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

Department of Veterans Affairs
Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) guidelines are based on the best information available at the time of publication. The guidelines 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 (CPG) 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 recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation with a patient-centered approach.

These guidelines are not intended to represent VA or DoD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both within these guidelines does not guarantee coverage of civilian sector care.

Version 6.0 – 2023

Prepared by

Management of Type 2 Diabetes Mellitus Work Group

With support from

Office of Quality and Patient Safety, Veterans Health Administration

and

Clinical Quality Improvement Program, Defense Health Agency

Version 6.0 – 2023[a]

Based on evidence reviewed through April 11, 2022

[a] Suggested citation: VA/DoD Clinical Practice Guideline. (2023). Management of Type 2 Diabetes Mellitus. Washington, DC: U.S. Government Printing Office.

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I. Introduction

The VA and DoD Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the VA/DoD Health Executive Committee "on the use of clinical and epidemiological evidence to improve the health of the population . . ." across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of CPGs for the VA and DoD populations.(1) Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and wellbeing.

In 2017, VA and DoD published a CPG for the Management of Type 2 Diabetes Mellitus in Primary Care (2017 VA/DoD DM CPG), which was based on evidence reviewed through 2016. Since the release of that CPG, the evidence base on type 2 diabetes mellitus (T2DM) has expanded. Consequently, the EBPWG initiated the update of the 2023 VA/DoD DM CPG in 2021. This updated CPG's use of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach reflects a more rigorous application of the methodology than previous iterations.(2) Therefore, the strength of some recommendations might have been modified because of the confidence in the quality of the supporting evidence (see Evidence Quality and Recommendation Strength).

This CPG provides an evidence-based framework for evaluating and managing care for adult patients with T2DM toward improving clinical outcomes. Successful implementation of this CPG will

- Assess the patient's condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care;
- Emphasize the use of patient-centered care and shared decision making;
- Minimize preventable complications and morbidity; and
- Optimize individual health outcomes and quality of life (QoL).

II. Background

A. Description of Type 2 Diabetes Mellitus

Diabetes mellitus (DM) is a disease caused by an absolute or relative insulin deficiency resulting in hyperglycemia. Type 1 DM (T1DM) is due to deficient insulin production and secretion and can present across the lifespan, with older patients often having a more indolent presentation that has been referred to as latent autoimmune diabetes of adults. In contrast, T2DM is due to progressive insulin deficiency on a background of insulin resistance. The underlying insulin resistance seen in T2DM is thought to be because of genetic factors and obesity, especially increased visceral adiposity, frequently accompanied by ectopic fat accumulation within organs such as the liver, pancreas, and

skeletal muscle. Prediabetes refers to the development of dysglycemia that does not reach the threshold for a diagnosis of diabetes. Gestational diabetes mellitus (GDM) is diabetes diagnosed in the second or third trimester of pregnancy that is typically not clinically overt. A variety of other causes of DM include diabetes due to monogenetic defects, including maturity-onset diabetes of the young; diabetes due to pancreatic diseases, such as chronic pancreatitis or cystic fibrosis; diabetes due to other endocrinopathies, including acromegaly or Cushing's syndrome; diabetes due to auto immune conditions; and diabetes due to medications.(3) This guideline focuses on T2DM and prediabetes.

Several criteria have been developed to diagnose T2DM and prediabetes. Prediabetes is usually seen on the continuum in the progression from normoglycemia to eventual T2DM.(3) Hyperglycemia insufficient 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. Both IFG and IGT are forms of prediabetes. 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 a rise in the incidence of retinopathy. However, differences exist among laboratories in the acceptable variability of HbA1c test values (i.e., accuracy and precision). Additionally, evidence suggests that racial or ethnic differences might exist such that HbA1c test results are sometimes incongruent with fasting blood glucose concentrations.(3, 4) Racial differences were reported among participants in the Diabetes Prevention Program (DPP); despite having comparable measures of glycemia, African Americans had significantly higher HbA1c levels (6.2%) than Whites (5.8%).(4) Therefore, these differences should be considered when a diagnosis of DM is suggested by HbA1c values between 6.5% and 7.0% or when making treatment decisions based on small changes in HbA1c. Racial differences might impact the relationship between HbA1c and glycemia.(3)

One may consider screening for T2DM or prediabetes in adults who are overweight or obese (body mass index [BMI] ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors, including the following.

