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CLINICAL PRACTICE GUIDELINE

Management of Type 2 Diabetes Mellitus: Synopsis of the Department of Veterans Affairs and Department of Defense Clinical Practice Guideline

Paul R. Conlin, MD; Brian V. Burke, MD; Curtis Hobbs, MD; Kathryn M. Hurren, PharmD; Adam Edward Lang, PharmD; John W. Morrison, DO; Lance Spacek, MD; Evan N. Steil, MD; Sharon A. Watts, DNP; Jane E. Weinreb, MD; and Leonard M. Pogach, MD

Abstract

The US Department of Veterans Affairs (VA) and the US Department of Defense (DoD) approved a joint clinical practice guideline for the management of type 2 diabetes. This was the product of a multidisciplinary guideline development committee composed of clinicians from both the VA and the DoD and was overseen by the VA/DoD Evidence Based Practice Work Group. The development process conformed to the standards for trustworthy guidelines as established by the National Academy of Medicine. The guideline development committee developed 12 key questions to guide an evidence synthesis. An independent third party identified relevant randomized controlled trials and systematic reviews that were published from January 2016 through April 2022. This evidence synthesis served as the basis for drafting recommendations. Twenty-six recommendations were generated and rated by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Two algorithms were developed to guide clinical decision-making. This synopsis summarizes key aspects of the VA/DoD Clinical Practice Guideline for diabetes in 5 areas: prediabetes, screening for co-occurring conditions, diabetes self-management education and support, glycemic treatment goals, and pharmacotherapy. The guideline is designed to help clinicians and patients make informed treatment decisions to optimize health outcomes and quality of life and to align with patient-centered goals of care.

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Type 2 diabetes mellitus (T2DM) is a highly prevalent disease both globally and in the United States, including among active-duty military and military veterans. Approximately 29 million Americans are diagnosed with diabetes, most with T2DM, representing 11.3% of the US population and about 13% of adults.[1] About 1 in 3 American adults has prediabetes, many of whom are unaware of their diagnosis.[2] In the US Department of Veterans Affairs (VA), nearly 1 in 4 veterans receive care for diabetes, of whom about 70% are 65 years and older.[3] Diagnosed diabetes among active-duty service members in the US Department of Defense (DoD) ranges from 8.3% to 13.6%. More disease burden exists among nonactive service members and retirees, for whom the prevalence is 15% (45 to 64 years old) to 33% (65 to 74 years old).[4]

Type 2 diabetes mellitus frequently occurs with other comorbid conditions that influence its course, complications, and treatment. Chronic hyperglycemia increases risks for microvascular complications, such as retinopathy, nephropathy, and neuropathy. The confluence of chronic hyperglycemia

From the Department of Veterans Affairs Boston Healthcare System, Boston, MA (P.R.C.); Department of Veterans Affairs Medical Center, Dayton, OH (B.V.B.); Madigan Army Medical Center, Tacoma, WA (C.H.); Department of Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI (K.M.H.); Department of Primary

Affiliations continued at the end of this article.

with features of metabolic syndrome, including hyperlipidemia and hypertension, significantly increases the risk of macrovascular complications, such as ischemic heart disease, stroke, and peripheral artery disease. Type 2 diabetes mellitus often clusters with obesity-related conditions that also affect its management.

The VA/DoD Clinical Practice Guideline (CPG) for the management of T2DM is designed to assist primary care clinicians with an evidence-based framework to evaluate and to treat patients with T2DM. This article summarizes several key recommendations to help clinicians and patients make informed treatment decisions that align with patient-centered goals of care.

GUIDELINE DEVELOPMENT PROCESS

The VA Evidence Based Practice Work Group collaborated with the Clinical Quality Improvement Program, Defense Health Agency, to oversee the guideline development process, which adhered to the standards for trustworthy guidelines as established by the National Academy of Medicine. The methodology used in developing this CPG follows the *Guideline for Guidelines*,[5] an internal document of the Evidence Based Practice Work Group that outlines procedures for developing and submitting VA/DoD CPGs.

A guideline development committee composed of subject matter experts (herein referred to as the CPG Work Group) included primary care clinicians (internal medicine and family medicine), diabetes educators, endocrinologists, nurse practitioners, nutritionists, pharmacists, and social workers. Co-champions were selected to lead the CPG Work Group (2 each from VA and DoD). The Lewin Group, ECRI, Sigma Health Consulting, and Duty First Consulting were contracted by VA to assist with the guideline development process.

Conflicts of interest were managed as described in the *Guideline for Guidelines*. Formal disclosures were completed at least twice by CPG Work Group members and guideline development contractors. Each CPG Work Group meeting began with a request for members and contractors to disclose any new conflicts of interest. The disclosure process included information about financial and intellectual interests or relationships with manufacturers of commercial products, providers of commercial services, or other commercial interests that could be perceived to influence contributions to the CPG. Random web-based audits were conducted for instances of potential or actual conflicts of interest among the CPG Work Group and the guideline development contractors. No conflicts of interest were identified.

