Clinical Practice Guideline

Management of Diabetes Mellitus (DM)

GUIDELINE SUMMARY 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 - Aug 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 each module is designed for use by primary care providers in an ambulatory care setting, the modules can also be used to coordinate and standardize care within subspecialty teams and as a teaching tool for students and house staff. 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 (i.e., <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 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 incorporates current evidence using digital imaging as a method of screening for retinopathy
- Finally, similar to the sections of the guideline addressing management of dyslipidemia and hypertension, the original Module [R] 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**

TABLE OF CONTENTS

MODULE D – CORE

SUMMARY OF RECOMMENDATIONS

General

1. Children with diabetes should be referred to a pediatric diabetic team (a pediatric endocrinologist, if available, or a management team with substantial experience in the management of children with diabetes) for consultative care.
2. 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.
3. Women with diabetes who are planning pregnancy should be educated about the different options of diabetes management during the pregnancy and referred to a maternal fetal medicine provider before, or as early as possible, once pregnancy is confirmed.
4. 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)
5. Diabetes mellitus (DM) management should be evaluated in the context of the patient's total health status.
6. Urgent or semi-urgent medical conditions, including severe hypo- or hyperglycemia, must be treated before long-term disease management principles are applied.
7. Determine and document if diabetes mellitus is type 1 or 2.

Aspirin Therapy

8. Prescribe aspirin therapy (75 to 325 mg/day) for all adult patients with diabetes type 2 and evidence of cardiovascular disease. [A]
9. 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]
10. 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]
11. 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]

Management of Diabetes

1. If the individualized HbA_1c is not at target, refer to **Module G – Glycemic Control.**
2. Measure blood pressure on every diabetes visit. If systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) is ≥90 mmHg, refer to the VA/DoD Clinical Practice Guideline for the Management of **Hypertension.**
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).**
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).**
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.**

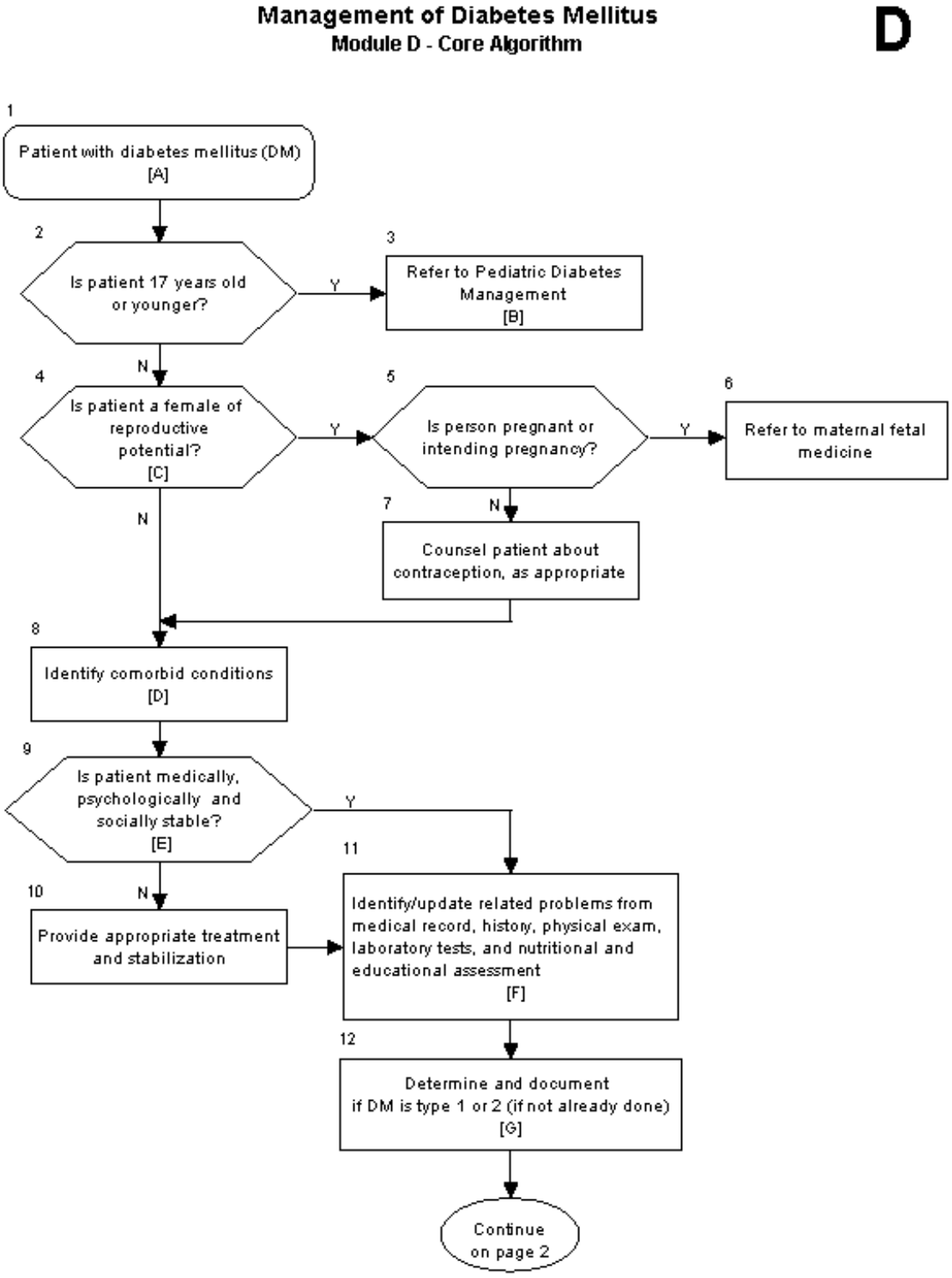
7. If the patient needs additional nutritional or lifestyle education, refer to **Module M – Self-Management and Education.**
8. If the patient is a candidate for an **influenza vaccine**, administer it in season. (See CDC recommendations)
9. Administer pneumococcal pneumonia vaccine if indicated. (See CDC recommendations)
10. If the patient is using tobacco, refer to the VA/DoD Clinical Practice Guideline for the Management of **Tobacco Use Cessation.**