- First-degree relative with T2DM(3)
- Member of a high-prevalence population (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)(3)
- Hypertension (blood pressure [BP] ≥140/90 mmHg or on therapy for hypertension)(3)
- High-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L), a triglyceride (TG) level >250 mg/dL (2.82 mmol/L), or both(3)
- History of cardiovascular disease (CVD)(3)

- Women with polycystic ovary syndrome(3)
- History of GDM(3) or history of delivering babies weighing >9 pounds (about 4 kg)
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)(3)
- Physical inactivity/sedentary lifestyle(3)
- Patients with human immunodeficiency virus(5)
- All adults over age 45

Consider, as well, screening in patients on medications increasing risk of T2DM, including antipsychotics, glucocorticoids, or statins.

The United States Preventive Service Task Force (USPSTF)[2] and the American Diabetes Association (ADA)[3] also suggest screening in all adults starting at age 35.(3, 6)

Table 1 summarizes the diagnosis criteria used by this Work Group.

Table 1: Criteria for the Diagnosis of Diabetes Mellitus and Prediabetes (7)

Status	Fasting Plasma Glucose [a,b] or HbA1c[c, d]
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% OR Two-hour plasma glucose on 75g OGTT of >200 mg/dl
Prediabetes	FPG ≥100 mg/dL **and** <126 mg/dL on two occasions **OR** HbA1c ≥5.7–6.4% **and** FPG ≥100 mg/dL (5.5 mmol/L) and <126 mg/dL (7.0 mmol/L) **OR** Two-hour plasma glucose on 75g OGTT of 140–199 mg/dL (7.8–11.0 mmol/L) (IGT)
Normal	FPG <100 mg/dL (<5.5 mmol/L) HbA1c <5.7%

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

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

[b] FPG is the preferred diagnostic test, but either of the two listed is acceptable. In the absence of unequivocal hyperglycemia with acute metabolic decompensation, one of these tests should be done on different days.

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

[d] The VA/DoD DM CPG recommends that when HbA1c values between 6.5% and 7.0% suggest diagnosis of diabetes mellitus, this observation should be confirmed with fasting plasma glucose levels to improve diagnostic specificity because HbA1c can vary among racial groups with comparable measures of glycemia.

An oral glucose tolerance test (OGTT) is not commonly used to diagnose DM. Although both the ADA and the American Association of Clinical Endocrinology guidelines include the OGTT as a diagnostic criterion for T2DM, it is cumbersome and needs better reproducibility, making it less useful for routine diagnosis than fasting plasma glucose (FPG) or A1C.

B. Epidemiology and Impact on the General Population

Both globally and within the United States (U.S.), T2DM is a highly prevalent disease, including within military and Veteran populations. Globally, a marked increase has occurred in T2DM prevalence from approximately 151 million in 2000 to 537 million individuals in 2021 affected worldwide.(8) The number of Americans with diagnosed DM in 2022 has followed a similar trend, with approximately 29 million diagnosed and approximately 8.5 million undiagnosed individuals, impacting 11.3% of the U.S. population and about 13% of adults. The vast majority (~95%) of Americans with diabetes have T2DM.(9) Overall, approximately one in eight American adults has diabetes, and about one in three has prediabetes,(10) many of whom are unaware of their diagnosis.

In the MHS, the prevalence of diagnosed DM ranged from 7.3–11.2% in 2006 and from 8.3–13.6% in 2010.(11) Although the prevalence among active duty Service members remained stable, a significant increase was observed over time among non-active Service members.(11) In 2010, the prevalence among non-active duty military men and women was 15.0% and 13.3%, respectively, for those age 45–64 years, 32.9% and 26.9%, respectively, for those age 65–74 years, and 31.5% and 25.7%, respectively, for those age 75 years and older.(11) According to the VHA, nearly one in four Veterans (1.6 million individuals) currently receiving VA care has DM. Veterans 65 years and older comprise 70% of those with diabetes, reflecting the older age distribution of this population.(12)

