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

Department of Veterans Affairs

Department of Defense

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

Prepared by:

The Management of Type 2 Diabetes Mellitus in Primary Care Work Group

With support from:

The Office of Quality, Safety and Value, VA, Washington, DC
&
Office of Evidence Based Practice, U.S. Army Medical Command

Version 5.0 – 2017

Based on evidence reviewed through March 2016

Table of Contents

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 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]

[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. About this Clinical Practice Guideline

This guideline represents a significant step toward improving the treatment and management of patients with DM in the VA and DoD. As with other CPGs, however, challenges remain, including evidence gaps, the need to develop effective strategies for guideline implementation and to evaluate the effect of guideline adherence on clinical outcomes. This guideline is intended for VA and DoD healthcare practitioners including physicians, nurse practitioners, nurses, physician assistants, dietitians/nutritionists, diabetes educators, pharmacists, and others involved in the care of Service Members or Veterans with DM.

As elaborated in the qualifying statement on page one, this CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on information available by March 2016 and is intended to provide a general guide to best practices. The guideline can assist care providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment and patient values and preferences, for the care of an individual patient.

A. Methods

The current document is an update to the 2010 DM CPG. The methodology used in developing the 2017 CPG follows the *Guideline for Guidelines*,[1] an internal document of the VA and DoD EBPWG. The

[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 (CKD) in Primary Care. 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/

Guideline for Guidelines can be downloaded from http://www.healthquality.va.gov/policy/index.asp. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions), and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the development and submission of a new or updated DM CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and writing and publishing a guideline document to be used by providers within the VA/DoD healthcare systems. Specifically, the Champions and Work Group members for this guideline were responsible for identifying the key questions (KQs) of the most clinical relevance, importance, and interest for the management of patients with DM. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level and quality of the evidence. The amount of new scientific evidence that had accumulated since the previous version of the CPG was also taken into consideration in the identification of the KQs. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified two clinical leaders as Champions for the 2017 DM CPG. Leonard Pogach, MD, MBA is the Champion from the VA and Maj Jeffrey A. Colburn, MD is the Champion for the DoD. Maj Colburn replaced the previous DoD Champion who left the Work Group after the in-person Work Group meeting in June 2016 due to a conflict of interest (COI).

The Lewin Team, including the Lewin Group, Duty First Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and conduct the evidence review. The first conference call was held in December 2015, with participation from the contracting officer's representative, leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence Based Practice, and the Champions. During this call, participants discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing and prioritizing specific research questions on which to base a systematic review (SR) about the management of DM. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of DM, from which Work Group members were recruited. The specialties and clinical areas of interest included endocrinology, internal medicine, nutrition, pharmacy, health education, nursing, medical management, ambulatory care, and family practice.

The guideline development process for the 2017 CPG update consisted of the following steps:

1. Formulating and prioritizing KQs
2. Conducting a patient focus group
3. Conducting the SR

4. Convening a face-to-face meeting with the Champions and Work Group members
5. Drafting and submitting a final CPG about the management of DM to the VA/DoD EBPWG

Appendix A provides a detailed description of each of these tasks.

a. Grading Recommendations

The Champions and Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system 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:[15]

- Confidence in the quality of the evidence
- Balance of desirable and undesirable outcomes
- Patient or provider values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Using this system, the Champions and Work Group determined the relative strength of each recommendation (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 give a weak recommendation.

They also determined the direction of each recommendation (For or Against). 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 …”)

The grade of each recommendation made in the 2017 DM CPG can be found in the section on Recommendations. Additional information regarding the use of the GRADE system can be found in Appendix A.

It is important to note that the GRADE system grades the strength of recommendations based on four domains—(1) confidence in the quality of evidence; (2) balance of benefits and harms; (3) patient values and preferences; and (4) other considerations, which can include resource use, equity and acceptability. Most other grading systems, such as U.S. Preventive Services Task Force (USPSTF), use only two domains—(1) certainty of net benefit and (2) magnitude of net benefit (i.e., balance of benefits and harms). Thus, differences in recommendations across guidelines may reflect differences in the grading system used as well as differences in the evidence reviewed and/or how the strength of the evidence is evaluated by the Work Group.

b. Reconciling 2010 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous guidelines based on new evidence, or as scheduled, subject to time-based expirations.[16] For example, the USPSTF has a process for refining or otherwise updating its recommendations pertaining to preventive services.[17] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed, or revised within the past five years.

The DM Guideline Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition to those new and updated recommendations, the Guideline Work Group considered, without complete review of the relevant evidence, the current applicability of other recommendations that were included in the previous 2010 DM CPG, subject to evolving practice in today's environment.

A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE).[18,19] These categories, along with their corresponding definitions, were used to account for the various ways in which previous recommendations could have been updated. In brief, the categories took into account whether or not the evidence that related to a recommendation was systematically reviewed, the degree to which the recommendation was modified, and the degree to which a recommendation is relevant in the current patient care environment and within the scope of the CPG. Additional information regarding these categories and their definitions can be found in Appendix A. The categories for the recommendations included in the 2017 version of the guideline can be found in the section on Recommendations. The categories for the recommendations from the 2010 DM CPG are noted in Appendix F.

The CPG Work Group recognized the need to accommodate the transition in evidence-rating systems from the 2010 DM CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system), the CPG Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2010 guideline to the GRADE system. As such, the CPG Work Group considered the strength of the evidence cited for each recommendation in the 2010 DM CPG as well as harms and benefits, values and preferences, and other implications, where possible. The CPG Work Group referred to the available evidence as summarized in the body of the 2010 DM CPG and did not re-assess the evidence systematically. In some instances, peer-reviewed literature published since the 2010 DM CPG was considered along with the evidence base used for that CPG.

Where such newer literature was considered when converting the strength of the recommendation from the USPSTF to the GRADE system, it is referenced in the discussion that follows the corresponding recommendation, as well as in Appendix E.

The CPG Work Group recognizes that, while there are practical reasons for incorporating findings from a previous SR, previous recommendations,[20] or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive SR and, therefore, may introduce bias.

c. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the CPG. The process for developing the initial draft is described in more detail in Drafting and Submitting the Final Clinical Practice Guideline.

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group members, the draft was sent out for peer review and comment. The draft was posted on a wiki website for a period of 14 business days. The peer reviewers comprised individuals working within the VA and DoD health systems as well as experts from relevant outside organizations designated by the Work Group members. External organizations that participated in the peer review included the following:

- Academy of Nutrition and Dietetics
- Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA)
- Coverage and Analysis Group, Centers for Medicare and Medicaid Services (CMS)
- Geisel School of Medicine, Dartmouth College
- Health Resources and Services Administration (HRSA)
- National Institute on Aging, National Institutes of Health (NIH)
- Office of Rural Health Policy, U.S. Department of Health and Human Services (HHS)

The VA and DoD Leadership reached out to both the internal and external peer reviewers to solicit their feedback on the CPG. Reviewers were provided a hyperlink to the wiki website where the draft CPG was posted. For transparency, all reviewer feedback was posted in tabular form on the wiki site, along with the name of the reviewer. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made throughout the CPG development process were made in accordance with the evidence.

B. Summary of Patient Focus Group Methods and Findings

When forming guideline recommendations, consideration should be given to the values of those most affected by the recommendations. Patients bring perspectives, values, and preferences into their healthcare experience, and more specifically their DM care experience, that vary from those of clinicians. These differences and the variability between patients' perspectives can affect decision making in various situations, and should thus be highlighted and made explicit due to their potential to influence a recommendation's implementation.[21,22] Focus groups can be used as an efficient method to explore ideas and perspectives of a group of individuals with an a priori set of assumptions or hypotheses and collect qualitative data on a thoughtfully predetermined set of questions.

Therefore, as part of the effort to update this CPG, VA and DoD Leadership, along with the DM CPG Work Group and Lewin, held a patient focus group on March 8, 2016, at the VA Puget Sound Health Care System - American Lake Division in Tacoma, Washington. The aim of the focus group was to further the understanding of the perspective of patients receiving treatment for DM within the VA and/or DoD healthcare systems. The focus group explored patient perspectives on a set of topics related to management of DM in the VA and DoD healthcare systems, including patients' knowledge of DM treatment options, views on the delivery of care, patients' perspective on their needs and preferences, and the impact of DM on their lives.

It is important to note the focus group was a convenience sample and the Working Group recognizes the limitations inherent in the small sample size. Less than 10 people were included in the focus group consistent with the requirements of the federal Paperwork Reduction Act, 1980. The Work Group acknowledges that the sample of patients included in this focus group may not be representative of all VA and DoD patients receiving treatment for DM. Patient perspective and input provided, while invaluable, is not generalizable given the broad characteristics of various key demographic groups of persons with DM. Further, time limitations for the focus group prevented exhaustive exploration of all topics related to DM treatment in the VA and DoD and the patients' broader experiences with their care. Thus, the Working Group made decisions regarding the priority of topics to discuss at the focus group. These limitations, as well as others, were considered throughout the use of the information collected from the discussion for guideline development.

Recruitment for participation in the focus group was managed by the Champions and VA and DoD Leadership, with assistance from coordinators at the facility at which the focus group took place.

The following concepts are aspects of care that are important to patients that emerged from the discussion. These concepts were needed and important parts of the participants' care and added to the Work Group's understanding of patient values and perspectives. Additional details regarding the patient focus group methods and findings can be found in Appendix D.

DM CPG Patient Focus Group Concepts	
A.	Using shared decision-making, consider all treatment options and develop a treatment plan based on the balance of risks, benefits, and patient-specific goals, values, and preferences.
B.	Guide patients on the self-management of their DM and glucose monitoring, including benefits and risks, and their expectations.
C.	Educate and involve family caregivers and co-workers in accordance with patient preferences regarding core knowledge of DM management.
D.	Within and between VA and DoD healthcare systems, work with appropriate providers to ensure continuity of high-quality care and timely referral to an endocrinologist.
E.	Create a support system for patients with DM such as online groups, chats, other support groups, and diabetes education classes to enhance involvement and support among patients with DM.

C. Conflict of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential COI in the past 24 months. Verbal affirmations of no COI were used as necessary during meetings throughout the guideline

development process. The project team was also subject to random web-based surveillance (e.g., ProPublica).

If a project team member reported a COI (actual or potential), measures were in place to mitigate the introduction of bias into the guideline development process. Identified COIs would be reported to the Office of Evidence Based Practice and disclosed to the EBPWG in tandem with their review of the evidence and development of recommendations. The EBPWG and the DM CPG Work Group would then determine whether or not action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If deemed necessary, action to mitigate the COI was taken by the Champions and Office of Evidence Based Practice, based on the level and extent of involvement.

In order to mitigate the risk of bias while maximizing the contributions of those with expertise in a specific area of DM, the Champions asked Work Group members to disclose relevant relationships during related guideline development discussions. Members with potential COIs contributed to the discussions related to their particular areas of expertise as well as the overarching guideline document in order to ensure differing viewpoints and experiences were adequately represented.

The initially appointed DoD Champion disclosed a COI at the in-person meeting and VA and DoD Leadership determined the COI would preclude him from continuing his role on the DM CPG Work Group. Maj Jeffrey A. Colburn, already a DM CPG Work Group member, was selected as the new DoD Champion. The work on the guideline when the initial DoD Champion was present was reviewed and steps were taken to ensure that no biases were introduced and that the initial work on the DM CPG with the former DoD Champion did not negatively affect the objectivity of the DM CPG development.

D. Scope of this Clinical Practice Guideline

Regardless of setting, any patient in the VA/DoD healthcare systems should be offered access to the interventions that are recommended in this guideline after taking into consideration the patient's specific circumstances.

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.

The literature review encompassed interventional studies (primarily randomized controlled trials [RCTs]) and observational studies published between January 2009 and March 2016, and targeted nine KQs focusing on the means by which the delivery of healthcare could be optimized for patients with DM. KQ7 required updated searches through June 14, 2016. The selected KQs were prioritized from many possible KQs. Due to resource constraints, a review of the evidence in all important aspects of care for patients with DM was not feasible for the update of this CPG. For example, treatments specific to obese patients, such as bariatric surgery, are not addressed in this CPG but are addressed in the VA/DoD

Clinical Practice Guideline for Screening and Management of Overweight and Obesity (VA/DoD Obesity CPG).[8]

E. Highlighted Features of this Clinical Practice Guideline

The 2017 edition of the VA/DoD Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus in Primary Care is the fourth update to the original CPG. It provides practice recommendations for the care of patients with DM. A particular strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from the broad spectrum of clinicians engaged in the treatment and management of patients with DM.

The framework for recommendations in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of treatment, the potential for variation in patient values and preferences, and other considerations such as resource use and equity. Applicability of the evidence to VA/DoD populations was also taken into consideration. A structured algorithm accompanies the guideline to provide an overview of the recommendations in the context of the flow of patient care and clinician decision making and to assist with training providers. The algorithm may be used to help facilitate translation of guideline recommendations into effective practice.

F. 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.[23] 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 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.[24] When properly executed, SDM [25,26] may decrease patient anxiety, increase trust in clinicians,[27] and improve treatment adherence.[28] 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)

[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/

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.

G. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of local needs and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the course of an episode of care.

Although this CPG represents the recommended practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and to inform optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new evidence particularly relevant to clinical practice.

IV. Guideline Work Group

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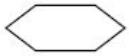
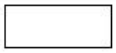
V. Algorithm

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:

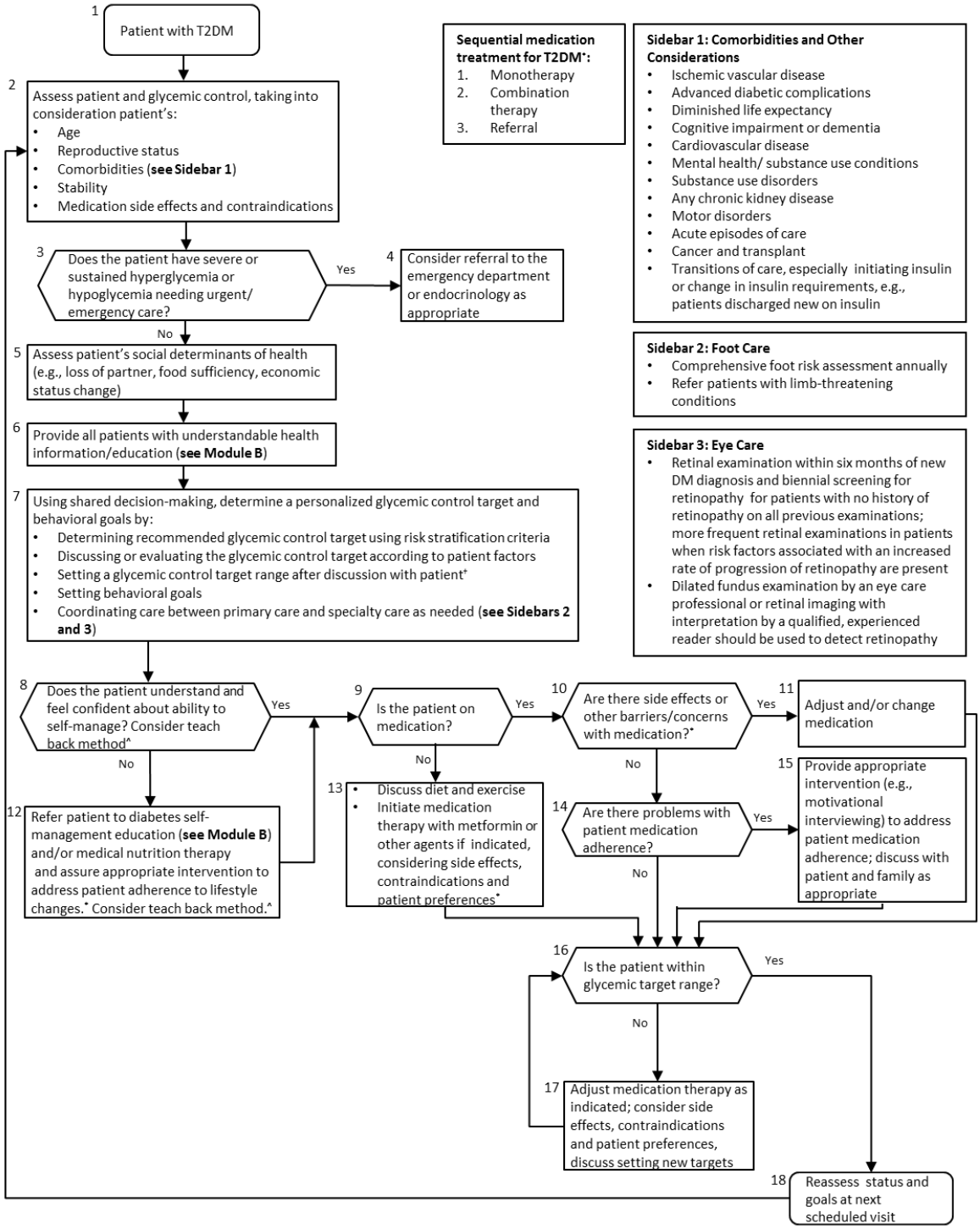
- An ordered sequence of steps of care
- Relevant observations and examinations
- Decisions for consideration
- Actions to be taken

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.[29]

	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.

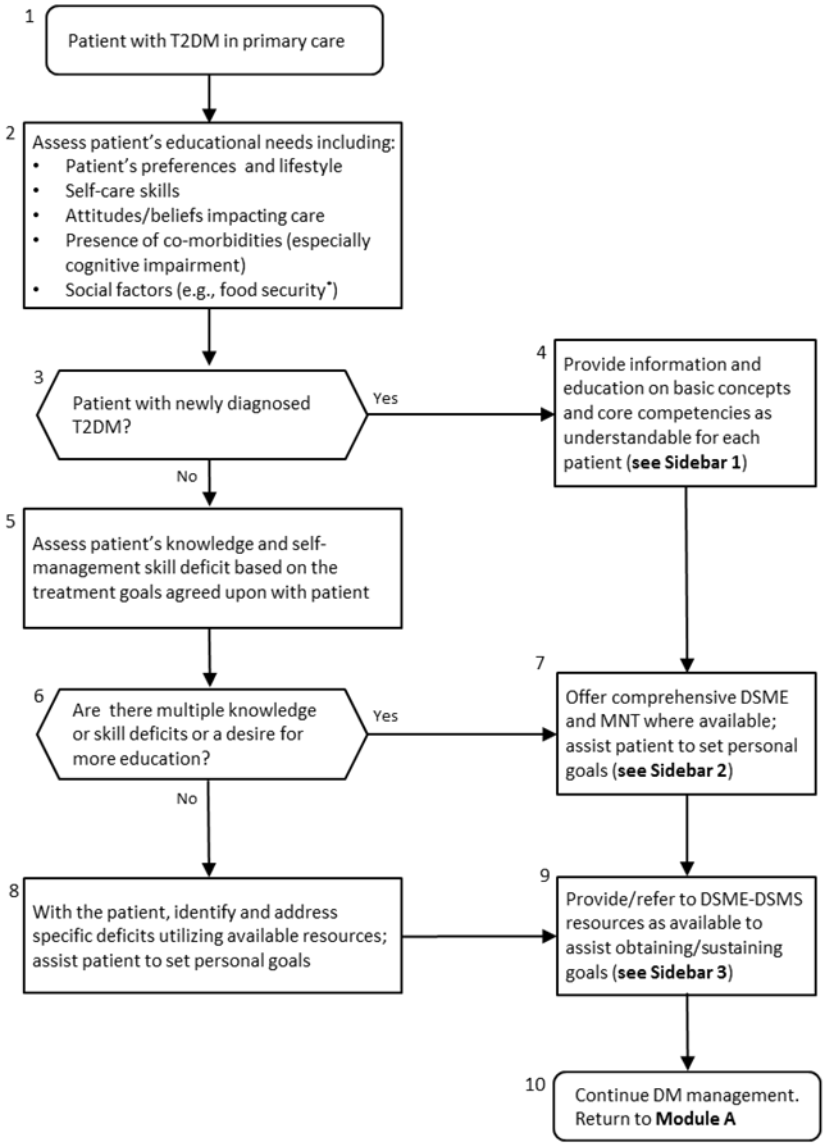
A. Algorithm

a. Module A: General Care and Treatment



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



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)

VI. Recommendations

#	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
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

#	Recommendation	Strength*	Category†
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

*For additional information, please refer to Grading Recommendations.
†For additional information, please refer to Recommendation Categorization and Appendix F.

A. General Approach to T2DM Care

Recommendation

1. We recommend shared decision-making to enhance patient knowledge and satisfaction. **(Strong for | Reviewed, New-added)**

Discussion

SDM is the process by which the patient and family in conjunction with the provider of care come to an agreement about a plan of care and treatment. Key principles include the patient/family readiness, provision of benefits and harms of all options in understandable tools, and incorporation of preferences.[25,26] SDM includes eight steps: 1) Ask – identify Issues; 2) Prioritize – explore what the patient wants; 3) Assess – look for barriers to the SDM; 4) Advise – benefits, risks of patient choice; 5) Acknowledge – criteria of the basis for the decision; 6) Assist- explore the options; 7) Make the decision; and 8) Evaluate – how did the choice work? Be prepared to review and revisit as needed. Is the patient satisfied with the outcome?[25]

Confidence in the quality of evidence was high regarding SDM for improving patients' knowledge, satisfaction and engagement with their treatment plan.[30-32] A prescribed type of approach to SDM is not well defined in the literature for individual patient groups and represents a research gap in this area. Patient preference must be a consideration. However, the studies utilized for this recommendation noted patients may have varying responses to their clinical providers when approached to engage in SDM processes. Patients that are diagnosed with DM may respond differently to SDM depending on personal goals, life experiences, and coping strategies.[30-32] SDM should not be used just for a patient with stable glycemic controls; it should be used to assist those patients that may not be able or willing to make those lifestyle changes and decisions that affect their health condition at any time during the course of their disease. This should include, at a minimum, diagnosis, difficulties in management, and times of transition or development of complications.[32]

Shared understanding is critical to the SDM process. Health coaching and motivational interviewing strategies can assist clinicians to understand patients' perceptions, values and beliefs regarding their condition, treatment and self-management options, particularly when patients appear to be reluctant to fully participate in decisions and care. Studies indicate there may be other approaches that use health coaching and motivational interviewing approaches to promote medication compliance/adherence and follow through. Using motivational interviewing techniques can make it easier to understand the specific level of patients' perception of the disease process and their comfort level discussing this process. Motivational interviewing is one of the techniques that may be used in the process of SDM. It provides a communication skill which may be lacking in some patient arenas. When a provider uses motivational interviewing skills it may increase the dialogue between provider and patient thus developing a trust level more rapidly and more effectively.

Sharing healthcare decisions requires a healthcare system which supports the process, and patients, providers, and healthcare team members who are encouraged to share decisions. The benefits of SDM usually outweigh the harms with increase in patient satisfaction and treatment "buy-in" regarding the ways and methods to reach that particular goal or treatment plan.[30] When patient preferences are considered, it reinforces a trusted therapeutic relationship and creates "good-will" as a shared responsibility for patient health outcomes.

SDM may be time intensive as the provider has to create an environment of consideration and goal formation. Clinical training in these communication skills may be a win as research indicates that patients most likely to participate in this SDM process are comfortable speaking with their providers and have some level of knowledge of their specific disease process.[33] Our challenge is to help patients understand how they can successfully manage DM and partner with their providers and healthcare teams to share their goals and preferences to individualize healthcare decisions. Providing system supports, SDM tools, and assuring that providers and teams can use patient-centered communication skills will increase patients' willingness to share decisions. These factors are the key to SDM.

Recommendation

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)

Discussion

Diabetes Self-Management Education (DSME) and Diabetes Self-Management Support (DSMS) provide a framework involving a collaborative, on-going, interactive process focusing on the patient with DM to gain knowledge, modify behavior, and successfully manage the disease. The process requires ongoing interactive information-sharing between the diabetes team and the patient.

The goal of diabetes education in SDM is to ensure the patient has sufficient knowledge and skills to achieve the treatment goals they agreed upon with their healthcare provider. Participants in the patient focus group emphasized the importance of DSME and that understanding diabetes is important for self-management of the disease. A strong message from the focus group was that clinicians need to account for the specific circumstances (e.g., cognitive impairment, changing life situations, culture/belief system) of each patient, have detailed knowledge about the various treatment options, and plan accordingly for each patient.

The reviewed literature acknowledged the value of DSME-DSMS to facilitate patient management, improve patient outcomes, as well as reduce overall diabetes-related costs. DSME is differentiated from traditional education which is didactic and tends to be delivered in lecture format only.[34] DSME as described in the literature is a dynamic process that provides knowledge and self-management skill-building activities based on individual needs, attitudes, beliefs, and ever-changing life situations.[34,35] The content of DSME varied between studies, but the following topics were consistently covered during study interventions: knowledge about diabetes and treatment options, medications, nutrition, exercise, hypoglycemia, monitoring of glucose and HbA1c, psychosocial and behavioral components, risk reduction, foot care, smoking cessation, chronic complications, and sick day management.[35-39]

DSME may be delivered via various modalities, including group sessions/discussion, telephone, web-based technology, multimedia presentations, teach-back, and role play. The reviewed literature addressed various modes of delivery and varied in the content of educational materials and time allotted for the intervention (varied from 1 to >20 hours), as well as the specific population subgroups that were studied. Due to wide variability in the evidence reviewed, the Work Group classified the

confidence level for the quality of evidence as low. Most studies favored group DSME over usual care (individual visit with primary care provider).[34,36,40] When comparing different modalities of providing DSME, the evidence identified positive patient outcomes for DSME delivered in group settings, individual settings, or using technology-based systems (e.g., telephone, internet).[38,41,42] Pillay et al. concluded that the greater the time spent with the patient was associated with improved outcomes and there is a need to provide DSME, DSMS, and/or behavioral programs to assist with lifestyle change.[40]

DSME-DSMS may be provided individually or in a group, based on available resources. Group-based DSME-DSMS is cost-effective and provides foundational support for individuals with diabetes to meet and discuss common issues.[34,36] Individual education can be time and resource intensive, but should be considered especially for individuals with special needs (e.g., cognitive issues, hearing or sight impairment). While the evidence did not favor group over individual DSME, individuals with poor glycemic management benefitted more from individual interventions than those with good glycemic management.[39] A combination of group and individual DSME-DSMS may be effective in providing general information and developing personalized goals/treatment plans more efficiently.

Success of DSME in the literature was dependent on program intensity and the delivery personnel or format.[34] DSME-DSMS was shown to require substantial contact time and a support component to train individuals in self-care skills. Tailoring DSME to ethnic minorities was shown to be beneficial.[35]

Resources to provide DSME will vary greatly and may be limited at some facilities due to inadequate staffing or lack of trained personnel. When DSME is not easily available, refer to the network based on your organization's policies. Other options may include community-based programs, web-based education, or phone applications.[43]

This Work Group studied one SR,[43] one network meta-analysis,[40] and three RCTs [37,38,44] in an effort to evaluate the effectiveness of technology-based DSME programs to aid in guiding this recommendation.

In the SR by Pal et al., technology-based DSME was significantly more effective at six months (-0.2%, 95% CI: -0.4 to -0.1), however, the effect diminished over time and was shown to not be significant beyond six months (-0.1%, 95% CI: -0.3 to 0.1).[43] Patients who received technology-based DSME reported greater self-efficacy at six to 18 months relative to patients in the control group.

Tang et al. assessed the effectiveness of internet-based DSME in a group of 415 patients with an average age of 54 years.[44] Internet-based DSME was associated with greater HbA1c reductions at six months (internet-based: Mean Difference [MD] -1.32; usual care [standard-of-care treatment with reminders for annual laboratory tests and screenings]: MD -0.66, $p < 0.001$); however, at 12 months follow-up, these differences lost statistical significance (internet-based: MD -1.14; usual care: MD -0.95, $p=0.133$). However, treatment satisfaction at 12 months was greatest in patients who received internet-based DSME relative to patients who received usual care ($p < 0.001$).[44]

In summary, the reviewed research demonstrated that internet-based DSME is comparable to the traditional in-person group DSME class for improvement in HbA1c outcomes.