The CPG Work Group used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to create each recommendation and to determine its strength. GRADE requires that recommendations be evidence based and not founded on expert opinion alone. GRADE uses 4 domains to inform the strength of each recommendation: confidence in the quality of the evidence; balance of desirable and undesirable outcomes; patient values and preferences; and other considerations, as appropriate (eg, resource use, equity, acceptability, feasibility, subgroup considerations).[6]

The CPG Work Group developed 12 key questions to guide an evidence synthesis, conducted by ECRI, which served as the basis for drafting its recommendations (Appendix Table). The evidence synthesis included randomized controlled trials and systematic reviews from January 2016 through April 2022. In some instances, there was insufficient evidence on which to base a recommendation. In such instances, the CPG Work Group could choose to include a statement of insufficient evidence or to remain silent. Nineteen new recommendations were generated, 3 recommendations from the 2017 CPG were replaced, and 4 prior recommendations were amended and carried forward. A total of 26 recommendations were proposed (Table 1). Two treatment algorithms were also developed to guide clinical decision-making and implementation (Appendix Figures 1 and 2 and accompanying Tables). These algorithms also refer clinicians to other VA/DoD CPG documents developed for patients with

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TABLE 1. VA/DoD Clinical Practice Guideline Recommendations for Diabetes Mellitus

Topic	No.	Recommendation	Strength of Evidence
Prediabetes	1.	In adults with prediabetes, we suggest aerobic exercise (such as walking 8 to 9 miles a week) and healthy eating (with a goal weight loss >3%) to achieve a reduction in body fat mass, weight loss, and improvement in fasting blood glucose concentration.	Weak for
	2.	In adults with prediabetes who have participated in healthy lifestyle modification and remain at high risk for progression to type 2 diabetes mellitus, we suggest evaluating patient characteristics (eg, age, life expectancy, co-occurring conditions, BMI, other risk factors) and offering metformin or other select medications to reduce the risk of progression from prediabetes to type 2 diabetes mellitus.	Weak for
Telehealth	3.	In adults with type 2 diabetes mellitus, we suggest offering health care delivered through telehealth interventions to improve outcomes.	Weak for
Management of type 2 diabetes mellitus	4.	There is insufficient evidence to recommend for or against routine screening or using a specific tool to screen for or to diagnose diabetes distress.	Neither for nor against
	5.	In adults with type 2 diabetes mellitus and co-occurring nonalcoholic fatty liver disease, we suggest that clinicians should assess for fibrosis using a noninvasive tool (eg, Fibrosis-4).	Weak for
	6.	In adults with type 2 diabetes mellitus, there is insufficient evidence to recommend for or against routine screening for fall risk and cognitive impairment to improve outcomes.	Neither for nor against
	7.	In adults with type 2 diabetes mellitus, we recommend diabetes self-management education and support.	Strong for
	8.	For adults with type 2 diabetes mellitus, we suggest using high glycemic variability over time (eg, fluctuation in HbA_{1c} or fasting blood glucose concentration) as a prognostic indicator for risk of hypoglycemia, morbidity, and mortality.	Weak for
	9.	We suggest setting an individualized HbA_{1c} target range based on the clinician's appraisal of the risk-benefit ratio, patient characteristics, presence or absence of type 2 diabetes mellitus complications, comorbidities, and life expectancy.	Weak for
	10.	We suggest an HbA_{1c} range of 7.0% to 8.5% for most patients if it can be safely achieved.	Weak for
	11.	In insulin-treated adults with type 2 diabetes mellitus who are not achieving glycemic goals, we suggest real-time continuous glucose monitoring to decrease hypoglycemia and to improve HbA_{1c}.	Weak for
Non-pharmacotherapy	12.	For adults with type 2 diabetes mellitus, we suggest a Mediterranean-style diet to improve glycemic control, body weight, and hypertension.	Weak for
	13.	For adults with type 2 diabetes mellitus, we suggest a nutrition intervention strategy providing 13% to 50% of total daily calorie intake from carbohydrates for diabetes management.	Weak for
	14.	For adults with type 2 diabetes mellitus, we suggest a vegetarian dietary pattern for glycemic control and weight loss.	Weak for
	15.	For adults with type 2 diabetes mellitus, we suggest against intermittent fasting.	Weak against
	16.	In adults with type 2 diabetes mellitus, we suggest regular physical activity to improve glycemic control, including but not limited to aerobic exercise, resistance training, and tai chi.	Weak for
	17.	In adults with stress related to type 2 diabetes mellitus, we suggest offering a mindfulness-based stress reduction program for short-term improvement.	Weak for
	18.	For adults with type 2 diabetes mellitus and diabetes distress, there is insufficient evidence to recommend for or against the use of acupuncture, biofeedback, hypnosis, guided imagery, massage therapy, yoga, or tai chi to improve outcomes.	Neither for nor against