Often, T2DM is preceded by prolonged asymptomatic hyperglycemic period where microvascular and macrovascular damage occurs. T2DM occurs with other comorbid conditions that influence the disease's pathogenesis, course, complications, and treatment. Insulin resistance, which often develops in the context of obesity, is a cardinal feature of T2DM. The increased prevalence of T2DM is closely associated with the increased prevalence of obesity in the U.S. Currently, ~42% of Americans are considered obese; diabetes is present in 6.6% of normal weight, 10.3% of overweight, and 23.3% of obese individuals. Briefly, when white adipose tissue lipid storage capacity is exceeded, lipids accumulate in ectopic sites (e.g., liver, skeletal muscle) and activate cellular pathways that impair insulin signaling.(13) Diets, therapies, and activities that promote weight loss often decrease ectopic lipid accumulation and increase insulin sensitivity. T2DM often develops as one of many obesity-related conditions, including non-alcoholic fatty liver disease (NAFLD), and obstructive sleep apnea. In addition, chronic hyperglycemia increases the risk of developing

microvascular complications, such as retinopathy, nephropathy, and neuropathy. Additionally, the confluence of hyperglycemia and insulin resistance with other features of metabolic syndrome, including hyperlipidemia and hypertension, significantly increases the risk for macrovascular complications, including CVDs, such as ischemic heart disease, stroke, and peripheral vascular disease.(14) Other co-occurring conditions, such as chronic obstructive pulmonary disease (COPD), substance use disorder (SUD), and depression, can affect the management of T2DM. For guidance on addressing these comorbidities, see the respective VA/DoD CPGs for managing COPD, SUD, Overweight and Obesity (OBE), and Major Depressive Disorder.[a, b, c, d] Finally, T2DM and poor glycemic control might increase the risk of mortality from COVID-19 infection, and COVID-19 infection might itself increase the risk for development of T2DM in male veterans.(15, 16)

T2DM is a major contributor to 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 managing CVD risk factors and co-occurring conditions or comorbidities, refer to the VA/DoD CPGs for the Management of Hypertension, Chronic Kidney Disease (CKD), Dyslipidemia, and OBE.[e, f, g, d] The total costs of diagnosed DM in the U.S. were $327 billion in 2017, including $237 billion for direct medical costs and $90 billion in reduced productivity.(17) Direct costs in the VHA and MHS are unknown.

III. Scope of This Guideline

This CPG is based on published clinical evidence and related information available through 2022. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). Although the CPG is intended to improve quality of care and clinical outcomes (see Introduction), it is not intended to define a standard of care (i.e., mandated or strictly required care).

[a] 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/.
[b] 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/.
[c] See the VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity (OBE), available at https://www.healthquality.va.gov/guidelines/CD/obesity/.
[d] 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/.
[e] See the VA/DoD Clinical Practice Guideline for the Management of Hypertension (HTN), available at https://www.healthquality.va.gov/guidelines/cd/htn/index.asp.
[f] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease (CKD), available at https://www.healthquality.va.gov/guidelines/CD/ckd/index.asp.
[g] 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/.

A. Guideline Audience

This CPG is designed primarily to assist primary care clinicians in managing patients with T2DM. As applicable, this guideline could also be used by other members of the health care team involved in the care of Service members, beneficiaries, or Veterans with T2DM.

B. Guideline Population

The patient population of interest for this CPG is adults (≥18 years) with T2DM who are eligible for care in the VA or DoD health care delivery systems and those who receive care from community-based clinicians. It is not intended to guide the care of pregnant or nursing women or patients with T1DM.

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline Update

The 2023 VA/DoD Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus (VA/DoD DM CPG) was developed with the active engagement of a multidisciplinary team of clinicians whose expertise and broad perspectives helped create a document that addresses clinically relevant topics related to the diagnosis and treatment of T2DM in the ambulatory care setting. This CPG includes a number of updates from the 2017 VA/DoD DM CPG. The Work Group developed 12 key questions (KQ) to guide an evidence synthesis. From this evidence, 19 new recommendations were generated. Three recommendations from 2017 were replaced and four recommendations were amended and carried forward. In drafting its recommendations, the Work Group considered the strength of evidence, the balance of desired outcomes with potential harms, the potential for variation in patient values and preferences, and considerations such as resource use and equity.

Some of the recommendations are noteworthy or new, and the strength of the evidence recommendation is noted.

