# VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN PRIMARY CARE

**Department of Veterans Affairs**

**Department of Defense**

## Clinician Summary

### QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

Variations in practice will inevitably and appropriately occur when clinicians 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 the setting of any particular clinical situation.

These guidelines are not intended to represent Department of Veterans Affairs or TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

**Version 5.0 – 2017**

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# I.  Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the "…Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration and Military Health System," by facilitating the development of clinical practice guidelines for the VA and DoD populations.[1] This clinical practice guideline (CPG) is intended to provide healthcare providers with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients with diabetes mellitus (DM), thereby leading to improved clinical outcomes.

The first VA/DoD CPG for the Management of Diabetes Mellitus, based upon earlier iterations in 1997 and 2000, was published in 2003.[2] It established a risk stratification approach for setting individualized target goals based upon life expectancy, comorbid conditions, patient preferences, and absolute benefits and potential risks of therapy.[2] It also emphasized the risks of hypoglycemia. In 2010, the VA and DoD published a CPG for the Management of Diabetes Mellitus (2010 DM CPG), which was based on evidence reviewed through June 2009. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of DM. Follow-up of major clinical trials of intensive therapy, as well as advances in physiological, behavioral, nutritional, and pharmacological research have led to the emergence of new strategies to manage and treat patients with DM.

Consequently, a recommendation to update the 2010 DM CPG was made and the update to the 2010 DM CPG was initiated in 2015. The updated CPG includes evidence-based recommendations and additional information on the management of DM. It is intended to assist healthcare providers in all aspects of patient care, including diagnosis, treatment, and follow-up. The system-wide goal of evidence-based guidelines is to improve the patient's health and well-being by guiding health providers, especially in primary care, to the management pathways that are supported by evidence. The expected outcome of successful implementation of this guideline is to:

- Emphasize shared decision-making to establish patient goals

- Assess the patient's situation and determine, in collaboration with the patient, the treatment methods to achieve the goals.

- Reduce the risk of preventable complications while improving quality of life (QoL).

# II.  Background

## A.  Description of Diabetes Mellitus

Diabetes mellitus is a disease caused by an absolute or relative insulin deficiency resulting in hyperglycemia. Type 1 DM (T1DM) is due to insulin secretion deficiency not resulting from insulin resistance, while type 2 DM (T2DM) is due to insulin resistance that can eventually also result in insulin secretion deficiency. The insulin resistance resulting in T2DM is thought to be due to excess adiposity, especially central distribution of adiposity, but can be due to other factors, such as corticosteroid treatment or Cushing's syndrome. Gestational diabetes (GDM) is DM present during pregnancy. Other

more unusual types of DM also exist, such as maturity onset diabetes of the young (MODY), latent autoimmune diabetes of adult (LADA) and those related to pancreatic disease or acromegaly, but the current guideline is focused on T2DM.

Several criteria exist to diagnose T2DM and prediabetes based on biomarker levels. The criteria used by this Work Group are summarized in Table 1. Prediabetes is a condition where blood glucose levels are higher than normal but the patient does not meet the criteria for DM.[3] Hyperglycemia not sufficient to meet the diagnostic criteria for DM 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 use of hemoglobin A1c (HbA1c) in the diagnosis of diabetes is derived from a study of the linear relationship between HbA1c values and microvascular complications, specifically retinopathy, with the diagnostic level occurring at the inflection point of rise in incidence. However, differences among laboratories in the acceptable variability of HbA1c test values, as well as evidence suggesting that there may be racial/ethnic differences, suggests that reliance upon HbA1c test results alone are not congruent with fasting blood glucose levels.[4,5] Racial differences were reported among participants in the Diabetes Prevention Program. Despite having comparable measures of glycemia, African Americans had significantly higher HbA1c levels (6.2%) than Whites (5.8%).[6] The VA/DoD DM CPG recommends that HbA1c values between 6.5%-7.0% be confirmed with fasting plasma glucose levels to improve diagnostic specificity.

**Table 1: Criteria for the diagnosis of diabetes mellitus and prediabetes [6]**

| Status | Fasting Plasma Glucose [1,2] or Hemoglobin A1c [3] |
|---|---|
| **Diabetes Mellitus** | FPG ≥ 126 mg/dL (7.0 mmol/L) on two occasions |
| | **OR** |
| | HbA1c ≥ 6.5% with a confirmatory FPG ≥ 126 mg/dL (7.0 mmol/L) |
| | **OR** |
| | HbA1c ≥ 7.0% on two occasions |
| **Prediabetes** | FPG ≥ 100 mg/dL **and** < 126 mg/dL on two occasions |
| | **OR** |
| | HbA1c ≥ 5.7% **and** FPG ≥ 100 mg/dL and < 126 mg/dL (7.0 mmol/L) |
| | **OR** |
| | 2-hr plasma glucose 140-199 mg/dL (7.8-11.0 mmol/L) (IGT) |
| **Normal** | FPG < 100 mg/dL <br> HbA1c < 5.7% |

Abbreviations: dL: deciliter; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; hr: hour; IGT: impaired glucose tolerance; L: liter; mg: milligram; mmol: millimole

[1] Fasting is defined as no caloric intake for at least eight hours.

[2] 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.

[3] Using a clinical laboratory (not a point-of-care) methodology standardized to the National Glycohemoglobin Standardization Program (NGSP)

An oral glucose tolerance testing (OGTT) is most commonly done to diagnose gestational diabetes.

Patients with one or more of the following risk factors are at higher risk for T2DM:

- Age ≥ 45 years

- Family history (first-degree relative with DM)

- Member of a high-prevalence population (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)

- Prediabetes (HbA1c ≥ 5.7% [39 mmol/mol], fasting blood glucose 100-125 mg/dl IGT [7], or IFG on previous testing)[1]

- Hypertension (blood pressure ≥ 140/90 mmHg or on therapy for hypertension)[1]

- High-density lipoprotein cholesterol (HDL-C) level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride (TG) level > 250 mg/dL (2.82 mmol/L)[1]

- History of cardiovascular disease (CVD)[1]

- Overweight (body mass index [BMI] ≥ 25 kg/m$^2$ or ≥ 23 kg/m$^2$ in Asian Americans)[1]

- Abdominal obesity[1]

- Women with polycystic ovary syndrome (PCOS)[1]

- History of GDM or history of delivering babies weighing > 9 lbs (about 4 kg)

- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

- Physical inactivity/sedentary lifestyle

- Patients using antipsychotics or statins

## B.    Epidemiology and Impact

The prevalence of diabetes is increasing around the world, mostly due to the increase in obesity and sedentary lifestyles.[8] The number of Americans with diagnosed DM has increased four-fold between 1980 and 2014.[9] In the United States (U.S.), a total of 29.1 million people, or 9.3% of the population, have DM (type 1 or type 2), of which 21 million are diagnosed and 8.1 million are undiagnosed.[10]