Continued on next page

TABLE 1. Continued

Topic	No.	Recommendation	Strength of Evidence
Pharmacotherapy	19.	For adults with type 2 diabetes mellitus with atherosclerotic cardiovascular disease, we recommend glucagon-like peptide 1 receptor agonists or sodium-glucose cotransporter 2 inhibitors with proven cardiovascular benefits to decrease the risk of major adverse cardiovascular events.	Strong for
	20.	For adults with type 2 diabetes mellitus at high risk of atherosclerotic cardiovascular disease (ie, chronic kidney disease, left ventricular hypertrophy, heart failure), we suggest glucagon-like peptide 1 receptor agonists or sodium-glucose cotransporter 2 inhibitors with proven cardiovascular benefits to decrease the risk of major adverse cardiovascular events.	Weak for
	21.	For adults with type 2 diabetes mellitus and heart failure, we recommend a sodium-glucose cotransporter 2 inhibitor to prevent hospital admissions for heart failure.	Strong for
	22.	For adults with type 2 diabetes mellitus and chronic kidney disease, we recommend sodium-glucose cotransporter 2 inhibitors with proven renal protection to improve renal outcomes.	Strong for
	23.	For adults with type 2 diabetes mellitus and chronic kidney disease who are not good candidates for a sodium-glucose cotransporter 2 inhibitor, we recommend a glucagon-like peptide 1 receptor agonist with proven renal protection to improve macroalbuminuria.	Strong for
	24.	In adults with type 2 diabetes mellitus who have cardiovascular disease or renal disease, we suggest that the addition of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist be considered, even if the patient has already achieved an individualized target range for glycemic control.	Weak for
	25.	In adults with type 2 diabetes mellitus, especially those 65 years and older, we suggest prioritizing drug classes other than insulin, sulfonylureas, or meglitinides to minimize the risk of hypoglycemia if glycemic control can be achieved with other treatments.	Weak for
	26.	In adults with type 2 diabetes mellitus who have co-occurring cognitive impairment or risk of falls, there is insufficient evidence to recommend for or against specific treatment strategies for glucose lowering to reduce the risk of harms.	Neither for nor against

BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; VA/DoD, Department of Veterans Affairs/Department of Defense.

chronic kidney disease (CKD), dyslipidemia, hypertension, ischemic heart disease, and obesity.

The CPG Work Group identified subject matter experts from VA, DoD, and other organizations to review a near-final CPG draft. All feedback was evaluated, and the CPG was modified where justified, in accordance with the evidence.

HIGHLIGHTED GUIDELINE UPDATES

Some of the CPG recommendations are noteworthy. Real-time continuous glucose monitoring is suggested as an adjunct to diabetes care in insulin-treated patients to reduce hypoglycemia risk and to improve hemoglobin A_{1c} (HbA_{1c}) (recommendation 11). Patients with T2DM and cardiovascular disease (CVD) or renal disease should receive medications associated with proven benefits to reduce disease-specific outcomes, complications, and mortality (eg, sodium-glucose cotransporter 2 inhibitor [SGLT2i] and glucagon-like peptide 1 receptor agonist [GLP-1 RA] medications) (recommendations 19 to 24). For older adults, clinicians should prioritize medications other than insulin and sulfonylureas to achieve glycemic goals and to reduce hypoglycemia risk (recommendation 25). High glycemic variability over time is a prognostic indicator for risks of hypoglycemia, morbidity, and mortality (recommendation 8). The CPG also

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suggests against intermittent fasting for weight reduction in T2DM (recommendation 15).

PREDIABETES

In adults with prediabetes, the CPG Work Group suggests aerobic exercise, such as walking 8 to 9 miles a week, and healthy eating with a weight loss goal of at least more than 3% to reduce fat mass and weight and to improve fasting blood glucose concentration (recommendation 16). Two studies of lifestyle modifications in people with prediabetes affirmed the benefits of aerobic exercise and weight loss on fasting blood glucose, glucose tolerance, and insulin sensitivity.[7,8]

The CPG Work Group also considered options for pharmacotherapy in patients at high risk for progression to T2DM. In adults who have attempted healthy lifestyle interventions and remain at high risk for progression to T2DM, offering pharmacotherapy to reduce this risk should be considered. The evidence review showed several medications with similar effects on preventing progression from prediabetes to diabetes. There were no substantial differences between metformin, pioglitazone, acarbose, and liraglutide in their effects on diabetes prevention.[9-15] The CPG Work Group concluded that metformin is preferred, given its safety and tolerability profile, but other medications may be alternatives on the basis of patients' characteristics and preferences (recommendation 2). Clinicians and patients should engage in shared decision-making when discussing medications for diabetes prevention, particularly in older adults or in the setting of lower life expectancy, because the benefits from diabetes prevention accrue over years. Many adults older than 75 years will experience no harms from prediabetes. The use of different treatments to prevent diabetes is an area of active research without current consensus.