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

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

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

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
N
Counsel patient about contraception, as appropriate
N
8
Identify comorbid conditions
[D]
9
Is patient medically, psychologically and socially stable?
[E]
Y
11
10
N
Provide appropriate treatment and stabilization
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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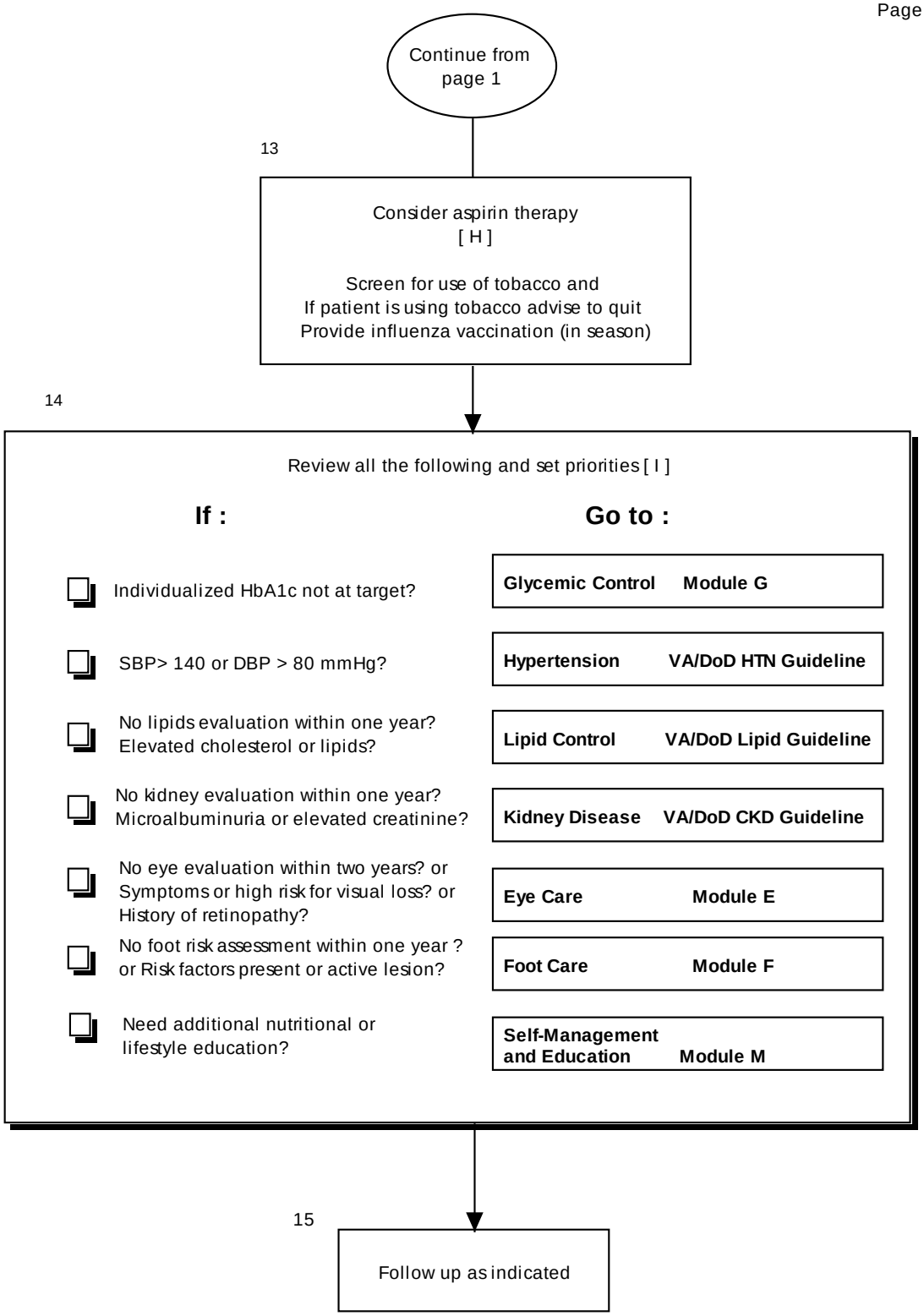

Continue from page 1
13
Consider aspirin therapy
[H]
Screen for use of tobacco and
If patient is using tobacco advise to quit
Provide influenza vaccination (in season)
14
Review all the following and set priorities [I]
If :
Go to :
Individualized HbA1c not at target?
Glycemic Control Module G
SBP> 140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