- Real-time continuous glucose monitoring might be a valuable adjunct to reduce the risk of hypoglycemia and improve HbA1c in insulin-treated T2DM patients. (Weak for)
- Intermittent fasting is not useful for weight reduction in patients with T2DM. (Weak against)
- High glycemic variability (e.g., as measured by HbA1c and fasting glucose) is a prognostic indicator for risks of hypoglycemia, morbidity, and mortality. (Weak for)
- Patients with T2DM with cardiovascular and renal diseases should receive medications associated with proven benefits for these indications to reduce disease-specific outcomes, complications, and mortality. (Strong for)

- Among older adults with T2DM, clinicians should prioritize medications other than insulin and sulfonylureas to achieve glycemic management goals and reduce risk of hypoglycemia. (Weak for)

Finally, the 2023 VA/DoD Type 2 Diabetes Mellitus CPG applied rigorous criteria for reviewing evidence compared with prior versions of this CPG. The GRADE methodology carefully define how data will be interpreted. It applies rating criteria that assign strength of evidence to critical outcomes, which might result in some recommendations being excluded or downgraded (see Evidence Quality and Recommendation Strength). However, these methods protect the integrity of the VA/DoD Type 2 Diabetes Mellitus CPG and ensure the recommendation statements are true to the underlying evidence.

B. Components of the Guideline

This CPG provides clinical practice recommendations for the care of patients with T2DM (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group has identified as needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and quick reference guide, which can be found at https://www.healthquality.va.gov/index.asp.

C. Racial and Ethnic Demographic Terminology in This Guideline

Demographic terms referring to an individual's race or ethnicity (e.g., Hispanic, Latino or Latina, Asian, Native American, Black, African American, White, Caucasian) can be ambiguously defined and understood, reflecting diverse geographies, histories, cultures, and experiences. Aligned with the recent Executive Order on Further Advancing Racial Equity and Support for Underserved Communities through the Federal Government,[h] the Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and to promote inclusivity, clarity, and consistency. However, to represent accurately the evidence on which this CPG is based, the Work Group generally deferred to racial and ethnic terminology as reported in the published systematic reviews (SR), clinical trials, and other studies comprising that evidence when summarizing or otherwise referring to those studies. Consequently, usage of demographic terms in this CPG might appear inconsistent.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group:

[h] Executive Order on Further Advancing Racial Equity and Support for Underserved Communities Through The Federal Government | The White House

Paul Conlin, MD, and Leonard Pogach, MD, from VA and Curtis Hobbs, MD, and Evan Steil, MD, from DoD.

The Work Group comprised individuals with the following areas of expertise: psychiatry, psychology, internal medicine, nursing, primary care, pharmacy, mental health counseling, and social work. Table 2 lists the Work Group and Guideline Development Team members.

This CPG Work Group, led by the Champions, was tasked with

- Determining the scope of the CPG;
- Crafting clinically relevant KQs to guide the systematic evidence review;
- Identifying discussion topics for the patient focus group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, and Duty First Consulting, was contracted by VA to help develop this CPG.

Table 2. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Paul Conlin, MD (Champion)**
	Leonard Pogach, MD, MBA, FACP (Champion)
	Brian Burke, MD
	Angela Giles, DBH, LCSW, DAPA
	Kathryn Hurren, PharmD, CDCES
	Mary Julius, RDN, LD, CDCES
	Sei Lee, MD, MAS
	Peter Reaven, MD
	Varman Samuel, MD, PhD
	Lance Spacek, MD
	Sharon Watts DNP, FNP-BC, CDCES
	Jane Weinreb, MD

Organization	Names*
Department of Defense	**Curtis Hobbs, MD, FACP (Champion)**
	Evan Steil, MD, MBA, MHA, FAAFP (Champion)
	Adam Edward Lang, PharmD
	Susan McReynolds, RDN, CD, CDCES
	John W. Morrison, Jr. DO, MPH, FACP
	Felicia Sherlin, RN
	Tiffany Williams, DNP
	Tracy Worrell, RN
VA Evidence Based Practice, Office of Quality and Patient Safety Veterans Health Administration	James Sall, PhD, FNP-BC
	Jennifer Ballard-Hernandez, DNP, RN, FNP-BC
	René Sutton, BS, HCA
	Eric Rodgers PhD, FNP-BC
Clinical Quality Improvement Program Defense Health Agency	Elaine P. Stuffel, MHA, BSN, RN
	Cynthia F. Villarreal, BSN, RN
The Lewin Group	Cliff Goodman, PhD
	Erika Beam, MS
	Savannah Kucera, MPH
	Charlie Zachariades, MSc
	Andrea Dressel, BS
	Amanda Heinzerling, MS
ECRI	Stacey Uhl, MS
	Ilya Ivlev, MD, PhD, MBI
	Allison Gross, MLIS
Sigma Health Consulting	Frances M. Murphy, MD, MPH
	James G. Smirniotopoulos, MD
Duty First Consulting	Kate Johnson, BS
	Rachel Piccolino, BA
	Anita Ramanathan, BA

*Additional contributor contact information is available in Appendix G.