SCREENING FOR CO-OCCURRING CONDITIONS

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of fat in the liver that is not attributable to alcohol consumption or other secondary causes of fatty liver. Type 2 diabetes mellitus is a risk factor for fatty liver disease and its more severe form, nonalcoholic steatohepatitis. Advanced liver fibrosis increases the risk of complications such as decompensated cirrhosis, hepatocellular carcinoma, and liver-related death. Patients with T2DM are susceptible to these complications and may experience worse outcomes compared with the general population.[16-19] The terminology for this condition has changed over time, and recent proposals have suggested the term metabolic dysfunction–associated steatotic liver disease. The CPG evidence synthesis used the term NAFLD to identify published studies. Therefore, recommendations are based on these reports, and the term NAFLD was retained to align with the published studies.

The clinical utility of screening patients with T2DM for NAFLD is determined by disease prevalence, accuracy of diagnostic tools, and availability of effective treatments. In this context, clinical utility represents the full impact of the screening framework, starting from diagnosis and culminating in the impact of therapy on patient-oriented outcomes. The CPG Work Group assessed both the clinical utility of screening for NAFLD and the diagnostic accuracy of various testing methods. The evidence synthesis found no studies evaluating the clinical utility of screening for NAFLD in patients with T2DM. Although T2DM is clearly a risk factor for NAFLD and disease progression, prospective trials showing that screening improves clinical outcomes are lacking. Concerns also exist about potential harms from unnecessary testing and treatments as a result of false positives and incidental findings. Whereas the potential benefits of screening for NAFLD are promising, additional studies are needed to clarify the effects on patient-oriented outcomes as well as potential unintended consequences associated with screening.

In contrast, assessing for advanced liver fibrosis in patients with T2DM and NAFLD has implications for staging and prognosis. Noninvasive methods should be prioritized

when possible. Magnetic resonance elastography and transient elastography with ultrasound may diagnose advanced fibrosis noninvasively. However, the evidence review found no studies evaluating their diagnostic accuracy in T2DM. Clinical prediction models using demographic and laboratory data, such as fibrosis 4 index (FIB-4), NAFLD fibrosis score, ratio of aspartate aminotransferase/alanine aminotransferase, and aspartate aminotransferase to platelet ratio index, have been studied. These tests do have lower performance in T2DM compared with the general population. The FIB-4 is preferred because it performs more favorably in comparison to other prediction models in T2DM (recommendation 5). Caution should be exercised in using FIB-4 in older patients as supporting evidence is based on individuals younger than 65 years.[20-22]

Diabetes Distress

Diabetes distress refers to a range of negative emotions experienced by individuals with diabetes, including guilt, anger, sadness, and feelings of helplessness.[23] Increased distress can adversely affect glycemic management. However, the evidence review did not show consistent benefits from screening for diabetes distress. The CPG Work Group concluded that there is insufficient evidence to recommend for or against screening or using a specific tool to screen for or to diagnose diabetes distress (recommendation 4).

Falls and Cognitive Impairment

Falls of older adults can lead to serious injuries and even death.[24] Cognitive impairment is also linked to higher mortality and increases the likelihood of falls.[25] Various organizations have recommended screening older adults with T2DM for fall risk and cognitive impairment. However, the evidence review did not identify studies showing the usefulness of screening patients with T2DM for fall risk or cognitive impairment. The CPG Work Group acknowledged some potential benefits but concluded that there is insufficient evidence to support or to discourage routine screening for fall risk and cognitive impairment in adults with T2DM (recommendation 6).

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT, LIFESTYLE CHANGES, AND MEDICAL NUTRITION THERAPY

Diabetes self-management education and support (DSMES) has an important place in the care of adults with T2DM. It is a dynamic process that provides knowledge and self-management skill building based on individual needs, attitudes, beliefs, and life situations.[26-28] Studies with a moderate quality of evidence show that DSMES improves glucose levels, blood pressure, diabetes knowledge, and self-care behaviors. The CPG Work Group recommends that all patients with T2DM be offered ongoing individualized DSMES (recommendation 7). Various modalities (eg, in-person or telehealth) may be used, according to available resources, and tailored to patients' preferences, learning needs, and abilities (recommendation 3), and they may be offered to both patients with T2DM and patients with prediabetes.