In the military population enrolled in the Military Health System (MHS), the prevalence of diagnosed DM ranged from 7.3% to 11.2% in 2006 and from 8.3% to 13.6% in 2010.[11] Although the prevalence among Active Duty Service Members remained stable, a significant increase was observed over time among Non-Active Duty Service Members.[11] In 2010, the prevalence among Non-Active military men and women were 15.0% and 13.3% respectively for those aged 45-64 years, 32.9% and 26.9% respectively for those aged 65-74 years, and 31.5% and 25.7% respectively for those aged 75 years and older.[11] According to the Veterans Health Administration (VHA), nearly one in four Veterans (1.6 million individuals) who are receiving care from the VA has DM. Veterans 65 years and older comprise 70% of those with diabetes, reflecting the older age distribution of this population.[12]

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[1] Associated with insulin resistance

DM can cause microvascular complications such as retinopathy, nephropathy, and neuropathy as well as macrovascular complications, including ischemic heart disease, stroke, and peripheral vascular disease.[13] In addition to the complications of T2DM, conditions such as chronic obstructive pulmonary disease (COPD), substance use disorder (SUD), and depression can affect the management of DM. For guidance on how to address those comorbidities, see the respective VA/DoD Clinical Practice Guidelines for the Management of COPD, SUD and Major Depressive Disorder (MDD).[2,3,4] DM is a major cause of morbidity and mortality in the U.S. It is associated with a two-fold to four-fold increased risk for atherosclerotic CVD, resulting in substantial morbidity and mortality from coronary events. For the management of CVD risk factors, refer to the VA/DoD Clinical Practice Guidelines for the Management of Hypertension, Chronic Kidney Disease (CKD), and Dyslipidemia.[5,6,7] The total costs of diagnosed DM in the U.S. were $245 billion in 2012, including $176 billion for direct medical costs and $69 billion in reduced productivity.[14] Direct costs in the VHA and MHS are not known.

## III.   Scope of this CPG

This CPG is designed to assist providers in managing or co-managing patients with T2DM. Moreover, the patient population of interest for this CPG is adults who are eligible for care in the VA and DoD healthcare delivery systems, which includes Veterans, deployed and non-deployed Active Duty Service Members, and their adult family members, and retirees and their beneficiaries or dependents. This CPG does not provide recommendations for the management of DM in children, adolescents, or pregnant/nursing women.

## IV.   Shared Decision-making and Patient-centered Care

Throughout this VA/DoD CPG, the authors encourage clinicians to focus on shared decision-making (SDM). The SDM model was introduced in *Crossing the Quality Chasm,* an Institute of Medicine (now the National Academy of Medicine) report, in 2001.[15] It is readily apparent that patients with DM, together with their clinicians, make decisions regarding their plan of care and target glycemic range; however, these patients require sufficient information to be able to make informed decisions. Clinicians must be skilled at presenting their patients with understandable and actionable information regarding both individual treatments and levels and locations of care.

Therefore, the VA/DoD CPG recommendations are intended to promote SDM and be patient-centered. VA/DoD CPGs encourage clinicians to use SDM to individualize treatment goals and plans based on patient capabilities, needs, goals, prior treatment experience, and preferences. Good communication between

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[2] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (COPD). Available at: http://www.healthquality.va.gov/guidelines/CD/copd/

[3] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders (SUD). Available at: http://www.healthquality.va.gov/guidelines/MH/sud/

[4] See the VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder (MDD). Available at: http://www.healthquality.va.gov/guidelines/MH/mdd/

[5] See the VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Hypertension in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/CD/htn/

[6] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care (CKD). Available at: http://www.healthquality.va.gov/guidelines/CD/ckd/

[7] See the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction. Available at: http://www.healthquality.va.gov/guidelines/CD/lipids/

healthcare professionals and the patient is essential and should be supported by evidence-based information tailored to the patient's needs. Use of an empathetic and non-judgmental (versus a confrontational) approach facilitates discussions sensitive to gender, culture, and ethnic differences. The information that patients are given about treatment and care should be culturally appropriate and also available to people with limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory, or learning disabilities. Family involvement should be considered if appropriate, especially in elderly patients.[16] When properly executed, SDM [17,18] may decrease patient anxiety, increase trust in clinicians,[19] and improve treatment adherence.[20] Improved patient-clinician communication can be used to convey openness to discuss any future concerns.

As part of the patient-centered care approach, clinicians should review the outcomes of previous self-change efforts, past treatment experiences, and outcomes (including reasons for treatment drop-out) with the patient. Lastly, they should involve the patient in prioritizing problems to be addressed and in setting specific goals regardless of the selected setting or level of care.

## V.    Guideline Work Group

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# VI. Algorithm

This CPG includes an algorithm which is designed to facilitate understanding of the clinical pathway and decision-making process used in management of DM. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format may promote more efficient diagnostic and therapeutic decision making and has the potential to change patterns of resource use. Recognizing that some clinical care processes are non-linear, the algorithm format allows the provider to follow a simplified linear approach in assessing the critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Relevant observations and examinations
- Decisions for consideration
- 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 and arrows connect the numbered boxes indicating the order in which the steps should be followed.[21]

| | |
|---|---|
| | 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. |
| | Rectangles represent an action in the process of care. |

# A. Module A: General Care and Treatment

**1** Patient with T2DM

**2** Assess patient and glycemic control, taking into consideration patient's:
- Age
- Reproductive status
- Comorbidities (**see Sidebar 1**)
- Stability
- Medication side effects and contraindications

**3** Does the patient have severe or sustained hyperglycemia or hypoglycemia needing urgent/ emergency care? — **Yes** → **4** Consider referral to the emergency department or endocrinology as appropriate

**No**

**5** Assess patient's social determinants of health (e.g., loss of partner, food sufficiency, economic status change)

**6** Provide all patients with understandable health information/education (**see Module B**)

**7** Using shared decision-making, determine a personalized glycemic control target and behavioral goals by:
- Determining recommended glycemic control target using risk stratification criteria
- Discussing or evaluating the glycemic control target according to patient factors
- Setting a glycemic control target range after discussion with patient†
- Setting behavioral goals
- Coordinating care between primary care and specialty care as needed (**see Sidebars 2 and 3**)

**8** Does the patient understand and feel confident about ability to self-manage? Consider teach back method^ — **Yes** → **9** Is the patient on medication? — **Yes** → **10** Are there side effects or other barriers/concerns with medication?* — **Yes** → **11** Adjust and/or change medication

**No** (from 8)

**No** (from 9)

**No** (from 10)

**12** Refer patient to diabetes self-management education (**see Module B**) and/or medical nutrition therapy and assure appropriate intervention to address patient adherence to lifestyle changes.* Consider teach back method.^