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA/DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(18) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(19) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction).(20)

1. Confidence in the quality of the evidence
2. Balance of desirable and undesirable outcomes
3. Patient values and preferences
4. Other considerations, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). 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 incorporates the four domains.(21) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

In some instances, insufficient evidence exists on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this finding is expressed in the CPG might vary. In such instances, the Work Group might include among its set of recommendations a statement of insufficient evidence for an intervention that might be in common practice although it is unsupported by clinical evidence and particularly if other risks of continuing its use might exist (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might decide to exclude this type of statement about an intervention. For example, the Work Group might remain silent where an absence of evidence occurs for a rarely used intervention. In other cases, an intervention might have a favorable balance of benefits and harms but might be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in Table 3.

Table 3. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest . . .
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

That a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence based and still important to clinical care) is important to note. The strength of each recommendation is shown in the Recommendations.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations; the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies might be inherently more difficult (e.g., randomized controlled trials [RCT]) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted might more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2, 22) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of 2017 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(23) For example, the USPSTF has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every 5 years for either an update or reaffirmation.(24)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(25, 26) Table 4 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the

degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2023 CPG recommendation categories can be found in Recommendations. Appendix F outlines the 2017 VA/DoD DM CPG's recommendation categories.

Table 4. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012)(25) and Garcia et al. (2014)(26)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(18) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care)(27) as well as to disclosure statements (i.e., standard disclosure form completed at least twice by CPG Work Group members and the guideline development team).(18) The disclosure form inquires regarding relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were subject to random web-

based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments, ProPublica).

No COIs were identified among the CPG Work Group or the guideline development team. If an instance of potential or actual COI had been reported, it would have been referred to the VA and DoD program offices and reviewed with the CPG Work Group Champions. The VA and DoD program offices and the CPG Work Group Champions would have determined whether and, if so, what further action was appropriate (e.g., excusing Work Group members from selected relevant deliberations or removal from the Work Group). Disclosure forms are on file with the VA Office of Quality and Patient Safety and are available on request.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(22, 28) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on December 15, 2021. The focus group aimed to gain insights into patients with DM of potential relevance and incorporate these insights into the CPG, as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care and impacts of their care on their lives.

The patient focus group comprised a convenience sample of four people. There were two males and two females. One participant was a Veteran who received care from the VA health system, and three participants received care from the DoD health system. The Work Group acknowledges this convenience sample is not representative of all patients with DM within the VA and DoD health care systems and, thus, findings are ungeneralizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix D. Patient focus group participants were provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified experts from VA and DoD health care systems and outside organizations generally viewed as experts in the respective field to review it. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual health care providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient with T2DM. The Work Group submits suggested performance metrics for VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in the Department of Veterans Affairs and the Department of Defense

A. Patient-Centered Care

Intended to consider patient needs and preferences, guideline recommendations represent a whole/holistic health approach to care that is patient centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and wellbeing.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.(29, 30) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and wellbeing goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to sex culture, ethnicity, and other differences.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making, a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(31) Shared decision making is emphasized in *Crossing the Quality Chasm,* an Institute of Medicine, now NAM, report in 2001 (32) and is inherent within the whole/holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels or settings of care or both, especially where patient heterogeneity in weighing risks and benefits might exist. Veterans Health Administration

and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to managing T2DM. Many Veterans, active duty Service members, and their families have one or more co-occurring conditions. Because T2DM is sometimes accompanied by co-occurring conditions, managing T2DM collaboratively with other care providers is often best. Some co-occurring conditions might require early specialist consultation to determine necessary changes in treatment or to establish a common understanding of how care will be coordinated. This approach might entail reference to other VA/DoD CPGs (e.g., for Chronic Kidney Disease, Overweight and Obesity, Hypertension, Dyslipidemia, and Pregnancy).[i]

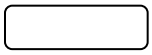
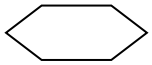
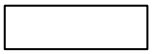
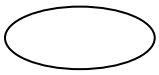
VIII. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision-making process used in managing patients with T2DM. This algorithm format represents a simplified flow of the management of patients with T2DM and helps foster efficient decision making by providers. It includes

- Steps of care in an ordered sequence,
- Decisions to be considered,
- Decision criteria recommended, and
- Actions to be taken.