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.*

*Pa*tients 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*

MODULE S - SCREENING FOR DIABETES

SUMMARY OF RECOMMENDATIONS

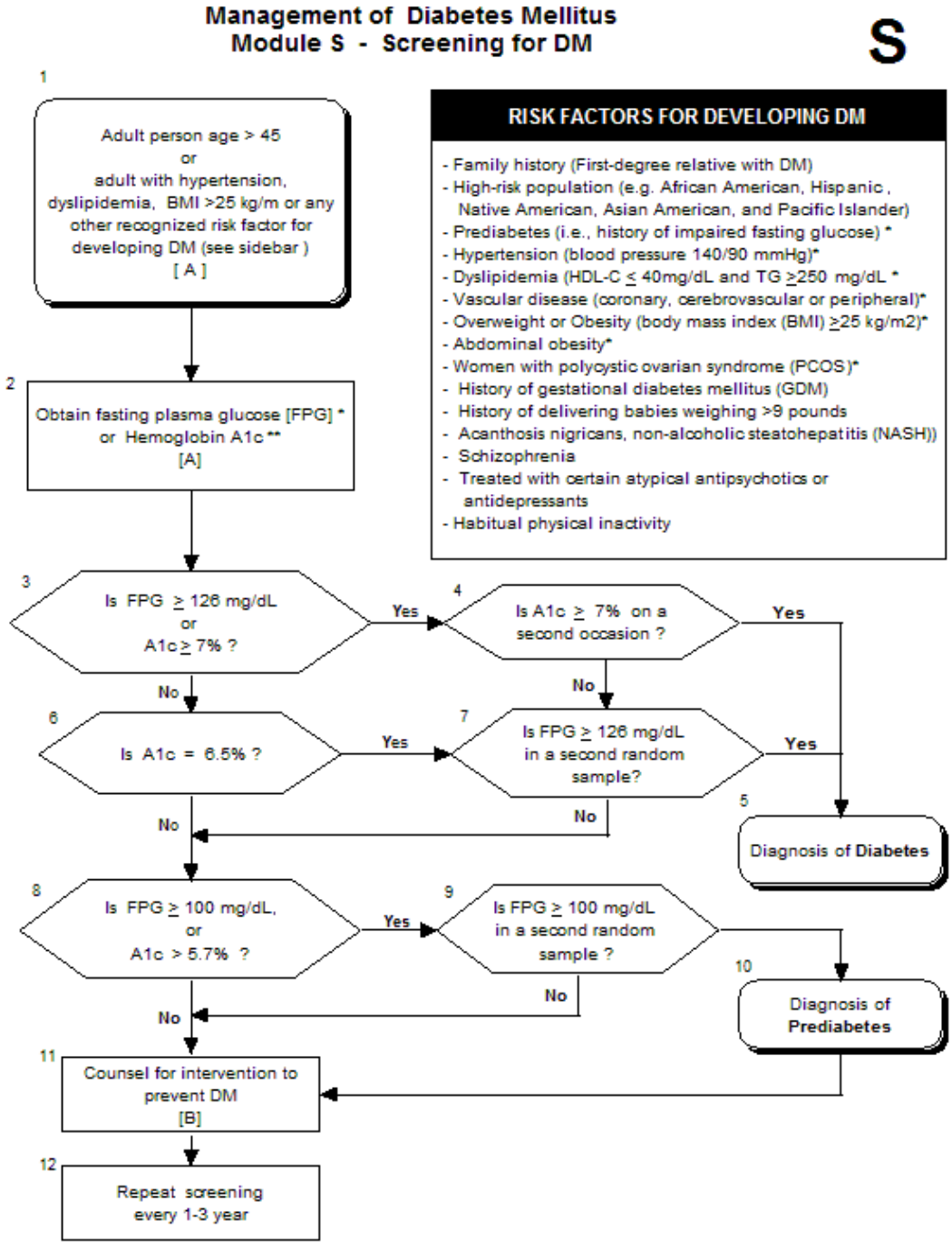
Screening

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 is not recommended to be used in the primary care setting. [C]
9. Random plasma glucose is not recommended as a routine screening test. [C]

Prevention of Diabetes

10. 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.
11. 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]
12. 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]
13. 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]

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 G - GLYCEMIC CONTROL

SUMMARY OF RECOMMENDATIONS

ASSESSMENT

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 in the following conditions:
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.

GLYCEMIC TARGET RANGE

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]

5. Risks of a proposed therapy should be balanced against the potential benefits, based upon the patient's medical, social, and psychological status.
6. The patient and provider should agree on a specific target range of glycemic control after discussing the risks and benefits of therapy.
7. 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.

CONSULTATION/ REFERRAL

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.

TREATMENT OPTIONS

1. Patients 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.
3. 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 diabetic clinic team with multidisciplinary resources (e.g., diabetologist, diabetes nurse, educator/manager, and registered dietitian) for institution and adjustment of insulin therapy.
4. 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.
5. Patients with diabetes should be regularly assessed for knowledge, performance skills, and barriers to self-management.
6. 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).
7. 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).
8. Individual treatment goals must be established with the patient based on the extent of the disease, comorbid conditions, and patient preferences.

Non-pharmacological Therapy

1. 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.
2. 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.
3. If treatment goals are not achieved with diet and exercise alone, drug therapy should be initiated while encouraging lifestyle modifications.

Pharmacotherapy

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]

Combination Therapy

6. Metformin + sulfonylurea is the preferred oral combination for patients who no longer have adequate glycemic control on monotherapy with either drug. [A]
7. 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]
8. 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]
9. Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management. [I]

Insulin Therapy

10. 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]
11. Use intermediate- or long-acting insulin to provide basal insulin coverage. [B]
12. Insulin glargine or detemir may be considered in the NPH insulin-treated patient with frequent or severe nocturnal hypoglycemia. [B]
13. Use regular insulin or short-acting insulin analogues for patients who require mealtime coverage.
14. 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.

Continuous Subcutaneous Insulin Infusion (CSII)

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]

Hospitalized Patients

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 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]

RESPONSE TO THERAPY

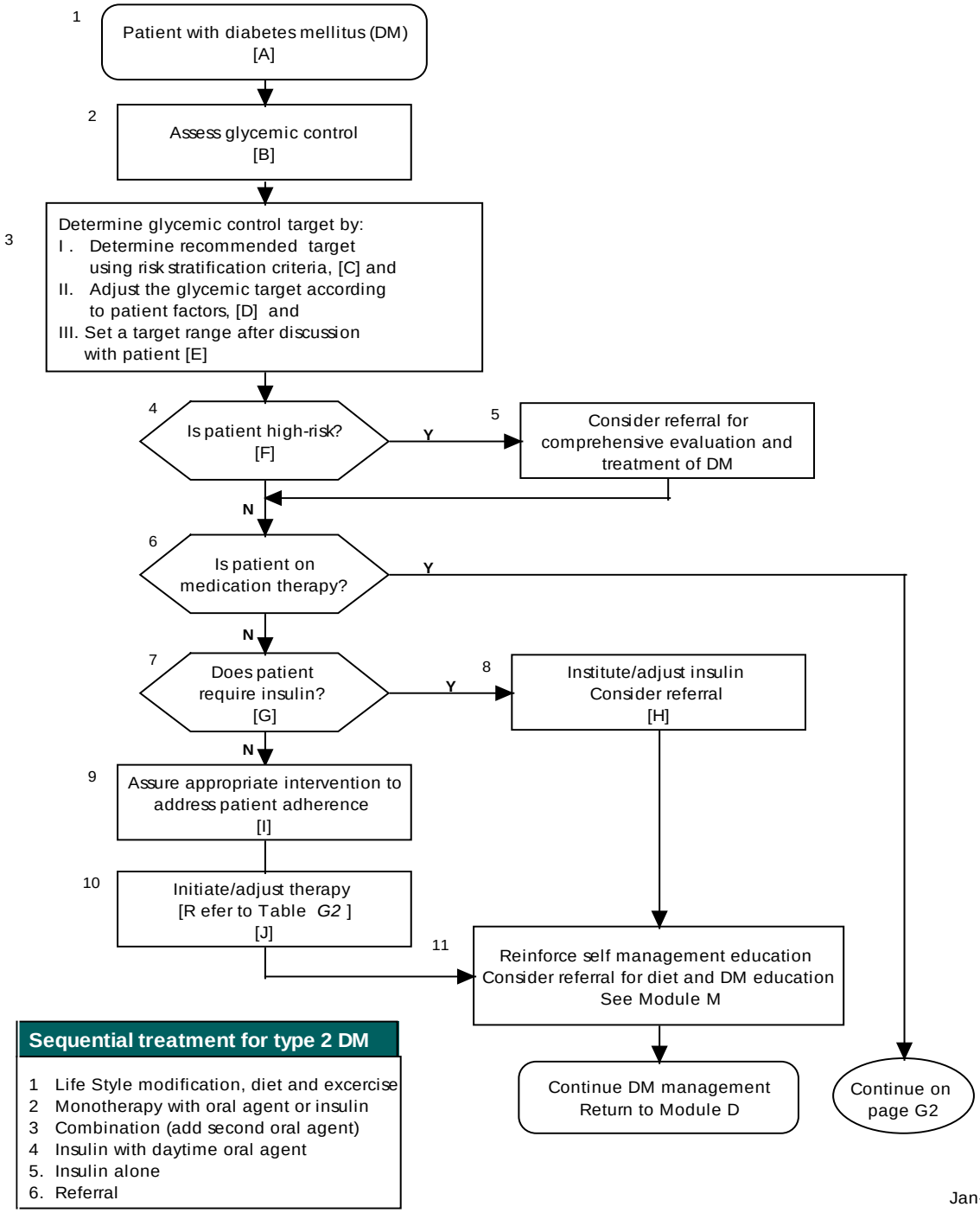
1. The patient with recurrent or severe hypoglycemia should be evaluated for precipitating factors that may be easily correctable (e.g., missed meals, exercise, incorrect administration of insulin—dosage or timing).
2. If the patient does not achieve his/her target range, the provider should identify barriers to patient adherence to the treatment regimen (e.g., miscommunication, lack of education or understanding, financial/social/psychological barriers, and cultural beliefs).
3. If barriers are identified referral to a case manager or behavioral/financial counselor should be considered as appropriate.
4. 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.