**13**
- Discuss diet and exercise
- Initiate medication therapy with metformin or other agents if indicated, considering side effects, contraindications and patient preferences*

**14** Are there problems with patient medication adherence? — **Yes** → **15** Provide appropriate intervention (e.g., motivational interviewing) to address patient medication adherence; discuss with patient and family as appropriate

**No** (from 14)

**16** Is the patient within glycemic target range? — **Yes** → **18** Reassess status and goals at next scheduled visit

**No**

**17** Adjust medication therapy as indicated; consider side effects, contraindications and patient preferences, discuss setting new targets

**Sequential medication treatment for T2DM*:**
1. Monotherapy
2. Combination therapy
3. Referral

**Sidebar 1: Comorbidities and Other Considerations**
- Ischemic vascular disease
- Advanced diabetic complications
- Diminished life expectancy
- Cognitive impairment or dementia
- Cardiovascular disease
- Mental health/ substance use conditions
- Substance use disorders
- Any chronic kidney disease
- Motor disorders
- Acute episodes of care
- Cancer and transplant
- Transitions of care, especially initiating insulin or change in insulin requirements, e.g., patients discharged new on insulin

**Sidebar 2: Foot Care**
- Comprehensive foot risk assessment annually
- Refer patients with limb-threatening conditions

**Sidebar 3: Eye Care**
- Retinal examination within six months of new DM diagnosis and biennial screening for retinopathy for patients with no history of retinopathy on all previous examinations; more frequent retinal examinations in patients when risk factors associated with an increased rate of progression of retinopathy are present
- Dilated fundus examination by an eye care professional or retinal imaging with interpretation by a qualified, experienced reader should be used to detect retinopathy
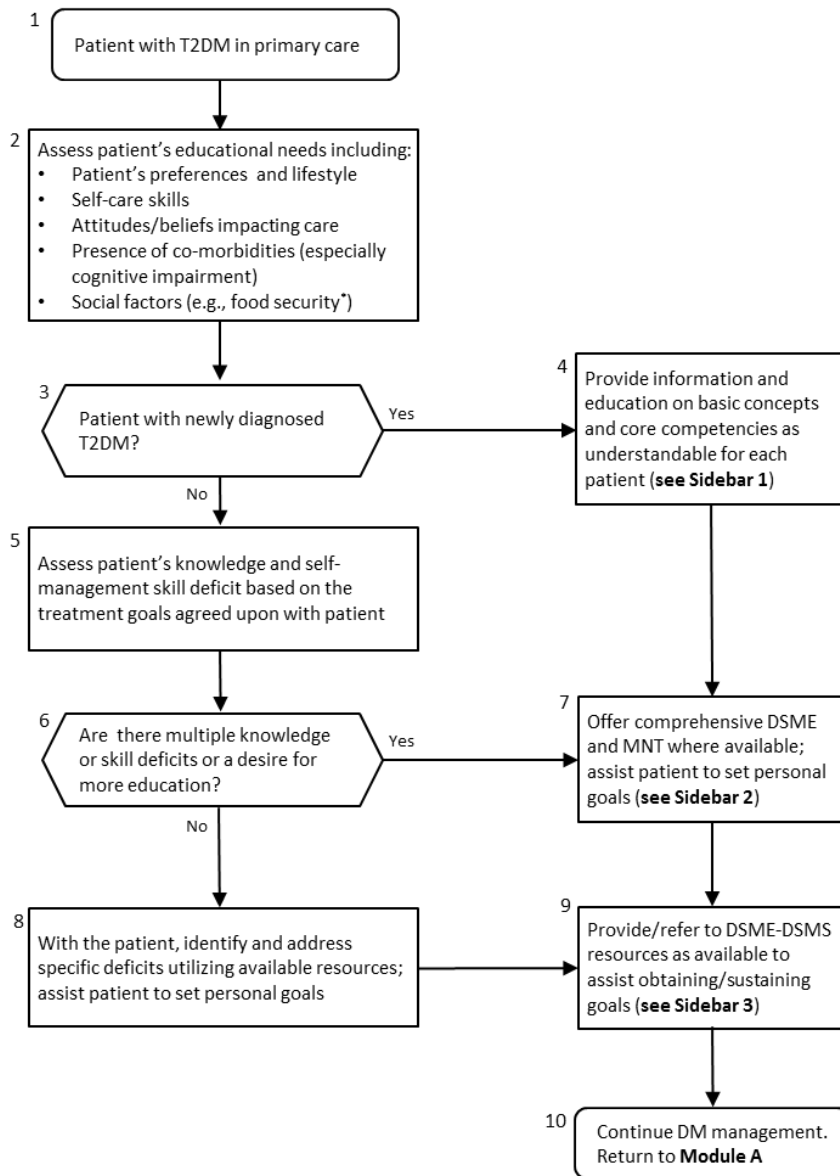
Abbreviations: T2DM: Type 2 diabetes mellitus
*For sequential treatment of DM, see Figure 1
†Target range incorporates the known variation in the HbA1c test from the laboratory used by the patient
^Use the Teach-Back Method: Tool #5. Content last reviewed February 2015. Agency for Healthcare Research and Quality, Rockville, MD.
http://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/healthlittoolkit2-tool5.html

## B.    Module B: Diabetes Self-Management Education

**1** Patient with T2DM in primary care

**2** Assess patient's educational needs including:
- Patient's preferences and lifestyle
- Self-care skills
- Attitudes/beliefs impacting care
- Presence of co-morbidities (especially cognitive impairment)
- Social factors (e.g., food security*)

**3** Patient with newly diagnosed T2DM?

Yes →

**4** Provide information and education on basic concepts and core competencies as understandable for each patient (**see Sidebar 1**)

No ↓

**5** Assess patient's knowledge and self-management skill deficit based on the treatment goals agreed upon with patient

**6** Are there multiple knowledge or skill deficits or a desire for more education?

Yes →

**7** Offer comprehensive DSME and MNT where available; assist patient to set personal goals (**see Sidebar 2**)

No ↓

**8** With the patient, identify and address specific deficits utilizing available resources; assist patient to set personal goals

**9** Provide/refer to DSME-DSMS resources as available to assist obtaining/sustaining goals (**see Sidebar 3**)

**10** Continue DM management. Return to **Module A**

**Sidebar 1: Basic Education/Core Competencies (Survival Skills)**
- Prescribed medication information
- How to recognize and treat hypoglycemia/hyperglycemia
- Basic nutrition
- Sick day/ when to call the provider