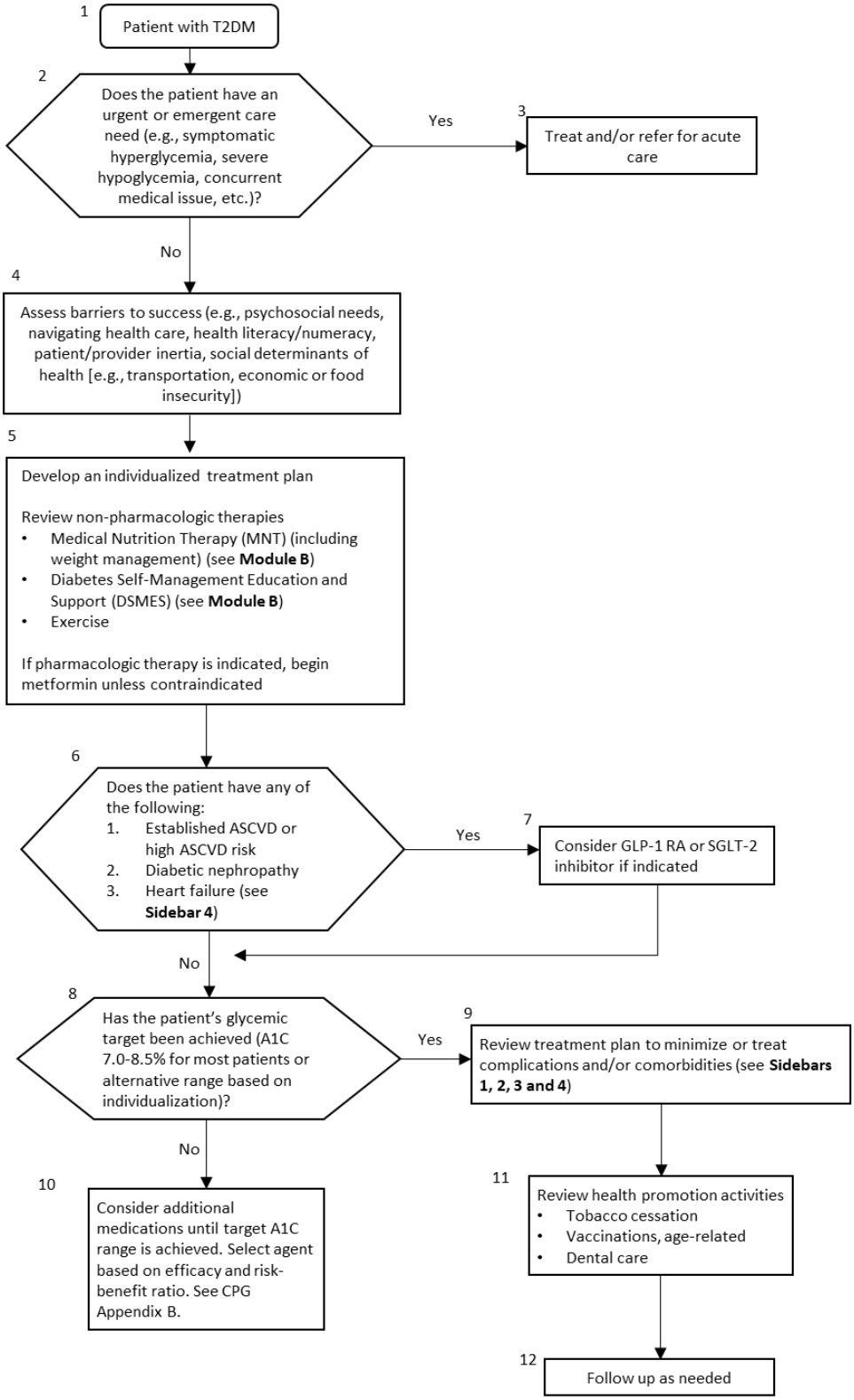
The algorithm is a step-by-step decision tree. Standardized symbols display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(33) Sidebars 1–8 provide more detailed information to assist in defining and interpreting elements in the boxes.

[i] The VA/DoD Clinical Practice Guidelines are available at https://www.healthquality.va.gov/.