Therapeutic lifestyle changes are also a cornerstone of T2DM treatment, either alone or in combination with pharmacotherapy. Exercise and medical nutrition therapy are key to improving glucose levels, weight, and CVD risk factors.[29-33] The CPG Work Group reviewed impacts of regular physical activity including aerobic exercise, resistance training, and tai chi. The quality of evidence was low but showed improvements in glucose levels with general exercise, supervised aerobic exercise training, yoga, resistance training, and tai chi.[34-37] Additional benefits include improved quality of life, weight loss, gait stability and balance, and increased muscle strength. The CPG Work Group suggests regular physical activity to improve glycemic control in adults with T2DM (recommendation 16).

Healthy eating and limiting alcohol intake are advocated for all patients with T2DM.[24] Several dietary interventions have a favorable impact on glucose levels, weight, and CVD risk factors.[29-33] A Mediterranean-

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style diet is the most effective dietary approach,[30,31] and this dietary pattern is suggested (recommendation 12). Various levels of carbohydrate intake have also been studied in T2DM. The evidence to support a specific macronutrient distribution is weak, but interventions that limit daily carbohydrates to 13% to 50% of calorie intake improve HbA_{1c}, blood pressure, and body weight.[30,32,38,39] The CPG Work Group suggests this carbohydrate intake range as part of a nutrition strategy (recommendation 13) but acknowledges that sustaining low carbohydrate intake is difficult.

Individuals with T2DM who follow a vegetarian dietary pattern (including vegan to lacto-ovo-vegetarian) also achieve improved glycemic control and weight loss.[33] The CPG Work Group suggests a vegetarian diet may be used (recommendation 14). Individuals who choose a vegetarian or vegan dietary pattern may benefit from referral to a registered dietitian to review the potential need for nutritional supplements.

Intermittent fasting, which includes within-day fasting or longer periods of hypocalorie intake, is associated with modest weight loss but has no significant effects on fasting glucose concentration, HbA_{1c}, lipid levels, waist circumference, and blood pressure.[40] In contrast, potential harms of intermittent fasting include risks of hypoglycemia and dehydration, and it may reinforce maladaptive behaviors associated with some eating disorders. The CPG Work Group suggests against intermittent fasting for adults with T2DM (recommendation 15).

GLYCEMIC GOALS

Central to the concept of patient-centered diabetes care is the use of shared decision-making in setting individualized HbA_{1c} target ranges based on anticipated benefits and harms (recommendation 9). Indeed, the VA/DoD CPG for diabetes has consistently proposed HbA_{1c} target ranges for specific groups of patients since 2003. The evidence supporting current HbA_{1c} target ranges has not changed, but the standards for guideline development have evolved and require slightly different conclusions from the same evidence.

Many trials have compared more stringent with less stringent glycemic management strategies. Most of these trials were unable to achieve and to sustain HbA_{1c} levels below 7% through the end of the study in more intensively treated patients.[41-43] Two studies reached and sustained HbA_{1c} levels between 6% and 7%.[44,45] Treatment to more stringent HbA_{1c} goals lowered risk of microvascular complications (ie, retinopathy and nephropathy). However, those benefits were counterbalanced by risks of hypoglycemia, weight gain, and all-cause mortality. Some results were inconsistent between studies with similar patient demographic characteristics and treatments. Important subgroups, such as older adults and those with multiple risk factors for hypoglycemia, showed no clear differences in outcomes. These findings add uncertainty to the assumption that patient characteristics can be used to define high- and low-risk subgroups. The CPG Work Group considered these uncertainties and concluded that achieving and sustaining HbA_{1c} levels between 7% and 8.5% in most patients with T2DM is proven to lower risks of major diabetes complications with an acceptable safety profile compared with higher or lower HbA_{1c} targets (recommendation 10).

To complement recommendations 9 and 10, the CPG Work Group developed guiding principles to help clinicians and patients establish individualized HbA_{1c} target ranges by shared decision-making (Table 2). Target ranges should consider a patient's age, presence or absence of comorbidities and diabetes complications, and life expectancy. Target ranges with upper and lower bounds highlight the importance of considering risks associated with both hyperglycemia and hypoglycemia. The CPG Work Group continues to hold that absent microvascular complications and with longer life expectancy (ie, >10 to 15 years), a lower HbA_{1c} goal (ie, 6.0% to 7.0%) is reasonable if it can be achieved safely. In treating to lower HbA_{1c} goals, clinicians may opt for newer medications associated with a lower