FOLLOW-UP

1. Patients should be scheduled for appropriate follow-up to evaluate response, tolerability to therapy, goal re-assessment, and management of acute and chronic problems:
    - The frequency of follow-up-visits for patients with diabetes who are meeting treatment goals and who have no unstable chronic complications should be individualized
    - When there is a sudden change in health status or when changes are made to the treatment regimen, follow-up within one month or sooner may be appropriate
2. Treatment goals should be periodically reassessed based upon patient-specific factors, including changes in the patient's health status, adverse drug reactions, adherence to therapy, and preferences.

MANAGEMENT OF DIABETES MELLITUS
Module G - Glycemic Control

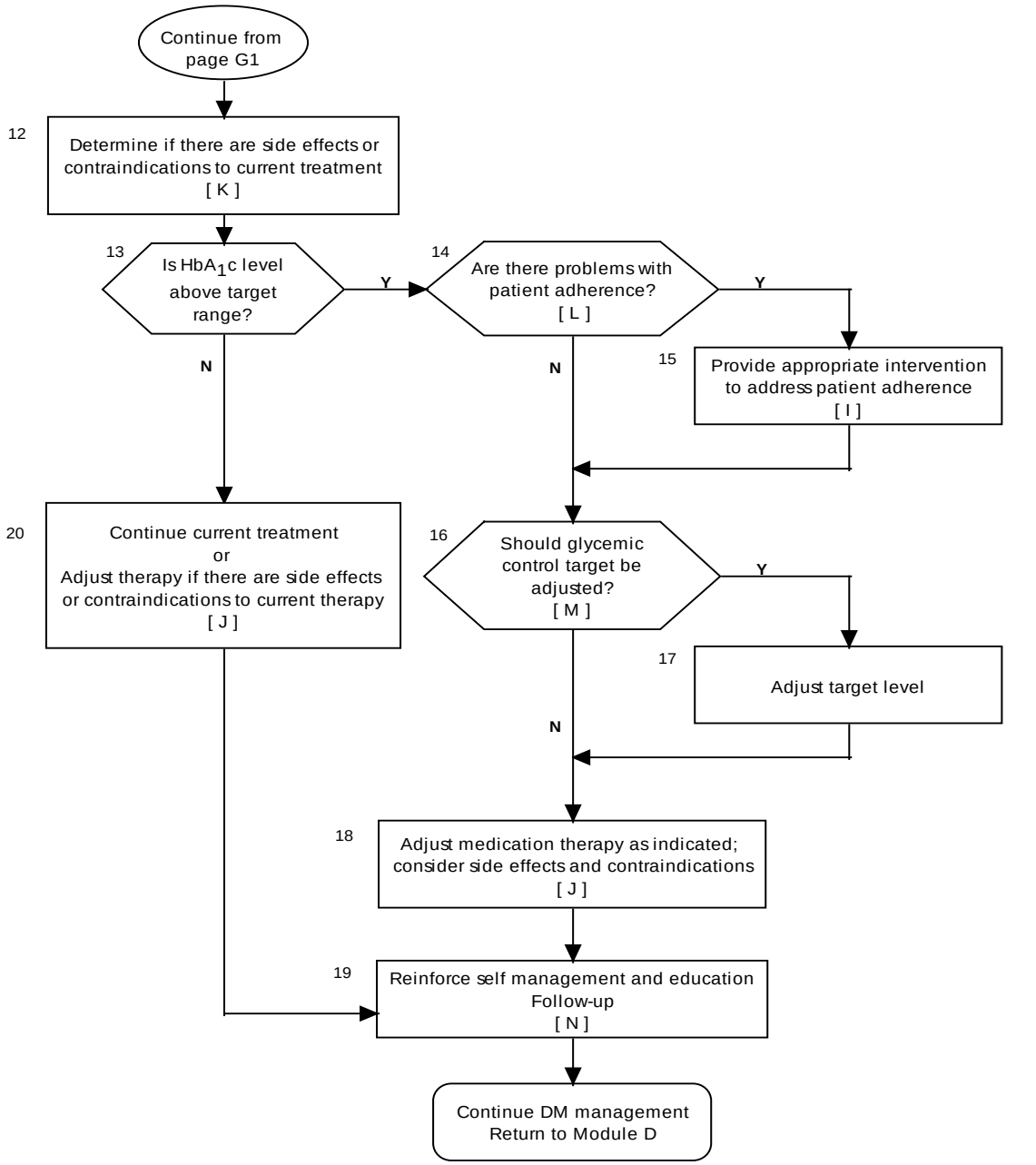
G1



Jan-03

MANAGEMENT OF DIABETES MELLITUS
Module G - Glycemic Control

G2



Jan-03

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).