**Sidebar 2: Comprehensive DSME**
- Diabetes disease process/ treatment options
- Nutrition/eating healthy
- Physical activity
- Medications in diabetes
- Self-monitoring blood glucose
- Prevention/treatment of hypoglycemia/hyperglycemia
- Prevention/screening of acute and chronic complications (eye/heart/nerve/kidney/dental)
  - Lab tests
  - Foot care/foot exam
  - Smoking cessation
  - Immunizations
- Psychosocial issues/concerns
- Tools/strategies to identify/incorporate patient's goals/preferences

**Sidebar 3: DSMS**
- Ongoing support
  - Assess personal goal status, knowledge, skills; re-educate as necessary
  - Resources: community, primary care follow-up
- Offer "refresher" education when:
  - Change of regimen
  - Life event
  - Change in health/cognitive/social status

Abbreviations: DSME: Diabetes self-management education; DSMS: Diabetes self-management support; MNT: Medical nutrition therapy; T2DM: Type 2 diabetes mellitus
*Food security: "In the past month, was there any day when you or anyone in your family went hungry because you did not have enough money for food?" (Reference: Kleinman RE, Murphy JM, Wieneke KM, et al. "Use of a single-question screening tool to detect hunger in families attending a neighborhood health center." Ambul Pediatr. 7.4 (2007): 278-84)

# VII.  Recommendations

The following recommendations were made based on a systematic evidence review and consideration of four decision domains as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach as detailed in the section on Methods. These domains include: confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient or provider values and preferences, and other implications, as appropriate (e.g., resource use, equity, acceptability).

| # | Recommendation | Strength | Category |
|---|---|---|---|
| **A.  General Approach to T2DM Care** | | | |
| 1. | We recommend shared decision-making to enhance patient knowledge and satisfaction. | Strong for | Reviewed, New-added |
| 2. | We recommend that all patients with diabetes should be offered ongoing individualized diabetes self-management education via various modalities tailored to their preferences, learning needs and abilities based on available resources. | Strong for | Reviewed, New-replaced |
| 3. | We suggest offering one or more types of bidirectional telehealth interventions (typically health communication via computer, telephone or other electronic means) involving licensed independent practitioners to patients selected by their primary care provider as an adjunct to usual patient care. | Weak for | Reviewed, New-replaced |
| **B.  Glycemic Control Targets and Monitoring** | | | |
| 4. | We recommend setting an HbA1c target range based on absolute risk reduction of significant microvascular complications, life expectancy, patient preferences and social determinants of health. | Strong for | Reviewed, New-added |
| 5. | We recommend developing an individualized glycemic management plan, based on the provider's appraisal of the risk-benefit ratio and patient preferences. | Strong for | Reviewed, Amended |
| 6. | We recommend assessing patient characteristics such as race, ethnicity, chronic kidney disease, and non-glycemic factors (e.g., laboratory methodology and assay variability) when interpreting HbA1c, fructosamine and other glycemic biomarker results. | Strong for | Reviewed, New-added |
| 7. | We recommend an individualized target range for HbA1c taking into account individual preferences, presence or absence of microvascular complications, and presence or severity of comorbid conditions (See Table 2). | Strong for | Reviewed, New-replaced |
| 8. | We suggest a target HbA1c range of 6.0-7.0% for patients with a life expectancy greater than 10-15 years and absent or mild microvascular complications, if it can be safely achieved (See Table 2). | Weak for | Reviewed, New-replaced |
| 9. | We recommend that in patients with type 2 diabetes, a range of HbA1c 7.0-8.5% is appropriate for most individuals with established microvascular or macrovascular disease, comorbid conditions, or 5-10 years life expectancy, if it can be safely achieved (See Table 2). | Strong for | Reviewed, New-added |
| 10. | We suggest a target HbA1c range of 8.0-9.0% for patients with type 2 diabetes with life expectancy <5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self-management attributable to e.g., mental status, disability or other factors such as food insecurity and insufficient social support. (See Table 2). | Weak for | Reviewed, New-replaced |
| 11. | We suggest that providers be aware that HbA1c variability is a risk factor for microvascular and macrovascular outcomes. | Weak for | Reviewed, New-added |

| # | Recommendation | Strength | Category |
|---|---|---|---|
| **C. Non-pharmacological Treatments** | | | |
| 12. | We recommend offering therapeutic lifestyle changes counseling that includes nutrition, physical activity, cessation of smoking and excessive use of alcohol, and weight control to patients with diabetes (See VA/DoD CPGs for obesity, substance use disorders, and tobacco use cessation). | Strong for | Not Reviewed, Amended |
| 13. | We recommend a Mediterranean diet if aligned to patient's values and preferences. | Strong for | Reviewed, New-added |
| 14. | We recommend a nutrition intervention strategy reducing percent of energy from carbohydrate to 14-45% per day and/or foods with lower glycemic index in patients with type 2 diabetes who do not choose the Mediterranean diet. | Strong for | Reviewed, New-added |
| **D. Inpatient Care** | | | |
| 15. | We recommend against targeting blood glucose levels <110 mg/dL for all hospitalized patients with type 2 diabetes receiving insulin. | Strong against | Reviewed, Amended |
| 16. | We recommend insulin be adjusted to maintain a blood glucose level between 110 and 180 mg/dL for patients with type 2 diabetes in critically ill patients or those with acute myocardial infarction. | Strong for | Reviewed, Amended |
| 17. | We recommend against the use of split mixed insulin regimen for all hospitalized patients with type 2 diabetes. | Strong against | Reviewed, New-added |
| 18. | We suggest a regimen including basal insulin and short-acting meal time or basal insulin and correction insulin for non-critically ill hospitalized patients with type 2 diabetes. | Weak for | Reviewed, New-added |
| 19. | We suggest providing medication education and diabetes survival skills to patients before hospital discharge. | Weak for | Reviewed, Amended |
| **E. Selected Complications and Conditions** | | | |
| 20. | We recommend performing a comprehensive foot risk assessment annually. | Strong for | Not Reviewed, Amended |
| 21. | We recommend referring patients with limb-threatening conditions to the appropriate level of care for evaluation and treatment. | Strong for | Not Reviewed, Amended |
| 22. | We recommend a retinal examination (e.g., dilated fundus examination by an eye care professional or retinal imaging with interpretation by a qualified, experienced reader) be used to detect retinopathy. | Strong for | Not Reviewed, Amended |
| 23. | We suggest screening for retinopathy at least every other year (biennial screening) for patients who have had no retinopathy on all previous examinations. More frequent retinal 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. | Weak for | Not Reviewed, Amended |
| 24. | We recommend that all females with pre-existing diabetes or personal history of diabetes and who are of reproductive potential be provided contraceptive options education and education on the benefit of optimizing their glycemic control prior to attempting to conceive. | Strong for | Not Reviewed, Amended |
| 25. | We recommend that all females with pre-existing diabetes or personal history of diabetes who are planning pregnancy be educated about the safest options of diabetes management during the pregnancy and referred to a maternal fetal medicine provider (when available) before, or as early as possible, once pregnancy is confirmed. | Strong for | Not Reviewed, Amended |

# VIII. Glycemic Control Targets and Monitoring

Setting HbA1c target levels with patients is often the major treatment goal in the management of T2DM. Table 2 provides general guidance for target ranges, based on patient's comorbidities and life expectancy that are consistent with Recommendations 7-10.

