactic acidosis when used in patients for whom the drug is contraindicated • Transient dose-related GI symptoms (nausea, vomiting, bloating, flatulence, anorexia) • Decrease in vitamin B12 levels

Alpha-glucosidase Inhibitors Acarbose Miglitol	< 1.0%	Negligible risk as monotherapy	• Allows for flexible meal dosing • Dose taken with first bite of each main meal • If patient misses or adds a meal, omit or add a dose respectively • Use not recommended if serum creatinine > 2.0mg/dl • Contraindicated in the presence of intestinal complications (e.g., inflammatory bowel disease, colonic ulceration, intestinal obstruction, digestion or absorption disorders) • Acarbose is contraindicated in patients with cirrhosis (miglitol pharmacokinetics are not altered in cirrhosis and may be used) • Weight neutral • Serum transaminase should be checked every 3 months during first year of treatment and periodically thereafter • To reverse hypoglycemia (usually only in setting of combination therapy),treat with oral glucose, not sucrose • Moderately expensive	• GI symptoms (diarrhea, abdominal pain, flatulence) which can limit adherence to therapy • AST/ALT elevation
Meglitinides Repaglinide Nateglinide	1.0-2.0% (repaglinide) < 1.0% (nateglinide)	Minimal-moderate risk (although less so than SU in context of missed meals)	• Allows for flexible meal dosing • Taken 1-30 minutes before a meal • Unknown long-term outcomes • If patient misses or adds a meal, omit or add a dose respectively • Do not use in patients who have failed sulfonylurea therapy or combine with sulfonylurea • Co-administration of repaglinide with gemfibrozil is contraindicated • Use repaglinide cautiously in hepatic impairment or severe renal impairment • Use nateglinide cautiously in moderate to severe hepatic impairment • Expensive	• Weight gain • Hypoglycemia

Thiazolidinediones Pioglitazone Rosiglitazone	1.0-1.5%	Negligible risk as monotherapy	• Contraindicated in New York Heart Association Class III and IV heart failure • Do not initiate in patients with active liver disease or ALT > 2.5 x the upper limit of normal • Slow onset of action (6-12 weeks for full effect) • May restore ovulation in premenopausal anovulatory females • Rosiglitazone not recommended in combination with insulin • Not recommended in symptomatic heart failure • Periodic monitoring of serum transaminases • Increase HDL-C (3-5mg/dL) • Very expensive	• Edema • Weight gain • Decrease hemoglobin/ hematocrit • Fractures in females (rare) • Exacerbate heart failure • Macular edema (rare) • Increase LDL-C
GLP-1 agonists Exenatide	1.0%	Minimal - moderate risk	• Weight loss • Unknown long-term outcomes • Not recommended in patients with: -Prior history of pancreatitis -Creatinine clearance less than 30 mL/min, end stage renal disease, or receiving dialysis - Gastrointestinal disease, severe (eg, gastroparesis) • Instruct patients to contact their provider if they experience persistent severe abdominal pain which may be accompanied by vomiting (may indicate pancreatitis) • Discontinue use if pancreatitis suspected • Not a substitute for insulin in insulin requiring patients. Do not use in type 1 diabetes for treatment of diabetic ketoacidosis • Use with caution in patients receiving oral medications that require rapid gastrointestinal absorption • Very expensive	• GI effects (nausea, vomiting, diarrhea) • In combination with a sulfonylurea, may increase the risk of hypoglycemia • Dehydration • Pancreatitis, acute, including hemorrhagic and necrotizing pancreatitis; post marketing cases, including fatalities, have been reported • Anaphylaxis, angioedema, hypersensitivity reactions • Reports of altered renal function

Amylin analogs Pramlintide	<1.0%	Moderate - significant risk	• Used as adjunctive therapy in those who have failed to achieve adequate glycemic control despite individualized insulin therapy • Use in patients receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes team • Unknown long-term outcomes • Increased injection burden • Slight weight loss • Black Box Warning: increased risk of insulin-induced severe hypoglycemia (usually seen within 3 hours following a pramlintide injection). Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk. • Contraindicated in those with confirmed diagnosis of gastroparesis or hypoglycemia unawareness • Pramlintide should NOT be considered if patient: - Has HbA1c > 9% - Has shown poor compliance with insulin regimen - Requires drugs that stimulate gastrointestinal motility - Has had recurrent episodes of severe hypoglycemia requiring assistance within past 6 months - Pediatric patients • Do not mix pramlintide and insulin in the same syringe; must be administered as separate injections • Administer subcutaneously into abdominal or thigh areas at sites distinct from concomitant insulin injections (do not administer into arm due to variable absorption) • Administer concomitant oral agents, where rapid GI absorption is a critical determinant of effectiveness, at least 1 hour prior to or 2 hours after pramlintide injection • When drawing up doses from vial, inadvertent calculation of dose based on “units” rather than mL has resulted in overdose of pramlintide • Very expensive	• Nausea • Hypoglycemia • Injection site reactions

Dipeptidyl peptidase-4 Inhibitors Sitagliptin Saxagliptin	<1.0%	Negligible risk as monotherapy	• Weight neutral • Dose adjustment needed for renal impairment • Unknown long-term outcomes • Very expensive	• Hypersensitivity reactions • Possible increased risk of upper respiratory infections

* *Table is not intended to be inclusive of all clinical considerations and adverse events, but rather to highlight some of the major points*

‡ *Drug Classes are listed according to number of years since approval of the first agent in that class*

§ *Patients who are drug therapy naïve or have higher baseline* HbA_1c *values may have a greater reduction in* HbA_1c *than values shown in the table*

Appendix G-4

Comparison of Insulin Preparation [a, b]

Insulin	Onset (hours)	Peak (hours)	Duration (hours)	Compatible Mixed With	Appearance / Role
Prandial (bolus) Insulin					
RAPID-ACTING					
Aspart (Novolog®)	0.17-0.33	0.67-0.83	3-5	NPH [c]	Clear / covers insulin needs at the time of the injection.
Lispro (Humalog®)	0.25-0.50	0.5-1.5	3-5	NPH	
Glulisine (Apidra®)	0.33-0.50	0.5-1.5	3-4	NPH in subcutaneous use only (but not in IV or infusion pump)	
SHORT-ACTING					
Regular (Novolin R®, Humulin R®)	0.5-1	2-5	5-8	NPH	Clear / covers insulin needs for meals eaten within 30-60 minutes.
Basal Insulin					
INTERMEDIATE-ACTING					
NPH (Novolin N®, Humulin N®)	1-1.5	4-12	24	Regular	Cloudy / covers insulin needs for about half the day or overnight. Often combined with rapid- or short-acting insulin.
LONG-ACTING					
Glargine (Lantus®)	1.1	- [d]	20-24	Not to be mixed with other insulins	Clear / covers insulin needs for about 1 full day. Often used, when needed, with rapid- or short-acting insulin
Detemir (Levemir®)	1-2	6-8	Up to 24	Not to be mixed with other insulins	
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 / generally taken twice a day before mealtime.
75% intermediate/25% lispro (Humalog mix 75/25) 50% intermediate/50% lispro (Humalog mix 50/50)				Not to be mixed with other insulins	
70 % insulin aspart protamine recombinant; 30% insulin aspart recombinant (Novolog mix 70/30) 50 % insulin aspart protamine recombinant; 50% insulin aspart recombinant (Novolog mix 50/50)				Not to be mixed with other insulins	

a Adapted from Facts and Comparisons 4.0; available at: www.online.factsandcomparisons.com/Insulin.mht and Web MD available at: http://diabetes.webmd.com/diabetes-types-insulin. Accessed 16 June 2009.