The individuals who participated in the patient focus group shared similar and intertwined goals and preferences, including maintaining their current work, minimizing treatment side effects, maintaining a functional life, and improving QoL. A key suggestion made by the focus group participants was to create a formal support system for patients with diabetes such as web-based, online chats, or other types of support groups and diabetes education classes to enhance involvement and support.

Incorporation of online learning into the DSME model appears to allow expansion of options for individual learners with diabetes who may prefer an online program over an in-person group program. Online learning allows the learner to engage in topics of personal interest and reinforce concepts by repeating online classes during asynchronous, flexible times. It also allows learners, family members, and co-workers the ability to acquire needed information without taking time away from their work schedule.

The literature supports using alternative delivery systems of DSME to provide support and maximize learning while presenting core curriculum. The goal of an internet-based strategy is not to replace group or individualized DSME programs but to allow adult learners the ability to flexibly engage and invest in their diabetes care needs.

DSMS is a recent concept as of this CPG update, and not yet consistently defined or supported in the literature. Broadly defined, DSMS is the notion of ongoing support of the individual after receiving DSME. While the literature reviewed did not specifically address DSMS, programs that provided ongoing support (e.g., periodic follow-up, evaluating and re-establishing goals, support groups) showed better outcomes after the initial educational intervention than isolated educational events.[34-36] As stated, DSME is a dynamic, on-going process where educational needs will vary and fluctuate with changes to medication regimens, medical conditions, and life situations.[34,35] Positive patient outcomes, such as improved HbA1c levels, increases in physical activity, emotional stability, and decreased BMI typically peaked at three to six months; but without ongoing support programs in place, the benefits will likely decline.[40,43] This was further validated by the patient focus group who advocated for on-going support to enhance self-management. The expectation, then, should be to use SDM to reassess patient treatment goals and educational needs. Ideally, this should be conducted at each visit and addressed accordingly using education resources available to the medical treatment facility.

Evidence shows that self-management training is effective, but most reviews called for further research by way of well-designed and long-term studies. Computer-based diabetes self-management interventions have limited evidence supporting their use and more research is needed for design, delivery and effectiveness. There is also a need to identify effective modalities (e.g., internet, satellite) to provide education in areas where an educator is not available.

Recommendation

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)

Discussion

Available telehealth studies were limited and heterogeneous in design and outcome; telehealth had a different meaning in each study. Moreover, most studies looked at telehealth as an adjunct to usual care. Tildesley et al. conducted a small study in which 46 patients were randomized to an internet-based glucose monitoring system (IBGMS) uploaded every two weeks to a secure, commercially available website plus conventional care with endocrinology or to conventional care with endocrinology only.[45] There was a statistically significant decrease in HbA1c for the IBGMS group (adjusted HbA1c difference -1.3%) compared to the control group (adjusted HbA1c difference -0.1%) for up to six months of follow-up. However, patients were returned to conventional care after six months and the effect was not sustainable at the 12-month mark. Luchsinger et al., the only large study in the evidence base (N=2,169), evaluated registered nurse (RN) case management telehealth versus usual care in patients aged ≥ 55 years.[46] The intervention included a home telemedicine unit with a web-enabled computer and modem connection to an existing telephone line. Patients in the telehealth intervention had statistically significant sustained reductions of HbA1c over five years of follow-up, but the difference in HbA1c reduction was not clinically significant (telemedicine: mean 7.09 ± 0.06 versus usual care: mean 7.38 ±0.06; treatment effect: 0.29, 95% CI: 0.12 to 0.46).

Two other studies involved primary care providers utilizing telehealth. Holbrook et al. (N=511) evaluated a web-based diabetes tracker shared between patients and their primary care providers.[47] There was a statistically significant improvement in HbA1c, but not in quality of life, in the intervention group compared to the control group. Wakefield et al. (N=108) evaluated the effectiveness of short-term targeted use of remote data transmission on treatment in patients who had out of range HbA1c measurements.[48] Transmitted data was reviewed by the clinic RN and if issues were identified, they were shared with the provider. There was no significant difference in changes in HbA1c from baseline to six months of follow-up. Pacaud et al. compared three models of education and communication support in newly diagnosed patients (N=68): web static (virtual appointments using asynchronous communication) versus web interactive (electronic communication and virtual appointments using synchronous and asynchronous communication) versus a control group (face-to-face education, both synchronous and asynchronous).[49] There were no overall significant differences among the three groups.

The evidence review focused on the comparative effectiveness of telehealth requiring physician interaction or supervision versus standard patient management in improving T2DM-related outcomes. However, only three of the five studies identified involved physician interaction and the quality of this evidence was graded as low. One study evaluated patient education only via telehealth.[49] Another study, graded as moderate quality, utilized a RN for case management.[46] Based on the evidence, the Work Group determined a team approach incorporating all licensed independent providers was warranted, which is reflected in the recommendation language.

In summary, data on telehealth outcomes were variable from no benefit to some statistically significant, but clinically insignificant benefits. Yet, no single study showed harm associated with telehealth; outcomes were either neutral or a little to moderately beneficial. Confidence in the quality of the evidence regarding the effectiveness of diabetes telehealth education and support is limited. Improvements were seen in HbA1c when patients had the ability to upload glucose monitoring device

data for review by the RN case manager or provider. Dedication of this resource to high-risk elevated HbA1c populations may help control outcomes where utilized.

B. Glycemic Control Targets and Monitoring

Recommendation

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)

Discussion

Consensus suggests that, for summarizing evidence, estimates of absolute risk, rather than relative risk should be consistently provided for both benefits and harms or burdens.[50-52] The scientific basis for presumed benefits and harms derives from the absolute differences in achieved mean updated HbA1c levels (not a single point in time) between intervention and control groups and meaningful outcomes in clinical trials over a time period of many years.

As a clinical example on how framing of trial results differs, we use the results from the United Kingdom Prospective Diabetes Study 33 (UKPDS) which showed that the major benefit of lowering HbA1c from 7.9% (average) to 7.0% (average) over 10 years for recent onset disease was prevention of advanced microvascular complication, predominantly laser photocoagulation (absolute risk reduction [ARR] was 3.1/100 persons treated for 10 years).[53] The ARR of any microvascular complication was 5.0/100 and the number needed to treat was 19.6. The relative risk reduction was a 37% decrease in risk for microvascular complications and was continuous and without a threshold.[53,54] However, the ARR for each 1% reduction in HbA1c was less at lower levels of initial HbA1c. The microvascular benefit was sustained for 10 years after the trial was completed, although the average HbA1c values converged in the treatment groups.[55]

There were three major trials conducted in the 2000s that tested the hypothesis that intensive glycemic control (target goal of <7%) improved cardiovascular outcomes in patients with T2DM. Action to Control Cardiovascular Risk in Diabetes (ACCORD) [56], Veteran Affairs Diabetes Trial (VADT) [57], and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [58] trials were conducted to answer the question of the macrovascular benefit of intensive control in patients with diabetes of longer duration.

Over the course of the randomized trial frame of the studies, there was no cardiovascular benefit in ADVANCE or VADT and there was increased mortality in ACCORD, leading to early termination of the study. After 10 years of follow-up, patients in VADT had 8.6 fewer major cardiovascular events but no survival benefit.[57] There was no cardiovascular benefit in the long-term follow-up of subjects in ADVANCE.[58] However, a microvascular benefit was observed during the follow-up period. For ADVANCE, the in-trial reductions in the risk of end stage renal disease (ESRD) (7 versus 20 events, hazard ratio [HR]: 0.35, p=0.02) persisted after 9.9 years of overall follow-up (29 versus 53 events, HR: 0.54, p <0.01). These effects were greater in earlier-stage CKD (p=0.04) and at lower baseline systolic blood pressure levels

(p=0.01). The effects of glucose lowering on the risks of death, cardiovascular death, or major cardiovascular events did not differ by levels of kidney function (p >0.26).[58]

These studies have established that the microvascular benefit of intensive control in patients who were older than those enrolled in the UKPDS with longer duration of diabetes was less than in the UKPDS study. Macrovascular benefits were not observed. These studies establish that intensive control in an older population with established disease should not be routinely implemented.

Three SRs have examined the effect of intensive glycemic control compared to standard/conventional glycemic control in managing adults with T2DM and the recommendations in this guideline are consistent with the individual RCTs and follow-up studies.[59-61]

Three medications—metformin, empagliflozin, and liraglutide—have demonstrated a medication-specific benefit on cardiovascular outcomes in patients with T2DM at high risk for cardiovascular events.[62-64] However, while each of these medications lower average blood glucose, the mechanism remains unknown and the improved cardiovascular outcomes cannot be ascribed to intensive glycemic control.

In recommending a target HbA1c goal for an individual patient, the clinician should take into account the patient's diabetes status (e.g., new onset, intermediate duration, long standing), diabetes complications, and an estimate of the life expectancy of the patient. We recommend that physicians discuss the magnitude of expected benefit using principles of ARR or number needed to treat, not relative risk. The aforementioned studies can provide an order of magnitude of expected benefit, especially in older adults.[53-61] Additionally, comorbid conditions and social determinants of health that could impact harms need to be assessed.

Patient preferences for a target range are dependent upon individual assessments of the risks and benefits of tighter glucose control as well as the use of medications to control hyperglycemia and impact upon lifestyle. SDM is a key process in setting HbA1c target ranges, as discussed in Recommendation 1.

We recommend a target HbA1c range rather than an all or none HbA1c target value for several reasons:

1) The clinical trials upon which the benefit of glycemic control is based use an updated HbA1c value over time; this cannot be generalized to maintaining an HbA1c value less than any single level.
2) Additionally, a single HbA1c measurement even from a high quality laboratory has a range around it (i.e., coefficient of variation [CV]). In many laboratories, sequential HbA1c values that are within 0.5% HbA1c are not significantly different unless the assay CV is less than 3%, ideally 2%.[65] Comparing HbA1c tests performed in different clinical laboratories introduces another source of error, as does use of point-of-care testing, which tends to have higher CV than laboratory assays.
3) There may be racial differences between estimated average glucose (eAG) and HbA1c values in patients with T2DM based upon 7-point glucose testing.[66]
4) Disease states that alter red blood cell turnover may falsely raise or lower HbA1c values discordant with actual blood glucose levels.

Recommendation

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)

Discussion

The most effective diabetes treatment plan is individualized to the patient. The benefits and risks of therapy are different for each patient, depending upon the individual's medical, social, psychological status, and personal goals and preferences. Understanding the patient's goals, lifestyle, and preferences helps the provider and team work collaboratively with the patient to create a personalized diabetes care plan that integrates the patient's values and preferences into the provider's assessment of the risk-benefit ratio.[26] Thus, the risks of a proposed therapy are balanced against the potential benefits. The partnership between the patient, provider, and healthcare team optimally begins at the time of initial diagnosis. The provider and team should stress that although diabetes is a serious condition, the patient can successfully manage it with attention to medications, diet, and physical activity. The other important part of this initial message is that there are a number of ways that diabetes can be successfully treated and that the best treatment plan is one that meets the patient's needs and preferences so that the patient will be more likely to take steps to successfully manage his or her diabetes each day. Patients should be encouraged to work with their provider and team to share decision making regarding glycemic targets, therapies, and goals of treatment.[31] Given the limited time available for visits, the healthcare team can gain useful information to help them tailor the risks and benefits of possible treatment plans to the individual patient.

Given these considerations, the Work Group advocates for an individualized approach based on the patient's absolute risk for developing microvascular complications balanced against known comorbidities, projected life expectancy, presence or absence of pre-existing microvascular complications, the risk of polypharmacy with attendant drug-drug interactions, exposure to medications with limited post-marketing experience, the risk of and ability to perceive hypoglycemia, possible benefits to other comorbidities (such as beneficial effects on weight or hypertension), and patient preferences.[67]

Recommendation

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)

Discussion

If the provider suspects the HbA1c to be discordant from the patient's true level of glycemia, the provider should collect and interpret actual glucose levels to inform clinical decisions. Many factors affect the measurement of HbA1c besides the level of glycemia.[68] Some of these are well established. For example, since HbA1c is dependent upon duration of erythrocytes exposure to glucose, conditions that alter erythrocyte life span will affect the measured level of HbA1c.[69,70] Iron deficiency anemia, which prolongs red cell life and exposes the cell to glucose for a longer period of time, is associated with false elevations of HbA1c.[71] In contrast, conditions that reduce red cell life span (e.g., hemolytic

anemia) may result in falsely low HbA1c levels. A variety of other conditions may result in alterations in HbA1c measurement (e.g., CKD). Hemoglobin variants can result in either falsely elevated or falsely lowered HbA1c, depending on the specific assay used.[4,5,72] In addition, oral hypoglycemic agents (metformin or sulfonylureas) may alter the relationship between blood glucose levels and HbA1c, although the clinical significance is unclear.[73] There are racial/ethnic differences in HbA1c levels for a given level of glycemia. African Americans have, on average, about 0.4% higher HbA1c levels than Whites and this difference cannot be explained by measured differences in glycemia or sociodemographic factors, clinical factors, access to care, or quality of care.

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]

Racial differences have also been reported in patients with longer duration of diabetes. In the A Diabetes Outcome Progression Trial (ADOPT), baseline HbA1c levels adjusted for age, sex, and BMI were 0.7% higher in African Americans (8.0% ± 1.1) than Whites (7.3% ± 0.8) despite comparable fasting glucose levels (153 mg/dL versus 151 mg/dL).[74]

Whether these differences are of sufficient magnitude to alter therapy (e.g., use different HbA1c target levels depending upon race), is still a matter of controversy.[75,76] Further research is required to determine if racial/ethnic differences in HbA1c vary depending on the level of glycemic control, its clinical significance, and most importantly, implications for therapy. In light of this, the VA/DoD DM CPG continues to recommend that a new diagnosis of diabetes be based upon a confirmatory fasting blood glucose level ≥126 mg/dL if the initial HbA1c value is between 6.5% and 6.9%.

How and where the HbA1c level is measured can also affect the result because of intra-laboratory variation (the variation in test accuracy and precision) and inter-laboratory variation (variation related to using different methodologies for the tests themselves). The National Glycohemoglobin Standardization Program (NGSP) not only establishes standards but also reports on intra-laboratory variation, typically expressed as CV. Of particular note is that point-of-care measurements of HbA1c (e.g., fingerstick HbA1c tests) tend to have higher levels of CV, indicating that they may produce less accurate results. An analytical CV ≤2% will produce a 95% probability that a difference of ≥0.5% HbA1c between successive patient samples is due to a significant change in glycemic control (when HbA1c is 7% [53 mmol/mol]).[65] Therefore, using HbA1c for diagnosis and treatment requires a highly accurate methodology of a degree not required by regulation and that may vary among laboratories. Consequently, providers and patients need to be aware that HbA1c results can differ based upon laboratory factors as well as clinical factors.

Assessing the impact of these patient characteristics and non-glycemic factors that affect HbA1c levels allows for better individualization of management. For example, treatment decisions based upon HbA1c alone without consideration for glucose monitoring may result in unnecessary initiation or intensification of therapy. Thus, we recommend that treatment goals involve target ranges for HbA1c rather than levels above or below a specific target value for most persons with diabetes. This approach may avoid unnecessary intensification of medication due to random fluctuations within the range

related to laboratory variation. This recommendation allows for individualized treatment plans and is consistent with patient values.

Data on other markers are lacking and continuous glucose monitoring is out of the scope of this CPG.

Recommendations

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)

Discussion

A substantial body of evidence demonstrates a direct relationship between glucose control and microvascular complications (e.g., retinopathy, neuropathy, nephropathy). Higher levels of HbA1c carry greater risk of complications and lowering HbA1c prospectively reduces risk.[53,64,77] The relationship between HbA1c and the risk of microvascular complications is continuous, and may accelerate with HbA1c levels >9%.[78] There is no apparent threshold above which benefits are not accrued by lowering HbA1c. However, in contrast to the relative risk of reduction of microvascular complications, which remains constant across HbA1c levels, the ARR is less at lower levels of mean achieved HbA1c than at higher levels.[54] Conversely, there are no data on the lower limit for achieved HbA1c, albeit there are strong data on the risks of hypoglycemia, as HbA1c is targeted to near normal levels for patients receiving insulin.[59] Lower levels of HbA1c (closer to 6%) may be reasonable in patients treated with metformin alone.

Microvascular complications develop over an extended period of time. Thus, the subset of individuals with longer life expectancy and absent or mild microvascular complications (e.g., early background retinopathy, microalbuminuria, mild neuropathy) are most likely to benefit from tight HbA1c control (i.e., 6.0-7.0%), see Table 2.

Diabetes also confers substantial risk of CVD, but there is no evidence that lowering HbA1c to <8.5% reduces mortality, although it reduces the risk of non-fatal myocardial infarction (MI).[79] Indeed, in clinical trials of patients treated to HbA1c levels <7% [79-81], not only was there no benefit on CVD risk but one trial showed increased mortality during the course of the RCT.[80] Consistent with these findings, three SRs comparing intensive and conventional glucose control showed no significant differences in all-cause mortality or death from CVD, but did demonstrate significant risk reduction for microvascular complications such as nephropathy, retinopathy, and lower extremity amputation.[59-61]

In some circumstances, aggressive glucose management may cause harms due to medication therapy. This is particularly true for patients with T2DM treated with insulin. Intensive glucose control significantly increases the risk of severe hypoglycemia (e.g., requiring help from another person) by two-fold when compared to conventional control. Follow-up of ACCORD study patients for a median of 8.8 years showed a significant 20% increased relative risk of death from cardiovascular events with intensive glycemic control, but the absolute risk difference of 0.13% per year was minimal, compared to standard, glycemic control.[82] Intensive control is also associated with increased weight gain.[81] It remains unknown if the risk/benefit ratio for intensive glucose control will differ with newer medications and/or extend to include macrovascular benefits. However, the FDA does provide clinical alerts regarding complications of individual or classes of medications for complications including osteoporosis, congestive heart failure, urinary tract infections, dehydration, and acute kidney injury, among others. The risk of complications may be exacerbated by underlying comorbid conditions.

Safely achieving intensive control requires attention to the risk factors for hypoglycemia. In addition to the higher risk of hypoglycemia with specific drugs (insulin and sulfonylureas), factors associated with risk of hypoglycemia include advanced age (especially >75 years), cognitive impairment, and chronic renal insufficiency (including causes unrelated to diabetic nephropathy).[83-85] Additional factors associated with hypoglycemia risk include lack of appropriate glucose monitoring, inadequate diabetes education, lack of family and social support systems, and food insufficiency. As a result of these factors, some patients may have life expectancies exceeding 10 years, yet be considered for less intensive glycemic control.

The results of recent trials of intensive glycemic control evaluating cardiovascular outcomes can help to inform the target HbA1c range of a patient population that is unlikely to benefit from intensive control (HbA1c 6.0-7.0%). Three major intensive control studies were designed to evaluate cardiovascular outcomes (ACCORD [56], VADT [57], and ADVANCE [58]), but varied somewhat in study populations, definition of intensive control, and intervention strategies. Nonetheless, the overall results did not show a reduction in macrovascular disease outcomes with intensive glucose control, while it did show a significantly increased risk of hypoglycemia. The target HbA1c in the standard control arm in ACCORD was 7.0-7.9%, in ADVANCE the achieved HbA1c was 7.3%, and in VADT the achieved HbA1c in the standard control group averaged 8.4%. By considering the severity of diabetes complications, comorbid conditions, and estimation of life expectancy, clinicians can recommend a glycemic target range to be discussed with the individual patient. This is especially important for patients who would not have been candidates for the RCT because of decreased life expectancy, significant comorbid conditions, and social determinants of health that place them at greater risk for adverse events from medication therapy.

Newer therapeutic options have been introduced since these major trials were completed, and further research is needed to understand which populations may benefit from the effects of newer therapies on macrovascular disease outcomes and/or lower HbA1c targets.

In summary, the reviewed evidence supports a clinically significant benefit from intensive glycemic control (HbA1c 6.0-7.0%) in individuals with longer life expectancy, short duration of diabetes, and absent or mild microvascular complications. Life expectancy estimates are not always reliable, but can be estimated based on information discussed between patients and providers such as functional status, history of multiple recent hospitalizations, organ failure (advanced renal disease, liver disease, or heart failure), cancer diagnoses and their treatment plans, and advanced medical directives. For most patients with established microvascular or macrovascular disease, comorbid conditions, or less than 10 years life expectancy, it is reasonable to achieve a target HbA1c between 7.0-8.5%, after discussion of the risks and benefits, see Table 2. For patients with a life expectancy <5 years, the upper limit of HbA1c should reflect the need to avoid symptoms of hyperglycemia. As discussed in Recommendation 6, HbA1c is influenced by many factors, including age, race/ethnicity and anemia/hemoglobinopathies. In considering upper target levels, especially for individuals with comorbid conditions and limited life expectancy, the Work Group balanced benefit, safety, and preferences, and set that level at 9.0%. Preferably, decisions on intensification of therapy should be based on glucose levels and not HbA1c values. Additionally, there should be consideration of hyperglycemic and hypoglycemic symptoms, and patient preferences, especially regarding initiation or change in insulin dosage. The overarching purpose of these four recommendations is to move away from a one-size-fits-all approach, to individualized treatment plans and HbA1c target range that are tailored to a patient's unique characteristics and goals of care. The target range should be reviewed at least annually, or as a result of a request by the patient or healthcare team, or as a result of changes in the patient's medical status.

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 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.

Recommendation

11. We suggest that providers be aware that HbA1c variability is a risk factor for microvascular and macrovascular outcomes.
    (Weak for | Reviewed, New-added)

Discussion

HbA1c variability refers to variation in glycemic control over the long-term as assessed by measurement of HbA1c, not the day-to-day variation in blood glucose levels. A variety of measures of HbA1c variability were used including the standard deviation (SD) (how much values differ from the group mean) and also as a CV (the ratio of SD to the mean).

An SR of 13 studies found consistent associations between HbA1c variability and micro- and macrovascular complications and mortality in T1DM and T2DM.[86] The association was greatest with mortality. However, the quality of evidence was low because of high risk of bias due to concerns regarding the small number of studies for analyses, the observational nature of the studies, retrospective design of some studies, unclear or short follow-up periods, and lack of adjustment for some potential confounders. Notably, the number of HbA1c measurements per patient ranged from three to a median of 79 and follow-up periods were similarly variable. More recently, a retrospective study involving Veterans (N >50,000) showed a similar association with mortality as well as MI and stroke over a mean period of 3.3 years.[87]

Although HbA1c variability is an independent predictor of adverse health outcomes compared to mean HbA1c alone, there is insufficient information to make any statement about a causal effect of HbA1c variability on these outcomes. Thus, it is unknown whether reducing HbA1c variability will have beneficial or adverse effects. Further research is necessary to assess whether HbA1c variability would be useful clinically for risk stratification and whether it might be a valuable therapeutic target.

The benefits of assessment of HbA1c variability outweigh the harms, and data from the patient focus group and elsewhere indicate that there is an interest among patients to have more information about DM management and optimal treatment. There are implications for resource use and feasibility related to the effort required to obtain the necessary data to calculate the degree of variability. There may be particular implications for DoD due to changes related to deployment (operations tempo [OPTEMPO]).

Further research is required to determine the best measures of HbA1c variability and practical means to communicate them, whether or not there is a dose-response relationship of magnitude of variability or exposure to variability, and most importantly whether interventions to reduce HbA1c variability affects outcomes.

C. Non-pharmacological Treatments

Recommendation

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)

Discussion

All patients with diabetes should be given lifestyle counseling. Lifestyle changes counseling is indicated for all diabetes patients and should include nutrition guidance, physical activity, cessation of smoking and excessive use of alcohol, and weight control.[88-91] Based on the VA/DoD Obesity CPG, the definition of comprehensive lifestyle intervention is, "interventions that combine three critical lifestyle components (i.e., dietary, physical activity and behavioral components) and include at least 12 intervention sessions over a 12-month period (See Recommendations 7, 10, 18, 23, 24, 31 and Appendix G in the VA/DoD Obesity CPG[9]).

The confidence in the quality of evidence for this recommendation is moderate and the benefits of therapeutic lifestyle changes counseling outweigh the harms/burden of implementing it. Among the included studies in the Ajala et al. SR, three of the diets were compared to standard or control diet (high protein diet versus standard protein diet, lower carbohydrate diet versus control diet, and Mediterranean diet versus control diet); the others compared one diet to a different diet (American Diabetes Association [ADA] diet versus ADA plus peanuts diet, Atkins diet versus ADA diet, high-protein diet versus low protein diet, lower carbohydrate diet versus control diet, low fat diet versus low glycemic load diet, Mediterranean diet versus control diet, vegan and vegetarian diets versus conventional diabetes diet). Only two of the diets were effective in weight management.[92] A referral to a dietitian to support dietary changes should occur.[93] There are benefits beyond glycemic control. The only harm identified is a potential increased risk of injury with physical activity. A patient's preferences and current level of health and comorbidities will vary and therefore must be taken into consideration.

The medical nutrition therapy (MNT) process consists of distinct, interrelated steps:

- Nutrition Assessment: The registered dietitian nutritionist (RDN) collects and documents information such as food or nutrition-related history; biochemical data, medical tests and procedures; anthropometric measurements, nutrition-focused physical findings and client history.
- Diagnosis: Data collected during the nutrition assessment guides the RDN in selection of the appropriate nutrition diagnosis.
- Intervention: The RDN then selects the nutrition intervention that will be directed to the etiology of the nutrition problem and aimed at alleviating the signs and symptoms of the diagnosis.
- Monitoring/Evaluation: The final step of the process is monitoring and evaluation, which the RDN uses to determine if the patient/client has achieved, or is making progress toward, the planned goals.

Resource considerations include the cost of diabetic nurse educators, RDNs, and behaviorists. It is also expensive, inconvenient, and time consuming for patients to adhere to therapeutic lifestyle changes. Resource availability to achieve goals varies (e.g., access to a smoking cessation class). Other factors, such

[9] 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/

as socioeconomic issues (especially food insecurity), conflicts with the patient's preference and culture, and impact on family members must also be taken into consideration.

For the management of obesity, in particular bariatric surgery, see the VA/DoD Obesity CPG.[10] For smoking cessation and alcohol use, see the VA/DoD CPG for Treating Tobacco Use and Dependence and the VA/DoD SUD CPG.[11,12]

Further research studies are required to address sustainability over the long-term (greater than five years). Research is also needed on effective methods to implement the interventions.

Recommendation

13. We recommend a Mediterranean diet if aligned to patient's values and preferences. **(Strong for | Reviewed, New-added)**

Discussion

The ideal distribution of the three main food components, carbohydrates, proteins and fats, remains unclear. Dietary recommendations for improving glycemic outcomes often have focused on individual macronutrients, specifically carbohydrate reduction. Although carbohydrate reduction is well researched as a strategy for glycemic control, recent studies have focused on overall dietary patterns and the link to chronic disease control, prevention, and treatment. As such, a Mediterranean-style dietary pattern has been shown to be effective in improving glycemic control, delaying the time to first pharmacological intervention, in addition to reducing cardiovascular risk factors and weight in individuals with T2DM.[92]

Despite known variation in the cuisine of Mediterranean countries, certain characteristic features are commonly used to describe a traditional Mediterranean diet: high intake of vegetables, fruits, nuts, unrefined grains, and olive oil; moderate intake of fish and poultry; low or moderate intake of wine; and low intake of red meat, processed meat, dairy, and sweets.

In a meta-analysis of nine RCTs, Huo et al. found that a Mediterranean diet significantly reduced HbA1c and fasting glucose levels in patients with T2DM.[94] A similar SR by Esposito et al. found a 0.47% reduction in HbA1c favoring a Mediterranean diet compared to usual care or a low-fat diet.[95]

A Mediterranean diet has also been linked to improved cardiovascular outcomes and weight loss. Huo et al. found a significant reduction in total cholesterol and triglyceride levels and increased HDL-C in those following a Mediterranean diet along with an average of weight loss of 0.29 kg.[94]

Only three of the reviewed studies were based on the U.S. population and the availability of foods commonly consumed as part of a Mediterranean diet may be perceived as difficult or challenging for

[10] 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/

[11] See the VA/DoD Clinical Practice Guideline for Treating Tobacco Use and Dependence. Available at: http://www.healthquality.va.gov/guidelines/CD/mtu/

[12] 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/

individuals in the VA/DoD population. To improve compliance, MNT should be aligned with the patients' values and preferences and focused on attainable and sustainable dietary modifications.