## Table 2: Determination of average target HbA1c level over time [1,2,3,4,5,12]

| Major Comorbidity[6] or Physiologic Age | Microvascular Complications | | |
| --- | --- | --- | --- |
| | Absent or Mild [7] | Moderate [8] | Advanced [9] |
| **Absent*** > 10-15 years of life expectancy | 6.0-7.0%[†] | 7.0-8.0% | 7.5-8.5%[‡] |
| **Present [10]** 5-10 years of life expectancy | 7.0-8.0%[†] | 7.5-8.5% | 7.5-8.5%[‡] |
| **Marked [11]** <5 years of life expectancy | 8.0-9.0%[‡] | 8.0-9.0%[‡] | 8.0-9.0%[‡] |

*Progression to major complications of diabetes is likely to occur in individuals with longer than 15-20 years of life expectancy. Therefore, goal ranges are more beneficial early in disease in younger individuals, or healthier older adults with a longer life expectancy.

†Without significant side effects, including but not limited to hypoglycemia.

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

**HbA1c laboratory considerations:**

[1] Based upon the NGSP reference standard. Clinicians need to obtain information regarding the coefficient of variation (CV) from the methodology used at their site. As an example, an HbA1c of 8.0% from a laboratory with a CV of 3% would be within a 7.76-8.24% range 13 out of 20 times (1 standard deviation), and would be between a 7.53-8.47% range 19 out of 20 times (2 standard deviations).

[2] The HbA1c range reflects an "HbA1c average goal" over time. Intensification or relaxation of therapy should be undertaken based upon individual clinical circumstances and treatment options.

[3] A medication change in response to a single HbA1c test that encompasses the "goal" is discouraged, especially if it is discordant with self-monitoring of blood glucose (SMBG) results.

[4] African Americans, on average, have higher HbA1c levels than Whites and this difference cannot be explained by measured differences in glycemia. Caution is recommended in changing medication therapy based upon HbA1c results, especially for patients on insulin therapy, without correlation with SMBG results.

[5] For all of the above reasons, the VA/DoD DM CPG does not recommend the use of estimated average glucose.

**Comorbid illness considerations:**

[6] Major comorbidity includes, but is not limited to, any or several of the following active conditions: significant CVD, severe CKD, severe COPD, severe chronic liver disease, recent stroke, and life-threatening malignancy.

[7] Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria, and/or mild neuropathy.

[8] 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).

[9] 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, orthostatic hypotension).

[10] Major comorbidity is present, but is not end-stage and management is achievable.

[11] Major comorbidity is present and is either end-stage or management is significantly challenging. This can include mental health conditions and substance/opioid use.

**Social determinant considerations:**

[12] Social determinants of health, including social support, ability to self-monitor on insulin, food insufficiency, and cognitive impairment need to be considered. Additionally, side effects of medications and patient preferences need to be considered in a process of shared decision-making.

# IX.  Pharmacological Therapy

When individualized glycemic goals are not achieved with nonpharmacological therapy such as diet and physical activity, adjunctive therapy with medications is indicated (see Recommendation 5). The magnitude of the reduction in HbA1c necessary to achieve goals should be considered when choosing medications and when assessing hypoglycemia risk, weight gain, patient preferences, administration burden, and cost (see Recommendations 4 and 7).

For treatment of DM in obese patients, see the VA/DoD Obesity CPG.[8]

## *Considerations*

The evidence for pharmacological treatment options for T2DM was not systematically reviewed as part of this guideline update; therefore, formal recommendations could not be made. The rationale to not systematically review the evidence for pharmacotherapy was that the evidence in this area is rapidly evolving and therefore any recommendations made may be outdated during the lifetime of this guideline. In lieu of recommendations, the following considerations are offered based on usual care and recent SRs performed by other groups. Where applicable, users of this guideline are asked to refer to their respective agencies for guidance/criteria on the use of pharmacotherapy for T2DM that are based on the most current evidence.

The following considerations are based on usual care and SRs performed by other groups:

1. When selecting an agent, consideration must be given to efficacy, contraindications, drug interactions, comorbidities, and potential side effects. Discuss with patients the various treatment options and arrive at a shared treatment plan.

2. Insulin should be considered as initial therapy in any patient with hyperglycemia with significant symptoms, if ketosis is present, and in newly diagnosed or previously unrecognized T1DM.

3. Metformin should be given as the first-line agent unless there are contraindications.

4. In patients with metformin intolerance or contraindications, other drug classes can be considered. These include (not in order of preference): alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, insulin, meglitinides, sodium glucose co-transporter 2 (SGLT2) inhibitors, sulfonylureas (SU), and thiazolidinediones (TZDs).

5. When initial therapy no longer provides adequate glycemic control, addition of a second-line agent from another class rather than substitution is usually necessary. Substitution can be reserved for intolerance/adverse effect to a drug. Combination of two anti-hyperglycemic drugs has the benefit of reducing hyperglycemia by working on different mechanisms that cause hyperglycemia (refer to Figure 1). Some agents are not generally used in combination or have not been studied in combination (refer to Table 14).  Although the evidence is clear on the relative efficacy of the various medications, their usage needs to be guided by clinical considerations.

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[8] See the VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity. Available at: http://www.healthquality.va.gov/guidelines/CD/obesity/

6.  Addition of basal insulin to existing regimen should be considered, particularly if the desired decrease in HbA1c is not likely to be achieved by use of combination therapy.

7.  Patients and their families should be instructed to recognize and confirm their understanding of signs and symptoms of hypoglycemia and its management.

8.  Given that new studies and FDA alerts will be published subsequent to the release of this guideline, clinicians should refer to the criteria for use published by the VA Pharmacy Benefits Management program (VA PBM) and the Department of Defense Pharmacy and Therapeutics Committee (DoD P&T).

## Figure 1: Sequential Treatment of Type 2 Diabetes*



Abbreviations: DPP-4: dipeptidyl peptidase-4; DSME: diabetes self-management and education; GLP-1: glucagon-like peptide-1; SGLT2: sodium glucose co-transporter 2

*Bile acid sequestrants, bromocriptine quick release, and pramlintide are uncommonly used agents in the management of diabetes and are not included in this guideline.