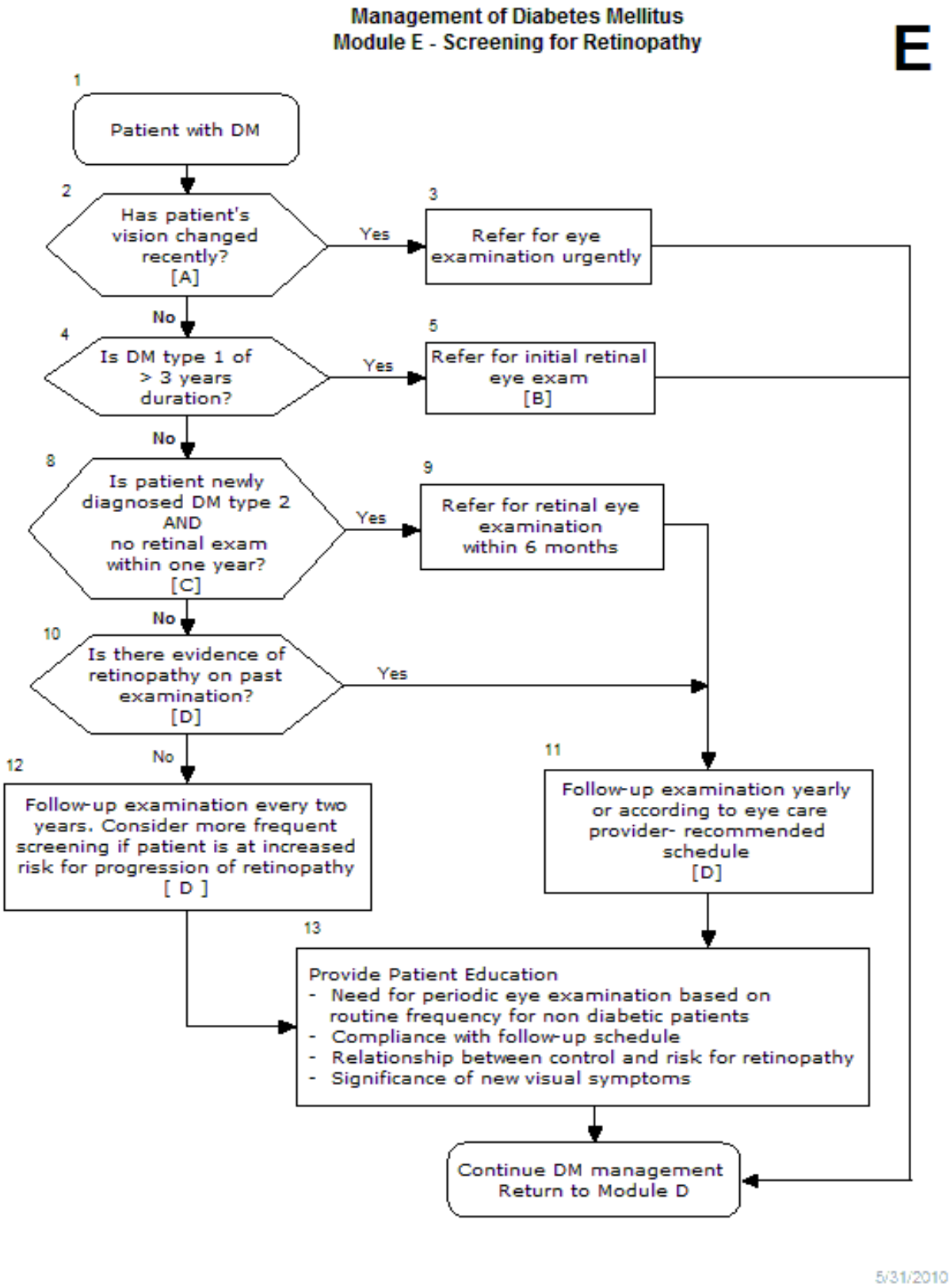
b The time course of action is intended as a general guide as many factors may influence these parameters (e.g., type of preparation, dose, site of administration, and patient related variables).

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

d No pronounced peak; small amounts of insulin glargine are released slowly, resulting in a relatively constant concentration/time profile over 24 hours.

MODULE E– EYE CARE

ALGORITHM


Management of Diabetes Mellitus
Module E - Screening for Retinopathy
E
1
Patient with DM
2
Has patient's vision changed recently? [A]
Yes
3
Refer for eye examination urgently
No
4
Is DM type 1 of > 3 years duration?
Yes
5
Refer for initial retinal eye exam [B]
No
8
Is patient newly diagnosed DM type 2 AND no retinal exam within one year? [C]
Yes
9
Refer for retinal eye examination within 6 months
No
10
Is there evidence of retinopathy on past examination? [D]
Yes
No
12
Follow-up examination every two years. Consider more frequent screening if patient is at increased risk for progression of retinopathy [D]
11
Follow-up examination yearly or according to eye care provider- recommended schedule [D]
13
Provide Patient Education
- Need for periodic eye examination based on routine frequency for non diabetic patients
- Compliance with follow-up schedule
- Relationship between control and risk for retinopathy
- Significance of new visual symptoms
Continue DM management
Return to Module D
5/31/2010

MODULE E– EYE CARE

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 or a change in ocular function should be urgently referred to an eye care provider.

DISCUSSION

Symptoms such as blurring or loss of vision, severe pain or light sensitivity, double vision, distortion, floaters, or light flashes may indicate a serious ocular problem. Such complaints require urgent referral to an eye care provider. Visual symptoms clearly associated with fluctuations in blood glucose should be distinguished from those that are not, as the former will typically resolve as glycemic control is improved. Nevertheless, it is prudent to seek consultation with an eye care provider in all instances where there has been a sudden change in vision.

B. Refer patients with Type 1 DM for Initial Eye Retinal Examination

OBJECTIVE

Establish the timing of the initial ocular evaluation for patients with early onset DM or type 1 DM at a later age.

RECOMMENDATIONS

1. Patients with either early diabetes onset (age <30 years) or type 1 diabetes at a later age should have an initial examination when the time from diabetes diagnosis is >3 years. [B]

DISCUSSION

The risk for retinopathy in patients with type 1 diabetes becomes significant after 3 to 5 years of disease. Patients are unlikely to develop clinically apparent retinopathy within 3 years of onset, but the prevalence rises steadily after that and may approach 30% by the fifth year (Klein et al., 1984a & 1984b). Patients who do develop retinopathy within 3 years of diagnosis may progress more rapidly than those who do not (Malone et al., 2001). Patients who develop type 2 diabetes in youth or as young adults are also at risk for developing retinopathy although incidence rates are generally lower up to approximately 5 years after diagnosis (Krakoff et al. 2003). Thus, it is recommended that the initial screening for the presence of retinopathy not be deferred beyond 3 years in individuals with onset of diabetes in youth or young adulthood or in individuals with type 1 diabetes at later ages.

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	Initial Screening for Retinopathy in patients with Type 1 Diabetes with early onset (age <30 years) should begin annual evaluations when the duration of the diabetes diagnosis is greater than 3 years	Klein et al., 1984a & 1984b Malone et al., 2001 Krakoff et al., 2003	I	Fair	B

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

C. Refer Patient with Type2 DM for Initial Eye Retinal Examination

OBJECTIVE

Establish the timing of the initial ocular evaluation for patients with type 2 DM.

BACKGROUND

Patients with newly diagnosed type 2 DM may have had several years of sub-clinical or clinical diabetes prior to being diagnosed. Retinopathy can develop during this time and up to 40 percent of patients will have evidence of diabetic eye disease at the time their diabetes is diagnosed. Although the prevalence of vision threatening retinopathy at the time of diagnosis is very low, there is a 3-4 percent prevalence of proliferative retinopathy within the first few years of disease. Consequently, it is recommended that patients with new onset type 2 DM who have not had a dilated eye examination within the prior 12 months should have one performed within 6 months.

RECOMMENDATIONS

1. Patients who are newly diagnosed with type 2 DM and have not had an eye exam within the past 12 months should have a retinal examination performed within 6 months [B]
2. A retinal examination (e.g. dilated fundus examination by an eye care professional or retinal imaging with interpretation by a qualified, experienced reader) should be used to detect retinopathy. [A]

DISCUSSION

The quality of the eye examination is a critical factor in the ability to detect early retinopathy, thus only qualified eye care professional or trained readers using validated imaging techniques should be utilized for retinopathy screening and surveillance. Ophthalmoscopy should be performed through dilated pupils using high magnification and stereo viewing. Fundus photography is also highly sensitive in detecting clinically significant retinopathy and when combined with interpretation by an experienced reader, may exceed the sensitivity of ophthalmoscopy in retinopathy detection. Non-mydriatic digital retinal imaging (i.e. fundus photography through a non-dilated pupil) also provides excellent sensitivity. In some cases small pupils and/or media opacities will cause image degradation (Whited et al., 2006). The combination of non-mydriatic digital retinal imaging with referral to an eye care specialist for patients in whom image quality is sub-optimal is an appropriate screening strategy as it can achieve a very high level of sensitivity in the detection of retinopathy. In some cases, selective use of mydriatic eye drops to facilitate improved image quality will enhance the diagnostic utility of digital retinal imaging.