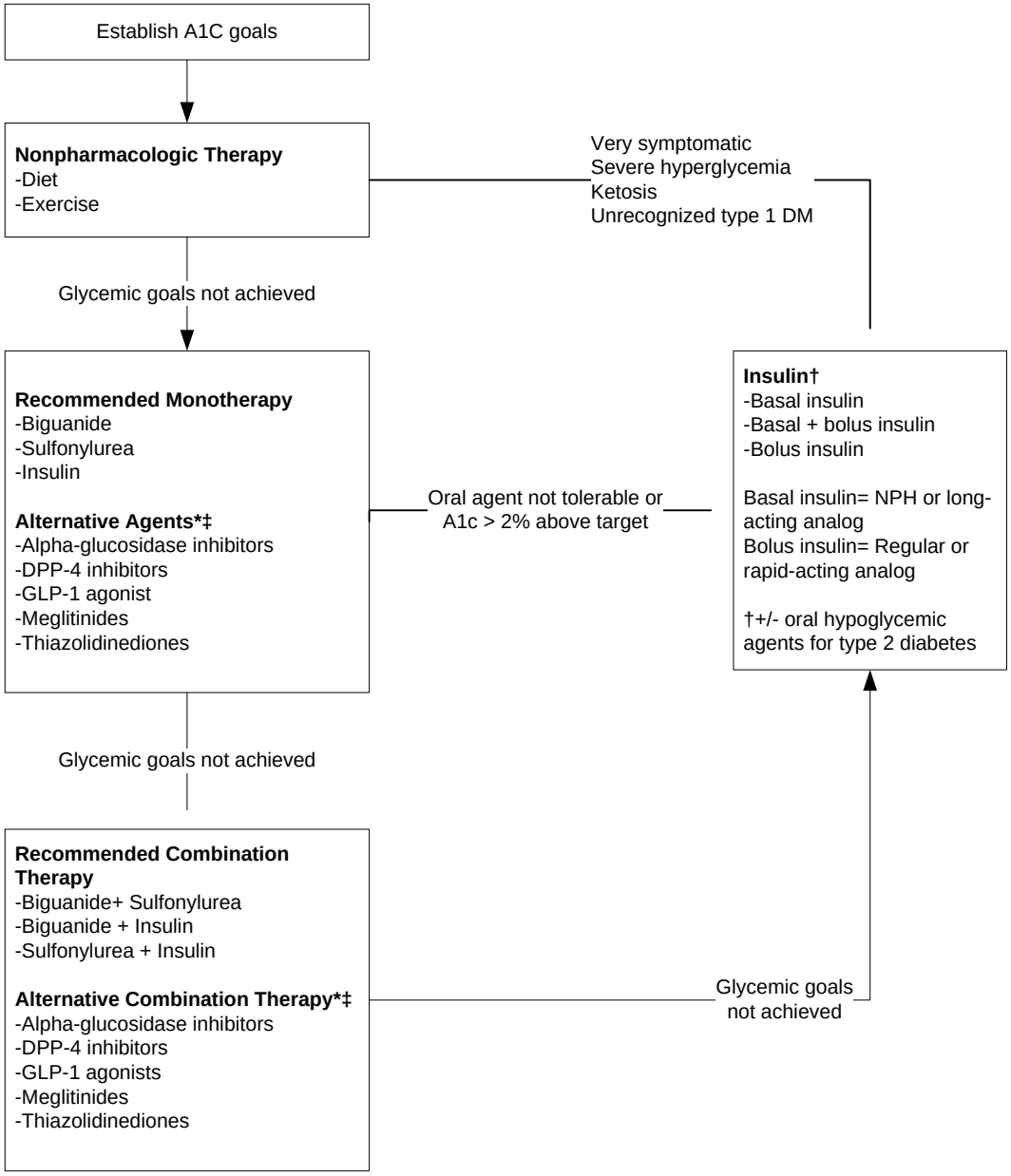
(d) Major comorbidity includes, but is not limited to, any or several of the following active conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent stroke, and life-threatening malignancy.

(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.

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

APPENDIX G-1

Measurements of Glycemic Control

The correlation between tests of glycemic control and HbA_1c, even using the National Glycohemoglobin Standardization Program (NGSP) 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 Glycohemoglobin Standardization Program (NGSP). 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 HbA_1c 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 NGSP 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 NGSP 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 NGSP 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	• 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 used, when needed, 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 combined, 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.