‡Consider a trial of metformin extended-release in those with persistent adverse gastrointestinal effects from metformin immediate-release

†Second-line agents listed alphabetically; not in order of preference

‡If applicable, refer to VA (http://www.pbm.va.gov/) or DoD (http://www.health.mil/PandT) guidance/criteria for further recommendations on use of these agents.

**Table 3: Alpha-glucosidase inhibitors**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| Acarbose Miglitol | 0.5 - 1% | Low | Weight neutral | ▪ Administer at the start of each main meal<br>▪ Titrate dose gradually to minimize GI effects<br>▪ GI side effects may be intensified in patients consuming large amounts of simple carbohydrates<br>▪ Reduces postprandial glucose values<br>▪ Not recommended in patients with significant renal impairment (SCr >2 mg/dL)<br>▪ Use with caution in hepatic impairment<br>▪ Contraindications: DKA, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, marked disorders of digestion or absorption conditions, cirrhosis (acarbose)<br>▪ Prevents breakdown of table sugar; therefore, a source of glucose (dextrose, D-glucose) should be readily available to treat symptoms of hypoglycemia | ▪ Flatulence; tend to abate with time<br>▪ Diarrhea and abdominal pain<br>▪ Dose-related increase in serum transaminases, usually asymptomatic, reversible (acarbose) | ▪ Inexpensive (acarbose)<br>▪ Moderately expensive (miglitol) |

Abbreviations: DKA: diabetic ketoacidosis; dL: deciliter; GI: gastrointestinal; HbA1c: hemoglobin A1c; mg: milligram; SCr: serum creatinine

**Table 4: Amylin analog**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| Pramlintide | 0.5 - 1% | High (especially in those with T1DM) | ↓Weight | <ul><li>Indicated to be co-administered with mealtime insulin</li><li>Reduces postprandial glucose values</li><li>Requires frequent pre- and post-meal and bedtime glucose monitoring</li><li>When initiating pramlintide, reduce mealtime insulin (including premixed insulin) dose by 50%; individualize subsequent insulin doses thereafter</li><li>Contraindicated in those with hypoglycemia unawareness and confirmed gastroparesis</li><li>Patients that should NOT be considered for pramlintide therapy:<ul><li>Poor compliance with current insulin regimen</li><li>Poor compliance with prescribed SMBG</li><li>HbA1c >9%</li><li>Recurrent severe hypoglycemic requiring assistance during the past 6 months</li><li>Require the use of drugs that stimulate GI motility</li><li>pediatric patients</li></ul></li><li>Injectable</li></ul> | <ul><li>GI effects (nausea, vomiting, anorexia)</li></ul> | Expensive |

Abbreviations: GI: gastrointestinal; HbA1c: hemoglobin A1c; SMBG: self-monitoring of blood glucose; T1DM: type 1 diabetes mellitus

**Table 5: Biguanides**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events /Side Effects | Cost |
|---|---|---|---|---|---|---|
| Metformin | 1 - 1.5% | Low | Weight neutral | ▪ Use well established<br>▪ Before starting metformin, obtain the patient's eGFR<br>▪ Metformin is contraindicated in patients with an eGFR below 30 mL/min/1.73 $m^2$<br>▪ Starting metformin in patients with an eGFR between 30-45 mL/min/1.73 $m^2$ is not recommended<br>▪ Obtain an eGFR at least annually in all patients taking metformin; in patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently<br>▪ In patients taking metformin whose eGFR later falls below 45 mL/min/1.73 $m^2$, assess the benefits and risks of continuing treatment; discontinue metformin if the patient's eGFR later falls below 30 mL/min/1.73 $m^2$<br>▪ Titrate dose gradually to minimize GI symptoms; a trial of metformin extended-release should be offered to patients experiencing continued GI effects<br>▪ Likely reduces CV events (UKPDS) | ▪ GI effects (diarrhea, nausea, abdominal cramping)<br>▪ Rare risk of lactic acidosis (risk is increased in patients with acute CHF, dehydration, excessive alcohol intake, renal impairment or sepsis)<br>▪ May impair vitamin B12 absorption; rarely associated with anemia | Inexpensive |

Abbreviations: CHF: congestive heart failure; CV: cardiovascular; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HbA1c: hemoglobin A1c; $m^2$: square meter; min: minute; mL: milliliter; UKPDS: United Kingdom Prospective Diabetes Study

**Table 6: Dipeptidyl-Peptidase 4 Inhibitors**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| Sitagliptin Saxagliptin Linagliptin Alogliptin | 0.5 - 1% | Low (↑ risk when combined with SU or insulin) | Weight neutral | ▪ May require dosage adjustment for renal impairment or concomitant use of strong CYP3A4/5 inhibitors (varies by product) ▪ Use of CYP3A4 or P-gp inducers with linagliptin is not recommended ▪ No cardiovascular benefits compared to placebo ▪ Not studied in patients with history of pancreatitis | ▪ Hypersensitivity reactions (e.g., urticaria, facial edema); post-marketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions ▪ Acute pancreatitis has been reported; discontinue if pancreatitis is suspected ▪ Severe and disabling arthralgia has been reported ▪ May increase risk for hospitalization for heart failure (saxagliptin and alogliptin) | Expensive |

Abbreviations: CYP3A4/5: Cytochrome P450 3A4; HbA1c: hemoglobin A1c; P-gp: P-glycoprotein; SU: sulfonylurea

## Table 7: Glucagon-like 1 peptide receptor agonists

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| Exenatide<br>Liraglutide<br>Lixisenatide<br><br>**Once weekly agents**<br>Exenatide<br>Albiglutide<br>Dulaglutide | 1 - 1.5% | Low<br>(↑ risk when combined with SU or insulin) | ↓ Weight | ▪ Reduces postprandial glucose values<br>▪ Contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2<br>▪ Consider other antidiabetic therapies in patients with a history of pancreatitis<br>▪ Use with caution in patients receiving oral medications that require rapid GI absorption<br>▪ Avoid use if patient has severe GI disease, including severe gastroparesis<br>▪ May require dosage adjustment for renal impairment (varies by product); exenatide should not be used if eGFR <30 mL/minute/1.73 m$^2$<br>▪ Injectable<br>▪ Liraglutide was shown to reduce the risk of cardiovascular events | ▪ GI effects (nausea, vomiting, diarrhea)<br>▪ Reports of renal impairment usually in association with nausea, vomiting, diarrhea<br>▪ Injection site reactions<br>▪ Post-marketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.<br>▪ Post-marketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema).<br>▪ Unconfirmed association with medullary cell carcinoma | Expensive |

Abbreviations: CYP3A4/5: Cytochrome P450 3A4; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HbA1c: hemoglobin A1c; m$^2$: square meter; mL: milliliter; SU: sulfonylurea