EVIDENCE TABLE

	Recommendation	Sources	LE	QE	SR
1	Initial Screening for Retinopathy in patients with Type 2 Diabetes who have not had an eye exam within the past 12 months and are newly diagnosed with type 2 DM should have a retinal examination performed within 6 months.	UKPDS 38 1998 Javitt et al., 1989, 1994, 1996 Nathan et al., 1991 Vijan et al., 2000	I	Fair	B
2	A retinal examination (e.g. dilated fundus examination by an eye care professional or retinal imaging with interpretation by a qualified, experienced reader) should be used to detect retinopathy.	Diabetic Retinopathy Study Research Group 1981 ETDRS Research Group 1993 DCCT Research Group, 1993 Harding SP, BMJ 1995	I	Good	A

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

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

OBJECTIVE

Establish a follow-up interval for patients based on the risk for retinopathy development or progression.

RECOMMENDATIONS

1. Patients who have had no retinopathy on all previous examinations should be screened for retinopathy at least every other year (biennial screening). More frequent retinal examinations in such patients should be considered when risk factors associated with an increased rate of progression of retinopathy are present. [B]
2. Patients with existing retinopathy should be managed in conjunction with an eye care professional and examined at intervals deemed appropriate for the level of retinopathy. [I]

DISCUSSION

The inability of symptoms alone to accurately predict the presence or severity of retinopathy necessitates regularly scheduled retinal examinations for patients with diabetes. Some patients will remain retinopathy-free for several years, but the course of diabetic eye disease cannot be reliably predicted for a given individual. Risk factors for progression of retinopathy include: poorly controlled HbA_1c (e.g. >9.0), rapid and substantial HbA_1c improvement (a decrease of approximately 2% or greater over <6 months), insulin use, the presence of microvascular disease including pre-existing retinopathy, nephropathy or cardiac autonomic neuropathy, longer duration of disease, hyperlipidemia, and poorly controlled blood pressure (e.g. systolic > 160 mm Hg). In light of these associations, it is prudent to perform more frequent retinal examinations in such patients. Clinicians should exert caution in extending biennial examinations to patients with factors associated with a higher likelihood of retinopathy progression.

Duration of disease is most strongly associated with retinopathy in individuals with type 1 DM. The prevalence of proliferative retinopathy approaches 30% after 15 years of diabetes and may rise to as much as 50% after 20 years. Although the prevalence of proliferative disease is lower in type 2 diabetes, the prevalence of any retinopathy approaches 75% in insulin-treated patients with longer duration of diabetes and the prevalence of proliferative retinopathy may exceed 20%. Different patients may exhibit separate and unique rates of retinopathy development or progression, but the likelihood of ocular involvement increases with duration of diabetes.

Macroalbuminuria (i.e. nephropathy) and lower extremity amputation are also associated with the presence of retinopathy. Although the relationship may not be causal, these patients typically have long-standing or advanced complications from diabetes and are likely to have other evidence of microvascular disease.

Pregnancy may be associated with rapid deterioration of existing retinopathy and a higher risk of progression to vision threatening disease. A woman with pre-existing diabetes who becomes pregnant should be examined at the time of diagnosis and if she has greater than minimal retinopathy, repeat examinations should be performed at 4-6 week intervals. Proliferative retinopathy or clinically significant macular edema should be treated promptly. Those with less severe retinopathy should be monitored closely throughout their pregnancy (i.e. during each trimester). In the absence of an eye examination within the previous twelve months, patients who are pregnant should have an expedited appointment for a retinopathy evaluation. In addition, regardless of the timing of the last eye examination, the patient's eye care provider should be notified of the pregnancy.

Retinopathy of any level can progress rapidly over the course of a year and occasionally even mild retinopathy will progress to proliferative retinopathy within that time frame. As follow-up intervals shorter than 12 months may be indicated for some of these individuals, patients with retinopathy who have not had a retinal exam within the previous year should be referred for an expedited retinal evaluation. Patients who have previously undergone laser therapy have already reached the stage of vision threatening diabetic eye disease. These patients require close follow up and in the absence of information to the contrary should be considered at high risk for vision loss and receive an expedited examination if they have not had one within the previous year.

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	Patients who have had no retinopathy on all previous examinations should be screened for retinopathy at least every other year (biennial screening). More frequent examinations in such patients should be considered when risk factors associated with an increased rate of progression of retinopathy are present. Patients with existing retinopathy should be managed in conjunction with an eye care professional and examined at intervals deemed appropriate for the level of retinopathy.	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

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

MODULE F – FOOT CARE

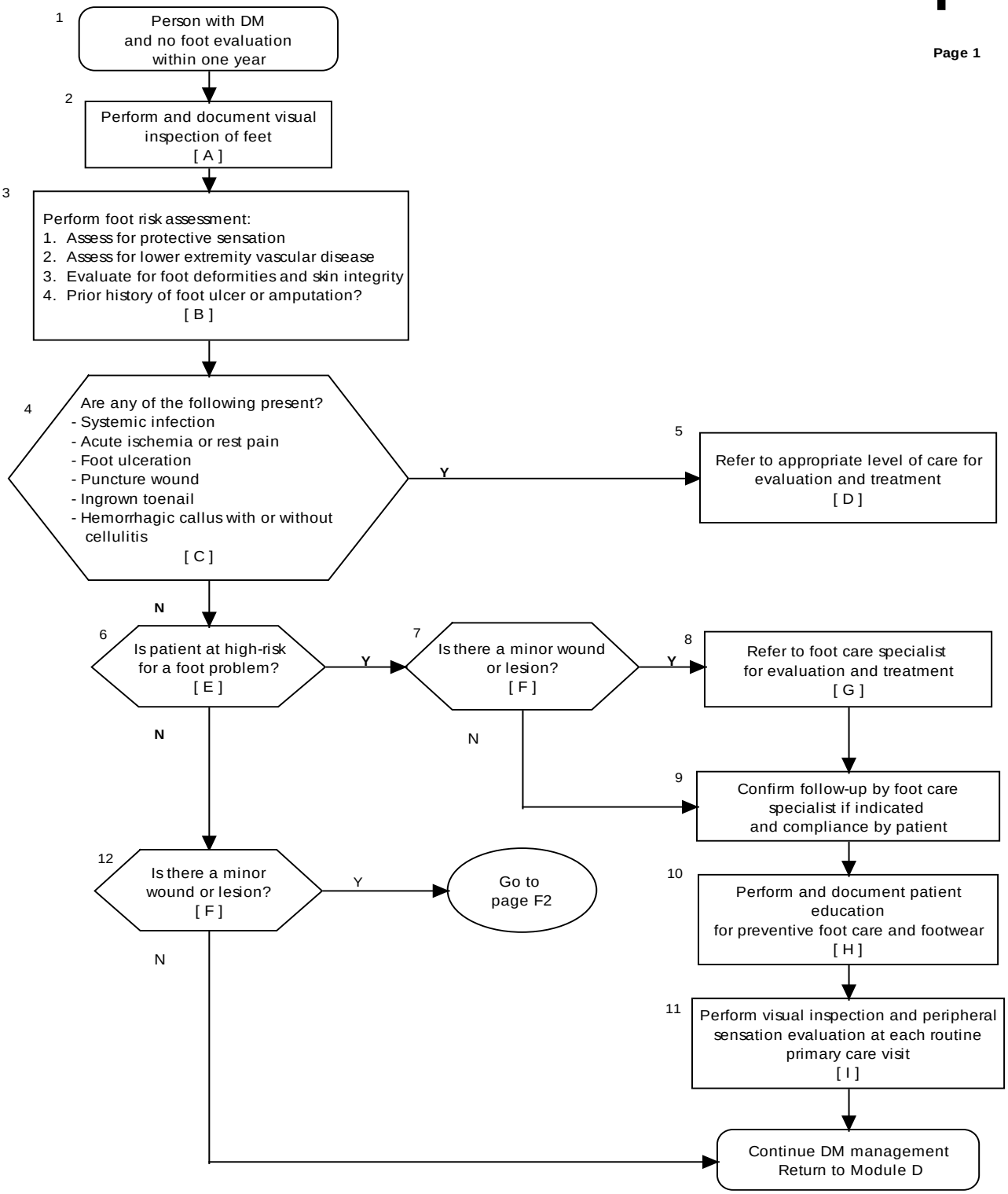
.