hypoglycemia risk to mitigate potential harms from near-normal glucose levels. However, many newer medications were not used in the major trials of stringent glycemic goals, so there is no specific evidence favoring their selective use and safety as part of more stringent glycemic treatment strategies.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) can improve glucose levels and reduce hypoglycemia in patients with type 1 diabetes mellitus. Evidence in T2DM is evolving. Glucose targets such as improving the time with glucose levels of 70 to 180 mg/dL [to convert glucose values to mmol/L, multiply by 0.0555] and reducing the time above 250 mg/dL can be achieved with CGM.[46] However, results may differ by the type of CGM device. Real-time CGM (ie, glucose readings automatically and continuously pushed to the user's receiver or smartphone) in T2DM has moderate-quality evidence showing decreased time in hypoglycemia and lowering HbA_{1c} but low-quality evidence for reducing time in hyperglycemia compared with fingerstick blood testing.[46-48] Intermittently scanned CGM and flash CGM without alarms (ie, requires scanning the device to obtain glucose data) have less evidence showing improved glycemic outcomes. Most studies with real-time CGM included patients taking insulin who were not at HbA_{1c} goals. It is unclear whether real-time CGM offers similar benefits for patients who have achieved HbA_{1c} goals or are not receiving insulin. The CPG Work Group suggests that in insulin-treated adults with T2DM who have not achieved glycemic goals, real-time CGM may be used to decrease hypoglycemia and to improve HbA_{1c} (recommendation 11). Impacts on patient satisfaction and quality of life with real-time CGM are lacking. It is also uncertain whether there are benefits when patients identify and treat subclinical hypoglycemia with CGM. The CGM technology is rapidly evolving, and research must continue to evaluate whether newer devices are superior to existing technologies. More rigorous studies of patient-centered outcomes (eg, quality of life, anxiety, and diabetes distress) and major clinical outcomes (eg, hospitalizations, vascular complications, and mortality) are needed.

Glycemic Variability

Glycemic variability can be measured within days and between days with CGM devices or between visits and over time by measuring the variation in fasting glucose concentration or HbA_{1c}. There is growing evidence that increased longer term glycemic variability—the between-visit variation in fasting glucose concentration or HbA_{1c}—is associated with increased risk for all-cause mortality, CVD, and hypoglycemia.[49-58] Glycemic variability may be affected by medication adherence, comorbidities, engagement with self-care, food insecurity, and financial and social supports. Associations between glycemic variability and adverse outcomes are independent of the type of treatment used (ie, oral medications or insulin). The evidence synthesis focused on variability between days or between visits for fasting glucose concentration and HbA_{1c}. Differing variability measures have been proposed. Coefficient of variation, the ratio of standard deviation to the mean, is more commonly cited. Increased risk of major adverse outcomes is associated with a coefficient of variation above 20% for between-visit fasting glucose concentration[51] and a coefficient of variation above 5% for HbA_{1c}.[53] The CPG Work Group suggests that high glycemic variability over time be used as a prognostic indicator for risk of hypoglycemia, morbidity, and mortality (recommendation 8). Steps to reduce glycemic variability may include reviewing medication and diet adherence, self-monitored glucose profiles, hypoglycemia symptoms, and possibly referring patients to diabetes specialists to identify remediable causes. Causal relationships between glycemic variability and outcomes should be studied to determine whether prospectively reducing variability affects outcomes.

PHARMACOTHERAPY FOR DIABETES

There is substantial evidence showing reduced CVD death, nonfatal myocardial

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TABLE 2. Determination of Hemoglobin A_{1c} (HbA_{1c}) Target Ranges[a,b]

Major comorbidity[c] or physiologic age	Microvascular complications		
	Absent or mild[c]	Moderate[c]	Advanced[c]
Absent[d] >10-15 years of life expectancy	6.0%-7.0%[e]	7.0%-8.0%	7.5%-8.5%[f]
Present[g] 5-10 years of life expectancy	7.0%-8.0%[e]	7.5%-8.5%	7.5%-8.5%[f]
Marked[h] <5 years of life expectancy	8.0%-9.0%[f]	8.0%-9.0%[f]	8.0%-9.0%[f]

[a]Laboratory Considerations
- HbA_{1c} assays should be based on the National Glycohemoglobin Standardization Program reference standard. Clinicians should obtain information about the coefficient of variation from the methodology used at their site.
- The HbA_{1c} range reflects an "HbA_{1c} average goal" over time. Intensification or relaxation of therapy should be undertaken on the basis of individual clinical circumstances and treatment options.
- We discourage medication changes in response to a single HbA_{1c} test result that falls slightly outside target ranges, especially if it is discordant with self-monitoring of blood glucose results.
- African Americans, on average, have HbA_{1c} levels about 0.4% higher than those of Whites, and this difference cannot be explained by measured differences in glycemia. Caution is recommended in changing medications on the basis of HbA_{1c} results that slightly exceed target ranges, especially for patients receiving insulin therapy, without considering self-monitoring of blood glucose results.
- The Department of Veterans Affairs/Department of Defense Clinical Practice Guideline for diabetes mellitus does not recommend the use of estimated average glucose values derived from HbA_{1c} levels.

[b]Social Determinants of Health Considerations
- Social determinants of health and factors such as social support, ability to self-monitor glucose, food insecurity, and cognitive impairment should be considered. In addition, adverse effects of medications and patients' preferences must be considered in a process of shared decision-making.