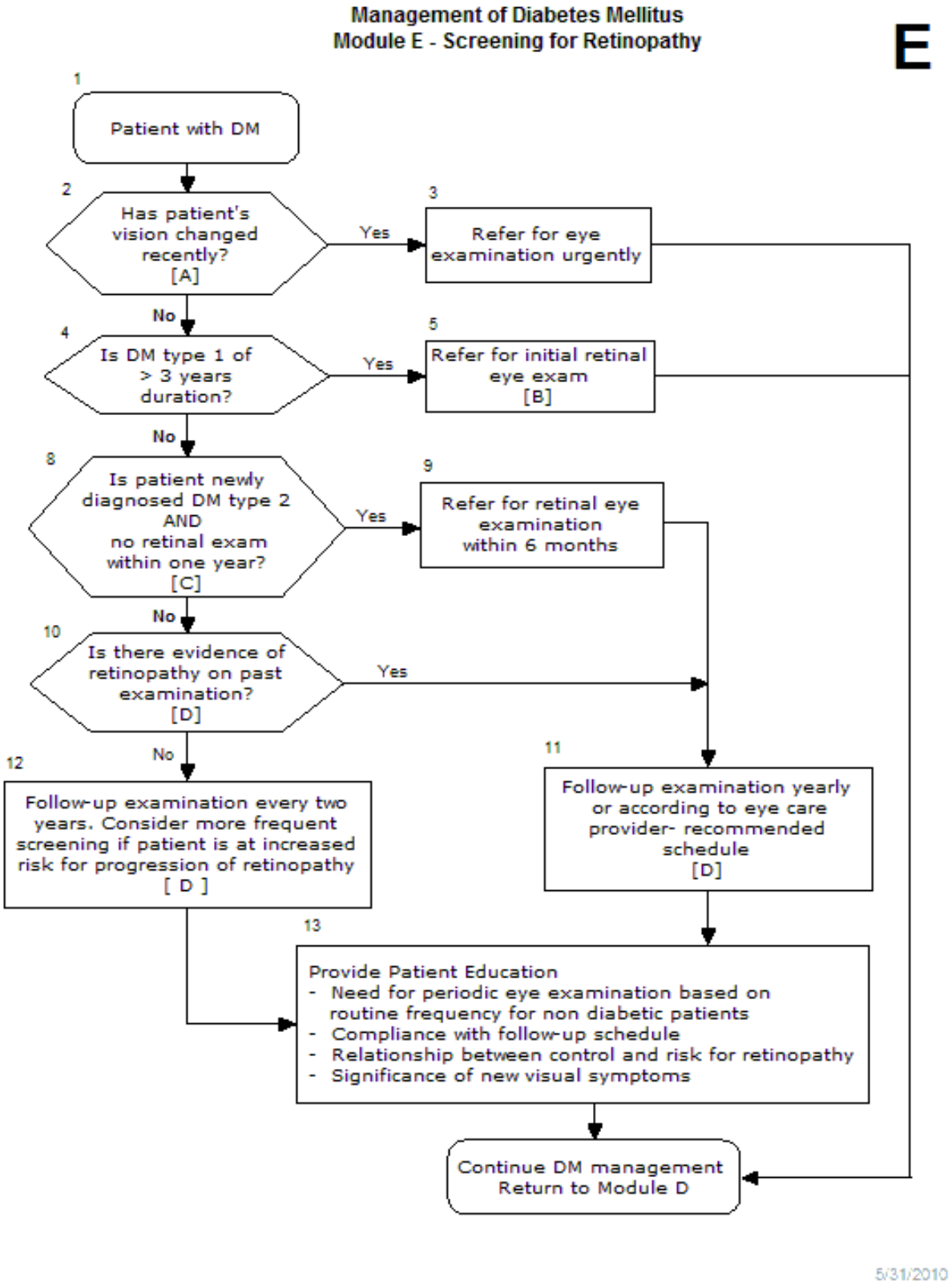
d No pronounced peak; small amounts of insulin glargine are released slowly, resulting in a relatively constant concentration/time profile over 24 hours.

MODULE E– EYE CARE

SUMMARY OF RECOMMENDATIONS

1. Patients with an acute change in vision or a change in ocular function should be urgently referred to an eye care provider.
2. Patients with 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]
3. Patients who are newly diagnosed with type 2 diabetes and have not had an eye exam within the past 12 months should have a retinal examination performed within 6 months. [B]
4. 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]
5. Patients who have had no retinopathy on all previous examinations may be screened for retinopathy 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]
6. 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]

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 F – FOOT CARE

SUMMARY OF RECOMMENDATIONS

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

Screening and Assessment

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

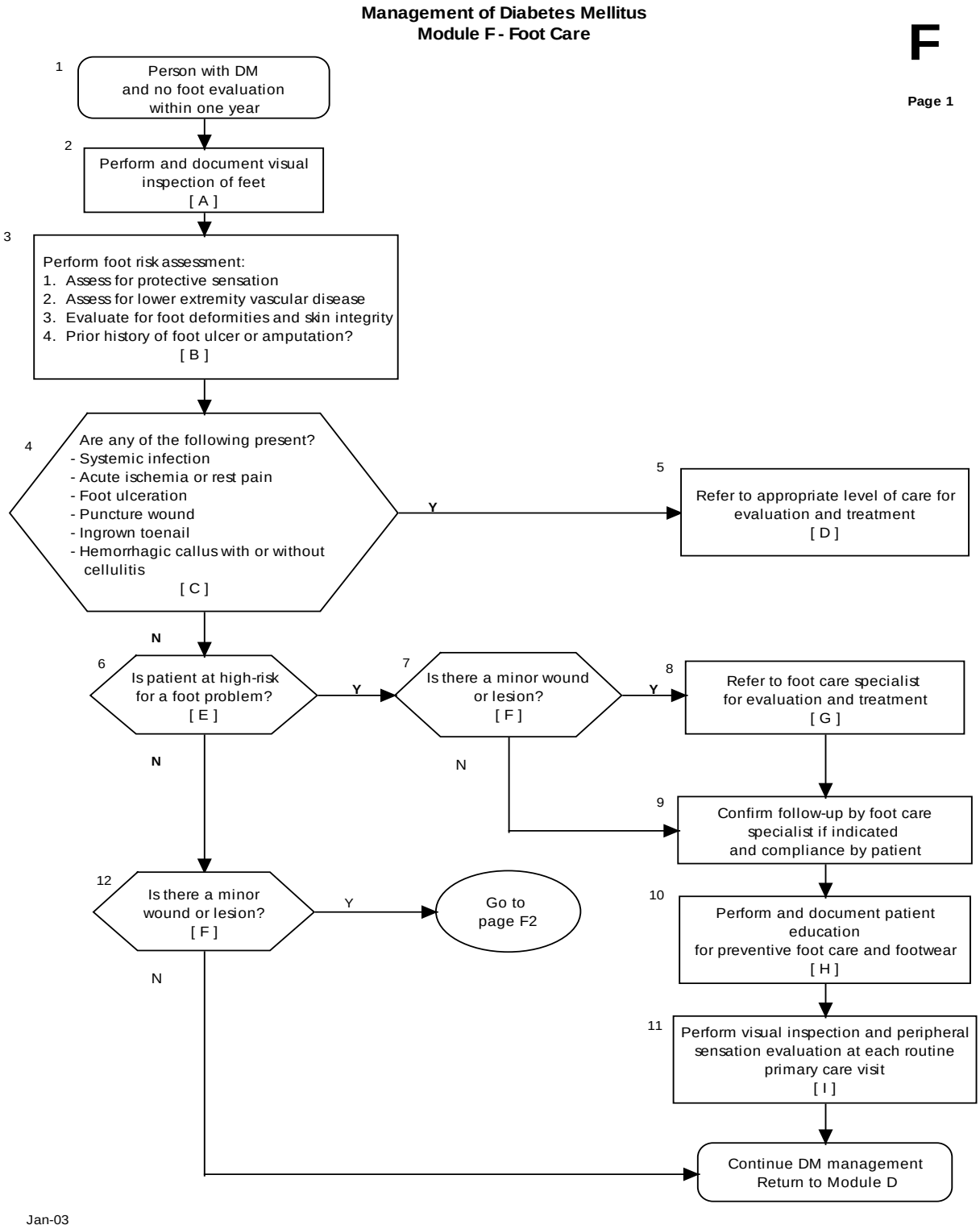
High-risk patients are defined as having at least one of the following characteristics:

- Lack of sensation to Semmes-Weinstein 5.07 monofilament at one or more noncallused plantar sites
- Evidence of LE arterial disease (absence of both dorsalis pedis and tibialis posterior pulses, dependent rubor with pallor on elevation, history of rest pain or claudication, and prior history of LE bypass surgery)
- Foot deformities (specifically hammer toes, claw toe, Charcot's arthropathy, bunions, and metatarsal head deformities)
- End stage renal disease
- History of foot ulcer or non-traumatic LEA

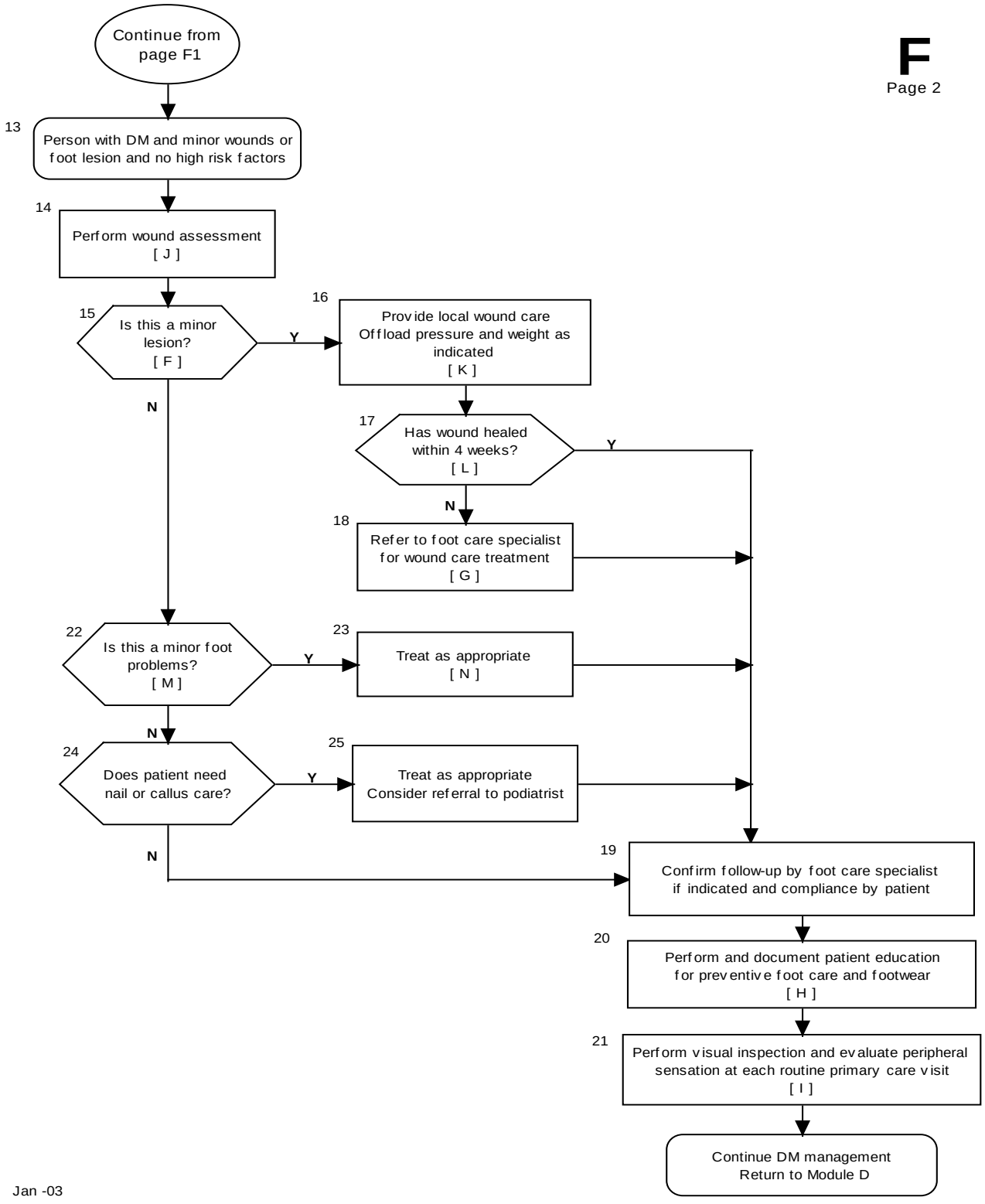
Treatment/Referral

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

ALGORITHM


Management of Diabetes Mellitus
Module F - Foot Care
F
Page 1
1
Person with DM
and no foot evaluation
within one year
2
Perform and document visual
inspection of feet
[A]
3
Perform foot risk assessment:
1. Assess for protective sensation
2. Assess for lower extremity vascular disease
3. Evaluate for foot deformities and skin integrity
4. Prior history of foot ulcer or amputation?
[B]
4
Are any of the following present?
- Systemic infection
- Acute ischemia or rest pain
- Foot ulceration
- Puncture wound
- Ingrown toenail
- Hemorrhagic callus with or without cellulitis
[C]
Y
5
Refer to appropriate level of care for
evaluation and treatment
[D]
N
6
Is patient at high-risk
for a foot problem?
[E]
Y
7
Is there a minor wound
or lesion?
[F]
Y
8
Refer to foot care specialist
for evaluation and treatment
[G]
N
N
9
Confirm follow-up by foot care
specialist if indicated
and compliance by patient
12
Is there a minor
wound or lesion?
[F]
Y
Go to
page F2
10
Perform and document patient
education
for preventive foot care and footwear
[H]
N
11
Perform visual inspection and peripheral
sensation evaluation at each routine
primary care visit
[I]
Continue DM management
Return to Module D
Jan-03