ALGORITHM

Management of Diabetes Mellitus
Module F - Foot Care

F

Page 1



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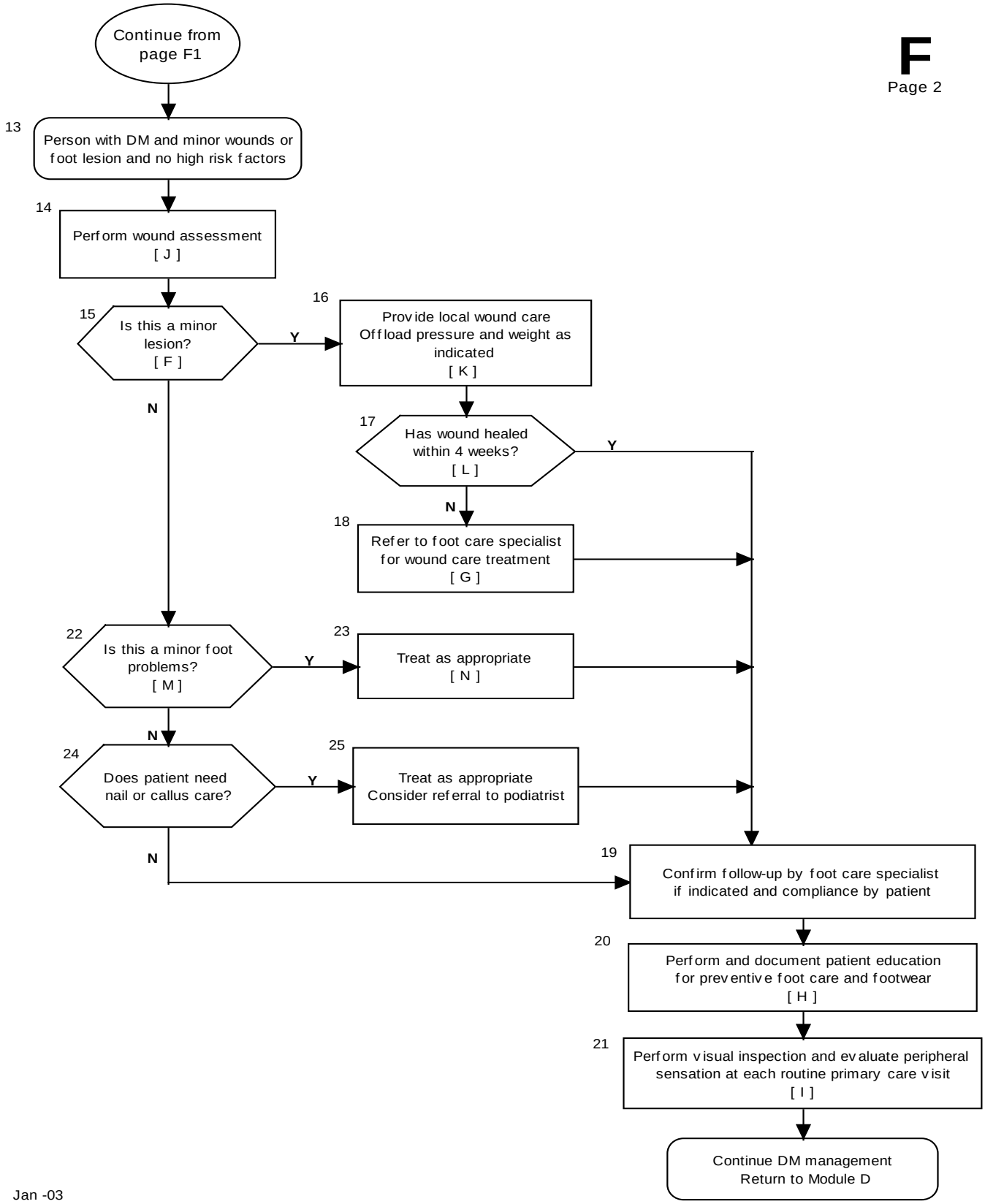
F
Page 2



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: [I]
   - 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 (including ADA), 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	LE	QE	SR
1	Visual inspection of the feet at every routine primary care visit.	ADA, 2002 Working Group Consensus	III	Poor	I

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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	LE	QE	SR
1	Foot risk assessment.	ADA, 2002 Mayfield et al., 1998 Mayfield et al., 2000	III II II	Fair	B

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (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 hemorrhagic 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, 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, 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 (Carringtonl. et al., 2001).

Foot Ulceration

Active foot ulcer - 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	LE	QE	SR
1	Assessment of peripheral vascular disease.	Carrington et al., 2001 Orchard , 1993	II-1 III	Fair	B
2	Evaluation for acute ischemia or rest pain.	Orchard , 1993	III	Poor	I
3	Evaluation for foot ulceration.	ADA, 2002 Brodsky , 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

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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.

Discussion

The patient with cellulitis, 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	LE	QE	SR
1	Referral for limb-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

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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.

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.

EVIDENCE

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

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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. Extra-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. Extra-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 an extra-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	LE	QE	SR
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

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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 recommended.
- 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	LE	QE	SR
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 in high-risk patient 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 of 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:* consider 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	LE	QE	SR
1	Local wound care.	ADA, 2000 Brodsky, 1991 Caputo et al., 1994 Eckman et al., 1995	III	Poor	I

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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	LE	QE	SR
1	Assessment of wound healing progress within 4 weeks.	ADA, 2000	III	Poor	I

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of 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. 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

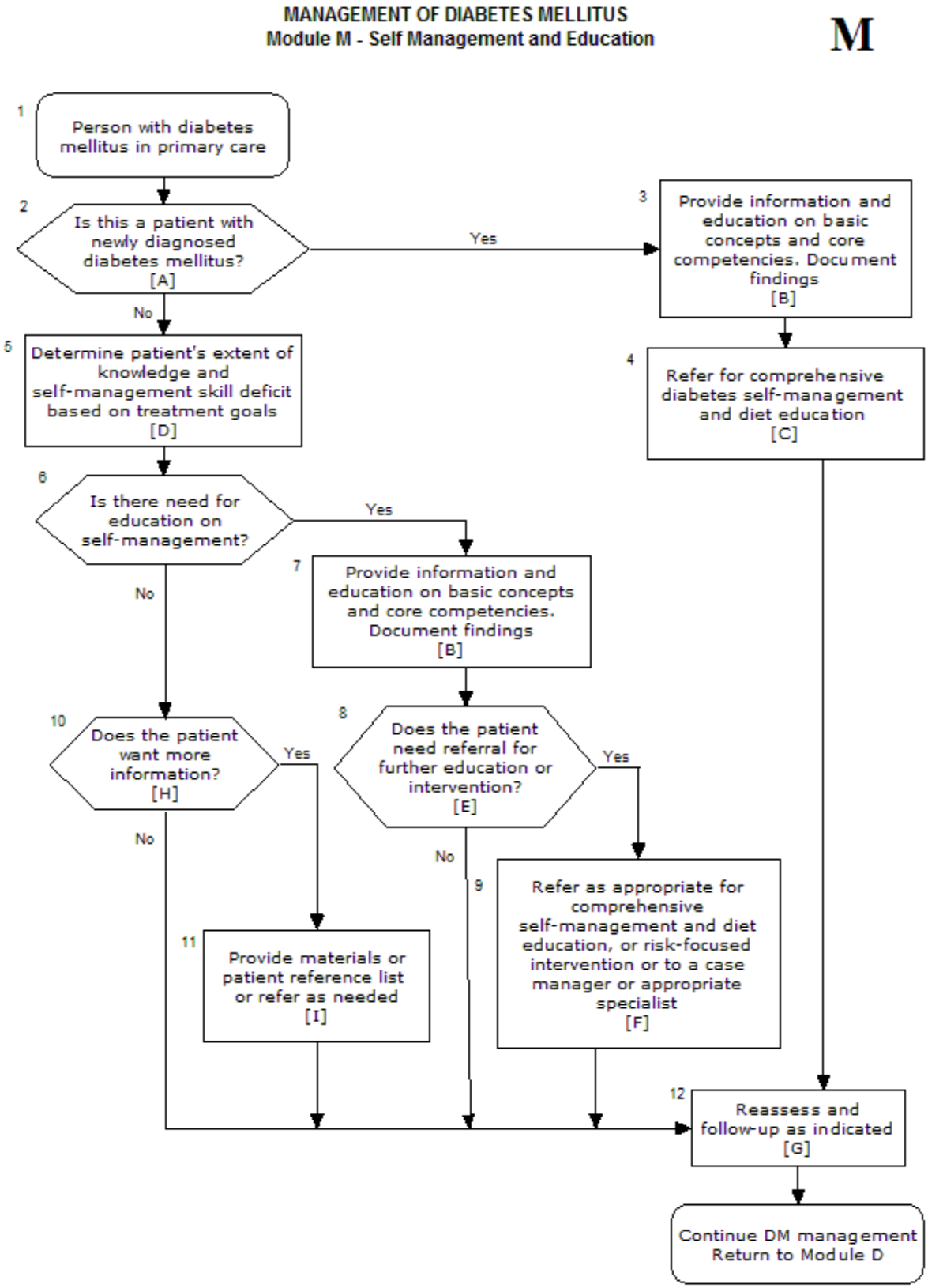
	Recommendation	Sources	LE	QE	SR
1	Treatment of minor foot problems, as appropriate.	Ahroni, 1993	III	Poor	I
		Barth et al., 1991	II		
		Fain & Melkus, 1994	III		
		Feste, 1991	III		
		Weir et al., 1994	III		