[c]Complications and Comorbid Illness Considerations
- Major comorbidity includes but is not limited to any or several of the following conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent cerebrovascular disease, and life-threatening malignant disease.
- Mild microvascular disease is defined by early background retinopathy, moderately increased albuminuria, mild neuropathy, or any combination of these.
- Moderate microvascular disease is defined by preproliferative (without severe hemorrhage, intraretinal microvascular anomalies, or venous bleeding) retinopathy, severely increased albuminuria, demonstrable peripheral neuropathy (sensory loss), or any combination of these.
- Advanced microvascular disease is defined by severe nonproliferative (with severe hemorrhage, intraretinal microvascular anomalies, or venous bleeding) or proliferative retinopathy, renal insufficiency (serum creatinine level >2.0 mg/dL; to convert to μmol/L, multiply by 88.4), insensate extremities, autonomic neuropathy (eg, gastroparesis, impaired sweating, orthostatic hypotension), or any combination

[d]Progression to major complications of type 2 diabetes mellitus is likely to occur in individuals with longer than 10 to 15 years of life expectancy. Therefore, lower ranges might be beneficial in younger individuals or older adults with a longer life expectancy.

[e]Consider higher target ranges if significant treatment-related adverse effects occur, including but not limited to hypoglycemia.

[f]Lower target ranges might be appropriate in some patients on the basis of other factors, balancing safety and tolerability of therapy.

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

[h]Major comorbidity is present and is either end stage or management is significantly challenging, including mental health conditions and substance or opioid use.

infarction, and nonfatal stroke in patients with T2DM and established CVD who are treated with GLP-1 RA or SGLT2i medications. The GLP1-RA class reduced major adverse CVD events by 12% during 2.6 to 3.9 years, and the SGLT2i class reduced similar events by 10% during 2.4 to 4.2 years.[59-61] Some GLP-1 RA (eg, liraglutide, dulaglutide, and semaglutide) and SGLT2i (eg, empagliflozin and canagliflozin) medications demonstrated benefits in individual trials. The CPG Work Group recommends using GLP-1 RA or SGLT2i with proven cardiovascular benefits to reduce the risk of major adverse CVD events in patients with T2DM and established CVD (recommendation 19).

Most patients enrolled in the GLP-1 RA and SGLT2i outcome trials had established CVD, but some trials also enrolled patients with high CVD risk. The data in patients with high CVD risk are less robust than

those in patients with established CVD. The CPG Work Group suggests use of GLP1-RA or SGLT2i with proven cardiovascular benefits in patients with high CVD risk (recommendation 20).

The SGLT2i medications also significantly reduce hospitalizations for heart failure.[60,61] The benefits are consistent across major patient subgroups including those with or without preexisting heart failure and CKD and in patients with reduced or preserved ejection fraction. The CPG Work Group recommends SGLT2i in patients with T2DM and heart failure to reduce heart failure hospitalizations (recommendation 21).

Two large systematic reviews showed that SGLT2i medications reduce the incidence of adverse kidney events by 38%.[60,61] Results were consistent across major patient subgroups including those with or without CVD and CKD. Empagliflozin, canagliflozin, and dapagliflozin demonstrated benefits in individual trials.[61-63] Of note, more than 80% of patients were concurrently prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at baseline, establishing the additive benefit of SGLT2i with these medications. The CPG Work Group recommends SGLT2i with proven renal protection to improve renal outcomes (recommendation 22).

There are no head-to-head studies comparing GLP-1 RA and SGLT2i on renal disease outcomes. A network meta-analysis in patients with and without albuminuria found SGLT2i had significantly lower risk of renal disease outcomes compared with GLP-1 RA.[64] However, not all patients are candidates for SGLT2i because of adverse effects or contraindications. Findings from systematic reviews showed that in patients with T2DM, GLP-1 RA also improved a composite kidney disease outcome by 21%,[65] with benefits largely driven by reduced onset of macroalbuminuria. This was significant in individual trials with liraglutide, semaglutide, dulaglutide, and efpeglenatide.[59,65] In contrast, GLP-1 RA did not slow declines in renal function or the need for renal replacement therapy.[65] Randomized clinical trials with renal outcomes as a primary end point in patients with CKD are not available for GLP-1 RA as for SGLT2i. Therefore, the CPG Work Group recommends use of GLP1 RA agents with proven renal protection to improve macroalbuminuria in patients with T2DM and CKD who are not candidates for SGLT2i (recommendation 23).