**Table 8: Insulin**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events / Side Effects | Cost |
|---|---|---|---|---|---|---|
| **Insulin (prandial)**<br>*Short-acting*<br>Regular<br>*Rapid-acting analog*<br>Lispro<br>Aspart<br>Glulisine<br><br>**Insulin (basal)**<br>*Intermediate-acting*<br>NPH<br>*Long-acting analogs*<br>Glargine<br>Detemir<br>Degludec<br><br>**Premixed**<br>NPH/Regular<br>Biphasic insulin aspart<br>Insulin lispro protamine/lispro<br>Insulin degludec/aspart | Variable | Moderate-high | ↑ Weight | ▪ Use well established<br>▪ Most effective at lowering elevated glucose<br>▪ Dosing can be individualized<br>▪ Beneficial effect on triglycerides and HDL-C<br>▪ Lower doses may be needed for renal and hepatic impairment<br>▪ Patient training needed | ▪ Hypersensitivity reactions<br>▪ Injection site reactions<br>▪ Anaphylaxis has been reported (rare) | ▪ Inexpensive (human insulin)<br>▪ Moderate to expensive (analogs) |

Abbreviations: HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; NPH: neutral protamine Hagedorn

**Table 9: Meglitinides**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| Nateglinide Repaglinide | 0.5 - 1% | Moderate | ↑ Weight | ▪ Administer with meals; scheduled dose should not be administered if a meal is missed to avoid hypoglycemia<br>▪ Reduces postprandial glucose values<br>▪ Use with caution in patients with moderate to severe hepatic impairment and severe renal impairment<br>▪ Use with caution in the elderly, debilitated, and malnourished patients; may be more susceptible to glucose-lowering effects<br>▪ Combination therapy with SU is not recommended, no additional benefit | ▪ Upper respiratory infection<br>▪ Flu-like symptoms | ▪ Inexpensive (repaglinide)<br>▪ Moderately expensive (nateglinide) |

Abbreviations: HbA1c: hemoglobin A1c; SU: sulfonylureas

**Table 10: Sodium glucose co-transporter 2 (SGLT2) inhibitors**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| Canagliflozin Dapagliflozin Empagliflozin | 0.5 – 1% | Low | ↓ Weight | ▪ Do not use if eGFR <45 mL/min/1.73 m$^2$ (empagliflozin/canagliflozin) or <60 mL/min/1.73 m$^2$ (dapagliflozin)<br>▪ Empagliflozin was shown to reduce the risk of cardiovascular events compared to placebo<br>▪ Decrease triglycerides<br>▪ Increase HDL-C<br>▪ Increase LDL-C | ▪ Urinary tract infections/urosepsis<br>▪ Genital mycotic infections (higher incidence in females and uncircumcised males)<br>▪ Increased risk for hypotension, orthostasis, volume depletion in elderly, those taking diuretics, or anti-hypertensives<br>▪ Decreased eGFR or increased serum creatinine may occur; elderly and those with preexisting renal impairment may be at greater risk<br>▪ Decrease in systolic blood pressure (~4-6 mmHg)<br>▪ DKA rare (presenting blood glucose levels may be below those typically expected for diabetic ketoacidosis (often <250 mg/dL).<br>▪ Decreased bone density and increased risk of bone fractures reported with canagliflozin | Expensive |

Abbreviations: DKA: diabetic ketoacidosis; dL: deciliter; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; m$^2$: square meter; mg: milligram; min: minute; mL: milliliter; mmHg: millimeter of mercury

**Table 11: Sulfonylureas**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| **Second Generation**<br>Glimepiride<br>Glipizide<br>Glyburide<br><br>**First generation agents seldom used**<br>Chlorpropamide<br>Tolazamide<br>Tolbutamide | 1 -1.5% | Moderate | ↑ Weight | ▪ Effectiveness diminishes with progression of T2DM due to continued beta cell destruction<br>▪ Use with caution in elderly and patients with hepatic or renal impairment<br>▪ Patients with G6PD may be at an increased risk of SU-induced hemolytic anemia | ▪ Allergic skin reactions<br>▪ SIADH has been reported<br>▪ Dose-related GI effects (nausea, diarrhea, constipation) | Inexpensive |

Abbreviations: G6PD: glucose-6-phosphate dehydrogenase deficiency; GI: gastrointestinal; HbA1c: hemoglobin A1c; SIADH: syndrome of inappropriate antidiuretic hormone secretion; SU: sulfonylurea; T2DM: type 2 diabetes mellitus

**Table 12: Thiazolidinediones**

| Drug Class | Average HbA1c Reduction | Potential for Hypoglycemia | Impact on Weight | Clinical Considerations | Adverse Events/Side Effects | Cost |
|---|---|---|---|---|---|---|
| Pioglitazone Rosiglitazone | 1 – 1.5% | Low (↑ risk when combined with SU or insulin) | ↑ Weight | ▪ Contraindicated in those with NYHA Class III or IV heart failure<br>▪ Use with caution in patients with NYHA Class I/II heart failure or patients with risk factors for heart failure<br>▪ Not recommended in symptomatic heart failure<br>▪ Do not use in patients with active bladder cancer; consider risk versus benefits of using pioglitazone in those with a history of bladder cancer<br>▪ Use with caution in premenopausal, anovulatory women; may result in resumption of ovulation, increasing risk of pregnancy<br>▪ Administer cautiously in those with abnormal liver function tests<br>▪ Pioglitazone may reduce CV events | ▪ Edema usually dose-related<br>▪ Cause or exacerbate heart failure (greater risk if used with insulin)<br>▪ Macular edema has been reported (may present with blurred vision or decreased visual acuity)<br>▪ Increased incidence of bone fractures in females occurring in the upper arm, hand and foot<br>▪ Liver injury has been reported; if ALT >3x ULN do not reinitiate therapy without another explanation for the liver test abnormalities | ▪ Inexpensive (pioglitazone)<br>▪ Moderately expensive (rosiglitazone) |

Abbreviations: ALT: alanine aminotransferase; CV: cardiovascular; HbA1c: hemoglobin A1c; NYHA: New York Heart Association; SU: sulfonylurea; ULN: upper limit of normal