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A).

MODULE M – SELF-MANAGEMENT AND EDUCATION

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.

ALGORITHM


MANAGEMENT OF DIABETES MELLITUS
Module M - Self Management and Education
M
1
Person with diabetes mellitus in primary care
2
Is this a patient with newly diagnosed diabetes mellitus? [A]
Yes
3
Provide information and education on basic concepts and core competencies. Document findings [B]
4
Refer for comprehensive diabetes self-management and diet education [C]
No
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?
Yes
7
Provide information and education on basic concepts and core competencies. Document findings [B]
No
8
Does the patient need referral for further education or intervention? [E]
Yes
No
9
Refer as appropriate for comprehensive self-management and diet education, or risk-focused intervention or to a case manager or appropriate specialist [F]
10
Does the patient want more information? [H]
Yes
No
11
Provide materials or patient reference list or refer as needed [I]
12
Reassess and follow-up as indicated [G]
Continue DM management
Return to Module D

MODULE M: SELF-MANAGEMENT& EDUCATION 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) as well as 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. The core competencies include:

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

(See Appendix M-1: Core Competencies [Survival Skills] for Patients with Diabetes).

DISCUSSION

Core competency education addresses basic principles of diabetes management. Individuals receiving insulin, and other high-risk populations may benefit from a comprehensive DSME program.

Patient education materials identified in the following appendices as well as other patient education materials can be made available to the patient in the office setting to assist the healthcare team in addressing additional concepts and information not included in the core competencies:

C. Refer for Comprehensive Diabetes Self-Management and Diet Education

OBJECTIVE

Provide or refer for comprehensive Diabetes Self-Management Education (DSME) and Medical Nutrition Therapy (MNT) education.

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.
2. DSME, including MNT education, 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

3. The education component should be tailored to the patient's needs and provided by healthcare professionals who are most knowledgeable in the topic. Regardless of setting, availability of a multidisciplinary team approach is highly desirable and could include, but is not limited to, a dietitian, certified diabetes educator, registered nurse, pharmacist, psychologist, exercise physiologist, physical therapist, social worker, endocrinologist, behaviorist, ophthalmologist, optometrist, physician, podiatrist, other healthcare professionals and paraprofessionals, or other specialized physicians based on the individual patient's needs.
4. The use of approaches such as group visits and telehealth should be considered in providing education.

DISCUSSION

DSME is the cornerstone of care for all individuals with diabetes who want to achieve successful health-related outcomes. The National Standards for DSME are designed to define quality diabetes self-management education that can be implemented in diverse settings and will facilitate improvement in healthcare outcomes (Mensing et al., 2000). These standards are reviewed and revised approximately every 5 years by key organizations and federal agencies within the diabetes education community to reflect advances in scientific knowledge and healthcare. The most recent revision was approved in March 2007 (Funnell et al., 2009) and identified 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) to achieve glycemic targets
- Monitoring blood glucose, monitoring blood or urine ketones (when appropriate), and using the results to improve control
- Preventing, detecting, and treating acute complications
- Preventing, detecting, and treating chronic complications
- Developing personal strategies to identify and address psychosocial issues and concerns
- Developing personal strategies to promote health and behavior change
- Promoting preconception, pregnancy, and gestational diabetes management when applicable.

While the importance of a multi-disciplinary approach has been demonstrated (Borgermans et al., 2009), demonstration of the effectiveness of each of the components of a comprehensive program awaits further study. However, their inclusion is recommended based on expert opinion and research. 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 & Goldstein, 1972; Rubin et al., 1998). Moreover, it is difficult to assess the unique contribution of education independent of other factors (Colagiuri & Eigenmann, 2009). 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. Ellis et al. (2004) conducted a systematic review (meta-analysis and meta-regression) of articles published from 1990 through 2000. Twenty-one RCTs with 2439 participants were included. Educational techniques represented included didactic teaching, dictated goal setting, negotiated goal setting, situational problem solving, cognitive reframing, and "other" unique teaching methods. The significant heterogeneity notwithstanding, this meta-analysis indicated that patient education improves glycemic control in patients with diabetes (net change in HbA_1c was 0.32). Change from baseline to post intervention HbA_1c was greater for intervention group and was significant for as long as 52 weeks, depending upon the type of analysis used. The meta-regression suggests that several attributes of patient education seem to predict improved glycemic control including face-to-face interaction, cognitive reframing teaching methods, and programs that integrated an exercise component.

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.

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

Davies et al., (2008) reported the results of a multicenter cluster randomized trial involving 824 adults with newly diagnosed type 2 diabetes (55% men, mean age 59.5 years) in 207 general practices in 13 primary care sites in the United Kingdom. The intervention was a six hour, community based, structured group education program provided by two trained healthcare educators and compared to usual care. The intervention resulted in greater improvements in weight loss and smoking cessation and positive improvements in beliefs about illness but no difference in HbA_1c levels up to 12 months after diagnosis.

There is some evidence-based work on the effectiveness of MNT. In a 6-month RCT evaluating the impact of MNT on glycemic control, Franz et al. (1995) reported that 94 patients who received 3 ongoing MNT visits from registered dietitians (RD) had a mean 10.5 point lower fasting plasma glucose (FPG) level compared to a 5.3 decrease in 85 patients who had a single visit with an RD and no improvement in 62 patients who did not receive any MNT from an RD. Education may also be given in different modes. See Annotation J.

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	Provision of comprehensive DSME and MNT education.	Davies et al., 2008	I	Good	A
		Ellis et al., 2004	I	Good	B
		Funnell et al., 2009	III	Good	B
		Colagiuri et al., 2009	II-2	Good	B
		Corabian & Harstall, 2001	II-2	Fair	B
		Miller et al., 2002	II-2	Fair	
		Norris et al., 2001, 2002a	III	Poor	
		Rickheim et al., 2002	I	Fair	B
2	Setting behavioral goals and determining a follow-up schedule with patient.	Garcia and Suarez, 1996	II-3	Fair	
		Glasgow et al., 1992	I	Good	
		Pascale et al., 1995	I	Good	
3	Assessment of patient's knowledge of DM and understanding about self-care.	DCCT, 1997	I	Good	A
		UKPDS 24, 1998			
4	Provision of specialized referrals when necessary.	Aubert et al., 1998	II-1	Fair	B
		Franz et al., 1995	II-2	Fair	
		Norris et al., 2002b	I	Good	
		Sikka et al., 1999	II-2	Fair	
5	Education provided in either individual or group settings.	Rickheim et al., 2002	I	Fair	B
		Scain et al., 2009	I	Fair	B
		Duke et al., 2009	I	Fair	B
		Raji et al., 2002	I	Good	B

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (see Appendix A)

D. 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. Documentation of the patient's learning needs, abilities including physical and cognitive limitations, or language barriers, preferences, cultural and religious practices, emotional barriers, health literacy and numeracy, desire and motivation to learn and/or change, and the financial implications of care choices.
3. Assessment and documentation of the patient's understanding of education.