The benefits of select SGLT2i and GLP-1 RA medications on CVD and renal diseases may be independent of changes in HbA_{1c}. There is a significant relationship between change in HbA_{1c} and major adverse CVD events with SGLT2i and GLP-1 RA,[66] but this relationship was driven solely by reductions in nonfatal stroke with GLP-1 RA. Risk reductions for heart failure, nonfatal myocardial infarction, and CVD death were independent of changes in HbA_{1c}. A systematic review found greater changes in HbA_{1c} associated with reduced incidence of macroalbuminuria,[67] but there was no significant relationship between HbA_{1c} change and a composite renal outcome. The CPG Work Group suggests that SGLT2i or GLP1-RA be considered in patients with T2DM and CVD or renal disease, even if the patient has already achieved an individualized HbA_{1c} target range for glycemic control (recommendation 24).

COMPARISON WITH OTHER GUIDELINES

The VA/DoD CPG for diabetes, like many other professional guidelines, used an evidence-based review of studies to guide its recommendations. Its goal is to help clinicians and patients implement proven treatment strategies to prevent or to delay acute and chronic complications of diabetes and to improve quality of life.

The VA/DoD CPG for diabetes acknowledges some racial/ethnic contrasts in hemoglobin glycation that can result in different relationships between HbA_{1c} and mean glucose concentration. The CPG proposes that clinicians obtain corroborating evidence from plasma glucose levels or HbA_{1c} levels when each is near diagnostic thresholds to establish an accurate diagnosis of diabetes. This view is not shared by all guidelines.

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The VA/DoD CPG also continues to apply a risk-stratified approach to setting individualized HbA_{1c} target ranges based on life expectancy, comorbidities, patients' preferences, and absolute benefits and risks.

The scope of the VA/DoD CPG for diabetes is focused on the population of adult patients who are eligible for care in the VA and DoD health care systems. This includes veterans, most of whom are older adults, as well as deployed and nondeployed active-duty service members, their adult family members, and retirees and their beneficiaries or dependents. This CPG does not provide recommendations for diabetes management in children, adolescents, or pregnant/nursing women, although each may be part of the patient catchment.

In comparing the VA/DoD CPG for diabetes with other diabetes guidelines, all agree on the need for shared decision-making in HbA_{1c} goal setting. The Endocrine Society[68] generally concurs with the VA/DoD CPG on glycemic targets. The American Diabetes Association[69] and the American Association of Clinical Endocrinologists[70] recommend lower HbA_{1c} targets for most adults with T2DM, if they are acceptable and achieved safely. Some also include targets for CGM-generated time-in-range to reduce glycemic variability. The American Diabetes Association has discrete recommendations for older adults in which HbA_{1c} targets are similar to the VA/DoD CPG for diabetes. The American Diabetes Association and Endocrine Society recommend routine screening for geriatric syndromes or cognitive impairment in older adults, whereas the VA/DoD CPG for diabetes found insufficient evidence to support these steps. All agree on prioritizing medications with lower hypoglycemia risk, particularly in older adults, and in recommending use of SGLT2i and GLP-1 RA in patients with CVD and CKD and SGLT2i in heart failure.

CONCLUSION

The VA/DoD CPG for diabetes provides an evidence-based framework for evaluating and treating adults with T2DM to minimize preventable diabetes-related complications and mortality and to align with patient-centered goals of care. The CPG will help clinicians and patients make informed treatment decisions, using shared decision-making, and create treatment plans that optimize health outcomes and quality of life.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CGM**, continuous glucose monitoring; **CKD**, chronic kidney disease; **CPG**, Clinical Practice Guideline; **CVD**, cardiovascular disease; **DoD**, Department of Defense; **DSMES**, diabetes self-management education and support; **FIB-4**, fibrosis 4 index; **GLP-1 RA**, glucagon-like peptide 1 receptor agonist; **GRADE**, Grading of Recommendations Assessment, Development, and Evaluation; **HbA_{1c}**, hemoglobin A_{1c}; **NAFLD**, nonalcoholic fatty liver disease; **SGLT2i**, sodium-glucose cotransporter 2 inhibitor; **T2DM**, type 2 diabetes mellitus; **VA**, Department of Veterans Affairs

Affiliations (Continued from the first page of this article.): Care, McDonald Army Health Center, Fort Eustis, VA (A.E.L.); 2nd Medical Battalion, Camp Lejeune, NC (J.W.M.); Department of Veterans Affairs South Texas Healthcare System, San Antonio, TX (L.S.); Medical Readiness Command—Europe, Sembach, Germany (E.N.S.); Office of Nursing Service, Department of Veterans Affairs Long Beach Healthcare System, Long Beach, CA (S.A.W.); Department of Veterans Affairs Greater Los Angeles

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Correspondence: Address to Paul R. Conlin, MD, Medical Service, VA Boston Healthcare System, 1400 VFW Pkwy, West Roxbury, MA 02132 (paul.conlin@va.gov).

ORCID

Paul R. Conlin: https://orcid.org/0000-0001-5720-0466

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