Although a Mediterranean diet has shown to improve glycemic control, weight, and cardiovascular outcomes in patients with T2DM more research is needed evaluating the effects and availability of the diet in the U.S. population, particularly in the VA and DoD.

Recommendation

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)

Discussion

A variety of dietary interventions have been shown to be effective for reducing HbA1c and other risk factors associated with complications of T2DM. There is increasing evidence that a lower carbohydrate diet improves glycemic control and leads to reduction in diabetes medication.[93,96] A lower carbohydrate diet was shown to achieve a greater reduction in triglycerides and increases in HDL-C in some studies suggesting the lower carbohydrate diet may be effective in reducing cardiovascular risk in patients with T2DM.[96]

While the bodies of evidence for Mediterranean diet and lower carbohydrate dietary approaches showed their effectiveness in patients with T2DM, the evidence in support of the Mediterranean diet was more uniform and robust than that for the lower carbohydrate dietary approaches. Therefore, we recommend the Mediterranean diet be offered first to patients. However, depending on patients' values and preferences, those who do not prefer the Mediterranean diet are offered lower carbohydrate dietary approaches.

During the VA/DoD Work Group analysis of multiple nutrition intervention strategies evaluating variable percentage of kilocalories (kcals) from carbohydrate, it was clear to the Work Group that in every study meeting GRADE requirements, the nutrition intervention strategy with a lower percent of energy coming from carbohydrate resulted in improved clinical surrogate markers. These markers included, but were not limited to HbA1c, self-monitoring of blood glucose (SMBG) values, post-prandial blood glucose, weight, reduction in pharmacological agent requirements, improved lipids, and improved blood pressure. While the Work Group is aware of the differences between the Academy of Nutrition and Dietetics' (AND) and our recommendations, our approach was based on our recent SR of the literature and considerations specific to the VA/DoD populations.

An SR of 20 RCTs compared dietary interventions including lower carbohydrate and low glycemic index diets.[92] Evidence showed both dietary interventions improved glycemic control. The majority of the lower carbohydrate diets reviewed comprised between 14-45% of energy from carbohydrate and 25-28% from protein. Another study, an RCT by Fabricatore et al., demonstrated that a Calorie-restricted, low glycemic index diet reduced HbA1c and promoted weight loss.[97]Improvement of glycemic control is independent of weight loss with lower carbohydrate diets. Low glycemic index diets provide patients with another alternative.

In a 16-week trial, Yancy et al. showed that a low carbohydrate, ketogenic diet resulted in improved glycemic control and discontinued or reduced diabetes medication for most participants.[98] It was noted in this study that patients using a low carbohydrate ketogenic diet should be under close medical supervision or be capable of self-adjusting medication. Evidence for a very low carbohydrate ketogenic diet is increasing both for T2DM and weight loss. Lower carbohydrate diets, especially those containing less than 70 grams carbohydrate per day, should be planned carefully to assure proper nutrition with the assistance of a dietitian.

Protein and fat replaces carbohydrate in a lower carbohydrate diet, which raises concern that increased dietary protein could cause deterioration in renal function in patients with advanced renal disease. Pedersen et al. compared a high protein diet to a standard protein diet which showed no evidence that increased protein intake (90-120 grams protein per day, 30% of energy from protein) had any adverse effect on renal function in patients with mild renal impairment (estimated glomerular filtration rate [eGFR] >40 mL/min/1.73 m^2).[99]

This recommendation allows for meal planning options to account for patient preferences. The patient focus group expressed the desire for providers to take into consideration patient treatment preferences. Utilizing SDM may benefit patients when initiating a dietary intervention. We suggest dietary education and behavioral counseling be facilitated by a RDN.[91] Studies show improved glycemic control and weight loss when intensive behavioral counseling and increased physical activity are combined with dietary interventions (see the VA/DoD Obesity CPG[13]).[93,96] There is no consensus on the definition of a low carbohydrate diet. Dietitians can offer lower carbohydrate options specifically tailored to the patient's needs, ensuring nutritional adequacy, and work with providers for timely adjustments of diabetes medications. For patients following a lower carbohydrate diet and who are taking hypoglycemia agents, management by an interdisciplinary team, including a dietitian, is recommended.

The quality of the evidence reviewed for this recommendation was low due to wide definition of components, imprecision, and limited duration and follow-up. Dietary intervention studies tend to compare diet versus diet rather than comparing diet versus control.

Carbohydrate reduction and low glycemic index are suggested dietary options in which the benefits outweigh harms. Adherence to these dietary interventions may be expensive, inconvenient, and time consuming for patients with T2DM. Family member preferences affect the level of success of dietary interventions. A referral to a RDN may facilitate patient education and promote a more effective dietary intervention. These guidelines do not completely address the role of protein as a macronutrient in patients with mild renal disease.[99] However, the progression of advanced CKD (Stage 3-4) might be delayed by protein restriction of 0.6-0.8 g/kg/d (see the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care [VA/DoD CKD CPG][14]).

[13] 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/

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

The VA/DoD population presents unique challenges of feasibility and acceptability of diet and lifestyle changes. Further research to determine new strategies that maximize adherence is needed for this population. Future research is needed to study the long-term effects of dietary modifications and specifically the implementation of a low glycemic index diet outside of the research setting. We did not address MNT in conjunction with pharmacotherapy because of lack of evidence. Research comparing initiating nutrition therapy as a first-line therapy versus pharmacotherapy is needed.

D. Inpatient Care

Recommendation

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)

Discussion

Hyperglycemia during hospitalization is associated with adverse outcomes independent of diabetes. Importantly, glucose lowering interventions have been shown to reduce morbidity and mortality in some critically ill populations. Most of the controversies in this setting have centered on the ideal and exact glucose target for hospitalized patients, as well as which populations would derive benefit from glucose lowering interventions. Evidence to support "tight" glycemic control (80-110 mg/dL) remains insufficient. Randomized trials examining glycemic control and/or insulin therapy are limited to the study of hospitalized patients with severe illness (e.g., intensive care unit [ICU], acute myocardial infarction (AMI), acute stroke). In the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, a blood glucose target of 180 mg/dL or less resulted in lower mortality (odds ratio [OR]=1.14) than did a target of 80 to 110 mg/dL in which hypoglycemia was more frequent (OR=14.7).[100] This data is often extrapolated to the inpatient setting at large, though there have been no controlled trials conducted in other settings evaluating "tight" control outcomes.

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial was a four-arm study examining both fluid resuscitation and "tight" glycemic control (80-110 mg/dL) in ICU patients with severe sepsis.[101] The trial was stopped early due to high rates of hypoglycemia (17% versus 4%). It is important to note that only 30% of the studied patients had a prior diabetes diagnosis; presumably, hyperglycemia in the remainder of the patients was of a different process (e.g., stress hyperglycemia of critical illness), though the results seem to suggest that targeting lower glucose levels with insulin in the ICU can result in concerning rates of hypoglycemia.

Hypoglycemia is the most common complication associated with aggressive inpatient glycemic control, and is one of the leading adverse outcomes limiting the quality of trials addressing the benefits of intensive glycemic control.[100,102,103] In a meta-analysis by Griesdale et al., among the trials that reported hypoglycemia, the pooled relative risk with intensive insulin therapy was 6.0 (95% CI: 4.5 to 8.0).[104] Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients.[105]

While lower glucose levels might physiologically result in benefit, it can be logistically challenging to achieve them without risking hypoglycemia. In recent publications on the topic and in common clinical practice there is a greater appreciation of risk of harms from hypoglycemia. For these reasons and due to evidence suggesting harm with lower glucose levels, the Work Group strongly recommends 110 mg/dL as the lower limit for inpatient control. Advancement in glucose monitoring technologies, such as continuous glucose monitors (CGM), may improve the capability to safely target lower glucose levels; however, performance of these devices in acutely ill hospitalized patients is not well studied.

Recommendation

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)

Discussion

Many of the trials examining insulin therapy in the hospital have specifically studied glucose-insulin-potassium (GIK) infusions with little or no regard to the glucose level or treatment of hyperglycemia. This is particularly evident in studies of patients with AMI. SRs have generally found that GIK interventions do not improve outcomes especially if glucose lowering is not a goal.[103,106-108]

Moderate levels of glycemic control have not been well studied. One of the earliest randomized trials of insulin therapy after AMI that predates more rigorous standards, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, was able to demonstrate reduced mortality rates with glucose lowering <180 mg/dL.[109] Among the patients with admission blood glucose levels ≥200 mg/dL who received the glucose-lowering intervention, mortality at one year decreased by 29%. A 58% relative reduction in hospital mortality in the intervention group was observed for the pre-defined sub-group of patients who were insulin naïve and low cardiovascular risk, but not for the intent-to-treat group. Nevertheless, since the intervention arm of DIGAMI included three months of intensive insulin therapy after discharge, it was not possible to discern whether the reduction in long-term morbidity and mortality was due to inpatient treatment, outpatient treatment, or the combination. DIGAMI-2 was designed to resolve this issue, but was not successful in achieving this primary goal due to insufficient power, and again, the inability to reach treatment goals.[110]

As standards of care have improved over the years, it has become increasingly difficult to design a study in which the control group is sufficiently more hyperglycemic than the intervention group to demonstrate a difference in outcome. The mean glucose at 24 hours of the control group in the DIGAMI-1 study was 211 mg/dL.[109] In contrast, the mean glucose of the control group in the recent NICE-SUGAR trial was 144 mg/dL. This has several implications. First, trials such as NICE-SUGAR are examining the effects of “tight” glycemic control versus “good” glycemic control, not poor glycemic control, and therefore the absence of treatment benefit observed cannot be used to justify hyperglycemia in the hospital setting. Second, a narrower gap between glucose levels in both groups requires a larger sample size, such as that of NICE-SUGAR, to have sufficient power to observe a significant benefit.

Other important differences among inpatient insulin therapy trials include variable glucose targets and unknown glycemic variability. For instance, a mean glucose of 140 mg/dL in one trial may represent an average of many hypoglycemic and hyperglycemic episodes which may have markedly different effects on outcomes than what is observed in another trial where mean glucose is 140 mg/dL with little SD. Such information is not provided by most trials and this lack of information also limits the interpretation of SRs that cannot account for these differences. Similarly, there are differences in protocols among trials. This includes frequency and method of glucose measurement. Trials where glucose is measured infrequently may underestimate the rate of hypoglycemia which could significantly impact outcomes. Furthermore, it has been demonstrated that point-of-care testing, although the most practical method, is often inaccurate in critically ill patients.

Lastly, it is important to note that while much of the controversy and attention has focused on the ideal glucose target, there are many ways in which the care of hospitalized individuals with diabetes and hyperglycemia can be improved. There is a growing body of literature examining the types and methods by which antidiabetic agents are applied in the hospital.[111-114] While the methods to achieve glycemic target were not systematically reviewed as part of the literature review, we note that in the studies reviewed, patients in the ICU were often treated with an insulin drip if their glycemia was above 180 mg/dL.

Glucose target considerations:

- In order to identify potentially harmful hyperglycemia and hypoglycemia, blood glucose monitoring may be ordered in hospitalized patients with diagnosed DM and/or hyperglycemia (blood glucose >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.
- Treatment goals should be periodically reassessed based upon patient specific factors, including changes in the patient's health status, adverse drug reactions, and patient preferences.
- Relative indications for raising the target glycemic goal include inability or unwillingness to adhere to a more intensive regimen, or an unacceptable risk of hypoglycemia relative to anticipated benefits of near-normal glycemia.
- If the target range remains appropriate but has not been reached, the provider and patient should identify the reasons why the target has not been achieved and take appropriate action.

Recommendation

17. We recommend against the use of split mixed insulin regimen for all hospitalized patients with type 2 diabetes.
    (Strong against | Reviewed, New-added)

Discussion

Split mixed insulin regimen is a twice-a-day insulin injection regimen with a fixed amount of mixed neutral protamine Hagedorn (NPH) insulin (intermediate-acting insulin) and regular insulin. This insulin regimen requires consistent meal times and compositions to avoid hypoglycemia. Only two small studies

could be identified to evaluate the effectiveness of split mixed insulin regimen versus basal-bolus insulin for hospitalized patients. It is important to note that the overall quality of evidence from these two trials is low to very low due to small sample sizes, poorly matched treatment arms, and concerns about generalizability to more broadly representative populations, including the VA/DoD patient population.

Bellido et al. enrolled a total of 72 patients to compare split mixed to basal-bolus, with early termination of the trial due to increased risk for hypoglycemia in the split mixed treatment group.[115] Variations between the baseline patient characteristics and meal plans make this evidence difficult to generalize to other patient populations, but the potential harm due to hypoglycemia is important to consider. Umpierrez et al. compared the use of a basal-bolus insulin regimen to a split mixed insulin regimen in 130 patients.[116] Rates of hypoglycemia did not significantly vary between treatment groups in this study. In both of these studies, baseline blood glucose and HbA1c did not vary between treatment groups, mean daily blood glucose measurements did not significantly vary between groups, and there were no differences between treatment groups according to length of hospital stay.[115,116]

These studies did not identify any benefit of using the split mixed insulin regimen over a basal-bolus insulin regimen for hospitalized patients. Split mixed regimens require consistent meal plans in order to avoid hypoglycemia, which is difficult to provide in the hospital. In conclusion, due to the potential harms of split mixed insulin and lack of any demonstrable benefit over basal-bolus insulin, we recommend against the use of split mixed insulin in hospitalized patients.

Recommendation

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)

Discussion

Key factors to consider in devising a glucose control strategy are pre-hospital total daily dose of insulin, calorie and carbohydrate intake, other factors that can decrease insulin sensitivity (e.g., physiologic stressors, corticosteroids) or increase insulin sensitivity (e.g., renal failure, liver failure), and ease of implementation.

The physiologic human pancreas constantly secretes some “basal” insulin while fasting, and releases a “bolus” of insulin to cover the glucose load associated with food intake to maintain euglycemia. In patients with insulin deficiency (e.g., T1DM, long-standing T2DM, pancreoprivic diabetes), providing these modes of insulin action and adding a “pre-meal supplemental correction” insulin to cover for unanticipated glucose elevations will best replicate this physiology with intermittent subcutaneous insulin. This is referred to as a basal-bolus plus correction regimen.

Basal-bolus plus pre-meal correction regimens are underutilized in the hospital, possibly due to their complexity, provider fear of hypoglycemia, and poorly established patient home total daily insulin dose. Thus, many patients are prescribed correction insulin only, dosed based upon a number of units assigned to treat a pre-specified glucose range on a scale or table called sliding scale insulin (SSI). While sliding scale only regimens may be easiest to start, in surgical patients, utilization of basal-bolus over SSI alone reduced the risk of post-surgical complications.[111]

In terms of ease, a simple basal insulin dose plus pre-meal correction scale may seem more approachable to providers and is supported by a single study in which general medical and surgical patients with T2DM treated with diet, oral antidiabetic agents, or low-dose insulin at home were shown to have similar glycemic control and frequency of hypoglycemic events on a basal-bolus plus correction versus basal-bolus regimen. Both regimens resulted in better glycemic control and in fewer treatment failures than did the use of SSI alone.[117]

Another practice that requires more study is the application of before-bed correction insulin. In a single RCT, before-bed correction did not improve pre-breakfast fasting glucose levels, overall glycemic control, length of hospitalization, or hospital complications. While before-bed correction did not lead to increased rates of hypoglycemia, this study was underpowered for this outcome, and the risks from hypoglycemia, added complexity, and increased nursing workload suggest that routine use of before-bed correction should not be used.[114]

Recommendation

19. We suggest providing medication education and diabetes survival skills to patients before hospital discharge.
    (Weak for | Reviewed, Amended)

Discussion

Although inpatient DSME is recommended by the Joint Commission, there is relatively little high quality supporting evidence for this recommendation. There are several potential times that DSME educators might target to provide care for patients with DM: at diagnosis, annually (to assess education, nutrition, and emotional needs), when new complicating factors influence self-management, and when transitions in care occur.[118] Diabetes care in the outpatient setting involves significant patient engagement, including dietary considerations, physical activity, home glucose testing, and medication management. The inpatient setting may provide an opportunity for providing education regarding self-management skills, including strategies ("survival skills") for addressing hypoglycemia and hyperglycemia, SMBG, and sick day management. Theoretically, providing education on self-management of diabetes could impact the overall quality of care. Conversely, the inpatient setting might not be ideal for providing such education. The patient will likely have competing medical concerns which precipitated the hospital admission, and the inpatient stay is frequently fast-paced and involves procedures and testing. Thus, it is also possible that such training would be ineffective because patients would be unable to reliably engage and comprehend the care management recommendations.

Observational studies suggest that there may be some benefit from inpatient DSME, but this evidence is prone to bias given the nature of the study.[119] One small RCT examined the effect of inpatient DSME on outpatient outcomes for up to a year.[120] Although most outcomes (patient satisfaction, hospital readmission, and glycemic control at 12 months) were not different between intervention (multi-disciplinary diabetes education) and control (usual care), there was an improvement in HbA1c at 12 months for insulin naïve patients who received the intervention. Despite being an RCT, this study was limited due to small sample size and imprecision, and was judged to be of very low quality evidence to support inpatient diabetes education. Another RCT compared patients who received diabetes education from a pharmacist prior to discharge to usual care.[121] The primary outcomes were medication

adherence (using refill data) at three months and glycemic control at four months after discharge. Patients receiving the intervention had greater medication adherence and better glycemic control at follow-up. However, this study was of low quality due to methodological issues and high dropout rate; the overall evidence to support inpatient diabetes education was very low.

There are significant gaps in the evidence to support recommendations for inpatient diabetes education. There is inadequate evidence to assess which patients with diabetes might benefit most from inpatient education; there are no high quality studies that have assessed for patient harms. Nonetheless, we suggest providing medication education, and basic information and skills ("survival skills") to patients before discharge. Although the strength of evidence for this recommendation is low, it is likely that benefits outweigh harms or burden.

E. Selected Complications

Recommendation

20. We recommend performing a comprehensive foot risk assessment annually.
    (Strong for | Not Reviewed, Amended)

Discussion

A foot risk assessment is recommended on an annual basis. A complete foot risk assessment includes:[122]

- Evaluation of the skin: breakdown, callus, erythema, tinea pedis
- Assessment of protective sensation using the Semmes-Weinstein 5.07 monofilament
- Evaluation for lower extremity vascular disease: pallor on elevation, dependent rubor, pitting edema, and pedal pulses
- Evaluation for foot and/or nail deformities, trauma
- Prior history of ulcers or amputations
- Evaluation of patient's footwear and socks

There are no harms associated with a diabetic foot risk assessment. It also offers the opportunity to reinforce the importance of regular foot exam by the patient. Patients with diabetes are at risk for developing peripheral neuropathy with loss of sensation. Patients who develop peripheral vascular disease or ESRD are considered high-risk for developing a foot ulcer.[122-124] There are moderate resources needed to accomplish this task, primarily the minimal cost of the monofilament and added time at the appointment.

Protective and prophylactic foot care and early detection of any deformity or skin breakdown may prevent the development of ulcers and risk of amputation. A person who has had a foot ulcer is at life-long risk of further ulceration.[122-124]

Peripheral vascular diseases are associated with diabetic bilateral amputation. Preventative foot care programs should focus on peripheral vascular assessment to identify patients at risk and on the development of timely intervention strategies.[125]

The tensile strength of mature scar tissue is about 80% of original tissue strength, thus increasing the chance of developing further ulceration. The patient should therefore be questioned about foot ulcer history. Further research is required to determine the effectiveness of patient/primary care team sensation testing as part of self-management and if this increased engagement decreases the frequency of poor foot outcomes.

Recommendation

21. We recommend referring patients with limb-threatening conditions to the appropriate level of care for evaluation and treatment.
(Strong for | Not Reviewed, Amended)

Discussion

The confidence in the quality of evidence for this recommendation is low. However, clinical observations on the natural course of untreated limb-threatening conditions suggest that the equipoise necessary to obtain stronger evidence, such as RCTs, does not exist, and recommendations therefore need to be based on lower levels of evidence. The practice of referring patients with limb-threatening conditions is supported by the Work Group, which concluded that the benefits most likely strongly outweigh any potential harm for the patient.[122] Additionally, most patients are expected to value an expert evaluation and opinion on a limb-threatening condition; therefore, patients' values and preferences are unlikely to vary significantly. There are, however, cost considerations associated with utilizing more specialty care and potential resource and equity issues regarding the availability of these specialists in smaller and remote communities. With these considerations, and considering that this is a recommendation carried forward from the previous version of the guideline, the Work Group felt that it was appropriate to maintain a strong recommendation. In the unfortunate circumstances when amputation is necessary, clinicians may want to refer to the VA/DoD Clinical Practice Guideline for the Rehabilitation of Lower Limb Amputation (VA/DoD Lower Limb Amputation CPG).[15]

Below is a non-exhaustive list of conditions that should prompt the primary care provider to consider a timely referral to a specialist.

Systemic or Ascending (Worsening) Infection

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

Although infection is not always clinically apparent, common signs and symptoms include perilesional warmth, erythema, purulent drainage, odor, and involvement of bone. Pain may or may not be present. There may or may not be lymphangitis and lymphadenopathy, and fever and white blood cell count may or may not be present. Sudden loss of glycemic control often heralds serious infections.[126]

[15] See the VA/DoD Clinical Practice Guideline for the Rehabilitation of Lower Limb Amputation. Available at: http://www.healthquality.va.gov/guidelines/Rehab/amp/

Vascular Compromise

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

Acute ischemia or rest pain –Evidence of arterial insufficiency: lower limb pain at rest, dusky/blue or purple/black color, gangrene, or cold extremity. Pain in the toes or forefoot may be relieved by dependency of the limb. Assessment is needed for prompt vascular/surgical intervention. Patients with acute arterial occlusion will present with pain, pallor, pulselessness, paresthesia, and/or paralysis.[126]

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

Foot Ulceration

Cutaneous erosion with a loss of epithelium that extends to or through the dermis can involve deeper tissue and is characterized by an inability to self-repair in a timely and orderly manner.[122,127-130]

Puncture Wound

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

Ingrown Toenail

Ingrown toenail presents as a nail plate that has pierced the surrounding periungual tissue with associated erythema and drainage or an area of thick or discolored callus. The primary care provider should consider referral to a podiatrist for excision of infected ingrown nails, especially in the case of high-risk patients.[131]

Hemorrhagic Callus with or without Cellulitis

Patients with hemorrhagic callus with or without cellulitis should be promptly referred to a foot care specialist for complete evaluation and treatment. The provider must determine if the cellulitis may be associated with callus tissue or necrotic tissue that may obscure an underlying ulceration or deeper infection. The callus tissue must be debrided to properly assess the extent of an underlying ulceration and possible deeper, more serious infection. Necrotic tissue must also be debrided to help eradicate the infection and determine the full extent of the infection.

Further research is required to better compare outcomes in patients being seen by specialists versus primary care for non-urgent conditions, such as ingrown toenails.

Recommendation

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)

Discussion

The quality of the eye examination is a critical factor in the ability to detect early retinopathy. Thus, only qualified eye care professionals or trained readers using validated imaging techniques should be utilized for retinopathy screening and surveillance. Ophthalmoscopy should be performed through dilated pupils using high magnification and stereo viewing. Fundus photography is also highly sensitive in detecting clinically significant retinopathy and, when combined with interpretation by an experienced reader, may exceed the sensitivity of ophthalmoscopy in retinopathy detection. Non-mydriatic digital retinal imaging (i.e., fundus photography through a non-dilated pupil) also provides excellent sensitivity.[132] In some cases small pupils and/or media opacities will cause image degradation.[133] The combination of non-mydriatic digital retinal imaging with referral to an eye care specialist for patients in whom image quality is sub-optimal is an appropriate screening strategy as it can achieve a high level of sensitivity in the detection of retinopathy. In some cases, selective use of mydriatic eye drops to facilitate improved image quality will enhance the diagnostic utility of digital retinal imaging.

Recommendation

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)

Discussion

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

Pregnancy may be associated with rapid deterioration of existing retinopathy and a higher risk of progression to vision threatening disease. A woman with pre-existing diabetes who becomes pregnant should be examined at the time of diagnosis and if she has greater than minimal retinopathy, repeat examinations should be performed at four to six week intervals. Proliferative retinopathy or clinically significant macular edema should be treated promptly. Those with less severe retinopathy should be monitored closely throughout their pregnancy (i.e., during each trimester). In the absence of an eye examination within the previous 12 months, patients who are pregnant should have an expedited appointment for a retinopathy evaluation. In addition, regardless of the timing of the last eye examination, the patient's eye care provider should be notified of the pregnancy.[134]

Patients with newly diagnosed T2DM may have had several years of sub-clinical or clinical diabetes prior to being diagnosed. Retinopathy can develop during this time and up to 40% of patients will have

evidence of diabetic eye disease at the time their diabetes is diagnosed. Although the prevalence of vision threatening retinopathy at the time of diagnosis is very low, there is a 3-4% prevalence of proliferative retinopathy within the first few years of disease. Consequently, it is recommended that patients with new onset T2DM who have not had a dilated eye examination within the prior 12 months should have one performed within six months.[135]

The inability of symptoms alone to accurately predict the presence or severity of retinopathy necessitates regularly scheduled retinal examinations for patients with diabetes. Some patients will remain retinopathy-free for several years, but the course of diabetic eye disease cannot be reliably predicted for a given individual. Risk factors for progression of retinopathy include: poorly controlled HbA1c (e.g., >9.0%), rapid and substantial HbA1c improvement (a decrease of approximately 2% or greater over <6 months), insulin use, the presence of microvascular disease including pre-existing retinopathy, nephropathy or cardiac autonomic neuropathy, longer duration of disease, hyperlipidemia, and poorly controlled blood pressure (e.g. systolic >160 mmHg). In light of these associations, it is prudent to perform more frequent retinal examinations in such patients. Clinicians should exert caution in extending biennial examinations to patients with factors associated with a higher likelihood of retinopathy progression.[135,136]

Retinopathy of any level can progress rapidly over the course of a year and occasionally even mild retinopathy will progress to proliferative retinopathy within that time frame. As follow-up intervals shorter than 12 months may be indicated for some of these individuals, patients with retinopathy who have not had a retinal exam within the previous year should be referred for an expedited retinal evaluation. Patients who have previously undergone laser therapy have already reached the stage of vision threatening diabetic eye disease.[135] These patients require close follow-up and in the absence of information to the contrary should be considered at high risk for vision loss and receive an expedited examination if they have not had one within the previous year.

Duration of disease is most strongly associated with retinopathy in individuals with T1DM. The prevalence of proliferative retinopathy approaches 30% after 15 years of diabetes and may rise to as much as 50% after 20 years. Although the prevalence of proliferative disease is lower in T2DM, the prevalence of any retinopathy approaches 75% in insulin-treated patients with longer duration of diabetes and the prevalence of proliferative retinopathy may exceed 20%. Different patients may exhibit separate and unique rates of retinopathy development or progression, but the likelihood of ocular involvement increases with duration of diabetes.[137]

Recommendations

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)

Discussion

Hyperglycemia in pregnancy results in significantly elevated risks of both fetal and maternal harm; many routine medications used in T2DM are contraindicated during pregnancy. Achieving glycemic control with recommended medications before pregnancy may prevent adverse outcomes and is encouraged whenever possible.[138] This can be best achieved through a coordinated effort between the patient, family, and care providers encompassing the patient's desires, lifestyle, advanced planning, and personal beliefs. Because of the high-risk nature of pregnancy complicated by diabetes and the need for intensive multidisciplinary monitoring and patient support, referral of women with diabetes to an expert high-risk perinatal team at the earliest possible opportunity must be considered as the standard of care. Ideally, such a referral should be made during the period of planned conception. While intervention studies will not be available to prove improved outcomes with diabetes management, significant fetal and maternal complications, including death and fetal demise, have been consistently associated with increasing HbA1c. As a result of these adverse outcomes, achieving a pre-pregnancy HbA1c of <7.0% is optimal. For further reference, please see the VA/DoD Clinical Practice Guideline for Management of Pregnancy [VA/DoD Pregnancy CPG][16]).