DISCUSSION

Diabetes self-management is an active, ongoing process that will change as patients' situations change. A useful framework for patient centered diabetes education includes the following self-care behaviors:

- Eating healthy foods
- Getting 30 to 60 minutes of physical activity on most days of the week
- Monitoring
- Taking medications
- Solving Problems
- Reducing risks
- Learning to cope with stress

E. 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.

BACKGROUND

Because primary care appointments frequently do not provide adequate time to address background and educational issues, referrals or additional appointments to address the patient's needs may be required. As patients often present with complex combinations of educational, treatment, coordination of care, psychosocial, and/or financial issues, they may benefit from a more in-depth, risk-focused education or intervention. When appropriate, refer for follow-up education in a comprehensive DSME program or to a provider/specialist to evaluate and address additional needs. Medication adherence should be addressed if patients are not meeting goals.

RECOMMENDATIONS

1. Conditions that may warrant risk-focused intervention include:
   - Markedly or persistently elevated HbA_1c (For appropriate HbA_1c target based on risk stratification, see Module G: Table G-1).
   - Progression to ESRD (e.g., stage 3-5 CKD)
   - Lower extremity complications
   - Pregnancy, or planned pregnancy, or woman of child bearing age
   - Impaired vision
   - Severe psychosocial or economic barriers
   - Cognitive impairment or frailty
   - Intensive insulin therapy

- Recurrent hypoglycemia or hypoglycemia unawareness
- Recent hospitalization for diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state 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.

F. 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: case manager, registered nurse, registered dietitian, pharmacist, psychologist, exercise physiologist, physical therapist, social worker, endocrinologist, ophthalmologist, optometrist, physician, podiatrist, behaviorist, other healthcare professionals, or paraprofessionals.
2. Refer to case manager for providing ongoing, detailed coordination of care for high-risk patients.

DISCUSSION

In the IDEATel study (Shea et al., 2009), nurse case managers were trained in diabetes management and in the use of computer-based case management tools to facilitate interactions through videoconferencing with a large, ethnically diverse sample of elderly Medicare beneficiaries with diabetes residing in medically underserved areas. Compared to the usual care group, the telemedicine case management intervention achieved sustained reductions in HbA_1c, LDL-cholesterol, and systolic and diastolic blood pressure levels over 5 years of follow-up. Differences (95% CI) in year 5 were 0.29 (0.12, 0.46)% for HbA_1c, 3.84 (0.08, 7.77) mg/dL for LDL cholesterol, 4.32 (1.93, 6.72) mm Hg for systolic blood pressure, and 2.64 (1.53, 3.74) mm Hg for diastolic blood pressure. Differences were present at 1 year of follow up and were sustained over five years for the three main endpoints. Multifactorial improvement has greater clinical significance than improvement in single risk factors. All-cause mortality did not differ over the 5 years of follow-up between the intervention and usual care.

King & Wolfe, (2009) compared the effectiveness of disseminating guidance from a central diabetes specialist clinic to primary care centers with access to midlevel provider services and usual care on HbA_1c, LDL cholesterol, and systolic blood pressure (SBP). Interventions included telephone consultations, bimonthly visits with diabetes specialists, and weekly diabetes clinics were made available. Mean HbA_1c values decreased from baseline by 0.46% in the active treatment group versus 0.06% in the control group; however, reductions in HbA_1c did not achieve statistical significance potentially because of the small sample size of the experimental group. Mean SBP values were significantly reduced in both groups; however, LDL-C was only significantly reduced in the control group, where more aggressive use of statins may have had an effect. Despite the inconsistencies in risk factor reduction, the study provided insights regarding the importance of electronic records and provider notifications, patient adherence, prioritization of provider resources by risk factor level among patients, and access to self-management education.

In a review of six trials involving 1382 participants who were followed for 6 to 12 months, Loveman et al., (2003) determined that HbA_1c in the intervention groups was not found to be significantly different from the control groups over a 12 month follow up period. One study demonstrated a significant reduction in HbA_1c in the presence of the diabetes specialist nurse/nurse case manager at 6 months. Significant differences in episodes of hypoglycemia and hyperglycemia between intervention and control groups were found in one trial. Where reported, emergency admissions and quality of life were not found to be significantly different between groups. No information was found regarding BMI, mortality, long term diabetic complications, adverse effects, or costs. The presence of a diabetes specialist nurse / nurse case manager may improve patients' diabetic control over short time periods, but from currently available trials the effects over longer periods of time are not evident. There were no significant

differences overall in hypoglycemic episodes, hyperglycemic incidents, or hospital admissions. Quality of life was not shown to be affected by input from a diabetes specialist nurse/nurse case manager.

Norris et al. (2002b) performed a systematic review of the effectiveness and economic efficiency of disease management and case management for people with diabetes in managed care organizations and community clinics in the United States and Europe. The evidence supported the effectiveness of disease management on glycemic control, screening for diabetic retinopathy, foot lesions and peripheral neuropathy, and proteinuria, and on lipid monitoring. The use of case management in managed care setting for adults with type 2 diabetes in the United States improved both glycemic control and provider monitoring of glycemic control. Moreover, case management was shown to be effective when delivered in conjunction with disease management, and with one or more additional educational, reminder, or support interventions.

EVIDENCE

	Recommendation	Sources	LE	QE	SR
1	Provision of specialized referrals when necessary.	Aubert et al., 1998 Franz et al., 1995 Sikka et al., 1999	II-1 II-2 II-2	Fair Fair Fair	B A
3	Use of case manager to improve outcomes	Loveman et al., 2003 § Machado et al., 2007 § Norris et al., 2002b §	I	Good	A

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation §=Systematic Review (see Appendix A)

G. 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

The importance of individualization and tailoring sessions to participants' needs has been amply documented (Colagiuri et al., 2009; Duke et al., 2009), but there is no definitive evidence to support specific frequencies of follow-up. Frequency of appointments has been reported from weekly to annually. Frequency of re-assessment should be based on the patient's and provider's perceptions 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.

H. 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.

I. 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.

J. Methods for Providing DSME

BACKGROND

There is a wide variety of means to provide self-management education and to promote self-management behaviors. Choose the method most consistent with the patient, clinical, and organizational contexts.

RECOMMENDATIONS

The following overriding principles were based on existing evidence used to guide the review and revision of the DSME Standards:

1. Diabetes education is effective for improving clinical outcomes and quality of life, at least in the short-term.
2. DSME has evolved from primarily didactic presentations to more theoretically based empowerment models.
3. There is no one "best" education program or approach; however, programs incorporating behavioral and psychosocial strategies demonstrate improved outcomes. Additional studies show that culturally and age appropriate programs improve outcomes and that group education is effective.
4. Ongoing support is critical to sustain progress made by participants during the DSME program.
5. Behavioral goal-setting is an effective strategy to support self-management behaviors.

DISCUSSION

Treatment Adherence

Vermeire et al., (2005) reviewed 21 studies assessing interventions aimed at improving adherence to treatment recommendations, not to diet or exercise recommendations, in people with Type 2 diabetes in primary care, outpatient, community and home, and hospital settings. Adherence measurement tools and outcomes evaluated in these studies were heterogeneous. Nurse-led interventions, home aids, diabetes education, pharmacy led interventions, adaptation of dosing, and frequency of medication taking showed a small effect on a variety of outcomes including HbA_1c. They concluded that the current efforts to facilitate adherence to treatment recommendations of people with type 2 diabetes demonstrated neither significant effects nor harm. Other reviews with different selection criteria have been somewhat more positive.