F
Page 2



Jan -03

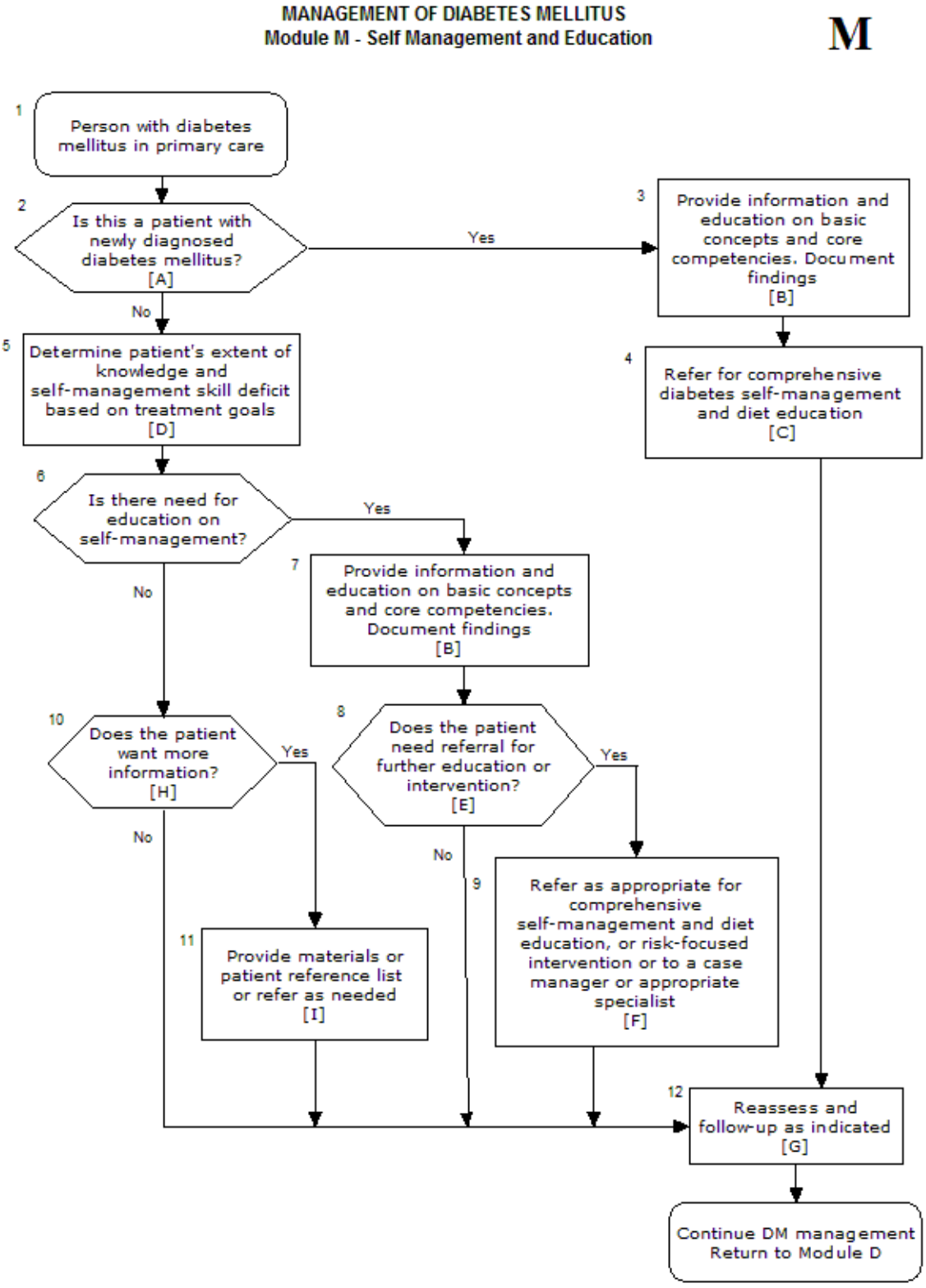
MODULE M – SELF-MANAGEMENT AND EDUCATION

SUMMARY OF RECOMMENDATIONS

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

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

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
No
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]
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
No
7
Provide information and education on basic concepts and core competencies. Document findings [B]
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

APPENDIX C:
ACRONYM LIST

A1c	see HbA_1c
ACEI	angiotensin converting enzyme inhibitor
AADE	American Association of Diabetes Education
ADA	American Diabetes Association
AER	albumin excretion rate
AGI	alpha glucosidase inhibitor
Alb/Cr	urine albumin/creatinine ratio
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AST/ALT	aspartate amino transferase/amino alanine transferase ratio
BIDS	bedtime insulin daytime sulfonylurea
BMI	body mass index
BP	blood pressure
BG	blood glucose
CAD	coronary artery disease
CAGE	alcohol abuse screening test mnemonic
CCB	Calcium channel blocker
CSII	continuous subcutaneous insulin infusion
CDC/CDCP	Centers for Disease Control and Prevention
CDE	certified diabetes educator
CHD	coronary heart disease
CHF	congestive heart failure
CHO	fast-acting carbohydrates
Clcr	creatinine clearance
CVA	cerebrovascular accident
CVD	cardiovascular disease
DBP	diastolic blood pressure
DCCT	Diabetic Control and Complication Trial
DHCCB	dihydropyridine calcium channel blockers
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DPP	NIH-funded Diabetes Prevention Program
DPP-4	dipeptidyl peptidase-4
DQIP	Diabetes Quality Indicator Project
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
GLP-1	glucagon-like peptide-1
HbA_1c	Hemoglobin marker (A_1c)
HCFA	Health Care Financing Administration
HCTZ	hydrochlorthiazide
HDL	high density lipoproteins
HDL-C	high density lipoproteins - cholesterol
HPLC	High pressure liquid chromatography

HTN	Hypertension
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
JNC VII	Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure
K/DOQI	National Kidney Foundation's Kidney Disease Outcome Quality Initiative
LDL	low density lipoproteins
LDL-C	low density lipoproteins-cholesterol
LE	lower extremity
LEA	lower extremity amputation
MDI	multiple daily injections
MI	myocardial infarction
MNT	medical nutrition therapy
NCEP	National Cholesterol Education Program
NCQA	National Committee for Quality Assurance
NGSP	National Glycohemoglobin Standardization Program
NPH	neutral protamine Hagedorn insulin
OGTT	oral glucose tolerance test
PDR	proliferative diabetic retinopathy
PPG	postprandial plasma glucose
PTH	parathyroid hormone
PUD	peptic ulcer disease
PVD	peripheral vascular disease
RD	registered dietitian
SBP	systolic blood pressure
Scr	serum creatinine
SU	sulfonylurea
SLE	Systemic Lupus Erythematosis
SMBG	self-monitoring of blood glucose
DSME	diabetes self-management education
SR	strength of recommendation
SUD	substance use disorder
TC	total cholesterol
TDI	total daily insulin
TG	triglycerides
TSH	thyroid stimulating hormone
TZD	thiazolidinedione