Fetal complications of maternal hyperglycemia include:[138]

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

Maternal complications that occur at above average rates in diabetic pregnancies include:[138]

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

In addition to providing intensive glycemic control, the clinician overseeing the management of pregnant women should:[138]

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

[16] See the VA/DoD Clinical Practice Guideline for Management of Pregnancy. Available at: http://www.healthquality.va.gov/guidelines/WH/up/index.asp

VII. 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 for a discussion of evidence regarding glycemic control). 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.[17]

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.

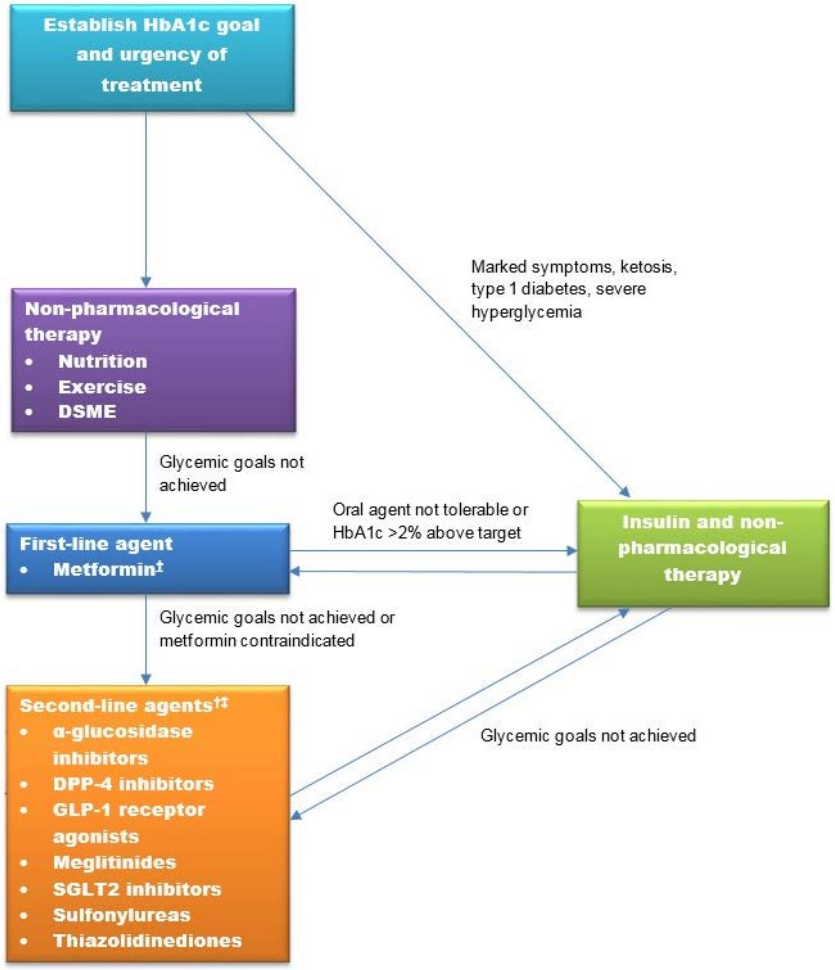
The following considerations are based on usual care and SRs performed by other groups:

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. (See Appendix B)
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 Appendix C). Although the evidence is clear on the relative efficacy of the various medications, their usage needs to be guided by clinical considerations.

[17] 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: Primary Action of Agents Used to Treat Hyperglycemia* [139]

Agent	Action	Results
α-glucosidase inhibitors	Inhibits intestinal α-glucosidase	Delays intestinal carbohydrate absorption/ digestion
DPP-4 inhibitors	Increases concentration of GLP-1 by slowing its inactivation via DPP-4 enzyme	Glucose dependent; ↑ insulin secretion Glucose dependent; ↓ glucagon secretion
GLP-1 agonists	Activates GLP-1 receptors	↑ glucose dependent insulin secretion ↓ glucose dependent glucagon secretion Slows gastric emptying
Insulin	Activates insulin receptors	↓ hepatic glucose production ↑ glucose uptake by fat and muscle cells
Meglitinides	Inhibits ATP-dependent potassium channels on pancreatic β-cells	↑ insulin secretion
Metformin	Activates AMP-kinase	↓ hepatic glucose production ↑ peripheral glucose uptake
SGLT2 inhibitors	Inhibits SGLT2 in proximal tubule thereby reducing reabsorption of filtered glucose	↑ urinary glucose excretion
Sulfonylureas	Inhibits ATP-dependent potassium channels by binding to specific sulfonylurea receptor on pancreatic β-cells	↑ insulin secretion
Thiazolidinediones	Activates PPAR-γ receptors in adipose tissue, skeletal muscle, liver	↓ hepatic glucose production ↑ peripheral glucose uptake

* Agents listed in alphabetical order

Abbreviations: AMP: 5' adenosine monophosphate-activated protein; ATP: adenosine triphosphate; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; PPAR: peroxisome proliferator-activated receptor; SGLT2: sodium glucose co-transporter 2

A. Summary of the Evidence - Monotherapy and Non-Insulin Two-Drug Combination Therapy

Three SRs by the Agency for Healthcare Research and Quality (AHRQ) have evaluated the comparative effectiveness and safety of diabetes medications.[140-143] The most recent review includes publications through December 2015. The evidence supports metformin as a first-line agent to treat T2DM based on its benefit-to-risk profile. A summary of the findings of the AHRQ reviews are summarized below.

a. Reduction in HbA1c

When used as monotherapy, metformin, SUs, TZDs, and repaglinide produced a similar reduction in HbA1c of about 1%. The α-glucosidase inhibitors and nateglinide reduced HbA1c to a lesser extent (approximately 0.5%).[140] The DPP-4 inhibitors were found to be less effective in lowering HbA1c compared to SU and metformin with treatment differences of 0.2% and 0.4%, respectively.[141-143]

The GLP-1 agonists and SGLT2 inhibitors were not included in the monotherapy assessments. The product labeling does not recommend the GLP-1 agonists as first-line therapy; however, they have been studied as monotherapy. Comparative trials with dulaglutide and once-weekly exenatide showed reductions in HbA1c comparable to metformin and pioglitazone and greater than sitagliptin.[144,145] Another trial showed greater reduction in HbA1c with liraglutide compared to glimepiride in patients

who were either diabetes treatment naïve or who were on prior SU at half-maximal dose.[146] As monotherapy, the average HbA1c reduction with the SGLT2 inhibitors is less than 1%. In a comparative study, empagliflozin was found to be comparable to sitagliptin.[147]

Metformin plus a second agent provided additional HbA1c lowering, ranging from 0.4% to 1.0% over metformin alone.[141-143] Comparisons of various two-drug metformin-based regimens show similar reduction in HbA1c (metformin + SU, metformin + TZD, metformin + DPP-4 inhibitor, metformin + SGLT2 inhibitor). However, metformin + GLP-1 agonists reduced HbA1c more than metformin + DPP-4 inhibitors (treatment difference: 0.65%).[142,143]

b. Weight

SUs, TZDs, and meglitinides are associated with weight gain, while the GLP-1 agonists and SGLT2 inhibitors are associated with weight loss. Metformin, DPP-4 inhibitors, and α-glucosidase inhibitors are generally considered to be weight neutral.

Direct comparison among the drugs associated with weight gain show the increase in weight is similar between SUs and meglitinides and less than TZDs. Among the weight neutral drugs, weight loss favored metformin compared to DPP-4 inhibitors.[141-143]

c. Hypoglycemia

SUs have a greater risk for hypoglycemia as monotherapy than metformin, TZDs, DPP-4 inhibitors, and GLP-1 agonists. In two-drug combination treatment comparisons, the risk of hypoglycemia with metformin + SU was greater than metformin + DPP-4 inhibitor, metformin + SGLT2 inhibitor, metformin + GLP-1 agonist, or metformin + TZD. The risk of hypoglycemia was similar between metformin monotherapy and two-drug regimens of metformin plus a second agent (TZD, DPP-4 inhibitor, SGLT2 inhibitor).[141-143]

d. Blood Pressure

Metformin, SUs, and TZDs had minimal effect on systolic and diastolic blood pressure.[140] The GLP-1 agonists and SGLT2 inhibitors decreased systolic blood pressure by 3-5 mmHg compared to metformin, SUs, and DPP-4 inhibitors.[142,143]

e. Gastrointestinal (GI) Adverse Effects

Metformin, GLP-1 agonists, and acarbose are associated with more GI side effects (e.g., nausea, vomiting, diarrhea) than SUs, TZDs, and DPP-4 inhibitors.[140-143] The SGLT2 were not included in the comparisons, but are typically not associated with increased GI side effects.

f. Lipids

The TZDs are associated with increase in low-density lipoprotein cholesterol (LDL-C) and metformin is associated with decrease in LDL-C. The SUs, DPP-4 inhibitors, acarbose, and repaglinide have little effect on LDL-C. In comparative analyses, metformin decreased LDL-C levels relative to SUs, DPP-4 inhibitors, and TZDs.[140,141]

Pioglitazone increased HDL-C more than rosiglitazone, metformin, and SUs. The effect on HDL-C with metformin was comparable to SUs or rosiglitazone and greater than DPP-4 inhibitors. However, the combination of metformin + rosiglitazone significantly increased HDL-C compared to metformin + SU.[141]

TZDs increased HDL-C whereas the other agents had little impact on HDL-C. Only rosiglitazone was shown to slightly increase triglycerides.

Lipids were not addressed in the most recent AHRQ review; therefore, comparative data for the GLP-1 agonists and SGLT2 inhibitors were not available. An SR and network meta-analysis found that GLP-1 agonists were associated with modest reduction in LDL-C and triglycerides, but no significant increase in HDL-C.[148]

Metformin, TZDs, SUs, DPP-4 inhibitors, acarbose, repaglinide, SGLT2 inhibitors, and GLP-1 agonists have been associated with various changes in lipid values as noted; however, whether these changes result in reductions in important clinical outcomes (fewer MIs, stroke, or improved total mortality) is unknown. Please refer to the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction [VA/DoD Dyslipidemia CPG].[18]

g. Cardiovascular Mortality and Morbidity

Metformin was associated with a lower risk for cardiovascular mortality compared to SUs. There were insufficient data to directly compare the other agents. Non-comparative long-term cardiovascular trials have been published for saxagliptin, alogliptin, sitagliptin, empagliflozin, liraglutide, and lixisenatide and are discussed later.

h. Other Adverse Effects

There were insufficient comparative data on other adverse effects associated with specific drugs or drug classes. Refer to Appendix B for adverse effects associated with each drug class.

B. Triple Therapy

A network meta-analysis evaluating triple therapy combinations found that the addition of a third agent to dual therapy results in further reduction of HbA1c. Changes in weight were consistent with what is expected for a given drug class. The odds of hypoglycemia increased when a third agent was added to dual therapy. The DPP-4 inhibitors had the lowest odds of hypoglycemia and SUs and insulin had the highest odds.[149]

Compared to dual therapy alone:

- The addition of a DPP-4 inhibitor to dual therapy further decreased HbA1c (estimated treatment difference: -0.56%, 95%CI: -0.70 to -0.42). There was no appreciable change in weight.
- The addition of a SGLT2 inhibitor to dual therapy further decreased HbA1c (estimated treatment difference -0.69%, 95%CI: -0.92 to -0.46) and decreased weight (estimated treatment difference: -1.79 kg, 95%CI: -3.03 to -0.55).

[18] 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/

- The addition of a GLP-1 agonist to dual therapy further decreased HbA1c (estimated treatment difference: -0.81%, 95%CI: -1.00 to -0.62) and decreased weight (estimated treatment difference: -1.85 kg, 95%CI: -2.85 to -0.89).
- The addition of a TZD to dual therapy further decreased HbA1c (treatment difference: -0.94%, 95%CI: -1.18 to -0.70), but increased weight (estimated treatment difference: 2.72 kg, 95%CI: 1.45 to 3.99).
- The addition of a SU to dual therapy further decreased HbA1c (treatment difference: -0.59%, 95%CI: -0.90 to -0.28), but increased weight (estimated treatment difference: 3.23 kg, 95%CI: 1.56 to 4.90).
- The addition of insulin to dual therapy further decreased HbA1c (treatment difference: -0.91%, 95%CI: -1.13 to -0.69), but increased weight (estimated treatment difference: 2.34 kg, 95%CI: 1.18 to 3.50).

Direct comparison of non-insulin containing triple therapy regimens

There are few head-to-head trials comparing non-insulin containing triple therapy regimens. Most trials compared a third agent as add-on to metformin + SU. All treatments provided additional HbA1c lowering; however, differences between treatments were relatively small. The impact on weight favored those drugs that are known to cause weight loss.

Table 4: Trials comparing non-insulin containing triple therapy regimens

Trial Author	Comparators (First drug – second drug)	Added-on to	Duration	HbA1c (treatment difference)	Weight (treatment difference)	Hypoglycemia
DeRosa [150]	DPP-4 versus SU	MET+TZD	52 weeks	Similar decrease	-6.5 kg	N/A
Liu [151]	TZD versus DPP-4	MET+SU	24 weeks	-0.23% (p=NS)	1.6 kg	N/A
Schernthaner [152]	SGLT2 versus DPP-4	MET+SU	52 weeks	-0.37% (95% CI: -0.50 to -0.25)	-2.4 kg	Similar
Home [153]	GLP-1 versus TZD	MET+SU	52 weeks	0.25% (95% CI: 0.10 to 0.40)	-4.8 kg	31.4% versus 21%

Abbreviations: CI: confidence interval; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; kg: kilograms; MET: metformin; N/A: Not applicable; NS: not significant; SGLT2: sodium glucose co-transporter 2; SU: sulfonylurea; TZD: thiazolidinedione

C. Insulin Therapy

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

- Type of diabetes
- Age
- Weight (presence or absence of obesity)
- Comorbid conditions

- Presence of autonomic neuropathy
- Concomitant medications (specifically beta-blockers)
- Patient's ability to perform SMBG and accurately inject insulin
- Complexity of management strategy (number of injections, variable dosing based on carbohydrate intake and pre-prandial glycemia)
- Risks of hypoglycemia and benefits of tight control, including psychosocial factors
- Magnitude and pattern of hyperglycemia
- Cost

Many patients with T2DM can achieve their glycemic target with a single bedtime injection of long-acting insulin or pre-meal split mixed insulin, often in combination with an oral agent. Some patients will require intensified regimens to achieve their target glycemic range. Early use of insulin should be considered in any patient with extreme hyperglycemia, even if transition to therapy with oral agents is intended as hyperglycemia improves. Other insulin options include adding basal insulin (NPH or long-acting analog) and continuing therapy with one or two oral agents, adding a premixed insulin while continuing insulin sensitizers (e.g., metformin) and discontinuing secretagogues, or adding rapid-acting insulin at mealtimes and continuing therapy with one or two oral agents.[154] The care of patients with T1DM or T2DM (needing insulin) should be individualized, in consultation with a multidisciplinary diabetes care team.

The GLP-1 agonists in combination with insulin were not addressed in the 2010 DM CPG and a brief summary of the evidence is provided. An SR and meta-analysis of 15 studies (N=4,348) of at least eight weeks duration addressed combination use of GLP-1 receptor agonists and basal insulin.[155] Eleven studies evaluated the addition of a GLP-1 agonist to basal insulin compared to basal insulin alone. Both treatment groups allowed the use of oral agents. Four studies compared a GLP-1 agonist to mealtime insulin. All patients had background basal insulin with or without oral agents. The primary endpoints were change in glycemic control, hypoglycemia, and weight between baseline and end of intervention.

GLP-1 agonist and basal insulin combination treatment compared to other anti-hyperglycemic treatments showed a mean reduction in HbA1c of 0.44% (95% CI: -0.60 to -0.29), increased likelihood of achieving target HbA1c $\leq$ 7% (relative risk: 1.92, 95% CI: 1.43 to 2.56), did not have an impact on the risk of hypoglycemia (0.99, 95% CI: 0.76 to 1.29) and a mean reduction in weight of -3.22 kg (95% CI: -4.90 to -1.54).

Limitations of the study included the long-term durability of the treatment (mean 24.8 weeks); potential risk of bias with some studies having open-label design and pharmaceutical industry funding; differences in GLP-1 agonist preparation (short-acting, twice-daily formulations, intermediate once-daily products, and long-acting weekly drugs); long-term durability, safety, and side effects of GLP-1 agonists have not been established; and the ideal timing for the start of treatment in the clinical course of the disease.[155]

Table 5: Insulin: Summary of Pharmacokinetics [139,156-161]

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

D. Cardiovascular Outcomes Trials

a. DPP-4 Inhibitors and Cardiovascular Outcomes

The long-term cardiovascular safety trials for saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus [SAVOR]), alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE]), and sitagliptin (Trial Evaluating Cardiovascular Outcomes with Sitagliptin [TECOS]) were conducted in patients with T2DM who had a history of, or were at high risk for, cardiovascular events. The results showed that there was no increase or decrease in the primary endpoint (composite of cardiovascular death, nonfatal MI, or nonfatal ischemic stroke) between the DPP-4 inhibitors and placebo.[162-164]

A secondary endpoint from the SAVOR trial found a higher risk of hospitalization for heart failure in patients receiving saxagliptin relative to placebo (HR=1.27, 95%CI: 1.07 to 1.51, p=0.007). Post-hoc analyses of SAVOR found that patients with Class 3 or 4 heart failure, or eGFR < 60mL/min were at a greater risk for hospitalization for heart failure. Hospitalization due to heart failure was not a predefined endpoint. In the EXAMINE trial for alogliptin, a post-hoc analysis found a numerically higher risk of hospitalization for heart failure in patients receiving alogliptin relative to placebo (HR=1.19, 95%CI: 0.90 to 1.58, p=0.220). A secondary endpoint in the TECOS trial found that the rate of hospitalization for heart failure did not differ between sitagliptin and placebo (HR=1.0, 95%CI: 0.83 to 1.20, p=0.98). It is unknown if true differences exist between agents as trials did not directly compare one agent to another and study populations and methodology differed. However, two large observational studies found the risk for hospitalization for heart failure was not greater with saxagliptin compared to sitagliptin.[165,166] The long-term trial for linagliptin (Cardiovascular Outcome Trial of Linagliptin Versus Glimepiride in Type 2 Diabetes [CAROLINA]) is ongoing and expected to be completed in 2019. This is the first comparative trial evaluating linagliptin and glimepiride in patients who have early T2DM and increased cardiovascular risk or established complications.

The labeling for saxagliptin and alogliptin state that the risks and benefits of saxagliptin or alogliptin should be considered prior to initiating treatment in patients at a higher risk for heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of saxagliptin/alogliptin.

Table 6: DPP-4 Cardiovascular Outcomes Trials

Study	Treatment Arms	Outcomes	Target Completion Date	Results
SAVOR-TIMI [163] N=16,500	Saxagliptin versus placebo	Time to first confirmed CV event (a composite defined as CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization)	Completed	Saxagliptin was non-inferior to placebo. Did not increase risk of CV death, MI, or stroke, but also did not add any benefits.
EXAMINE [164] N=5,400	Alogliptin versus placebo		Completed	Alogliptin was non-inferior to placebo for CV endpoints (composite of death from CV causes, nonfatal MI, or nonfatal stroke).
CAROLINA [167] N=6,115	Linagliptin versus glimepiride		February 2019	Pending
TECOS [162] N=14,000	Sitagliptin versus placebo		Completed	Sitagliptin was non-inferior to placebo for CV composite endpoint (first time MI, nonfatal stroke, unstable angina requiring hospitalization, or CV related death).

Abbreviations: CAROLINA: Cardiovascular Outcome Trial of Linagliptin versus Glimepiride in Type 2 Diabetes; CV: cardiovascular; EXAMINE: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; MI: myocardial infarction; SAVOR-TIMI: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction; TECOS: Trial Evaluating Cardiovascular Outcomes with Sitagliptin

b. Thiazolidinediones and Cardiovascular Outcomes

The long-term cardiovascular trial for pioglitazone (Prospective Pioglitazone Clinical Trial In Macrovascular Events [PROactive]) was conducted in patients with T2DM and who had evidence of macrovascular disease.[168] There was no significant difference between pioglitazone and placebo in the primary endpoint (composite of all-cause mortality, non-fatal MI [including silent MI], stroke, acute coronary syndrome, leg amputation, coronary revascularization, or revascularization of the leg) (HR=0.90, 95%CI: 0.8 to 1.02, p=0.095). The main secondary endpoint (composite all-cause mortality, non-fatal MI, and stroke) showed a significant reduction in events with pioglitazone compared to placebo (HR=0.84, 95%CI: 0.72 to 0.98, p=0.027).

Heart failure (non-adjudicated) was reported more often with pioglitazone (10.8%) than placebo (7.5%). Hospitalization for heart failure was also reported more frequently with pioglitazone (5.7%) than placebo (4.1%).

Another large trial (Insulin Resistance Intervention after Stroke [IRIS]) compared pioglitazone to placebo in patients with insulin resistance who had had a recent ischemic stroke or transient ischemic attack (TIA). There was a significant reduction in the primary outcome (fatal or nonfatal stroke or MI) with pioglitazone compared to placebo (HR=0.76, 95% CI: 0.62 to 0.93, p=0.007).[169]

In 2013, the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing medicines was removed by the FDA after determining that data from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial did not show an increased risk of MI. The long-term cardiovascular trial for rosiglitazone (RECORD) was a randomized, multicenter, open-label, non-inferiority trial. Patients with T2DM (N=4,447) who were receiving metformin or sulfonylurea and had

inadequate glycemic control were randomized to add-on rosiglitazone or placebo (control group). The primary end point was hospitalization or death from cardiovascular causes.

Results showed non-inferiority of rosiglitazone compared to placebo. The primary endpoint occurred in 321 patients in the rosiglitazone group and 323 patients in the control group over the 5.5 year follow up period (HR= 0.99, 95% CI: 0.85 to 1.16). Additional results showed non-inferiority for cardiovascular death (HR=0.84, 95% CI: 0.59 to 1.18), MI (HR=1.14, 95% CI: 0.80 to 1.63), and stroke (HR=0.72, 95% CI: 0.49 to 1.06). There was no significant difference between rosiglitazone and the control group regarding MI and death from cardiovascular causes or any cause. Similar to pioglitazone, heart failure leading to hospitalization was reported more often with rosiglitazone compared to placebo (HR=2.10, 95% CI: 1.35 to 3.27).

c. GLP-1 Receptor Agonists and Cardiovascular Outcomes

Liraglutide is the first of the GLP-1 class to show cardiovascular benefit (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER] trial) in patients with T2DM and high cardiovascular risk.[62] Lixisenatide with T2DM patients who had MI or who had been hospitalized for unstable angina, did not show cardiovascular benefit in the Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA] trial.[170]

The primary composite outcome in the liraglutide study (LEADER) was a time-to-event analysis of the first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke with a primary hypothesis of non-inferiority to placebo. The liraglutide group had significantly fewer patients with the primary outcome (HR=0.87, 95% CI: 0.78 to 0.97, p <0.001 for non-inferiority; p=0.01 for superiority). The rate of death due to cardiovascular causes (HR=0.78, 95% CI: 0.66 to 0.93, p=0.007) and death from any cause (HR=0.85, 95% CI: 0.74 to 0.97, p=0.02) was lower in the liraglutide group than in the placebo group. There were non-significant reduction in the rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure in the liraglutide group versus the placebo group.

The primary composite end point of the lixisenatide study (ELIXA) was cardiovascular death, MI, stroke, or hospitalization for unstable angina. Lixisenatide showed non-inferiority to placebo in the primary end-point event (HR=1.02, 95% CI: 0.89 to 1.17, p<0.001) but did not show superiority (p=0.81). The two groups showed no significant differences in the rate of hospitalization for heart failure (HR in the lixisenatide group=0.96, 95% CI: 0.75 to 1.23) or the rate of death (HR=0.94, 95% CI: 0.78 to 1.13).

Other cardiovascular safety trials with the GLP-1 class are ongoing (See Table 7).

Table 7: GLP-1 Cardiovascular Outcomes Trials*

Study	Treatment Arms	Outcomes	Target Completion Date
LEADER [62] N=9,000	Liraglutide versus placebo	Time to first confirmed CV event (a composite defined as CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization)	Completed: Reduced the risk of major adverse CV events
EXSCEL [171] N=14,000	Exenatide once weekly versus placebo		April 2018
HARMONY-OUTCOMES [172] N=9,400	Albiglutide versus placebo		May 2019
REWIND [173] N=9,622	Dulaglutide versus placebo		July 2018
ELIXA [170] N=6,000	Lixisenatide versus placebo		Completed: Not inferior to placebo in CV outcomes
SUSTAIN 6 [174] N=3,299	Semaglutide versus placebo		Completed: Reduced the risk of major adverse CV events

* Semaglutide was not FDA approved at the time this guideline was published.

Abbreviations: CV: cardiovascular; ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL: Exenatide Study of Cardiovascular Event Lowering; GLP-1: glucagon-like peptide-1; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI: myocardial infarction; REWIND: Researching Cardiovascular Events with a Weekly Incretin in Diabetes; SUSTAIN 6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

d. SGLT2 Inhibitors and Cardiovascular Outcomes

One long-term prospective cardiovascular outcomes trial has been completed with a SGLT2 inhibitor to date. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial evaluated the time to first event of cardiovascular death, non-fatal MI, or non-fatal stroke in patients randomized to empagliflozin or placebo.[63]

The primary composite outcome was statistically significant for patients in the empagliflozin group compared to placebo with a 32% relative risk reduction (2.6% ARR) in death from any cause in the pooled empagliflozin group. The number needed to treat was 39 patients for three years to prevent one death. In terms of death from cardiovascular causes, empagliflozin showed a 38% relative risk reduction (2.2% ARR). To prevent one death from cardiovascular causes, 45 patients would need to be treated for three years.

A predefined secondary outcome (composite of the primary outcome plus hospitalization for unstable angina) was also statistically significant in the empagliflozin arm revealing a 35% relative risk reduction (1.4% ARR) in hospitalization for heart failure. Seventy-one patients would need to be treated for three years to prevent one hospitalization. Of note, 77% of patients were taking statins concomitantly. This study only included patients with a high risk of CVD and did not include patients without CVD.[63]

Other cardiovascular safety trials with the SGLT2 inhibitor class are ongoing (See Table 8).

Table 8: SGLT2 Outcomes Trials

Study	Treatment Arms	Outcomes	Target Completion Date
CANVAS [175] N=4,330	Canagliflozin versus placebo	Time to first confirmed CV event (a composite defined as CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization)	February 2017
DECLARE-TIMI 58 [176] N=17,276	Dapagliflozin versus placebo	Time to first event included in the composite endpoint of CV death, MI or ischemic stroke	April 2019
EMPA-REG OUTCOME [63] N=7,064	Empagliflozin versus placebo	Time to first event of CV death, non-fatal MI, or non-fatal stroke	Completed; patients at high risk for CV events on empagliflozin had a lower rate of the primary composite CV outcome and of death from any cause compared to placebo

Abbreviations: CANVAS: Canagliflozin Cardiovascular Assessment Study; CV: cardiovascular; DECLARE-TIMI: Dapagliflozin Effect on Cardiovascular Events; EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MI: myocardial infarction; SGLT2: sodium glucose co-transporter-2

VIII. Knowledge Gaps and Recommended Research

During the course of guideline development, the Work Group identified important areas for future research to assist in the next DM CPG update.

Evidence shows that DSME is effective but most reviews called for further research by way of well-designed longitudinal studies. Research on comparative effectiveness of in-person versus technology-based education is needed. Investigation of effective modalities of DSME to provide education in areas where an educator is not available is also of interest.

Three major intensive control studies of target HbA1c were designed to evaluate cardiovascular outcomes (ACCORD [56], VADT [57], and ADVANCE [58]). Newer therapeutic options have been introduced since these major trials were completed, and further research is needed to understand the effects of intensive control with newer therapies on macrovascular disease outcomes.

Further research is also required to determine whether HbA1c varies with racial/ethnic differences depending on the level of glycemic control, their clinical significance, and most importantly, implications for therapy.