Telehealth/Electronics:

A wide variety of approaches have been used in delivery and support of computer-aided diabetes education and self-management programs. In a systematic review of 219 RCTs involving 3167 patients (92% adults), Austin Boren et al., (2006) identified three computerized approaches in the trials reviewed: Computerized touch screen assessment and instruction, computerized assessment with individualized counseling or feedback, and games or simulation; methods used in the control groups were variable. Outcome measures were grouped according to DSME core outcome measures: learning, behavior change, clinical improvement, and improved health status. Results

demonstrated that there were significant improvements in 47 percent of the outcomes measured (47 of 112 outcomes). However, the improvements that occurred during the learning period were not sustained long term.

Balas et al., (2004) reviewed RCTs and other study designs that evaluated the impact of various interventions including utilization of home glucose records in computer-assisted insulin dose adjustment and computer-assisted diabetes patient education. They found that small, pocket-sized dosage computers facilitated increased mobility and treatment adherence with therapy recommendations on demand and that remote diabetes control and counseling enhanced glycemic control.

In a systematic review of 68 RCTs and 30 observational studies involving frail elderly, 34 of which focused on telemonitoring and diabetes, Barlow et al. (2007) determined that benefits of telemonitoring of blood glucose data and transmitting data on system outcomes (clinic time, efficiency, or workflow) were inconsistent. Four researchers found that proactive support or case management by telephone improved clinical outcomes or reduced symptoms in people with diabetes and several researchers determined that regular telephone calls from nurses reduced or delayed hospital admissions and costs in people with diabetes, but the most effective frequency of telephone support remains uncertain. Findings regarding the impact of continuing telephone follow up on treatment adherence and quality of life, as well as the effects of education and support provided via email and the Internet were also inconsistent. Proactive telephone support or case management by telephone has been found to improve clinical outcomes or reduce symptoms in people with diabetes (Kim, 2003; Piette et al., 2000; Shea et al.,, 2006; Thompson et al.,, 1999; Wong et al.,, 2005) and continuing telephone follow up is also associated with improved adherence to treatment and self efficacy in people with diabetes (Gambling & Long, 2006; Maljanian et al., 2005). However, there were no improvements in quality of life in people with diabetes receiving telephone support (Piette et al., 2000) and adding video conferencing to telephone support and home visits had no effect on knowledge and medication adherence.

Botsis and Hartvigsen (2008) performed a similar review of 54 studies from 1996 to 2008, fourteen of which included elderly people with diabetes. Although not all studies measured the same outcomes, overall findings demonstrated reduced HbA1c, blood pressure and LDL cholesterol, fewer clinic visits, improved self care, lower health risk, reduction in hospitalizations, and improved quality of life when monitored and educated via telecommunication devices. Limitations in many of the studies were the small sample size and the short follow up period. Chumbler et al.,, (2004) found evidence that home telecare coordination strategies improved functional independence in veterans with chronic diseases. Elderly patients with diabetes had reduced HbA_1c values and reduced blood pressure and LDL cholesterol when monitored and educated via telecommunication devices (Dang et al., 2007; Shea et al., 2006). Barnett et al.,, (2006) found that diabetes patients required fewer clinic visits with daily telehealth monitoring. Trief et al., (2007) confirmed findings that teleheath approaches enhanced patients' understanding of the disease and consequently, their self-care behaviors.

DELIVERY OF EDUCATION IN GROUP SETTING

In a randomized trial, Rickheim et al. (2002) found that group or individualized diabetes education are equally effective methods of providing education and improving glycemic control.

In a systematic review of group-based diabetes education programs for adults with type 2 diabetes, Deakin et al. (2005) found that approach to and delivery of group education was highly diverse (e.g., underlying theoretical model, numbers/hours of sessions, length of intervention, venue, and individual(s) delivering intervention). Findings, however, suggested that group education improved glycemic control as evidenced by lower HbA_1C levels and fasting blood glucose levels and retention of diabetes knowledge at 4 to 6 months and 12 months. Additional group education sessions provided annually may extend benefits up to 2 to 4 years. Evidence also suggested that group education programs may reduce the requirement for diabetes medication, improve diabetes self-management skills, enhance patient self-empowerment skills, and improve food related aspects of quality of life. At longer term follow up (2 to 4 years), group education programs may still result in improved quality of life and reduce the progression to diabetic retinopathy.

As long as the health professional is trained to provide diabetes education, there was no evidence to suggest that location, size of group, duration of program, or type of provider delivering program impacted education effectiveness. There is less evidence, however, to support the effectiveness of programs delivered by lay health workers. Programs based on therapeutic patient education using the principles of empowerment, participation and adult learning have proved to be efficacious. As stated previously, offering annual educational programs has been observed to result in long-lasting benefits to health and psychosocial outcomes.

In three studies (525 patients combined) there was no effect on mortality (OR 1.2; CI 0.3 to 5.6, P = 0.77). Trento et al. (2001) found no significant difference between groups for retinopathy or foot ulcers at 2 years, but did find that

retinopathy progressed significantly more slowly for intervention group at 4 years. Overall reductions in HbA_1c varied from 0.8% to 1.6% at time points as long as 4 years, although most studies had follow-up of <1year. Similar effects were observed for blood glucose. Impact on body weight/BMI was inconsistent. In general, little difference was observed for lipid profiles and systolic blood pressure, although some studies showed significant systolic blood pressure lowering. Group visits were also associated with improvements in empowerment/self efficacy (Deakin et al., 2005). Little effect was observed on overall quality of life, but there was improvement in some subscales. However, Trento et al., (2001) reported no significant difference in QoL at 12 months, but significant improvement at 2 years (Trento et al., 2001; P <0.001) and at 4 years (Trento et al., 2002; P <0.009). Self-management activities increased in some studies for some activities but not others.

Group visits that combine education and care have also been utilized. This model of care delivery has also been referred to as cluster visits, cooperative healthcare clinics (CHCCs), and shared medical appointments (SMAs). In a review of all group visit articles published between 1974 and 2004, Jaber et al. (2006) identified 18 prospective observational studies and RCTs studies. Several studies involved patients with diabetes (Beck et al., 1997; Clancy et al., 2003, Sadur et al., 1999; Scott et al., 2004; Wagner et al., 2001). The differences in study application of the group visit model and the lack of specification regarding education rendered interpretation of results difficult, but in general, Jaber's results were consistent with the conclusions of the major and higher quality studies. That is, group visits improved satisfaction, quality of life, and quality of care indicators. Investigations exploring the effects of group visits on healthy behaviors and self efficacy demonstrated mixed results. In an RCT at an HMO, patients with poor glycemic control (HbA_1c > 8.5%) were eligible. Although the visits focused on education and self-management, the physician had the opportunity to make management decisions based upon clinical data gathered during the visits; and ongoing communication and diabetes management was provided during telephone calls made by nurses at least monthly. This extensive intervention was successful in improving glycemic control (HbA_1c improved by 1.3%) and lipid levels (Sadur et.al.1999. Similar results in a model that did not include the telephone calls were observed in a quasi-experimental study performed in the VA. (Kirsh et al., 2007). In a study at Group Health involving 58% of all patients with diabetes there was no effect on clinical outcomes overall, although sub-group analysis showed that patients who attended a larger number of sessions had better glycemic control and fewer disability days than those who attended fewer sessions. In another study, group visits compared with quarterly visits on unselected patients with diabetes showed improvement in HbA_1c compared to control, but this "improvement" was achieved because HbA_1c increased 0.9% in the control arm and remained stable in the intervention arm (Trento et al., 2001). Group visits are one means for providing social support which has shown positive effects, although a systematic review was unable to clarify which aspects of social support, and which active mechanisms behind it, are most effective for enhancing self-management and outcomes of care for people with type 2 diabetes.

Pharmacists

Wubben & Vivian, (2008) evaluated the impact of diabetes quality improvement strategies used by pharmacists in outpatient settings. The meta-analysis indicated that when pharmacists functioned as case managers there was an overall improvement in HbA_1c across a diverse group of patients and study designs. Because of heterogeneity, however, the researchers were not able to combine the results and identify conclusions about the effectiveness of the interventions or the essential elements necessary to improve patient outcomes.