**Table 13: Insulin: Summary of Pharmacokinetics [22-28]**

| Insulin | Onset | Peak | Duration | Half-life | Comments |
|---|---|---|---|---|---|
| **Prandial (bolus) Insulin** | | | | | |
| **Rapid-Acting** | | | | | |
| **Insulin aspart** | NovoLog: 0.2 to 0.3 hr NovoLog Mix 70/30: 10 to 20 mins | NovoLog: 1 to 3 hrs NovoLog Mix 70/30: 1 to 4 hrs | NovoLog: 3 to 5 hrs NovoLog Mix 70/30: 18 to 24 hrs | Subcutaneous: 81 min (NovoLog); ≈ 8 to 9 hrs (NovoLog Mix 70/30) | Appearance: clear; covers insulin needs at the time of the injection |
| **Insulin lispro** | Subcutaneous: 0.25 to 0.5 hr | Subcutaneous: 0.5 to 2.5 hrs | Subcutaneous: ≤5 hrs | Subcutaneous: ≈ 1 hr, IV: 51 to 55 mins | |
| **Insulin glulisine** | 5 to 15 mins | 1.6 to 2.8 hr | <5 hrs | IV: 13 mins, Subcutaneous: 42 mins | |
| **Short-Acting** | | | | | |
| **Regular insulin** | Subcutaneous: ≈ 0.5 hr, IV: 10 to 15 mins | Subcutaneous: 3 hrs | U 100: 4 to 12 hrs; U 500: up to 24 hrs | IV: 17 mins, Subcutaneous: 86 to 141 mins | Appearance: clear; covers insulin needs for meals eaten within 30-60 mins |
| **Basal Insulin** | | | | | |
| **Intermediate-Acting** | | | | | |
| **Insulin isophane (NPH)** | 1 to 1.5 hrs | 4 to 12 hrs | 14.5 hrs | ≈ 4.4 hrs | Appearance: cloudy; covers insulin needs for about half the day or overnight. Often combined with rapid- or short-acting insulin |
| **Long-Acting (Not be mixed with other insulins)** | | | | | |
| **Insulin detemir** | 3 to 4 hrs | None | Up to 24 hrs | 5 to 7 hrs | Appearance: clear; covers insulin needs for about 1 full day. Often used as needed, or with rapid- or short-acting insulin |
| **Insulin glargine** | Lantus: 3 to 4 hrs Toujeo: 6 hrs | None | Lantus: Up to 24 hrs Toujeo: ≥24 hrs | | |
| **Insulin degludec** | 1 hr | 9 hrs | At least 42 hrs | 25 hrs | |

| Insulin | Onset | Peak | Duration | Half-life | Comments |
|---|---|---|---|---|---|
| **Pre-Mixed Products** | | | | | |
| **70 NPH/30 Regular** | Not to be mixed with other insulins. Cloudy/generally taken twice a day before meals. | | | | |
| **50 NPH/50 Regular** | | | | | |
| **75 NPH/25 lispro** | | | | | |
| **50 NPH/50 lispro** | | | | | |
| **70 aspart/30 aspart** | | | | | |
| **50 aspart/50 aspart** | | | | | |

Abbreviations: hr: hour; IV: intravenous; min: minute; NPH: neutral protamine Hagedorn

**Table 14: FDA Approved/ Studied Combination Therapy[1,2] [28]**

| | AGIs | DPP-4 inhibitors | GLP-1 agonists | Insulin | Meglitinides | Metformin | SGLT2 inhibitors | SUs | TZDs |
|---|---|---|---|---|---|---|---|---|---|
| **AGIs** | N/A | | | | | | | | |
| **DPP-4 inhibitors** | | N/A | | | | | | | |
| **GLP-1 agonists*** | | | N/A | | | | | | |
| **Insulin** | X | X | X[†] | N/A | | | | | |
| **Meglitinides** | | | | | N/A | | | | |
| **Metformin** | X | X | X | X | X | N/A | | | |
| **SGLT2 inhibitors** | | X | | X | | X | N/A | | |
| **SUs** | X | X | X | X | | X | X | N/A | |
| **TZDs** | | X | X | X[±] | X | X | X | X | N/A |

Abbreviations: AGI: α-glucosidase; DPP4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium glucose co-transporter 2; SU: sulfonylurea; TZD: thiazolidinedione

[1] Agents listed in alphabetical order

[2]This table reflects FDA approved indications and/or well-studied combinations. All combinations have not been studied at this time and evidence is rapidly evolving.

*The data for GLP-1 agonists in combination with both basal and prandial insulin are very limited at this time.

†Exenatide once weekly + insulin is not recommended per product labeling.

±Rosiglitazone + insulin is not recommended per product labeling.

# X.    Methods

## A.    Strength of Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [29]

- Balance of desirable and undesirable outcomes

- Confidence in the quality of the evidence

- Values and preferences

- Other implications, as appropriate, e.g.,:

  - Resource use

  - Equity

  - Acceptability

  - Feasibility

  - Subgroup considerations

The framework below (Table 15) was used by the Work Group to guide discussions on each domain.

**Table 15. Evidence to Recommendation Framework**

| Decision Domain | Judgment |
|---|---|
| **Balance of desirable and undesirable outcomes** | |
| <ul><li>Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?</li><li>Are the desirable anticipated effects large?</li><li>Are the undesirable anticipated effects small?</li><li>Are the desirable effects large relative to undesirable effects?</li></ul> | <ul><li>Benefits outweigh harms/ burden</li><li>Benefits slightly outweigh harms/burden</li><li>Benefits and harms/burden are balanced</li><li>Harms/burden slightly outweigh benefits</li><li>Harms/burden outweigh benefits</li></ul> |
| **Confidence in the quality of the evidence** | |
| <ul><li>Is there high or moderate quality evidence that answers this question?</li><li>What is the overall certainty of this evidence?</li></ul> | <ul><li>High</li><li>Moderate</li><li>Low</li><li>Very low</li></ul> |
| **Values and preferences** | |
| <ul><li>Are you confident about the typical values and preferences and are they similar across the target population?</li><li>What are the patient's values and preferences?</li><li>Are the assumed or identified relative values similar across the target population?</li></ul> | <ul><li>Similar values</li><li>Some variation</li><li>Large variation</li></ul> |
| **Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)** | |
| <ul><li>Are the resources worth the expected net benefit from the recommendation?</li><li>What are the costs per resource unit?</li><li>Is this intervention generally available?</li><li>Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?</li><li>Is there lots of variability in resource requirements across settings?</li></ul> | <ul><li>Various considerations</li></ul> |

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains.[29] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.[30] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation in the full-text CPG.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

## B.    Recommendation Categorization

For use in the 2017 DM CPG, a set of recommendation categories was adapted from those used by the United Kingdom National Institute for Health and Clinical Excellence.[31,32] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2010 DM CPG. The categories and definitions can be found in Table 16.

**Table 16. Recommendation Categories and Definitions**

| Evidence Reviewed* | Recommendation Category* | Definition* |
|---|---|---|
| Reviewed | New-added | New recommendation following review of the evidence |
| | New-replaced | Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence |
| | Not changed | Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed |
| | Amended | Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made |
| | Deleted | Recommendation from the previous CPG that has been removed based on review of the evidence |
| Not reviewed | Not changed | Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed |
| | Amended | Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made |
| | Deleted | Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG |

*Adapted from the NICE guideline manual (2012) [31] and Garcia et al. (2014) [32]

Abbreviation: CPG: clinical practice guideline

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