More research is required to determine the best measures of HbA1c variability and practical means to communicate them, whether or not there is a dose-response relationship for magnitude of variability or exposure to variability and, most importantly, whether interventions to reduce HbA1c variability affect outcomes.

There is a gap in research studies on therapeutic lifestyle counseling for all patients with T2DM that address sustainability over the long-term (greater than five years) and effective methods to implement interventions.

Although a Mediterranean diet has been shown to improve glycemic control, weight, and cardiovascular outcomes in patients with T2DM, more research is needed to evaluate the effects and availability of the diet in the U.S. population, particularly in the VA and DoD populations. The VA/DoD population presents unique challenges regarding feasibility and acceptability of diet and lifestyle changes. Further research to determine new strategies that maximize adherence is needed for this population. Research is also needed to study the long-term effects of dietary modifications and specifically the implementation of a low glycemic index diet outside of the research setting. This CPG does not address MNT in conjunction with pharmacotherapy due to lack of evidence. Research comparing initiating nutrition therapy as a first-line therapy versus pharmacotherapy is needed.

Advancement in glucose monitoring technologies such as CGMs may improve the capability to safely target lower glucose levels, however, performance of these devices in acutely ill hospitalized patients is not well studied. Another practice that requires more study is the application of before-bed correction insulin for non-ICU hospitalized patients with T2DM.

There are significant gaps in the evidence to support recommendations for inpatient diabetes education. There is inadequate evidence to assess which patients might benefit most from inpatient DM education and there are no high quality studies that have assessed for patient harms.

Further research is required to determine the effectiveness of patient/lay person sensation testing as part of foot care self-management and if this increase in patient engagement decreases the frequency of poor foot outcomes. More studies are required to better compare outcomes of patients with limb-threatening conditions being seen by specialists versus primary care providers for non-urgent conditions, such as ingrown toenails.

Appendix A: Evidence Review Methodology

A. Developing the Scope and Key Questions

The Champions, along with the Work Group, were tasked with identifying KQs to guide the systematic review of the literature on DM. These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the AHRQ. Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [177]

P	Patients, Population, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions, Work Group, and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Due to resource constraints, all developed KQs could not be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority and those were included in the review. Table A-5 contains the final set of KQs used to guide the systematic evidence review for this CPG.

a. Population(s)

- Adults 18 years or older with T2DM treated in any VA/DoD primary care setting
- The KQs are specific to adults 18 years or older with T2DM treated in any VA/DoD primary care setting.
- KQ specific populations
    - KQ1: Middle-aged individuals with approximate average age of 60 years (Range: 40–75 years)
    - KQ2: Adult patients with T2DM and comorbid medical conditions such as cancer, CKD and diabetes, and other end stage conditions or patients with multiple comorbidities
    - KQ4a, KQ4b: Hospitalized adult patients with T2DM, excluding ICU settings
    - KQ7: Patients with T2DM and attention also given to subpopulations:

- African American patients
- Elderly (>65 years)
- Patients with CKD, including end-stage renal disease

- KQ8: Patients with T2DM and attention given to women contemplating pregnancy if available

b. Interventions

Table A-2 below lists the interventions that are covered in this SR. The interventions are listed according to the key questions they address.

Table A-2: Interventions

Key Question	Intervention(s)
1	Intensive glycemic control strategies—as defined by the study
2	Shared decision making strategies
3	Telehealth: ▪ Real-time communication ▪ Asynchronous communication ▪ Non-face-to-face communication ▪ Face-to-face communication e.g., mobile health, applications include self-directed versus guided, text messaging (SMS)
4a	Basal-bolus plus correction type insulin protocol, basal plus (or anything with basal-bolus)
4b	Managing glucose to 180 mg/dL
5	One or more of diabetes planning, management, and education interventions given at discharge or within certain period after discharge (e.g., phone calls, diabetes education, face-to-face visits, case management)
6	Higher long-term glucose variability (as defined by authors)
7	Patient characteristics that could affect test performances, such as ethnicity, race, older age, and CKD
8	Nutrition intervention strategies reviewed include: Interventions include: ▪ Low carbohydrate ▪ Low energy/low calorie ▪ Low fat ▪ Low glycemic index ▪ Medical nutrition therapy ▪ Carbohydrate counting ▪ Vegan ▪ Ketogenic ▪ Mediterranean ▪ Paleolithic
9	Interventions (e.g., online, technological including mobile apps, in-person including group and individual) designed to educate and support patients in self-management of diabetes

c. Comparators

Table A-3 lists the comparators of interest to this SR. The comparators are listed by the key question they address.

Table A-3: Comparators

Key Question	Comparator(s)
1	Standard glycemic control strategies
2	Standard patient management
3	Standard patient management
4a	Sliding scale insulin protocol, as well as the interventions outlined in Table A-2 (compare all three with each other)
4b	Managing glucose to 200 mg/dL
5	Absence of diabetes planning, management and education interventions given at discharge or within certain period after discharge
6	Lower long-term glucose variability (as defined by authors)
7	Patient characteristics not present
8	No MNT, one or more of the diets listed as interventions in Table A-2
9	Standard of care

d. Outcomes

Table A-4 lists the outcomes of interest to this SR. The outcomes are listed by the key question they address.

Table A-4: Outcomes

Key Question	Outcomes(s)
1	▪ Hypoglycemia ▪ Diabetes-related microvascular complications • Diabetic nephropathy • Diabetic retinopathy • Neuropathy ▪ Mortality ▪ Quality of life ▪ Cardiovascular outcomes • Congestive heart failure • Coronary artery disease • Stroke • MI
2	▪ Patient psychosocial coping (e.g., 17-item Diabetes-related Distress Scale) ▪ Adherence to medication management, other behavioral change (e.g., missing scheduled appointments or referrals) ▪ Measures of decisional conflict/discordance • Decisional Conflict Scale ▪ Standard diabetes outcomes (see list for KQ1, above)
3	▪ Adherence to regimen (pharmaceutical, behavioral) ▪ Standard diabetes outcomes (see list for KQ1, above)

Key Question	Outcomes(s)
4a	▪ Glucose variability ▪ Hypoglycemia ▪ Hyperglycemia ▪ Length of stay ▪ Mortality ▪ 30-day readmission ▪ Provider satisfaction
4b	▪ Hypoglycemia ▪ Dehydration ▪ Infection ▪ Length of stay
5	▪ HbA1c ▪ Length of stay ▪ 30-day readmission ▪ Patient psychosocial coping (e.g., 17-item Diabetes-related Distress Scale) ▪ Urgent care/emergency room visits
6	▪ Microvascular outcomes (nephropathy, retinopathy, neuropathy) ▪ Acute coronary events (e.g., MI, unstable angina) ▪ Peripheral vascular disease ▪ Stroke
7	For different tests (HbA1c, eAG, fructosamine, glycated albumin, 1,5-anhydroglucitol, and/or continuous glucose monitoring): ▪ Measurements of blood glycemic control including: fasting glucose, oral glucose tolerance test, 2-hour post-prandial test ▪ Report on standard measurement of diagnostic test performance, if available, including: sensitivity, specificity, positive predictive value, negative predictive value ▪ Patient-centered outcomes will be captured if available
8	▪ HbA1c ▪ Adherence to diet ▪ Blood pressure ▪ Dyslipidemia ▪ Hypoglycemia ▪ Hyperglycemia ▪ Weight change ▪ If information is available on progression to first use of pharmacotherapy
9	▪ HbA1c ▪ Hypoglycemia ▪ Patient satisfaction/coping ▪ Diabetes self-efficacy (e.g., confidence)

e. Timing

Twelve weeks for studies looking at outpatient populations (except KQ 8 and 9); for KQ 8 and 9 the minimum follow-up was six months. For studies looking at inpatients (KQs 4a and 4b), follow-up is during hospital stay and 30-days post-discharge.

f. Setting(s)

KQ 1-3, 6-9: Primary care; KQ 4, 5: Inpatient care

B. Conducting the Systematic Review

Extensive literature searches using the search terms and strategy included in Appendix H identified 5,012 citations potentially addressing the KQs of interest to this evidence review. Of those, 1,940 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, not a full-length article). Overall, 3,072 abstracts were reviewed with 2,328 of those being excluded for the following reasons: not an SR or clinical study, did not address a KQ of interest to this review, did not enroll a population of interest, or published prior to January 1, 2009. A total of 744 full-length articles were reviewed. Of those, 453 were excluded at a first-pass review for the following: not addressing a key question of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or SR, not meeting inclusion criteria for any key question, or being a duplicate. A total of 291 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 233 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below.

Overall, 58 studies addressed one or more of the KQs and were considered as evidence in this review. Table A-5 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram

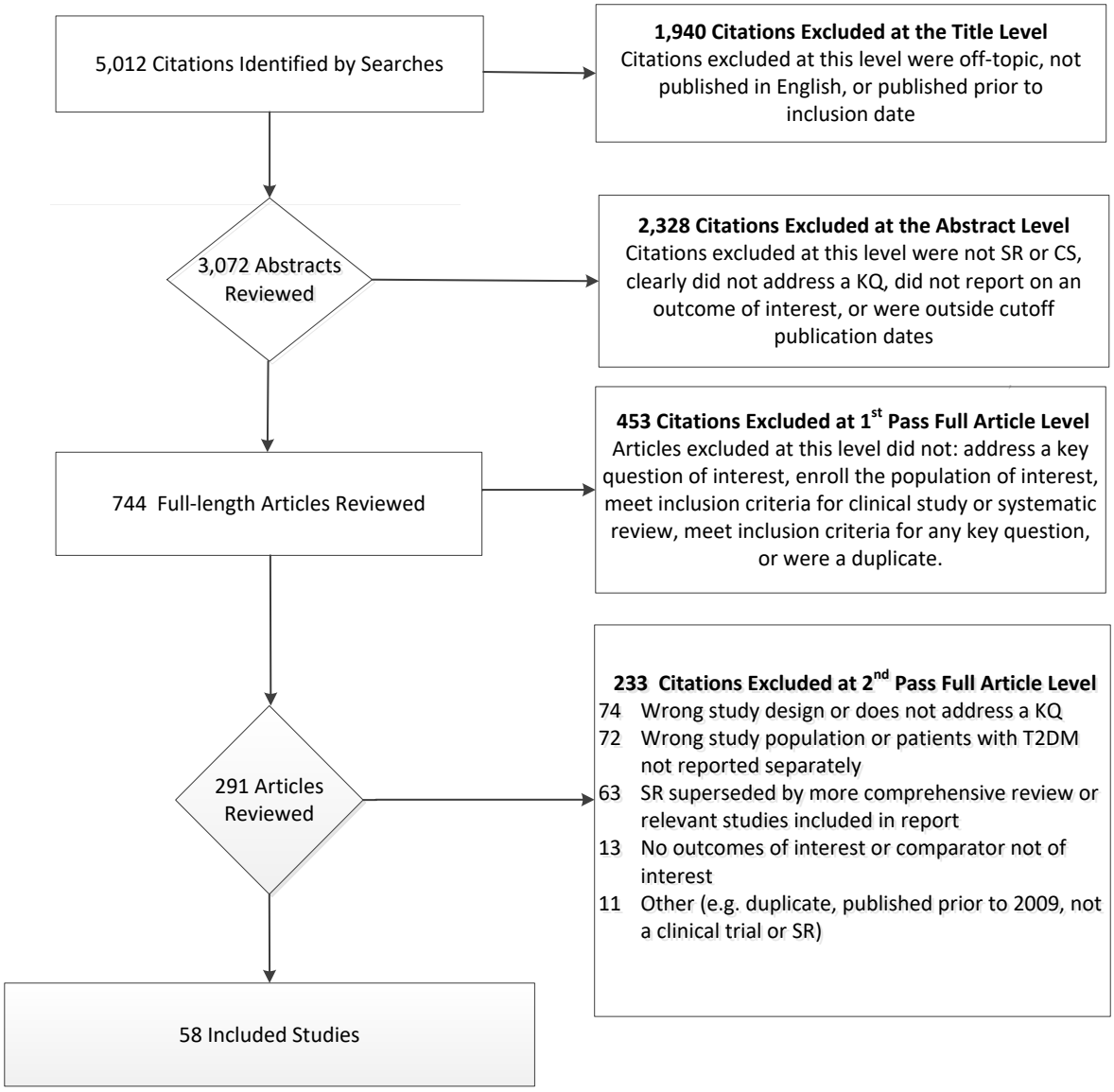


Table A-5. Evidence Base for Key Questions

Question Number	Question	Number of Studies and Type of Studies
1	In late middle-aged individuals (approximate average age of 60 years, typically in the range of 40–75 years) with T2DM, what are the benefits and harms of intensive glycemic control strategies relative to standard glycemic control strategies?	3 SRs 3 follow-up reports of RCTs 1 sub-study of an RCT
2	In patients with T2DM, is shared decision-making more effective than standard patient management in improving healthcare outcomes?	2 RCTs
3	In patients with T2DM, what is the comparative effectiveness of telehealth requiring physician interaction versus standard patient management in improving T2DM-related outcomes?	5 RCTs
4	a. In hospitalized patients with T2DM, excluding ICU settings, what is the comparative effectiveness of a basal-bolus plus correction insulin protocol and a sliding scale only insulin protocol for managing diabetes?	5 open-label RCTs
	b. In hospitalized patients with T2DM, excluding ICU settings, what is the comparative effectiveness of managing glucose to a goal of 180 mg/dL versus 200 mg/dL on hospital and short-term post-discharge outcomes?	No studies identified
5	In adult inpatients with T2DM, what components of diabetes care management (excluding glycemic control) during the inpatient or immediately post-discharge period are associated with improved outcomes? Are some bundled components more effective than others?	2 RCTs
6	Among patients with T2DM, does increased long-term glucose variability affect the severity of microvascular and macrovascular outcomes?	1 SR
7	What are the differences among individuals from different ethnicities, age groups, any comorbid conditions in how biomarkers, such as HbA1c, eAG, and other biomarkers reflect glycemic control in the previous weeks / months? Is the correlation consistent across the range of values for the biomarkers or is it non-linear?	11 observational studies
8	In adults with T2DM, what is the safety and effectiveness of medical nutrition therapy as monotherapy or in conjunction with pharmacotherapy in controlling HbA1c and glycemic oscillations?	5 SRs 10 RCTs
9	In adults with T2DM, what is the effectiveness of diabetes self-management education and support in controlling HbA1c in glycemia management and glycemic oscillations?	3 SRs 1 network meta-analysis 6 RCTs
	Total Evidence Base	**58 Studies**

a. Criteria for Study Inclusion/Exclusion

i. General Criteria

- Clinical studies or SRs published on or after January 1, 2009 to March 25, 2016, except for KQ7 (see Key Question Specific Criteria below.) If multiple SRs address a key question, we selected the most recent and/or comprehensive review. SRs were supplemented with clinical studies published subsequent to the SR.
- Studies must be published in English.

- Publication must be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- Intervention studies had a treatment or management style and were a prospective, randomized controlled trial with an independent control group, unless otherwise noted (see Key Question Specific Criteria below). The ideal diagnostic study compares clinical outcomes after diagnostic technology evaluation versus clinical evaluation, or compares clinical outcomes linked to different diagnostic technologies. Non-comparative diagnostic studies reporting only characteristics of the diagnostic test (e.g., sensitivity, specificity, repeatability) were excluded. However, non-comparative diagnostic studies that report a change in management strategy or patient outcomes (e.g., evidence of organic based disease patterns) were considered.
- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted. (see Key Question Specific Criteria below.)
- Study must have reported on an outcome of interest. Study must have enrolled a patient population in which at least 80% of patients had a diagnosis of T2DM. If the percentage is less than 80%, then data must have been reported separately for this patient subgroup.

ii. Key Question Specific Criteria

- For KQ 1, acceptable study designs included SRs, RCTs, including follow-up studies of RCTs, cohorts and pre-planned, prospective analyses of those studies. Retrospective analyses were not included.
- For KQs 2-4, 8, and 9, acceptable study designs included SRs of RCTs and/or individual RCTs.
- For KQ 5, acceptable study designs included SRs of acceptable study designs, individual RCTs or prospective nonrandomized controlled studies.
- For KQ 6, acceptable study designs included SRs of acceptable study designs, RCTs or prospective cohort studies that statistically compared outcomes for patients with T2DM and higher versus lower glucose variability. Large retrospective studies (200 patients minimum) that performed multivariate statistical analyses of the effect of higher and lower glucose variability on patient outcomes were also acceptable.
- For KQ7, it was determined after initial searches that the KQ required additional refinement and updated searches. Searches were updated to capture clinical studies or SRs published on or after January 1, 2009 to June 14, 2016.
- For KQ7, acceptable study designs included SRs, prospective blinded trials, cohort, or case-control studies comparing diabetes management metrics to HbA1c. For assessment of diagnostic accuracy, diagnostic cohort studies that compare a diagnostic test(s) to a reference standard (HbA1c) within the same patient were acceptable.
- For KQ9, trials set outside of the U.S. were considered to be out of scope, as the potential differences in education, support, cultural norms, and socioeconomic setting could

potentially limit applicability. Additionally, the minimum sample size per treatment arm was 50 patients.

b. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-6, below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix H.

Table A-6. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Bibliographic Databases		
The Cochrane Central Register of Controlled Trials (CENTRAL)	1/1/2009-4/11/16	Wiley
The Cochrane Database of Methodology Reviews (Methodology Reviews)	1/1/2009-4/11/16	Wiley
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	1/1/2009-4/11/16	Wiley
Database of Abstracts of Reviews of Effects	1/1/2009-4/11/16	Wiley
EMBASE (Excerpta Medica)	1/1/2009-4/4/16 KQ7 1/1/2009-6/14/16	Elsevier
Health Technology Assessment Database (HTA)	1/1/2009-4/11/16	Wiley
MEDLINE/PreMEDLINE	1/1/2009-4/4/16 KQ7 1/1/2009-6/14/16	OVIDSP
PubMed (In-process and Publisher records)	1/1/2009-4/4/16 KQ7 1/1/2009-6/14/16	NLM
Gray Literature Resources		
AHRQ	1/1/2009-4/11/16	AHRQ
Healthcare Standards database	1/1/2009-4/11/16	ECRI Institute
National Guideline Clearinghouse™	1/1/2009-4/11/16	AHRQ
National Institute of Health and Clinical Excellence	1/1/2009-4/11/16	NHS

C. Convening the Face-to-face Meeting

In consultation with the contracting officer's representative, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the Champions and Work Group members on June 21-24, 2016. These experts were gathered to develop and draft the clinical recommendations for an update to the 2010 DM CPG. Lewin presented findings from the evidence review of KQs 1-9 in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to categorize and carry forward recommendations from the 2010 DM CPG, modifying the recommendations as necessary. The members also developed new clinical practice recommendations not presented in the 2010 DM CPG, based on the 2016 evidence review. The subject matter experts were divided into three smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations during the face-to-face meeting, the Work Group members also revised the 2010 DM CPG algorithms to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2010, as necessary, to update the algorithms.

D. Grading 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:[15]

- 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 following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved QoL, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for DM, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rating of "High," "Moderate," "Low," or "Very Low."

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values," "some variation," or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resource use, equity, acceptability, feasibility, and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and, depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practically of the recommendation.

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

Table A-7. Evidence to Recommendation Framework

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

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.[15] 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.[178] 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.

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.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

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.[18,19] 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 A-8.

Table A-8. 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) [18] and Garcia et al. (2014) [19]

Abbreviation: CPG: clinical practice guideline

b. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as "New-added," "New-replaced," "Not changed," "Amended," or "Deleted."

"Reviewed, New-added" recommendations were original, new recommendations that were not in the 2010 DM CPG. "Reviewed, New-replaced" recommendations were in the previous version of the guideline, but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as "Reviewed, Not changed" were carried forward from the previous version of the CPG unchanged.

To maintain consistency between 2010 recommendations, which were developed using the USPSTF methodology, and 2017 recommendations, which were developed using the GRADE methodology, it was necessary to modify the 2010 recommendations to include verbiage to signify the strength of the recommendation (e.g., "We recommend," "We suggest"). Because the 2010 recommendations inherently needed to be modified at least slightly to include this language, the "Not changed" category was not used. For recommendations carried forward to the updated CPG with review of the evidence and slightly modified wording, the "Reviewed, Amended" recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive (i.e., not clinically meaningful) language changes deemed necessary. The evidence used

to support these recommendations was carried forward from the previous version of the CPG and/or was identified in the evidence review for the update.

Recommendations could have also been designated "Reviewed, Deleted." These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

c. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without a SR of the evidence. Due to time and budget constraints, the update of the DM CPG could not review all available evidence on management of DM, but instead focused its KQs on areas of new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated SR of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as "Not reviewed." If evidence had not been reviewed, recommendations could have been categorized as "Not changed," Amended," or "Deleted."

"Not reviewed, Not changed" recommendations refer to recommendations from the previous version of the DM CPG that were carried forward unchanged to the updated version. The category of "Not reviewed, Amended" was used to designate recommendations which were modified from the 2010 CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as "Not reviewed, Deleted" if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2017 version of the guideline are noted in the Recommendations. Recommendations 6, 9, 10, 12, 15, 17, 19, 20, 21, 22, 23, and 24 were carried forward from the 2010 DM CPG using this method. The categories for the recommendations from the 2010 DM CPG are noted in Appendix F.

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2010 DM CPG to support the amended "carried forward" recommendations. The Work Group also considered tables, appendices, and other sections from the 2010 DM CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14-20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in Peer Review Process. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket cards, and a patient summary. The final 2017 DM CPG was submitted to the EBPWG in April 2017.

Appendix B: Pharmacotherapy [1] [139]

A. 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 ▪ Titrate dose gradually to minimize GI effects ▪ GI side effects may be intensified in patients consuming large amounts of simple carbohydrates ▪ Reduces postprandial glucose values ▪ Not recommended in patients with significant renal impairment (SCr >2 mg/dL) ▪ Use with caution in hepatic impairment ▪ Contraindications: DKA, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, marked disorders of digestion or absorption conditions, cirrhosis (acarbose) ▪ 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 ▪ Diarrhea and abdominal pain ▪ Dose-related increase in serum transaminases, usually asymptomatic, reversible (acarbose)	▪ Inexpensive (acarbose) ▪ Moderately expensive (miglitol)

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

[1] Information is based on Work Group consensus, VA/DoD evidence-based reviews, and product package inserts. Average values shown; response is dependent on other factors such as whether drug therapy naïve, baseline HbA1c, concomitant anti-glycemic therapy, etc. Clinical considerations and adverse events/side effects are not intended to be inclusive of all information, but rather to highlight some of the key points. Refer to agency pricing sources for current cost information; lower pricing within a class may be available for agency preferred agents, or as new generics become available.

B. 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	▪ Indicated to be co-administered with mealtime insulin ▪ Reduces postprandial glucose values ▪ Requires frequent pre- and post-meal and bedtime glucose monitoring ▪ When initiating pramlintide, reduce mealtime insulin (including premixed insulin) dose by 50%; individualize subsequent insulin doses thereafter ▪ Contraindicated in those with hypoglycemia unawareness and confirmed gastroparesis ▪ Patients that should NOT be considered for pramlintide therapy: • Poor compliance with current insulin regimen • Poor compliance with prescribed SMBG • HbA1c >9% • Recurrent severe hypoglycemic requiring assistance during the past 6 months • Require the use of drugs that stimulate GI motility • pediatric patients ▪ Injectable	▪ GI effects (nausea, vomiting, anorexia)	Expensive

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

C. 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 ▪ Before starting metformin, obtain the patient's eGFR ▪ Metformin is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2 ▪ Starting metformin in patients with an eGFR between 30-45 mL/min/1.73 m^2 is not recommended ▪ 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 ▪ 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 ▪ Titrate dose gradually to minimize GI symptoms; a trial of metformin extended-release should be offered to patients experiencing continued GI effects ▪ Likely reduces CV events (UKPDS)	▪ GI effects (diarrhea, nausea, abdominal cramping) ▪ Rare risk of lactic acidosis (risk is increased in patients with acute CHF, dehydration, excessive alcohol intake, renal impairment or sepsis) ▪ 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

D. 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

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

F. Insulin

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

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

G. 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 ▪ Reduces postprandial glucose values ▪ Use with caution in patients with moderate to severe hepatic impairment and severe renal impairment ▪ Use with caution in the elderly, debilitated, and malnourished patients; may be more susceptible to glucose-lowering effects ▪ Combination therapy with SU is not recommended, no additional benefit	▪ Upper respiratory infection ▪ Flu-like symptoms	▪ Inexpensive (repaglinide) ▪ Moderately expensive (nateglinide)

Abbreviations: HbA1c: hemoglobin A1c; SU: sulfonylureas

H. 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) ▪ Empagliflozin was shown to reduce the risk of cardiovascular events compared to placebo ▪ Decrease triglycerides ▪ Increase HDL-C ▪ Increase LDL-C	▪ Urinary tract infections/urosepsis ▪ Genital mycotic infections (higher incidence in females and uncircumcised males) ▪ Increased risk for hypotension, orthostasis, volume depletion in elderly, those taking diuretics, or anti-hypertensives ▪ Decreased eGFR or increased serum creatinine may occur; elderly and those with preexisting renal impairment may be at greater risk ▪ Decrease in systolic blood pressure (~4-6 mmHg) ▪ DKA rare (presenting blood glucose levels may be below those typically expected for diabetic ketoacidosis (often <250 mg/dL). ▪ 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

I. Sulfonylureas

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

J. 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 ▪ Use with caution in patients with NYHA Class I/II heart failure or patients with risk factors for heart failure ▪ Not recommended in symptomatic heart failure ▪ Do not use in patients with active bladder cancer; consider risk versus benefits of using pioglitazone in those with a history of bladder cancer ▪ Use with caution in premenopausal, anovulatory women; may result in resumption of ovulation, increasing risk of pregnancy ▪ Administer cautiously in those with abnormal liver function tests ▪ Pioglitazone may reduce CV events	▪ Edema usually dose-related ▪ Cause or exacerbate heart failure (greater risk if used with insulin) ▪ Macular edema has been reported (may present with blurred vision or decreased visual acuity) ▪ Increased incidence of bone fractures in females occurring in the upper arm, hand and foot ▪ Liver injury has been reported; if ALT >3x ULN do not reinitiate therapy without another explanation for the liver test abnormalities	▪ Inexpensive (pioglitazone) ▪ Moderately expensive (rosiglitazone)

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

Appendix C: FDA Approved/ Studied Combination Therapy[1,2] [139]

	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.

Appendix D: Patient Focus Group Methods and Findings

A. Methods

On March 8, 2016, as part of the effort to update this CPG, the VA and DoD Leadership, along with the DM CPG Working Group, held a patient focus group at the VA Puget Sound Health Care System – American Lake Division. The focus group was comprised of five patients.

The aim of the focus group was to further the understanding of the perspective of patients receiving treatment for DM within the VA and/or DoD healthcare systems, as these patients are most affected by the recommendations put forth in the updated DM CPG. The focus group explored patient perspectives on a set of topics related to management of DM in the VA and DoD healthcare systems, including patients' knowledge of DM treatments and alternate treatment options, views on the delivery of care, and the impact of DM on the patients and the challenges it poses.

Participants for the focus group were recruited by Eric Rodgers, Director of the Evidence-based Practice Program, Office of Quality, Safety and Value for the Department of Veterans Affairs, Corinne Devlin, Chief, Office of Evidence-Based Practice Clinical Performance Directorate, and by the DM CPG Champions. Patient focus group participants were not intended to be a representative sample of VA and DoD patients who have experienced DM. However, recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the guideline development process. Patients were not incentivized for their participation or reimbursed for travel expenses.

The DM CPG Champions and Work Group developed a set of questions to help guide the focus group. The facilitator from Lewin led the discussion using interview questions prepared by the Work Group as a general guide to elicit the most important information from the patients regarding their experiences and views about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all of the listed questions were addressed.

At the time of the focus group, all five patients were receiving care in the VA healthcare system. Some of these patient participants had transitioned between multiple care settings, including from DoD to VA. The time since patients had been diagnosed with DM ranged from three weeks to 25 years at the time of the focus group. All patients had T2DM. Two patients stated that other members in their family had DM as well. One patient stated he was currently on insulin pump therapy.