In a review of 16 RCTs and 20 quasi-experimental studies Machado et al. (2007) determined that HbA1c is sensitive to pharmacists' interventions. Meta-analysis of data from 2247 patients in 16 studies found a significant reduction in HbA_1c levels in the pharmacists' intervention group ($1.00 \pm 0.28\%$; $p < 0.001$) but not in controls ($0.28 \pm 0.29\%$; $p = 0.335$). Pharmacists' interventions further reduced HbA1c values $0.62 \pm 0.29\%$ ($p = 0.03$) over controls. Diabetes education (69%) and medication management (61%) were the most frequently used interventions.

Doucette et al., (2009) compared the effectiveness of pharmacists administered interventions during up to 4 quarterly visits per patient with usual care in patients with diabetes who had completed at least 2 diabetes education sessions at a local diabetes education center. Nine Interventions included discussing medications, clinical goals, and self-care activities with patients and recommending medication changes to physicians when appropriate. The main outcome measures were 12-month changes in HbA_1c, LDL-C, blood pressure, and self-report of self-care activities. Compared with changes in the control group, patients who received interventions significantly increased the number of days per week that they engaged in a set of diet and diabetes self-care activities (1.25 and 0.73 more days/wk, respectively). The mean 12-month changes for HbA_1c, LDL-C, and blood pressure were not significantly different between the 2 study groups.

Specialist Nurses

Compared to non-diabetes specialist nurses, there are no studies to support that diabetes education provided by certified diabetes educators improves outcomes.

Community Health Workers

Community health worker (CHW) characteristics are often poorly reported (CHWs included in studies all were members of the local community and of the same ethnicity/race as the study subjects). Diabetes programs include community health workers as team members in a variety of roles. There are some preliminary data demonstrating improvements in participant knowledge and behavior as well as participant satisfaction with CHW contacts. Effects on physiological measures and health behaviors were mixed. Data on health related quality of life, healthcare utilization and economic efficiency were sparse. Some of the successful interventions were multi-component and some were limited primarily or exclusively to the CHW (Norris et al., 2006).

EVIDENCE TABLE

	Recommendation	Sources	LE	QE	SR
1	Education provided in either individual or group settings.	Rickheim et al., 2002	I	Fair	B
2	Telehealth/electronic interventions	Austin Boren S et al., 2006 Barlow et al., 2007 Balas et al., 2004	I	Fair	B
3	Group visits	Deakin et al., 2005 Jaber et al., 2006 Sadur et al.,1999 Wagner et al., 2001 Trento et al., 2001 Kirsh et al., 2007 van Dam et al., 2005 §	I	Fair	B
4	Nurse interventions	Loveman et al., 2003 § Marrero et al., 1995 Piette et al., 2000 Thompson et al., 1999	I	Fair	B
5	Pharmacist interventions	Machado et al., 2007 Wubben & Vivian, 2008	I	Fair	B

LE-Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation **§***=Systematic Review (see Appendix A)*

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.

MEDICATION EDUCATION

Education regarding diabetes medications should include (as appropriate):

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

SELF-MONITORING OF BLOOD GLUCOSE

Individualized 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

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.

SPECIAL CIRCUMSTANCES

- Sick day management
- When to seek further medical assistance
-

Additional resources are available at:

- 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/
- www.ndep.nih.gov

CORE COMPETENCIES AND 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 healthcare 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:

- 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.

APPENDICES

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APPENDIX A
GUIDELINE DEVELOPMENT PROCESS

This VA/DoD Diabetes Mellitus guideline update builds on the 2003 version. The development process follows a systematic approach described in "Guideline-for-Guidelines," an internal working document of the VA/DoD Evidence-Based Practice Working Group that requires an ongoing review of the work in progress.

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 2003 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 previous version of the guideline and the result of literature searches were reviewed by the Working Group through numerous conference calls and individual contributions to the document. 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 and by individual contributions to the document.

Experts from the VA and DoD internal medicine, endocrinology and primary care reviewed the final draft. Diabetes educators and other professionals involved in diabetes education teams also reviewed the draft. Finally the draft was posted on the Internet to solicit comment from providers from the VA and DoD healthcare system at large. Their feedback was integrated into the final document. Nonetheless, this document is a work in progress. It will be updated every two years, or when significant new evidence is published.

This 2010 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 ten 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://www.cebm.net)

- 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 (2002 through May 2009) and type of research (RCT and meta-analysis). For the CCTR, limits were set for date of publication (2002 through 2009).

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.

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.

Preparation of Evidence Tables

The results of the searches were organized in evidence reports, and copies of the original studies were provided to the WG for further analysis. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the VA and DoD healthcare systems.

The clinical experts and other researchers in healthcare 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.. Each of the evidence reports covered:

- Summary of findings
- Methodology
- Search terms
- Resources searched
- Summary table of findings
- Critical appraisal of each study

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 strength of recommendation [SR] was assigned for each recommendation, based on study design and significance of the quality of the evidence).

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 (2007). 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).

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

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 2002 through May 2009. 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 (Society for Medical Decision-Making Committee, 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 C: ACRONYM LIST

A1C	see HbA_1c
AADE	American Association of Diabetes Education
ACEI	angiotensin converting enzyme inhibitor
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
AUC	Area under the curve
BG	Blood Glucose
BID	twice daily
BMI	body mass index
BP	blood pressure
BPH	benign prostatic hyperplasia
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CDC/CDCP	Centers for Disease Control and Prevention
CDE	certified diabetes educator
CHCC	Cooperative health care clinic
CHD	coronary heart disease
CHF	congestive heart failure
CKD	Chronic Kidney Disease
Clcr	creatinine clearance
COPD	chronic obstructive pulmonary disease
CSII	continuous subcutaneous insulin infusion
CSII	continuous subcutaneous Insulin Injection
CVA	cerebrovascular accident
CVD	cardiovascular disease
DBP	diastolic blood pressure
DCCT	Diabetic Control and Complication Trial
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DN	diabetic nephropathy
DoD	Department of Defense
DPP	NIH-funded Diabetes Prevention Program
DPP-4	dipeptidyl peptidase-4
DSME	diabetes self-management education
eGFR	estimated glomerular filtration rate
EKG	electrocardiogram
ESRD	end stage renal disease
ETOH	ethanol
FBS	fasting blood glucose
FPG	fasting plasma glucose
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GHb	glycosylated hemoglobin
GI	gastrointestinal
GIK	Glucose Insulin Potassium
GLP-1	glucagon-like peptide-1

GU	genitourinary
HbA_1c	Hemoglobin marker (A_1c)
HCFA	Health Care Financing Administration
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 performance liquid chromatography
HTN	Hypertension
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IRMA	intraretinal microvascular anomalies
JNC 7	Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure
LDL	low density lipoproteins
LDL-C	low density lipoproteins-cholesterol
LE (Foot Care)	lower extremity
LEA	lower extremity amputation
MDI	multiple saily injections
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MICU	medical intensive care unit
MNT	medical nutrition therapy
MTF	medical treatment facility
NASH	non-alcoholic staetohepatitis
NCCB	nondihydropyridine calcium channel blocker
NCEP	National Cholesterol Education Program
NGSP	National Glycohemoglobin Standardization Program
N-Hanes	National Health & Nutrition Examination Study
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)
OGTT	oral glucose tolerance test
OHA	oral hypoglycemic agent
OQP	Office of Quality and Performance
PCKD	polycystic kidney disease
PCOS	polycystic ovarian syndrome
PDR	proliferative diabetic retinopathy
PG	postload glucose
POC	point of care
PPG	postprandial plasma glucose
PTH	parathyroid hormone
PUD	peptic ulcer disease
PVD	peripheral vascular disease
RCT	randomized controlled trial
RD	registered dietitian
RF	risk factor
RHI	regular human insulin
SBP	systolic blood pressure
Scr	serum creatinine
SFU	sulfonylurea
SICU	surgical intensive care unit

SMBG	self-monitoring of blood glucose
SME	self-management education
SUD	substance use disorder
TC	total cholesterol
TDD	total daily dose
TDI	total daily insulin
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
VA	Veterans Affairs
VHA	Veterans Health Administration
VISN	Veterans Integrated Services Network
WMD	weighted mean difference

APPENDIX D: BIBLIOGRAPHY

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