The following concepts are aspects of care that are important to these patients, which emerged from the focus group discussion. Each of these themes was an important and needed aspect of participants' healthcare.

B. Patient Focus Group Findings

a. Using shared decision-making, consider all treatment options and develop a treatment plan based on the balance of risks, benefits, and patient-specific goals, values, and preferences

- Use shared decision-making to develop an individualized treatment plan; discuss pros and cons (e.g., benefits, risks, side effects) of each treatment option in conjunction with each patient's goals, priorities, values, and preferences.
- Periodically re-evaluate and reassess the patient's medications as new drug formulations and devices are available.
- Re-evaluation of the side effects and titration of the medicines are important during shared decision-making.
- Discuss pharmacologic options in depth with the patient, including their willingness to take medications and their preferences for other treatments.

b. Guide patients for the self-management of their diabetes and glucose monitoring, including benefits and risks, and their expectations

- Guide and educate patients on the self-management of their diabetes.
- Educate patients on the reason for SMBG throughout the day.
- Consider the benefits, risks, and patients' expectations during the self-management of their diabetes.

c. Educate and involve family caregivers and co-workers in accordance with patient preferences regarding core knowledge of diabetes management

- Foster family involvement in shared decision-making and patient support in accordance with patient preferences and in a way that is beneficial to the patient.
- Educate and include family members early in treatment discussions, especially regarding core knowledge on management of diabetes.
- Build and maintain trust, respect, and support with the patient and their family.
- Educate patients' co-workers on the core knowledge on management of diabetes in accordance with patient preference.

d. Within and between VA and DoD healthcare systems, work with appropriate providers to ensure continuity of high-quality care and timely consult and/or referral to an endocrinologist as appropriate

- Clinicians should listen actively and be responsive to each patient's agenda during clinic visits.
- Provide seamless transitions in DM treatment within and between VA, DoD, and other healthcare systems; patients should not have to encounter delays in diagnosis of DM, changes in treatment regimens, or have to "start all over" when moving to another provider.
- Provide timely consult and/or referrals to endocrinologists as appropriate.

e. Create a support system for patients with diabetes such as online groups, chats, other support groups, and diabetes education classes to enhance involvement and support among patients with diabetes

- Inform patients about available resources for DM management such as diabetes education classes.
- Create a support system in the VA and DoD healthcare systems such as online groups, chats, and other support groups for patients with DM and other co-occurring conditions.

Appendix E: Evidence Table

Recommendation	2010 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
1. We recommend shared decision-making to enhance patient knowledge and satisfaction.	N/A	[32] **Additional References:** [25,26,30,31,33]	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.	I None	[34-38,40-44] **Additional Reference:** [39]	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.	C None None None None	[45-49]	Weak for	Reviewed, New-replaced
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.	N/A	[53-61] **Additional References:** [50-52,62-66]	Strong for	Reviewed, New-added

[1] The 2010 VA/DoD DM CPG used the USPSTF evidence grading system (http://www.uspreventiveservicestaskforce.org). Inclusion of more than one 2010 Grade indicates that more than one 2010 CPG recommendation is covered under the 2017 recommendation. The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. "None" indicates that the 2017 DM CPG recommendation replaced or amended a 2010 DM CPG recommendation for which there was no grade. "N/A" indicates that the 2017 DM CPG recommendation was a new recommendation, and therefore does not have an associated 2010 Grade.

[2] The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2017 guideline Work Group, the literature cited corresponds directly to the 2016 evidence review. For recommendations that have been carried over from the 2010 VA/DoD DM CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to either 1) studies that support the recommendation and which were identified through the 2016 evidence review, or 2) relevant studies that support the recommendation, but which were not systematically identified through a literature review.

[3] Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

[4] Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	2010 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
5. We recommend developing an individualized glycemic management plan, based on the provider's appraisal of the risk-benefit ratio and patient preferences.	C None	**Additional References:** [26,31,67]	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.	N/A	[6] **Additional References:** [4,5,65,68-76]	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).	A	[53,54,56-61,77,79-81] **Additional References:** [64,78,82-85]	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).	A	[53,54,56-61,77,79-81] **Additional References:** [64,78,82-85]	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).	N/A	[53,54,56-61,77,79-81] **Additional References:** [64,78,82-85]	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).	A	[53,54,56-61,77,79-81] **Additional References:** [64,78,82-85]	Weak for	Reviewed, New-replaced
11. We suggest that providers be aware that HbA1c variability is a risk factor for microvascular and macrovascular outcomes.	N/A	[86] **Additional Reference:** [87]	Weak for	Reviewed, New-added

Recommendation	2010 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
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).	None	[88-93]	Strong for	Not Reviewed, Amended
13. We recommend a Mediterranean diet if aligned to patient's values and preferences.	N/A	[92,94,95]	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.	N/A	[91-93,96,97,99] **Additional Reference:** [98]	Strong for	Reviewed, New-added
15. We recommend against targeting blood glucose levels <110 mg/dL for all hospitalized patients with type 2 diabetes receiving insulin.	A	[100,101,103,104] **Additional References:** [102,105]	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.	A	[103,106,108-112,114] **Additional References:** [107,113]	Strong for	Reviewed, Amended
17. We recommend against the use of split mixed insulin regimen for all hospitalized patients with type 2 diabetes.	N/A	[115,116]	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.	N/A	[111,114,117]	Weak for	Reviewed, New-added
19. We suggest providing medication education and diabetes survival skills to patients before hospital discharge.	I	[120,121] **Additional References:** [118,119]	Weak for	Reviewed, Amended
20. We recommend performing a comprehensive foot risk assessment annually.	None	[122-125]	Strong for	Not Reviewed, Amended
21. We recommend referring patients with limb-threatening conditions to the appropriate level of care for evaluation and treatment.	None	[122,126-131]	Strong for	Not Reviewed, Amended

Recommendation	2010 Grade[1]	Evidence[2]	Strength of Recommendation[3]	Recommendation Category[4]
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.	A	[133] **Additional Reference:** [132]	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.	B I	**Additional References:** [134-137]	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.	None	**Additional Reference:** [138]	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.	None	**Additional Reference:** [138]	Strong for	Not Reviewed, Amended

Appendix F: 2010 Recommendation Categorization Table

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
D	B	1	Children with diabetes should be referred for consultative care to a pediatric diabetic team that is knowledgeable and experienced in meeting the medical, psychosocial, and developmental needs of children with diabetes.	None	Not reviewed, Deleted	
D	B	2	The pediatric diabetic team should include a pediatric endocrinologist, if available, and/or a pediatrician, certified diabetes educator, registered nurse, registered dietitian, and social worker, all with expertise and specialized training in the comprehensive care of children with diabetes.	None	Not reviewed, Deleted	
D	C	1	All female patients with pre-existing diabetes and reproductive potential should be educated about contraceptive options, and strongly encouraged to plan and prepare for pregnancy, and to optimize their glycemic control prior to attempting to conceive.	None	Not reviewed, Amended	Recommendation 24
D	C	2	Women with diabetes who are planning pregnancy should be educated about the different options of diabetes management during the pregnancy and referred to maternal fetal medicine provider before, or as early as possible, once pregnancy is confirmed.	None	Not reviewed, Amended	Recommendation 25
D	C	3	Women with gestational diabetes mellitus (GDM) should be screened for diabetes 6-12 weeks postpartum and should follow-up with subsequent screening for diabetes or prediabetes (See Module S: Screening)	None	Not reviewed, Deleted	

[1] The first three columns indicate the location of each recommendation within the 2010 DM CPG.

[2] The 2010 Recommendation Text column contains the wording of each recommendation from the 2010 DM CPG.

[3] The 2010 VA/DoD DM CPG used the U.S. Preventive Services Task Force (USPSTF) evidence grading system. http://www.uspreventiveservicestaskforce.org The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. "None" indicates there was no grade assigned to the recommendation in the 2010 DM CPG.

[4] The Category column indicates the way in which each 2010 DM CPG recommendation was updated.

[5] For recommendations that were carried forward to the 2010 DM CPG, this column indicates the new recommendation(s) to which they correspond.

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
D	E	1	Urgent or semi-urgent medical conditions, including hypo- or hyperglycemia, and deficient renal function must be treated before long-term disease management principles are applied.	None	Not reviewed, Deleted	
D	E	2	The urgency of medical treatment, including the necessity for hospitalization, will depend upon the presence of ketoacidosis, dehydration, hyperosmolarity, infections, and other life threatening conditions.	None	Not reviewed, Deleted	
D	E	3	Psychiatric illness and marked socioeconomic hardship (e.g., homelessness, absence of a support system or reliable transportation, and unemployment) pose significant barriers to diabetic management. If such circumstances are identified, involvement of behavioral health, social services, and case management professionals may enhance patient compliance with treatment and follow-up.	None	Reviewed, Deleted	
D	E	4	The determination of stability is up to the judgment of the provider.	None	Not reviewed, Deleted	
D	F	1	In addition to a general medical examination, a complete evaluation of patients with DM will include: ▪ Information regarding the onset and duration of DM ▪ History of hospitalization(s) for diabetic events ▪ Review of glycemic control ▪ Measurement of serum lipids ▪ Identification of foot complications ▪ Identification of eye complications ▪ Screening for hypertension ▪ Screening for kidney disease ▪ Identification of macrovascular disease ▪ Identification of neurovascular disease ▪ Assessment of psychosocial status (including family support) ▪ Appraisal of self-management skills	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
D	F	2	On a follow-up visit, the evaluation should focus on updating new information and/or changes to the patient record (see Table D3 for a listing of the components of the evaluation).	None	Not reviewed, Deleted	
D	H	1	Prescribe aspirin therapy (75 to 325 mg/day) for all adult patients with type 2 diabetes and evidence of cardiovascular disease.	A	Not reviewed, Deleted	
D	H	2	Consider beginning aspirin therapy (75 to 325 mg/day) in patients age ≥ 40 with type 2 diabetes and one or more other cardiovascular risk factors.	B	Not reviewed, Deleted	
D	H	3	Consider individual evaluation for aspirin therapy for patients age 30 to 40 with type 2 DM, with other cardiovascular risk factors, or with type 1 DM for duration of disease longer than 2 years.	I	Not reviewed, Deleted	
D	H	4	When considering the value of antiplatelet therapy, the risks of hemorrhagic stroke or gastrointestinal bleeding must be balanced against the benefits of prevention of adverse cardiovascular outcomes.	I	Not reviewed, Deleted	
D	I	1	If the individualized HbA1c is not on target, refer to Module G – Glycemic Control	None	Not reviewed, Deleted	
D	I	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. (Also see Annotation J)	None	Not reviewed, Deleted	
D	I	3	Measure fasting lipids (TC, HDL-C, TG and calculated LDL-C) if not done within one year. If the patient has elevated cholesterol or lipids, refer to the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia (Lipids). (Also see Annotation K)	None	Not reviewed, Deleted	
D	I	4	Screen for proteinuria and assess kidney function if not done within one year. If the patient develops micro- or macroalbuminuria or decline in estimated glomerular filtration rate (eGFR), refer to the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease (CKD). (Also see Annotation L)	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
D	I	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.	None	Not reviewed, Deleted	
D	I	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.	None	Not reviewed, Amended	Recommendation 20
D	I	7	If the patient needs additional nutritional or lifestyle education, refer to Module M – Self-Management and Education.	None	Reviewed, Deleted	
D	I	8	If the patient is a candidate for an influenza vaccine, administer it in season. (See CDC recommendations)	None	Not reviewed, Deleted	
D	I	9	Administer pneumococcal pneumonia vaccine, if indicated. (See CDC recommendations)	None	Not reviewed, Deleted	
D	I	10	If the patient is using tobacco, refer to the VA/DoD Clinical Practice Guideline for the Management of Tobacco Use Cessation.	None	Not reviewed, Deleted	
D	J	1	Patients with diabetes with hypertension (systolic BP ≥140 or diastolic BP ≥90 mmHg) should: a). Begin anti-hypertensive therapy with angiotensin converting enzyme inhibitor (ACEI) or a diuretic b). If ACEI induced side effects occur, consider switching to an angiotensin receptor blocker (ARB) c). Use other preferred agents (beta blockers, long acting calcium channel blockers) as necessary, depending on other co-morbid conditions or compelling indications to achieve a blood pressure <140/80 mm Hg.	A	Not reviewed, Deleted	
D	J	2	Patients with diabetes with initial SBP <140 mmHg and DBP between 80 and 89 mmHg (within the “pre-hypertensive” category identified by JNC 7) may benefit from lowering diastolic blood pressure to < 80 mm Hg.	A	Not reviewed, Deleted	
D	J	3	Individuals with diabetes whose blood pressure is <140/80 mmHg who have clinical cardiovascular disease may benefit from ACEI therapy even without a reduction in blood pressure.	A	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
D	J	4	In patients with diabetes and kidney insufficiency (i.e., eGFR <60 mL/min/1.73 m^2) and proteinuria (i.e., >1 g/24h) there are some data suggesting that further BP lowering (<125/75 mm Hg) may slow progression of renal disease. Lower BP should be achieved, if feasible and practical, depending on the tolerance of medications and side effects of BP lowering.	B	Not reviewed, Deleted	
D	K	1	Patients with diabetes and patients with established coronary heart disease (CHD) should be screened for lipid abnormalities with fasting lipid profile (triglycerides and HDL-C or LDL-C).	None	Not reviewed, Deleted	
D	K	2	Patients with Type 2 DM are at significant increased risk of CVD compared with non-diabetic patients of similar age and should, therefore, be treated more aggressively according to secondary prevention protocols.	A	Not reviewed, Deleted	
D	K	5	LDL should be lowered to less than 100 mg/dL for patients with previous documented CHD or CVD equivalent (DM with other major risk factors) for secondary prevention.	A	Not reviewed, Deleted	
D	K	6	LDL should be lowered to less than 130 mg/dL for patients with DM without other major risk factors for secondary prevention.	C	Not reviewed, Deleted	
D	K	7	All patients with diabetes should be given lifestyle counseling. Lifestyle change is indicated in all patients with LDL-C > 100 mg/dL. Strategies include diet (dietary/nutritional management of fat and/or cholesterol intake or MNT consult), exercise, smoking cessation, cessation of excessive use of alcohol, and weight control.	None	Not reviewed, Amended	Recommendation 12
D	K	8	Elevated TG level (>400 mg) may be due to poor glycemic control. The most common secondary causes of hypertriglyceridemia are alcohol, diabetes, and hypothyroidism. Addressing these underlying conditions can improve or normalize triglyceride levels and failing to address these conditions can render therapy ineffective. Once glycemic control is improved, the TG level should be reassessed and addressed.	None	Not reviewed, Deleted	
D	K	9	Statin drug therapy should be initiated for patients with previous documented CHD or CVD equivalent (diabetes with other major risk factors) if baseline LDL-C is greater than or equal to 100 mg/dL.	A	Not reviewed, Deleted	

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Module	Section	Number				
D	K	10	Statin drug therapy should be initiated for patients with documented DM with no major risk factors if baseline LDL-C is greater than or equal to 130 mg/dL.	C	Not reviewed, Deleted	
D	K	11	Statin drug therapy should be considered for all patients with CHD or CVD equivalent (diabetes with other major risk factors) regardless of LDL-C baseline.	B	Not reviewed, Deleted	
D	K	12	Therapeutic lifestyle changes (TLC) should be recommended for ALL patients with dyslipidemia, regardless of risk or baseline LDL-C level.	C	Not reviewed, Deleted	
D	K	13	For secondary prevention of recurrent CVD events, non-pharmacologic therapy is always indicated, but it should not delay appropriate pharmacotherapy.	None	Not reviewed, Deleted	
D	K	14	Emphasis on therapeutic lifestyle changes (TLC) is an important component of primary prevention and is effective in reducing CVD risk by lowering LDL-C and blood pressure.	B	Not reviewed, Deleted	
D	K	15	Diet intervention should be the first step in lipid lowering therapy.	B	Not reviewed, Deleted	
D	K	16	Patients whose initial treatment is therapeutic lifestyle changes (TLC) should be given 3-6 months of dietary therapy prior to beginning medication and longer, if lipids are improving and nearing LDL thresholds.	B	Not reviewed, Deleted	
D	K	17	Therapeutic lifestyle changes (TLC) is provided in a step-wise approach focused on initiating TLC components and followed by subsequent evaluation of the effect on LDL-C and moving to intensify MNT as indicated.	None	Not reviewed, Deleted	
D	K	18	Statins are first line agents in primary and secondary prevention of CVD regardless of HDL-C or TG level.	A	Not reviewed, Deleted	
D	K	19	Moderate doses of formulary statins (to achieve an LDL-C reduction of 25% or greater) should be initiated unless a patient is considered to be at greater than usual risk for adverse events from statins (e.g., myopathy).	A	Not reviewed, Deleted	
D	K	20	For patients who cannot tolerate statins, niacin or resins should be considered for treatment.	A	Not reviewed, Deleted	

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Module	Section	Number				
D	K	21	There is insufficient clinical outcome evidence to recommend ezetimibe monotherapy for reduction of CV risk.	I	Not reviewed, Deleted	
D	K	22	Ezetimibe can be considered for lowering LDL-C in patients who are unable to tolerate other lipid-lowering drugs, or in combination with other drugs.	A	Not reviewed, Deleted	
D	K	23	The dose of statin should be adjusted at 6 to 12 week intervals until individual LDL-C goals are achieved or statin doses have been maximized.	I	Not reviewed, Deleted	
D	K	24	Niacin, fibrates, or fish oil (omega-3 fatty acids) supplements may be used in treatment of isolated hypertriglyceridemia.	B	Not reviewed, Deleted	
D	K	25	For secondary prevention gemfibrozil or niacin may be used in patients with isolated low HDL-C and normal LDL-C. [A-Gemfibrozil; B-Niacin]	None	Not reviewed, Deleted	
D	L	1	Patients with, diabetes, should be screened periodically for the presence of kidney disease.	C	Not reviewed, Deleted	
D	L	2	Testing for kidney disease includes urinalysis and estimation of the glomerular filtration rate (eGFR).	B	Not reviewed, Deleted	
D	L	3	Patients with diabetes who have a negative urine protein by dipstick should be tested for the presence of microalbuminuria.	B	Not reviewed, Deleted	
D	L	4	Definitions of Chronic Kidney Disease includes any of the following: a). Persistent decreased eGFR <60 ml/min/1.73 m^2 on two tests at least three months apart b). Proteinuria (> 1+) on dipstick or urine protein-to-creatine ratio > 0.2, confirmed on two tests at least three months apart c). Microalbuminuria defined as albumin-to-creatine ratio > 30, confirmed on two out of three urine tests in patients with diabetes mellitus (DM) d). Known structural kidney disease defined by imaging or pathologic examination (e.g., polycystic kidney disease [PCKD]) e). Estimated glomerular filtration rate (eGFR) is the preferred method to assess kidney function.	None	Not reviewed, Deleted	

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Module	Section	Number				
D	L	5	The severity of CKD should be classified based on the level of the glomerular filtration rate (GFR) (see Table D-9). Kidney function should be assessed by formula-based estimation of GFR (eGFR), preferably using the 4-variable Modification of Diet in Renal Disease (MDRD) equation.	A	Not reviewed, Deleted	
D	L	6	Microalbuminuria – in patients with diabetes – should be assessed using a laboratory method expressed as an albumin-to-creatinine ratio. If dipsticks designed to detect urinary microalbumin are used, positive tests should be followed by laboratory confirmation.	None	Not reviewed, Deleted	
D	L	7	The diagnosis of microalbuminuria cannot be reliably made in the presence of an acute medical condition. As far as it is practicable, the best possible metabolic control of diabetes should be achieved before evaluating for microalbuminuria. Patients should not be screened during intercurrent illness or after heavy exercise.	None	Not reviewed, Deleted	
D	L	8	It is important to consider other causes of increased albumin excretion, especially in the case of Type 1 diabetes present for < 5 years. In addition to the previously mentioned conditions, other causes can include menstrual contamination, vaginal discharge, uncontrolled hypertension, and heart failure.	None	Not reviewed, Deleted	
D	L	9	A 24-hour urine collection for protein and creatinine is not needed for quantitation of proteinuria, as it is more cumbersome for patients and prone to collection errors.	None	Not reviewed, Deleted	
D	L	10	24-hour urine collection may be considered for: pregnant women, extreme age and weight, malnutrition, skeletal muscle disease, paraplegia or quadriplegia, patients with a vegetarian diet and rapidly changing kidney function.	None	Not reviewed, Deleted	
D	L	11	Serum creatinine level should be used to estimate the GFR to identify patients at risk and develop appropriate management plans.	None	Not reviewed, Deleted	
D	L	12	Patients with diabetes with urine albumin/creatinine levels of ≥30 µg/mg in the random specimen should repeat the test to ensure that the level was not transiently elevated (by heavy exercise, urinary tract infection, acute febrile illness, or heart failure).	None	Not reviewed, Deleted	

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Module	Section	Number				
D	L	13	If a second test is ≥30 µg/mg, the patient has persistent microalbuminuria; if the second test is <30µg/mg, repeat the test a third time.	None	Not reviewed, Deleted	
D	L	14	Persons with diabetes and macroalbuminuria (i.e., urine Alb/creatinine ratio ≥300 µg/mg or 24-hour urine protein ≥300 mg/dL) should be assessed for level of kidney function as these levels of albuminuria indicate established to advanced diabetic kidney disease: a). Document the course of the albuminuria. It would be unusual to go from having normal urine to macroalbuminuria in less than one year in diabetic kidney disease b). Document if the blood pressure has been rising. As diabetic kidney disease progresses from micro- to macroalbuminuria, the blood pressure usually rises c). Document the presence of other diabetic complications, such as retinopathy. All patients with diabetes with macroalbuminuria should undergo an eye exam to screen for retinopathy (findings include microaneurysm, flame hemorrhage, and soft/hard exudates) (see Module E, Eye Care) because >90 percent of patients with macroalbuminuria from diabetes will also have at least mild retinopathy d). If the course has been atypical (i.e., rapidly progressive or no evidence of retinopathy), refer or consult with nephrology for further work-up e). Consider alternative explanations for reduced kidney function including pre-renal, renal, and post-renal causes f). Consider obtaining other tests and referral to specialists in nephrology or urology as indicated.	None	Not reviewed, Deleted	
D	L	15	Nephrology consultation for help in diagnosis and treatment is indicated in: a). Patients with eGFR <30 ml/min/1.73 m^2) to facilitate education and planning for renal replacement therapy (dialysis or kidney transplant). b). Patients with kidney function that is deteriorating rapidly (e.g., eGFR decline of 50 percent eGFR from previous measure over 6 months or less). c). Patients with metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism). d). Patients with CKD of unclear etiology after the initial work up, or a known or suspected kidney condition requiring specialized care (e.g., a glomerulonephritis).	None	Not reviewed, Deleted	

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Module	Section	Number				
D	L	16	Treatment of high blood pressure in DM-CKD should include identification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease and development of cardiovascular disease.	None	Not reviewed, Deleted	
D	L	17	(In patients with DM-CKD) Antihypertensive therapy should be adjusted to achieve blood pressure of < 130/80 mm Hg.	C	Not reviewed, Deleted	
D	L	18	All patients with CKD with hypertension should be offered life-style advice, including maintenance of normal body weight (body mass index 18.5 to 24.9 kg/m2), reduction in dietary sodium intake (< 2 g/day), regular aerobic physical exercise, smoking cessation, and limitation of alcohol intake.	B	Not reviewed, Deleted	
D	L	19	There is insufficient evidence to recommend the routine implementation of a low protein diet (< 0.6g/kg/day) to slow the loss of GFR in patients with CKD.	D	Not reviewed, Deleted	
D	L	20	(In patient with DM-CKD) A low protein diet may delay the onset of uremic symptoms in patients close to needing dialysis but this benefit must be weighed against the risk of protein malnutrition.	B	Not reviewed, Deleted	
D	L	21	ACEIs or ARBs are the preferred agent for patients with kidney disease and hypertension. ACEIs may be preferred based on cost. ARBs may be substituted for patients with an ACEI induced cough.	A	Not reviewed, Deleted	
D	L	22	Many patients (with DM-CKD) will require two or more medications to achieve their target blood pressure control. A diuretic should be used when a second blood pressure medication is needed, or if hyperkalemia occurs. Thiazide diuretics may be used if estimated GFR >30 ml/min/1.73 m^2, but loop diuretics are usually needed for patients with lower eGFR. Potassium-sparing diuretics should be used with caution in patients with CKD.	None	Not reviewed, Deleted	
D	L	23	An increase of serum creatinine, as much as 30 percent above baseline, after ACEI or ARB initiation is common. ACEIs or ARBs should not be discontinued for this situation, since these medications are renoprotective.	None	Not reviewed, Deleted	

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Module	Section	Number				
D	L	24	Patients with refractory hypertension, defined as inability to achieve goal blood pressure despite combination therapy with three drugs from complementary classes (including a diuretic), may benefit from an evaluation by a specialist in hypertension.	None	Not reviewed, Deleted	
D	L	25	Patients with non-DM CKD with hypertension or diabetes with macroalbuminuria should be treated with an ACEI or ARB to slow the progression of kidney disease [A] and reduce proteinuria.	A	Not reviewed, Deleted	
D	L	26	Patients with diabetes and microalbuminuria should be treated with an ACEI or ARB to slow the progression from microalbuminuria to macroalbuminuria, considered a surrogate for progression to CKD.	A	Not reviewed, Deleted	
D	L	27	(In patient with DM-CKD) ACEIs and ARBs should be initiated at low doses and titrated to moderate to high doses as used in clinical trials.	A	Not reviewed, Deleted	
D	L	28	There is insufficient evidence to recommend combination therapy with an ACEI and ARB to slow the progression of kidney disease except in a limited population of non-DM CKD.	I	Not reviewed, Deleted	
D	L	29	(In patient with DM-CKD) Creatinine and potassium levels should be monitored one to two weeks after initiation or after a change in dose of ACEI or ARB therapy and periodically to maintain a normal range.	C	Not reviewed, Deleted	
D	L	30	Treatment with an ACEI or ARB should not be initiated in patients with hyperkalemia (> 5.5).	D	Not reviewed, Deleted	
D	L	31	(In patients with DM-CKD) People who develop cough on an ACEI should be switched to an ARB. Some people who develop angioedema on an ACEI may be switched to an ARB but require careful monitoring since some may also develop angioedema on an ARB.	C	Not reviewed, Deleted	
D	L	32	In most patients (with DM-CKD), an ACEI or ARB should be continued unless: a). There is an acute GFR decline of > 30 percent within the first two weeks after initiation. b). Serum potassium is ≥ 6 mEq/L, despite appropriate treatment.	B	Not reviewed, Deleted	

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Module	Section	Number				
D	L	33	Patients with CKD should be monitored for complication of CKD: disorders of potassium balance, calcium and phosphate metabolism, acid base abnormalities, hematologic abnormalities, volume overload, and exposure to nephrotoxic drugs.	None	Not reviewed, Deleted	
D	L	34	Patients (with DM-CKD) may benefit from a dietary evaluation by a medical nutrition therapist and should be advised about a healthy diet and the preferred range of sodium, phosphate, and potassium in their diet.	C	Not reviewed, Deleted	
D	L	35	Patients with CKD and an eGFR >30 ml/min/1.73 m^2 with no associated co-morbidities should be followed up every 6 to 12 months.	None	Not reviewed, Deleted	
D	L	36	Patients with more advanced CKD should be referred to a nephrologist for consultation and/or continued follow-up.	None	Not reviewed, Deleted	
S	A	1	Screening for pre-diabetes or diabetes should be considered for all adults age ≥45.	B	Not reviewed, Deleted	
S	A	2	Screening for pre-diabetes or diabetes should be considered in younger adults who are overweight or obese (BMI ≥ 25 kg/m2) or are at high risk for DM based upon established risk factors (see Table S-1) at 1-3 year intervals.	B	Not reviewed, Deleted	
S	A	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 HbA1c or FPG results, and patient or clinician preferences.	I	Not reviewed, Deleted	
S	A	4	Fasting plasma glucose (FPG) is the preferred diagnostic test for pre-diabetes and DM and is also a component of diagnostic testing.	None	Not reviewed, Deleted	
S	A	5	HbA1c 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).	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
S	A	6	A diagnosis of DM is made if any of the following: a). Fasting plasma glucose (FPG) is ≥126 mg/dL on at least two occasions, or b). A single HbA1c reading of ≥ 6.5%, confirmed with a FPG ≥126 mg/dL. These tests can be done on the same or different days; or c). HbA1c 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.	B	Not reviewed, Deleted	
S	A	7	A diagnosis of pre-diabetes is made if any of the following: a). Fasting plasma glucose (FPG) readings with result < 126 mg/dL, but ≥100mg/dL on two occasions b). HbA1c 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 HbA1c.	B	Not reviewed, Deleted	
S	A	8	Although the oral glucose tolerance test can also be used for the diagnosis of diabetes, it's is not recommended in the primary care setting.	C	Not reviewed, Deleted	
S	A	9	Random plasma glucose is not recommended as a routine screening test.	C	Not reviewed, Deleted	
S	B	1	Patients with pre-diabetes should be counseled about the risks of progression to diabetes and the rationale for implementing preventive strategies. [A] Individuals with risk factors for diabetes who are not diagnosed with pre-diabetes should also be counseled and educated about how to reduce risks.	A	Not reviewed, Deleted	
S	B	2	Lifestyle modifications to prevent diabetes, including regular aerobic exercise and a calorie-restricted diet to promote and maintain weight loss, should be instituted in patients with pre-diabetes.	A	Not reviewed, Deleted	
S	B	3	An individualized goal to achieve and sustain weight loss of ≥ 5 percent of body weight should be set for patients with risk factor for diabetes and a BMI ≥ 25.	A	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
S	B	4	When lifestyle modifications have been ineffective at preventing a sustained rise in glucose, the patient may be offered pharmacologic therapy with a metformin or an alpha-glucosidase inhibitor (e.g., acarbose) to delay progression from pre-diabetes to a diagnosis of diabetes.	A	Not reviewed, Deleted	
G	B	1	HbA1c 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.	None	Not reviewed, Deleted	
G	B	2	Self Monitoring of Blood Glucose (SMBG) may be used to monitor glycemic control and adjust treatment.	B	Not reviewed, Deleted	
G	B	3	Patients, for whom SMBG is appropriate, should receive instruction on the proper procedure, the importance of documenting results, and basic interpretation and application of results to maximize glycemic control.	None	Not reviewed, Deleted	
G	B	4	SMBG results should be discussed with the patient to promote understanding, adjust treatment regimens, and facilitate treatment adherence.	B	Not reviewed, Deleted	
G	B	5	Remote electronic transmission of SMBG data should be considered as a tool to assess glycemic patterns.	C	Reviewed, New-replaced	Recommendation 3
G	B	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	Not reviewed, Deleted	
G	B	7	A combination of pre-and postprandial tests may be performed, up to 4 times per day.	C	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	B	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: a). Initiation of therapy and/or active adjustment of oral agents b). Acute or ongoing illness c). Detection and prevention of hypoglycemia when symptoms are suggestive of such, or if there is documented hypoglycemia unawareness d). Detection of hyperglycemia when fasting and/or post-prandial blood glucose (PPG) levels are not consistent with HbA1c.	None	Not reviewed, Deleted	
G	C	1	Treat diabetes more aggressively early in its course.	B	Not reviewed, Deleted	
G	C	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	Reviewed, Amended	Recommendation 5
G	C	3	Providers should recognize the limitations of the HbA1c measurement methodology reconciling the differences between HbA1c readings and self-monitoring results on a case-by-case basis.	None	Reviewed, Deleted	
G	C	4a	Setting the initial target range should consider the following: (see Table G-1) 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 HbA1c target of <7 percent, if it can be achieved without risk.	A	Reviewed, New-replaced Reviewed, New-replaced	Recommendation 7 Recommendation 8
G	C	4b	Setting the initial target range should consider the following: (see Table G-1) Any patient with diabetes should have a HbA1c target of <9 percent to reduce symptoms of hyperglycemia.	C	Not reviewed, Deleted	
G	C	4c	Setting the initial target range should consider the following: (see Table G-1) The patient with longer duration diabetes (more than10 years) or with comorbid conditions, and who require combination medication regimen including insulin, should have an HbA1c target of < 8 percent.	A	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	C	4d	Setting the initial target range should consider the following: (see Table G-1) 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 HbA1c target of 8-9 percent.	A	Reviewed, New-replaced	Recommendation 10
G	C	4e	Setting the initial target range should consider the following: (see Table G-1) Risk of hypoglycemia should be considered in recommending a target goal.	B	Not reviewed, Deleted	
G	D	1	Risks of a proposed therapy should be balanced against the potential benefits, based upon the patient's medical, social, and psychological status.	None	Not reviewed, Deleted	
G	E	1	The patient and provider should agree on a specific target range of glycemic control after discussing the risks and benefits of therapy.	None	Not reviewed, Deleted	
G	E	2	The patient should be assessed for knowledge, performance skills, and barriers (e.g., psychosocial, personal, or financial), and if necessary referred to a primary care case manager or endocrine/diabetes clinic to address barriers for achieving treatment goals.	None	Reviewed, New-replaced	Recommendation 3

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	F	1	The indications to consider a consultation or referral to specialty include patients who: a). Have type 1 DM; especially patients with history of hospitalizations for metabolic complications and/or patients who are receiving intensive insulin therapy b). Have new-onset insulin-requiring DM c). Have marked insulin resistance d). Have contraindications or intolerances to medications typically used in managing diabetes e). Have recurrent episodes of incapacitating hypo- and/or hyperglycemia f). Have poor recognition of hypoglycemia and who have a history of severe hypoglycemic reactions (including coma, seizures, or frequent need for emergency resuscitation) g). Have visual and/or renal impairment h). Have psychosocial problems (including alcohol or substance abuse) that complicate management i). Have HbA1c > 9.0 percent and are considered for aggressive management on an expedited basis j). Are not achieving glycemic control despite comprehensive treatment with complex regimen of combination pharmacotherapy including insulin k). Require evaluation or management beyond the level of expertise and resource level of the primary team	None	Not reviewed, Deleted	
G	G	1	The patient with type 1 diabetes mellitus (DM) must receive insulin replacement therapy.	None	Not reviewed, Deleted	
G	G	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.	None	Not reviewed, Deleted	
G	H	1	All patients with type 1 DM should be managed by a provider experienced in managing type 1 DM in a multidisciplinary approach or by a clinic team with multidisciplinary resources (e.g., diabetologist, diabetes nurse, educator/manager, and registered dietitian) for institution and adjustment of insulin therapy.	None	Not reviewed, Deleted	
G	H	2	When expeditious referral is not possible, the primary care provider should institute “survival” insulin therapy comprised of total daily insulin (TDI) 0.5 units/kg/day; half as basal insulin and half as meal time insulin.	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	I	1	Patients with diabetes should be regularly assessed for knowledge, performance skills, and barriers to self-management.	None	Reviewed, New-replaced	Recommendation 3
G	I	2	Patients with recurrent or severe hypoglycemia should be evaluated for precipitating factors that may be easily corrected (e.g., missed meals, incorrect administration of insulin [dosage or timing], and exercise).	None	Not reviewed, Deleted	
G	I	3	If psychosocial, personal, or financial barriers are identified, additional resources should be consulted, as applicable (e.g., mental health, medical social work, or financial counselors).	None	Reviewed, New-replaced	Recommendation 3
G	J	1	Individual treatment goals must be established with the patient based on the extent of the disease, comorbid conditions, and patient preferences.	None	Not reviewed, Deleted	
G	J	2	Institution of dietary modification and exercise alone is usually the appropriate initial management in patients with new onset type 2 diabetes, depending upon severity of symptoms, psychosocial evaluation, patient motivation, and overall health status. Encourage diet and exercise and lifestyle modifications.	None	Not reviewed, Deleted	
G	J	3	Use various approaches (e.g., individual or group, counseling, coaching, motivational interviewing) to promote healthful behaviors, such as healthful diet, adequate physical activity, and smoking cessation.	None	Not reviewed, Deleted	
G	J	4	If treatment goals are not achieved with diet and exercise alone, drug therapy should be initiated while encouraging lifestyle modifications.	None	Not reviewed, Amended	
G	J-1	1	(Monotherapy/ Initial therapy) 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	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	J-1	2	(Monotherapy/ Initial therapy) 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	Not reviewed, Deleted	
G	J-1	3	(Monotherapy/ Initial therapy) Metformin (preferred) or sulfonylureas (SU) should be given as first line agents unless there are contraindications.	A	Not reviewed, Deleted	
G	J-1	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	Not reviewed, Deleted	
G	J-1	5	Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management.	I	Reviewed, New-replaced	Recommendation 2
G	J-2	1	(Combination therapy/ Add-on) Metformin + sulfonylurea is the preferred oral combination for patients who no longer have adequate glycemic control on monotherapy with either drug.	A	Not reviewed, Deleted	
G	J-2	2	(Combination therapy/ Add-on) 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	Not reviewed, Deleted	
G	J-2	3	(Combination therapy/ Add-on) Addition of bedtime NPH or daily long-acting insulin analog to metformin or sulfonylurea should be considered, particularly if the desired decrease in HbA1c is not likely to be achieved by use of combination oral therapy.	A	Not reviewed, Deleted	
G	J-2	4	Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management.	I	Reviewed, New-replaced	Recommendation 2
G	J-3	1	Use of insulin therapy should be individualized, and managed by a healthcare team experienced in managing complex insulin therapy for patients with type 1 DM	I	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	J-3	2	Use intermediate- or long-acting insulin to provide basal insulin coverage.	B	Not reviewed, Deleted	
G	J-3	3	Insulin glargine or detemir may be considered in the NPH insulin-treated patient with frequent or severe nocturnal hypoglycemia.	B	Not reviewed, Deleted	
G	J-3	4	Use regular insulin or short-acting insulin analogues for patients who require mealtime coverage.	None	Not reviewed, Deleted	
G	J-3	5	Alternatives to regular insulin (aspart, lispro, or glulisine) should be considered in the following settings: a). Demonstrated requirement for pre-meal insulin coverage due to postprandial hyperglycemia AND concurrent frequent hypoglycemia b). Patients using insulin pump	B	Not reviewed, Deleted	
G	J-4	1	Continuous subcutaneous insulin infusion (CSII) therapy should only be initiated and managed by an endocrinologist/diabetes team with expertise in insulin pump therapy	None	Not reviewed, Deleted	
G	J-4	2	Continuous subcutaneous insulin infusion (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.	None	Not reviewed, Deleted	
G	J-4	2a	Continuous subcutaneous insulin infusion (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 poor glycemic control (including wide glucose excursions with hyperglycemia and serious hypoglycemia and those not meeting HbA1c goal) despite an optimized regimen using MDI in conjunction with lifestyle modification.	A	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	J-4	2b	Continuous subcutaneous insulin infusion (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 marked dawn phenomenon (fasting AM hyperglycemia) not controlled using NPH at bedtime, glargine or detemir.	B	Not reviewed, Deleted	
G	J-4	2c	Continuous subcutaneous insulin infusion (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 recurrent nocturnal hypoglycemia despite optimized regimen using glargine or detemir.	B	Not reviewed, Deleted	
G	J-4	2d	Continuous subcutaneous insulin infusion (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 circumstances of employment or physical activity, for example shift work, in which multiple daily injections (MDI) regimens have been unable to maintain glycemic control.	I	Not reviewed, Deleted	
G	J-4	3	Patients using continuous subcutaneous insulin infusion (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.	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	J-4	4	The use of continuous subcutaneous insulin infusion (CSII) over multiple daily injections (MDI) regimens is not recommended in most patients with type 2 diabetes.	D	Not reviewed, Deleted	
G	J-5	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	Not reviewed, Deleted	
G	J-5	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	Reviewed, Deleted	
G	J-5	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	Not reviewed, Deleted	
G	J-5	4	For patients with DM and/or hyperglycemia who are not medically stable or who are poorly controlled with oral anti-hyperglycemic medications at home, initiating insulin therapy should be considered. It is appropriate to continue pre-hospitalization insulin regimens, but reasonable to reduce the dose in order to minimize the risk of hypoglycemia. In the ICU, continuous intravenous insulin infusion is recommended. Scheduled subcutaneous insulin is appropriate in the non-ICU setting and may include a long-acting basal insulin as well as a nutritional insulin for those eating discrete meals or receiving enteral nutrition. A supplementary correction (sliding) scale is also recommended but correction scale insulin regimens as sole therapy are discouraged.	B	Reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	J-5	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	Reviewed, Amended	Recommendation 15 Recommendation 16
G	J-5	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	Not reviewed, Amended	
G	J-5	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	Reviewed, Amended	Recommendation 19
G	J-5	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	Not reviewed, Deleted	
G	K	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).	None	Not reviewed, Deleted	
G	L	1	If the patient does not achieve his/her target range, the provider should identify barriers to patient adherence to the treatment regimen (e.g., miscommunication, lack of education or understanding, financial/social/psychological barriers, and cultural beliefs).	None	Not reviewed, Deleted	
G	L	2	If barriers are identified, referral to a case manager or behavioral/financial counselor may be considered as appropriate.	None	Not reviewed, Deleted	
G	M	1	Treatment goals should be periodically reassessed based upon patient specific factors, including changes in the patient's health status, adverse drug reactions, adherence to therapy, and preferences.	None	Reviewed, Amended	Recommendation 5

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
G	N	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: a). The frequency of follow-up visits for the patient with diabetes who is meeting treatment goals and who has no unstable chronic complications should be individualized b). 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.	None	Not reviewed, Deleted	
G	N	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.	None	Reviewed, Amended	Recommendation 5
E	A	1	Patients with an acute change in vision or a change in ocular function should be urgently referred to an eye care provider.	None	Not reviewed, Deleted	
E	B	1	Patients with either early diabetes onset (age <30 years) or type 1 diabetes at a later age should have an initial examination when the time from diabetes diagnosis is >3 years.	B	Not reviewed, Deleted	
E	C	1	Patients who are newly diagnosed with type 2 DM and have not had an eye exam within the past 12 months should have a retinal examination performed within 6 months	B	Not reviewed, Deleted	
E	C	2	A retinal examination (e.g. dilated fundus examination by an eye care professional or retinal imaging with interpretation by a qualified, experienced reader) should be used to detect retinopathy.	A	Not reviewed, Amended	Recommendation 22
E	D	1	Patients who have had no retinopathy on all previous examinations should be screened for retinopathy at least every other year (biennial screening). More frequent retinal examinations in such patients should be considered when risk factors associated with an increased rate of progression of retinopathy are present.	B	Not reviewed, Amended	Recommendation 23
E	D	2	Patients with existing retinopathy should be managed in conjunction with an eye care professional and examined at intervals deemed appropriate for the level of retinopathy.	I	Not reviewed, Amended	Recommendation 23

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
F	A	1	The patient's feet should be visually inspected for: a). Breaks in the skin b). Erythema c). Trauma d). Pallor on elevation e). Dependent rubor f). Changes in the size or shape of the foot g). Nail deformities h). Extensive callus i). Tinea pedis j). Pitting edema	I	Not reviewed, Deleted	
F	B	1	A foot risk assessment must be performed and documented at least once a year. A complete foot risk assessment includes: a). Evaluation of the skin for breakdown b). Assessment of protective sensation using the Semmes-Weinstein 5.07 monofilament c). Evaluation for LE arterial disease d). Evaluation for foot deformity e). Prior history of ulcers or amputations. In addition, the patient's footwear should be evaluated.	None	Not reviewed, Deleted	
F	C	1	Evaluation should be performed for limb-threatening conditions, such as systemic infection, acute ischemia/rest pain, foot ulceration, puncture wound, ingrown toenail, and hemorrhagic callus with or without cellulitis.	None	Not reviewed, Deleted	
F	D	1	Patients with limb-threatening conditions should be referred to the appropriate level of care for evaluation and treatment.	None	Not reviewed, Amended	Recommendation 21
F	D	2	If the patient's symptoms limit his/her lifestyle, a vascular specialist should determine the appropriateness of surgical intervention on a patient-specific basis. Justification of vascular procedures should be based on the outcomes of the vascular interventions.	None	Not reviewed, Deleted	
F	E	1	Patients without limb-threatening conditions should be evaluated for their level of risk for LE foot ulcers and amputations.	None	Not reviewed, Deleted	
F	E	2	The existence of one of the following characteristics is sufficient to define the patient as high-risk for foot problem a). Lack of sensation to Semmes-Weinstein 5.07 monofilament at one or more noncallused plantar sites b). 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) c). Foot deformities (specifically hammer toes, claw toe, Charcot's arthropathy, bunions, and metatarsal head deformities) d). History of foot ulcer or non-traumatic LEA at any level.	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
F	E	3	The patient at high-risk should be referred to a foot care specialist for a more comprehensive evaluation and intensive treatment plan including patient education concerning foot care practices, hygiene, and footwear.	None	Not reviewed, Deleted	
F	F	1	Minor lesions or wounds that could possibly be treated by the primary care provider are blisters, erosions, and/or minor cuts that do not extend beyond subcutaneous tissue. Pulses are present, there are no signs of acute infection, and there is no severe lower limb pain and no sign of a worsening lesion.	None	Not reviewed, Deleted	
F	F	2	Patients with an ingrown toenail should be referred to a foot specialist for evaluation and treatment (see Annotation C, Ingrown Toenail).	None	Not reviewed, Deleted	
F	G	1	High-risk patients with a minor foot wound or lesion should be promptly referred to a foot care specialist (i.e., podiatrist, vascular surgeon, orthopedic surgeon, and other healthcare providers with demonstrated training, competence, and licensure in foot care) for evaluation and treatment.	None	Not reviewed, Deleted	
F	G	2	Footwear prescriptions should be based upon individual characteristics of foot structure and function.	None	Not reviewed, Deleted	
F	H	1	All patients and their families should receive self-management education for preventive foot care and selection of footwear. Instruction should include recommendations for daily foot inspection and preventive foot care, skin care, and use of emollients, nail care, and treatment for callus.	None	Not reviewed, Deleted	
F	I	1	Visual inspection and peripheral sensation testing in high-risk patient should be performed at each routine primary care visit for all patients (see Annotation A).	None	Not reviewed, Deleted	
F	J	1	Patients with diabetes with minor wounds or foot lesions should have a wound assessment.	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
F	J	2	The wound assessment includes: a). A review of anatomic, physical, and lesion characteristics including determination of circumference, depth, and involvement of deep structures b). Assessment for signs of infection including necrosis, sinus tracts, exudate, odor, presence of fibrin, and healthy granulation tissue c). Assessment of surrounding areas for signs of edema, cellulitis, or abscess.	None	Not reviewed, Deleted	
F	K	1	Patients with diabetes with uncomplicated minor lesions should receive local wound care. Primary care providers should attempt to offload weight-bearing on the affected extremity.	None	Not reviewed, Deleted	
F	K	2	Patients with diabetes with uncomplicated minor lesions must be followed at least monthly.	None	Not reviewed, Deleted	
F	L	1	Patients with diabetes treated for an uncomplicated wound should be assessed within four weeks from the initial wound assessment for appropriate reduction in lesion size and depth and appearance of healthy granulating tissue with no evidence of infection.	None	Not reviewed, Deleted	
F	M	1	Minor foot problems (e.g., onychomycosis, painful corn, dry skin, athlete's foot, minor calluses, uncomplicated nail trimming and improper foot hygiene) may be treated by a primary care provider in the office, or by the patient or family members at home (see Annotation F).	None	Not reviewed, Deleted	
F	N	1	Assure that patient and family members have received appropriate education regarding preventive foot care.	None	Not reviewed, Deleted	
F	N	2	Treat minor foot problems, as appropriate.	None	Not reviewed, Deleted	
M	B	1	Ensure that patients newly diagnosed with DM are provided with core competency education. The core competencies include: a). Acute complications (hyperglycemia and hypoglycemia) b). Medication education c). Self-monitoring of blood glucose and how to use the results d). Basic diet principles e). Sick day management f). When to seek further assistance (See Appendix M-1: Core Competencies [Survival Skills] for Patients with Diabetes).	None	Not reviewed, Deleted	
M	C	1	Patients newly diagnosed with diabetes should receive comprehensive DSME and education for MNT.	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
M	C	2	DSME, including MNT education, should be an interactive, collaborative, ongoing process involving patients with diabetes and educators and include the following four-step process: a). Assessment of the patient's educational needs b). Identification of the patient's specific self-management goals c). Education and behavioral interventions aimed at meeting the patient's goals d). Evaluation of the patient's progress towards the goals	None	Not reviewed, Deleted	
M	C	3	The education component should be tailored to the patient's needs and provided by healthcare professionals who are most knowledgeable in the topic. Regardless of setting, availability of a multidisciplinary team approach is highly desirable and could include, but is not limited to, a dietitian, certified diabetes educator, registered nurse, pharmacist, psychologist, exercise physiologist, physical therapist, social worker, endocrinologist, behaviorist, ophthalmologist, optometrist, physician, podiatrist, other healthcare professionals and paraprofessionals, or other specialized physicians based on the individual patient's needs.	None	Not reviewed, Deleted	
M	C	4	The use of approaches such as group visits and telehealth should be considered in providing education.	None	Reviewed, New-replaced	Recommendation 3
M	D	1	Assessment of the following factors should be completed to determine the extent of the patient's educational and skills deficit and his/her ability for self-management: knowledge of the diabetes disease process, treatment goals, management skills, cultural influences, health beliefs/behavior, attitudes, socioeconomic factors and barriers.	None	Not reviewed, Deleted	
M	D	2	Documentation of the patient's learning needs, abilities including physical and cognitive limitations, or language barriers, preferences, cultural and religious practices, emotional barriers, health literacy and numeracy, desire and motivation to learn and/or change, and the financial implications of care choices.	None	Not reviewed, Deleted	
M	D	3	Assessment and documentation of the patient's understanding of education.	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
M	E	1	Conditions that may warrant risk-focused intervention include: a). Markedly or persistently elevated HbA1c (For appropriate HbA1c target based on risk stratification, see Module G: Table G-1) b). Progression to ESRD (e.g., stage 3-5 CKD) c). Lower extremity complications d). Pregnancy, or planned pregnancy, or woman of child bearing age e). Impaired vision f). Severe psychosocial or economic barriers g). Cognitive impairment or frailty h). Intensive insulin therapy i). Recurrent hypoglycemia or hypoglycemia unawareness j). Recent hospitalization for diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state disease complexity	None	Not reviewed, Deleted	
M	F	1	Patients at high-risk may have needs beyond educational deficits and should be referred for focused attention by other services. Possible referrals could include, but are not limited to: case manager, registered nurse, registered dietitian, pharmacist, psychologist, exercise physiologist, physical therapist, social worker, endocrinologist, ophthalmologist, optometrist, physician, podiatrist, behaviorist, other healthcare professionals, or paraprofessionals.	None	Not reviewed, Deleted	
M	F	2	Refer to case manager for providing ongoing, detailed coordination of care for high-risk patients.	None	Not reviewed, Deleted	
M	G	1	When knowledge deficits continue to exist or a large number of lifestyle changes are necessary, frequent follow-up may be indicated.	None	Not reviewed, Deleted	
M	G	2	Recently learned diabetes skills or information should be re-evaluated no longer than 3 months after initial instruction. One possible method involves follow-up at earlier time points, e.g., 1 month.	None	Not reviewed, Deleted	
M	G	3	When appropriate, single behavioral goals should be identified and prioritized to increase the likelihood of the patient adopting lifestyle changes necessary to achieve treatment goals.	None	Not reviewed, Deleted	
M	J	1	Diabetes education is effective for improving clinical outcomes and quality of life, at least in the short-term.	None	Not reviewed, Deleted	
M	J	2	DSME has evolved from primarily didactic presentations to more theoretically based empowerment models.	None	Not reviewed, Deleted	

2010 Recommendation Location[1]			2010 Recommendation Text[2]	2010 Grade[3]	Category[4]	2017 Recommendation (if applicable)[5]
Module	Section	Number				
M	J	3	There is no one "best" education program or approach; however, programs incorporating behavioral and psychosocial strategies demonstrate improved outcomes. Additional studies show that culturally and age appropriate programs improve outcomes and that group education is effective.	None	Reviewed, New-replaced	Recommendation 2
M	J	4	Ongoing support is critical to sustain progress made by participants during the DSME program.	None	Not reviewed, Deleted	
M	J	5	Behavioral goal-setting is an effective strategy to support self-management behaviors.	None	Not reviewed, Deleted	

Appendix G: Participant List

Department of Defense	
Maj Jeffrey A. Colburn, MD, FACP (Champion) Staff Endocrinologist Diabetes Champion San Antonio Military Medical Center Fort Sam Houston, TX	Elizabeth (Liz) Rees Atayde, RN, MSN, FNP, CCM, CPHM Nursing, Medical Management Nurse Case Manager/ CPG Consultant US Army Medical Command Fort Sam Houston, TX
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Sharon A. Watts, DNP, FNP-BC, CDE ONS Clinical Nurse Advisor Chair, Office of Nursing Services and Diabetes Field Advisory Committee Veterans Hospital of Cleveland Cleveland, OH	

Appendix H: Literature Review Search Terms and Strategy

A. Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table H-1. Embase

Set #	Concept	Strategy
Type 2 Diabetes Mellitus		
1	T2DM – core set	'non insulin dependent diabetes mellitus'/exp OR 'adult onset diabetes' OR 'adult onset diabetes mellitus' OR 'diabetes mellitus type 2' OR 'diabetes mellitus type ii' OR 'diabetes mellitus, maturity onset' OR 'diabetes mellitus, non insulin dependent' OR 'diabetes mellitus, non-insulin-dependent' OR 'diabetes mellitus, type 2' OR 'diabetes mellitus, type ii' OR 'diabetes type 2' OR 'diabetes type ii' OR 'diabetes, adult onset' OR 'dm 2' OR 'insulin independent diabetes' OR 'insulin independent diabetes mellitus' OR 'ketosis resistant diabetes mellitus' OR 'maturity onset diabetes' OR 'maturity onset diabetes mellitus' OR 'maturity onset diabetes of the young' OR 'niddm' OR 'non insulin dependent diabetes' OR 'non insulin dependent diabetes mellitus' OR 'noninsulin dependent diabetes' OR 'noninsulin dependent diabetes mellitus' OR 'type 2 diabetes' OR 'type 2 diabetes mellitus' OR 'type ii diabetes' OR 'T2DM'
2		#1 AND [humans]/lim AND [English]/lim
3		#2 AND ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
4		#2 NOT #3
5		#4 AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [2009-2016]/py
Intensive Glycemic Control		
6	Intensive glycemic control	(('ACCORD' NEAR/2 (study OR trial)) OR 'Action to control cardiovascular risk in diabetes trial')
7		(('ADVANCE' NEAR/2 (study OR trial)) OR 'Action in diabetes and vascular disease')
8		(('VADT' NEAR/2 (study OR trial)) OR 'Veterans affairs diabetes trial')
9		#6 OR #7 OR #8
10		(intensive OR tight) NEAR/2 ('glycemic control' OR 'glycaemic control')
11		'intensive glucose lowering'
12		#9 OR #10 OR #11
13		#5 AND #12
14	Embase study type filters	('clinical article'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'dosage schedule comparison'/de OR 'drug dose comparison'/de OR 'evidence based medicine'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'multicenter study'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 3 clinical trial (topic)'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de OR 'systematic review (topic)'/de)

Set #	Concept	Strategy
15	ECRI broad trial filter	'randomized controlled trial'/exp OR 'randomization'/de OR 'double blind procedure'/de OR 'single blind procedure'/de OR 'placebo'/de OR 'latin square design'/de OR 'crossover procedure'/de OR 'triple blind procedure'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR blind OR sham)) OR 'latin square' OR isrctn* OR actrn* OR (nct* NOT nct)
16	ECRI broad meta-analysis filter	'meta-analysis/de OR 'research synthesis' OR pooled OR 'meta-analysis' OR 'meta-analytic'
17	ECRI systematic review filter	'systematic review'/de OR 'systematic review' OR search*:ab
18	Combine sets	#13 AND (#14 OR #15 OR #16 OR #17)
Shared Decision-making		
19	Decision making	'patient decision making'/de OR 'patient decision making' OR 'clinical decision making'/de OR 'clinical decision making' OR 'clinical decision-making' OR 'decision making'/de OR 'choice behavior' OR 'choice behaviour' OR 'decision making' OR 'decision making task' OR 'decision process'
20		shared
21		'patient-centered' OR patient* NEAR/2 (preference* OR priorit*) OR patient* NEAR/5 (shared OR sharing OR centered OR trust)
22		'diabetic patient'/de
23		Goal NEAR/2 set*
24	Combine sets	#5 AND #19 AND (#20 OR #21)
25		#21 AND #22
26		#23 AND (#5 OR #22)
27		#24 OR #25 OR #26
28	Limit to diabetes as a major concept	#27 AND ('non insulin dependent diabetes mellitus'/exp/mj OR diabet*:ti)
29		SDM AND ('non insulin dependent diabetes mellitus'/exp/mj OR diabet*:ti)
30		#28 OR #29

Set #	Concept	Strategy
Telehealth		
31	Telehealth	'telehealth'/exp
32		telehealth* OR telecare* OR telediagnos* OR telemonitor* OR telemanag* OR teleconsult* OR teledermatol* OR telehomecare* OR telematics OR telepathol* OR telepharm* OR telenurs* OR telepsychiatr* OR telestroke OR telesupport
33		(tele OR remote) NEAR/2 (health OR care* OR diagnos* OR monitor* OR manag* OR consult* OR home* OR nurs* OR dermatol* OR pathol* OR pharmac* OR nurs* OR psychiatr* OR stroke OR support)
34		'connected care' OR 'ehealth' OR 'e-health' OR 'e-connected' OR 'etherapy' OR 'e-therapy' OR 'mhealth' OR 'm-health' OR 'wired for health' OR 'virtual care' OR 'computer mediated therapy' OR 'econsult' OR 'e-icu' OR 'patient portal' OR video NEAR/2 (visit* OR consult*)
35		'health care'/exp/mj AND ('mass communication'/de OR 'e-mail'/de OR 'interactive voice response system'/de OR 'internet'/de OR 'mass medium'/de OR 'mobile phone'/de OR 'social media'/de OR 'telephone'/de OR 'text messaging'/de OR 'videoconferencing'/de OR 'wireless communication'/de OR 'online system'/de)
36		'health care'/exp/mj AND (internet*:ti OR computer*:ti OR web*:ti OR interactive*:ti OR telecommunication*:ti OR telephone*:ti OR phone*:ti OR sms:ti OR video*:ti OR email:ti OR 'e-mail':ti OR wireless:ti OR bluetooth:ti)
37		#31 OR #32 OR #33 OR #34 OR #35 OR #36
38	Combine sets	#5 AND #37
39		#38 AND #15 *[ECRI RCT filter]*
40		#38 AND #14 *[Embase study filter]*
41		#39 OR #40
Medical Nutrition Therapy		
42	MNT	#5 AND 'nutrition'/exp
43		#42 AND ('disease management'/lnk OR 'therapy'/lnk OR 'treatment outcome'/exp)
44		#5 AND 'diabetic diet
45		#5 AND 'diet therapy'/exp/mj
46		#5 AND ('MNT' OR 'medical nutrition therapy' OR 'medical nutrition therapies')
47		#5 AND ('MeDiet' OR (Mediterranean* NEAR/2 diet*) OR 'mediterranean diet'/de)
48		#5 AND (diet NEAR/2 ('low carbohydrate' OR 'low energy' OR 'low fat' OR 'low glycemic index' OR 'low glycaemic index' OR 'carbohydrate counting' OR 'carb counting' OR ada OR vegan OR nordic)):ti
49		#43 OR #44 OR #45 OR #46 OR #47 OR #48
50	Limit by study types	#49 AND ('randomized':ti OR 'randomised':ti OR 'randomized controlled trial'/de)
51		#49 AND ('systematic review'/de OR "systematic review" OR 'meta analysis'/de OR (meta* NEAR/2 (analysis OR analyses OR analytic)))
52		#50 OR #51
53	Limit to treatment of diabetes using subheading	#52 AND 'diabetes mellitus'/exp/dm_th

Set #	Concept	Strategy
54	Limit to nutrition as a major concept	#52 AND 'nutrition'/exp/mj
55	Combine sets	#53 OR #54
56	Eliminate phrase	Diet NEAR/2 'inadequately controlled'
57		#55 NOT #56
Self-management Education		
58	Patient education	'patient education'/de OR 'education, patient' OR 'patient education' OR 'patient education as topic' OR 'patient medication knowledge'
59		'education'/de OR 'diabetes education'/de OR 'health education'/de OR 'health promotion'/de
60		'teaching'/exp OR 'computer-assisted instruction' OR 'patient simulation' OR 'programmed instruction' OR 'programmed instruction as topic' OR 'programmed teaching' OR 'remedial school' OR 'remedial teaching' OR 'school, remedial' OR 'student teaching' OR 'teaching' OR 'teaching aid' OR 'teaching material' OR 'teaching materials' OR 'teaching method' OR 'teaching program' OR 'teaching programme' OR 'teaching, programmed' OR 'teaching, remedial'
61		(patient* OR adult* OR client* OR participant* OR individual* OR diabetes) NEAR/3 (train* OR educat* OR teach* OR instruct* OR inform* OR counsel* OR empower*)
62		#58 OR #59 OR #60 OR #61
63	Combine sets	#5 AND #62
64	Self-management	'self care'/exp OR 'self care' OR 'self management' OR 'self treatment'
65		'disease management'/de OR 'disease management' OR 'diseases management' OR 'disorder management' OR 'disorders management' OR 'illness management' OR 'management of disease' OR 'management of disorder' OR 'medical management' AND (self*:ti OR patient*:ti OR individual*:ti OR group*:ti)
66		self* NEAR/4 (care OR efficac* OR manag* OR monitor*)
67		#64 OR #65 OR #66
68	Blood glucose monitoring (BGM)	'blood glucose monitoring'/de OR 'blood glucose control' OR 'blood glucose monitoring' OR 'blood glucose self-monitoring' OR 'monitoring, blood glucose'
69		Blood NEAR/2 (glucose OR sugar) NEAR/3 monitor*
70		#68 OR #69
71	Combine sets – education & self management	#63 AND #67
72	Combine sets – education & BGM	#63 AND #70
73	Combine sets	#71 OR #72
74	Limit by study types	#73 AND ('randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de)
75		#73 AND ('randomised':ti OR 'randomized:ti' OR 'systematic review'/de OR 'systematic review' OR 'critical review' OR 'meta-analysis'/de OR meta NEAR/2 analy*)
76		#74 OR #75

Set #	Concept	Strategy
Metrics		
77	Blood glucose	'glucose blood level'/de OR 'blood glucose' OR 'blood glucose level' OR 'blood serum glucose' OR 'blood sugar' OR 'blood sugar level' OR 'glucosaemia' OR 'glucose blood level' OR 'glucose, blood' OR 'glucose, plasma' OR 'glucosemia' OR 'glycaemia' OR 'glycemia' OR 'normoglycaemia' OR 'normoglycemia' OR 'plasma glucose' OR 'postprandial glycaemia' OR 'postprandial glycemia' OR 'serum glucose' OR 'serum sugar' OR 'blood glucose monitoring'/de
78	Metrics	'continuous glucose monitoring' OR 'cgms' OR 'cbgms' OR 'cgm' OR 'cgbm'
79		'glycosylated hemoglobin'/exp OR 'hba1c' OR 'a1c' OR 'hgba1c'
80		'eag' OR 'estimated average glucose'
81		'fructosamine blood level'/exp OR 'fructosamine'/de OR fructosamine OR fbs
82		'1,5 anhydrosorbitol'/exp OR '1,5 anhydrosorbitol' OR '1,5-anhydroglucitol' OR '1,5-anydro-d-glucitol' OR '1,5-ag'
83		#78 OR #79 OR #80 OR #81 OR #82
84	Combine sets	#77 AND #83 AND [humans]/lim AND [English]/lim and [2009-2016]/py
85	Limiting concepts	'measure':ti OR 'measures':ti OR 'indices':ti OR indicator*:ti
86		(glycemic OR glycaemic) NEAR/2 indicator*
87		correlation*:ti OR relationship*:ti
88		#85 OR #86 OR #87
89	Combine sets	#84 AND #88
Metformin as 1st-line Therapy		
90	Drug therapy	'drug therapy' limiter
91	Metformin	'metformin'/de OR '1, 1 dimethylbiguanide' OR 'apophage' OR 'aron' OR 'benofomin' OR 'dabex' OR 'denkaform' OR 'deson' OR 'dextin' OR 'diabetase' OR 'diabetase s' OR 'diabetformin' OR 'diabetmin' OR 'diabetmin retard' OR 'diabetosan' OR 'diabex' OR 'diafat' OR 'diaformin' OR 'diaformina' OR 'diaformina lp' OR 'diametin' OR 'diamin' OR 'diformin' OR 'diformin retard' OR 'dimefor' OR 'dimethylbiguanide' OR 'dimethyldiguanide' OR 'dmgg' OR 'dybis' OR 'eraphage' OR 'espa-formin' OR 'euform retard' OR 'fluamine' OR 'flumamine' OR 'fornidd' OR 'fortamet' OR 'glafornil' OR 'glibudon' OR 'glifage' OR 'gliguanid' OR 'glucaminol' OR 'glucofage' OR 'glucofago' OR 'glucoform' OR 'glucoformin' OR 'glucohexal' OR 'glucoless' OR 'glucomet' OR 'glucomin' OR 'glucomine' OR 'gluconil' OR 'glucophage' OR 'glucophage forte' OR 'glucophage retard' OR 'glucophage sr' OR 'glucophage xr' OR 'glucophage xr extended release' OR 'glucophage-mite' OR 'glucotika' OR 'gludepatic' OR 'glufor' OR 'gluformin' OR 'glumeformin' OR 'glumet' OR 'glumetza' OR 'glupa' OR 'glustress' OR 'glyciphage' OR 'glycomet' OR 'glycon' OR 'glycoran' OR 'glyformin' OR 'glymet' OR 'haurymellin' OR 'hipoglucin' OR 'i-max' OR 'islotin' OR 'juformin' OR 'la 6023' OR 'la6023' OR 'maformin' OR 'meglucon' OR 'meguan' OR 'melbin' OR 'melformin' OR 'mellittin' OR 'mescorit' OR 'metaformin' OR 'metfogamma' OR 'metforal' OR 'metformin' OR 'metformin hydrochloride' OR 'metformine' OR 'methformin' OR 'metiguanide' OR 'metomin' OR 'metphormin' OR 'miformin' OR 'n` dimethylguanylguanide' OR 'n` dimethylguanylguanidine' OR 'n`, n` dimethyldiguanide' OR 'n, n dimethyl biguanidine' OR 'n, n dimethylbiguanide' OR 'n, n dimethylbiguanide retard' OR 'n, n dimethylbiguanidine' OR 'n, n dimethyldiguanide' OR 'n, n dimethylguanylguanidine' OR 'neoform' OR 'nndg' OR 'reglus-500' OR 'riomet' OR 'siamformet' OR 'siofor' OR 'thiabet' OR 'vimetrol' OR 'walaphage'
92	Combine sets	#90 OR #91

Set #	Concept	Strategy
93	Core diabetes set	#5
94	Combine sets	#92 AND #93
95	1st-line	(first OR '1st') NEAR/2 line
96	Combine sets	#94 AND #95
97	Limit by study type	#96 AND ('systematic review'/de OR 'systematic review' OR 'critical review' OR 'meta-analysis'/de OR meta NEAR/2 analy*)
98		#96 AND ('randomised':ti OR 'randomized:ti' OR 'randomized controlled trial'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'intermethod comparison'/de OR 'multicenter study'/de OR 'practice guideline'/de OR 'prospective study'/de)
99		#97 OR #98
Non-ICU Inpatient Insulin Management		
100	Inpatient	'hospital patient'/de OR 'hospital patient' OR 'hospitalised patient' OR 'hospitalised patients' OR 'hospitalized patient' OR 'hospitalized patients' OR 'in-hospital patient' OR 'in-hospital patients' OR 'inpatient' OR 'inpatients' OR 'patient, hospital' OR 'hospital care'/de OR inpatient*:ti OR hospital*:ti OR ward:ti
101		'after hospital stay' OR ('post-discharge' OR postdischarge) NEAR/2 ('glycemic control' OR 'glycaemic control')
102		#100 OR #101
103	ICU	'intensive care'/de OR 'care, intensive' OR 'critical care' OR 'intensive care' OR 'intensive therapy' OR 'therapy, intensive' OR 'icu' OR 'ccu'
104	Inpatient NOT ICU	#102 NOT #103
105	Non-ICU patients with diabetes	#4 AND #104
106	Insulin dosing	'insulin derivative'/exp OR 'carbamoylinsulin' OR 'carbamylinsulin' OR 'carbonyl bis methionyl insulin' OR 'diacetoacetyl insulin' OR 'diacetylinsulin' OR 'diaminosuberoyl insulin' OR 'insulin analog' OR 'insulin analogue' OR 'insulin derivative' OR 'insulins' OR 'methylthiocarbamoylinsulin' OR 'methylthiocarbamylinsulin' OR 'mononitroinsulin' OR 'polyalanylinsulin series' OR 'suberoyl insulin' OR 'succinyl insulin' OR 'triacetylinsulin' OR 'tricarbamylinsulin'
107		'insulin treatment'/exp OR 'insulin'/de OR 'actrapid insulin' OR 'actrapid mc' OR 'cross linked insulin' OR 'destripeptide insulin' OR 'fish insulin' OR 'humilin' OR 'iletin ii' OR 'immunoinsulin' OR 'in 105' OR 'in105' OR 'initard' OR 'insulin' OR 'insulin (animal source)' OR 'insulin actrapid' OR 'insulin hnc' OR 'insulin novo actrapid' OR 'insulin snc' OR 'insulina pronta lilly' OR 'insuline' OR 'insulinum' OR 'iodinated insulin' OR 'iszilin' OR 'maxirapid' OR 'monotard human' OR 'monotard insulin' OR 'neusulin' OR 'novolin' OR 'oralin' OR 'oro insulin' OR 'teleost insulin'
108		(fixed NEAR/2 (dose OR dosing)) OR (basal NEAR/5 correction) OR 'drug dose titration'/de OR (sliding NEAR/2 scale) OR (basal NEAR/2 bolus) OR (insulin NEAR/2 protocol)
109		(#106 OR #107) AND #108
110	Combine sets	#105 AND #109
111	Limit to RCTs, SRs, and Mas	#110 AND ('randomized':ti OR 'randomised':ti OR 'randomized controlled trial'/de)
112		#110 AND ('systematic review'/de OR "systematic review" OR 'meta analysis'/de OR (meta* NEAR/2 (analysis OR analyses OR analytic)))
113		#111 OR #112

Set #	Concept	Strategy
Non-ICU Inpatient Blood Glycemic Target		
114	Glycemic target	iatrogenic NEAR/5 (hypoglycemi* OR hypoglycaemi* OR hyperglycemi* OR hyperglycaemi* OR dysglycemi* OR dysglycaemi*)
115		(blood NEAR/2 (sugar OR glucose)) AND (moderate NEAR/3 control)
116		(glycemic OR glycaemic) NEAR/2 target*
117		'200 mg/dl' OR '11.1 mmol/l' OR '11.1 mmol/liter'
118		'hospital patient'/de AND 'glycemic control'/de
119		#114 OR #115 OR #116 OR #117 OR #118
120	Combine sets	#105 AND #119
121		#120 AND ('randomized':ti OR 'randomised':ti OR 'randomized controlled trial'/de)
122		#120 AND ('systematic review'/de OR "systematic review" OR 'meta analysis'/de OR (meta* NEAR/2 (analysis OR analyses OR analytic)))
123	Combine sets	#121 OR #122
124	Limit	#123 NOT (gestational OR 'pre-gestational' OR pregnan*):ti
Transitions of Care - Education		
125	Care management and education	(patient OR individual* OR group OR participant* OR diabetes) AND (educat* OR train* OR teach* OR instruct* OR inform* OR counsel* OR empower*)
126		((care OR transition*) NEAR/2 (management OR plan*))
127		'transitional care'/de OR transition*:ti
128		'dsme'
129		#125 OR #126 OR #127 OR #128
130	Combine sets	#105 AND #129
131	Limit to RCTs, SRs, and MA's	#130 AND ('randomized':ti OR 'randomised':ti OR 'randomized controlled trial'/de)
132		#130 AND ('systematic review'/de OR "systematic review" OR 'meta analysis'/de OR (meta* NEAR/2 (analysis OR analyses OR analytic)))
133	Controlled trials	#130 AND ((controlled OR control*) NEAR/2 group) OR controls:ab OR 'controlled trial'/de)
134	Combine sets	#131 OR #132 OR #133
Effect of Glucose Variability on Microvascular and Macrovascular Outcomes		
135	Complications	'diabetic angiopathy'/de OR 'diabetic nephropathy'/de OR 'diabetic neuropathy'/de OR 'diabetic retinopathy'/de OR 'diabetic cardiomyopathy'/de OR 'diabetic foot'/de
136		microvascular OR 'micro-vascular' OR 'macrovascular' OR 'macro-vascular' AND (disease* OR outcome* OR complication*)
137		'Kidney disease'/exp/mj
138		'peripheral vascular disease'/exp/mj
139		'heart disease'/exp/mj
140		#136 OR #137 OR #138 OR #139
141		#140 AND ('non insulin dependent diabetes mellitus'/exp OR diabet*:ti)
142		#135 OR #141

Set #	Concept	Strategy
143	Glycemic variability	'glycemic control'/de OR ((glycemic OR glycaemic) NEAR/2 control)
144		(glycemic OR glycaemic OR 'blood glucose') NEAR/2 (variab* OR oscillat* OR excursion* OR fluctuation*)
145		#143 OR #144
146	Combine sets	#142 AND #145
147	Combine sets	#5 AND #146

EMBASE.com Syntax:

* = truncation character (wildcard)

NEAR/*n* = search terms within a specified number (*n*) of words from each other in any order

NEXT/*n* = search terms within a specified number (*n*) of words from each other in the order specified

/ = search as a subject heading

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

mj = denotes a term that has been searched as a major subject heading

:de = search in the descriptors field (controlled terms and keywords)

:lnk = floating subheading

:it,pt. = source item or publication type

:ti. = limit to title

:ti,ab. = limit to title and abstract fields

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Diabetes	**EMBASE** 'diabetes'/exp 'non insulin dependent diabetes mellitus'/exp	adult onset diabet* 'diabetes mellitus type 2' 'diabetes mellitus type II' 'diabetes mellitus maturity onset' 'insulin independent diabetes' 'ketosis resistant diabetes' 'non insulin dependent' "noninsulin dependent" "non-insulin-dependent" DM2 NIDDM T2D T2DM "type 2" "type-2" "type II" "type-II"
Specific trials	**EMBASE**	ACCORD "Action to Control Cardiovascular Risk in Diabetes" ADVANCE "Action in diabetes and vascular disease" DIMORA (not sure of relevance – older patients) VADT "Veterans Affairs Diabetes Trial"
Care Management	**EMBASE** 'hospital discharge'/de 'transitional care'/de	'after hospital stay' Bundled DSME Post NEAR/1 hospital* 'post-discharge' 'postdischarge' Transition*:ti 'transition care'
Discharge planning and transition management	**EMBASE** 'Hospital discharge'/de 'Primary medical care'/de 'Health care planning'/de 'Health care access'/de	(discharge OR transition) NEAR/3 (plan* OR service* OR management) 'diabetes care' NEAR/3 'hospital discharge'

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Glucose measurement	**EMBASE** 'blood glucose monitoring'/de 'continuous glucose monitoring'/de 'glucose blood level'/de 'glycemic control'/de	eAG 'estimated average glucose' 'hospital monitored average glucose' HMAG Glycemic control Glycaemic control Glycemic excursions Glycaemic excursions Glycemic variability Glycaemic variability Glucose variability 1,5-anhydro-D-glucitol (1,5-AG) A1c CGMS 'continuous glucose monitoring' GA Gap measurement Glycation gap Glycosylation gap Glycated albumin adjGA FBS HbA1c HgA1c 'mean amplitude' MAGE 'M value'

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Glycemic variability and threshold	**EMBASE** 'glycemic control'/de	A1c variability Glycemic control Glycaemic control Glycemic excursions Glycaemic excursions Glycemic variability Glycaemic variability Glucose variability Glycosylated hemoglobin HbA1c variability 'lower threshold' '180 mg/dl' '200 mg/dl' '10.0 mmol/L' '10.0 mmol/liter' '11.1 mmol/L' '11.1 mmol/liter' Glycemic target Glycaemic target
Inpatient	**EMBASE** 'hospital patient'/de 'hospitalization'/de	hospital hospitalised hospitalized inpatient 'in-patient'
Inpatient insulin management	**EMBASE** 'hospital patient'/de 'insulin'/de	Reviewed related citations from PMID 24121872 Algorithmic titration Basal NEAR/2 bolus BBI Insulin NEAR/2 protocol Sliding NEAR/2 scale
Intensive glucose control		'glycemic control':ti 'glycaemic control':ti (intensive OR tight) NEAR/2 ('glycemic control' OR 'glycaemic control') 'intensive glucose lowering'

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Macrovascular outcomes	**EMBASE** 'diabetic cardiomyopathy'/de 'ischemic heart disease'/de 'peripheral vascular disease'/de	Acute coronary events CAD Cardiovascular outcome* Cerebrovascular accident* CHF Coronary artery disease Heart attack* Heart disease Heart failure Ischemic heart disease Macrovascular complication* MI Myocardial infarction Peripheral vascular disease Stroke* Unstable angina Mortality Quality of life QOL
Microvascular outcomes	**EMBASE** 'disease association'/de 'disease course'/mj 'diabetic angiopathy'/de 'diabetic foot'/de 'diabetic microangiopathy'/de 'diabetic nephropathy'/de 'diabetic neuropathy'/de 'diabetic retinopathy'/de 'microangiopathy'/de 'kidney disease'/exp/mj *[includes chronic kidney disease and kidney failure]* 'neuropathy'/de 'Retinopathy'/de	Chronic kidney disease CMD Coronary microvascular dysfunction Diabetic nephropathy Hypoglycem* Hypoglycaem* Macroalbuminuria Microalbuminuris Microvascular complication* Nephropath* Neuorpath* Renal failure Renal insufficiency Retinopath*

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Medical nutrition therapy	**EMBASE** 'nutrition'/exp *[Note: parent term for tree with diet and diet therapy. Includes terms for Mediterranean, Paleo and other specific diets]* 'caloric intake'/de 'food intake'/de 'Cereal'/de 'Dairy product'/de 'Drinking behavior'/de 'Egg'/de 'Legume'/de 'Meat'/de 'Red meat'/de 'Smoking habit'/de 'Tomato'/de 'Vegetable'/de 'Exercise'/de	Diet* 'MNT' 'Medical nutrition therapy' Mediterranean* NEAR/2 diet* 'MeDiet' Nutrition* 'ADA diet' 'carb counting' 'carbohydrate counting' 'DASH' 'Dutch Health Council diet' Ketogenic 'low carbohydrate' 'low energy' 'low fat' 'low glycemic index' 'low glycaemic index' 'Nordic diet' 'Paleo' 'Vegan' Specific trials: MEDINA MOLI-SANI study
Patient education	**EMBASE** 'Diabetes education'/de 'Health education'/de 'Health promotion'/de 'Patient education'/de	Individual One-on-one One-to-one Standard care (patient* OR adult* OR client* OR participant* OR individual*) NEAR/3 (train* OR educat* OR teach* OR instruct* OR inform* OR counsel* OR empower*)
Self management	**EMBASE** 'blood glucose self-monitoring'/exp 'Self care'/exp	Blood NEAR/2 (glucose OR sugar) 'Disease management' Self NEAR/4 (care OR efficacy* OR manag* OR monitor*)

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Shared decision-making	**EMBASE** 'diabetic patient'/de 'patient decision making'/de 'patient participation'/de 'clinical decision making'/de 'decision making'/de 'doctor patient relation'/de 'interpersonal communication'/de 'trust'/de	Choice* 'choice behavior' 'choice behaviour' Choose* 'clinical decision making' Decision* Decid* 'decision making' 'decision process' Deliberat* Goal NEAR/2 set* Option* Patient-centered Patient NEAR/2 (preferenc* OR priorit*) Patient NEAR/2 (shared OR sharing OR centered OR trust) Priorit* SDM 'Multiple chronic conditions' MCC Multimorbid* Reviewed related citations for PMIDs: 26645932 Utilization of a cloud-based diabetes management program for insulin initiation and titration enables collaborative decision making between healthcare providers and patients 26458383 Shared decision-making in diabetes care 26567256 Informed shared decision-making programme on the prevention of myocardial infarction in type 2 diabetes: a randomized controlled trial

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Telemedicine	**EMBASE** 'telehealth'/exp 'health care'/exp 'mass communication'/de 'e-mail'/de 'interactive voice response system'/de 'internet'/de 'mass medium'/de 'mobile phone'/de 'online system'/de 'social media'/de 'telephone'/de 'text messaging'/de 'videoconferencing'/de 'wireless communication'/de	Telecare* Teleconsult* Teledermatol* Telediagnos* Telehealth* Telehomecare* Telemanag* Telematics Telemonitor* Telenurs* Telepathol* Telepharm* Telepsychiatr* Telestroke Telesupport (tele OR remote) NEAR/2 (health OR care* OR diagnos* OR monitor* OR manag* OR consult* OR home* OR nurs* OR dermatol* OR pathol* OR pharmac* OR nurs* OR psychiatr* OR stroke OR support) Bluetooth Computer* Email 'e-mail' Interactive* Internet* Phone* SMS Telecommunication* Telephone* Video* Web* Wireless

Appendix I: Acronym List

Abbreviation	Definition
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AGI	alpha-glucosidase inhibitor
AHRQ	Agency for Healthcare Research and Quality
AMI	acute myocardial infarction
AMP	5' adenosine monophosphate-activated protein
ARR	absolute risk reduction
ATP	adenosine triphosphate
BMI	body mass index
CGM	continuous glucose monitor
CI	confidence interval
CKD	chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
CPG	clinical practice guideline
CV	coefficient of variation
CVD	cardiovascular disease
DIGAMI	Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DoD	Department of Defense
DPP-4	dipeptidyl peptidase-4
DSME	diabetes self-management education
DSMS	diabetes self-management support
eAG	estimated average glucose
EBPWG	Evidence-Based Practice Work Group
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
GDM	gestational diabetes mellitus
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	hemoglobin A1c

Abbreviation	Definition
HDL-C	high-density lipoprotein cholesterol
HHS	U.S. Department of Health and Human Services
HR	hazard ratio
HRSA	Health Resources and Services Administration
IBGMS	internet-based glucose monitoring system
ICU	intensive care unit
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
KQ	key question
LDL-C	low-density lipoprotein cholesterol
MD	mean difference
MDD	major depressive disorder
MET	metformin
MHS	Military Health System
MI	myocardial infarction
MNT	medical nutrition therapy
MODY	maturity onset diabetes of the young
N/A	not applicable
NICE	National Institute for Health and Care Excellence
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation
NIH	National Institutes of Health
NPH	neutral protamine Hagedorn
OGTT	oral glucose tolerance testing
OPTEMPO	operations tempo
PBM	Pharmacy Benefits Management program
PICOTS	population, intervention, comparison, outcome, timing and setting
PPAR	peroxisome proliferator-activated receptor
P&T	Pharmacy and Therapeutics Committee
QoL	quality of life
RCT	randomized controlled trial
RDN	registered dietitian nutritionist
RN	registered nurse
SD	standard deviation
SDM	shared decision-making
SGLT2	sodium glucose co-transporter 2
SMBG	self-monitoring of blood glucose
SR	systematic review
SU	sulfonylurea
SUD	substance use disorder
T1DM	type 1 diabetes mellitus

Abbreviation	Definition
T2DM	type 2 diabetes mellitus
TIA	transient ischemic attack
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
U.S.	United States of America
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VADT	Veteran Affairs Diabetes Trial

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