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered “Yes” or “No”
	Rectangles represent an action in the process of care
	Ovals represent a link to another section within the algorithm

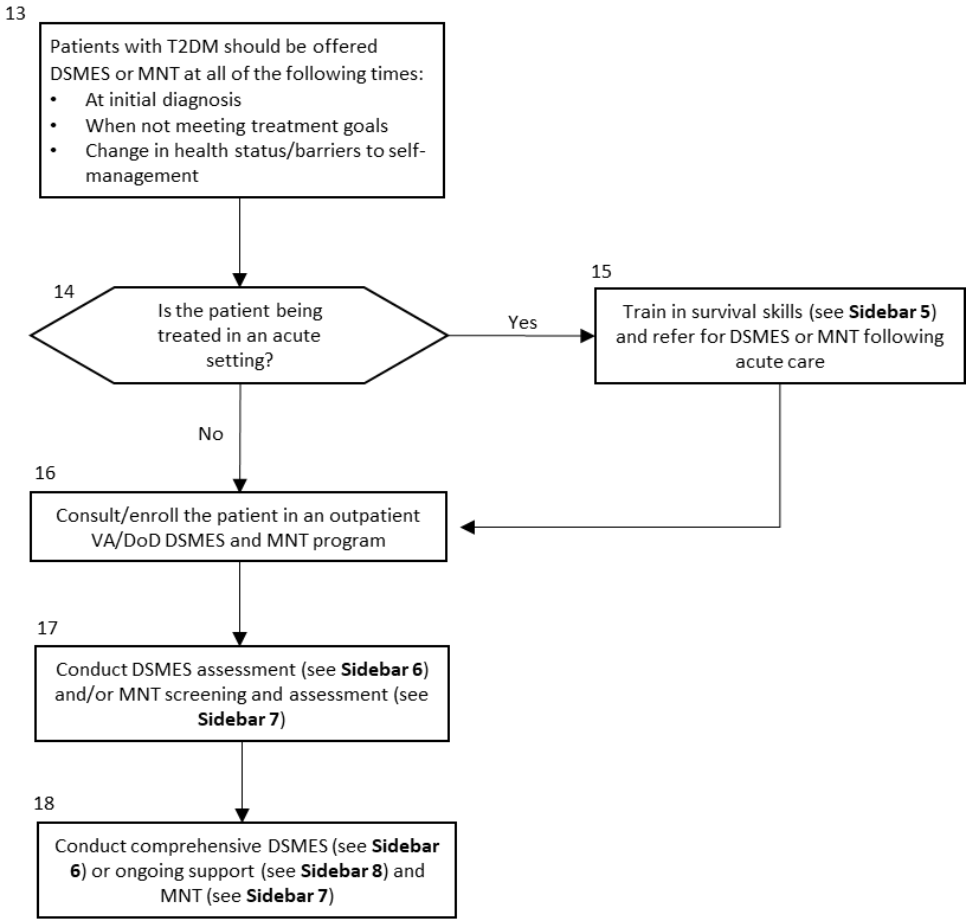
Appendix I contains alternative text descriptions of the algorithm.

A. Module A: T2DM Management



Abbreviations: ASCVD: atherosclerotic cardiovascular disease; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SGLT-2 inhibitor: sodium-glucose transporter 2 inhibitor; MNT: Medical Nutrition Therapy; T2DM: type 2 diabetes mellitus

B. Module B: Self-Management Education and Support



Abbreviations: DoD: Department of Defense; DSMES: diabetes self-management education and support; MNT: Medical Nutrition Therapy; T2DM: type 2 diabetes mellitus; VA: Department of Veterans Affairs

Sidebar 1: Neuropathy and Foot Care
• Perform a comprehensive lower extremity risk assessment (including monofilament) annually and as needed. • Refer patients with limb-threatening conditions. • Provide pain management as needed.

Sidebar 2: Retinopathy and Eye Care
• Provide BP, glycemic, and lipid management. • Provide a dilated fundus examination by an eye care professional or retinal imaging with interpretation by a qualified, experienced reader to detect retinopathy. • Obtain a retinal examination within 6 months of a new T2DM diagnosis and biennial screening for retinopathy for patients with no history of retinopathy on all prior examinations. • For some, more frequent retinal examinations might be indicated (e.g., patients with additional risk factors, existing retinopathy, risk factors for progression of retinopathy).

Abbreviations: BP: blood pressure; T2DM: type 2 diabetes mellitus

Sidebar 3: Nephropathy and Kidney Care

- Consider guideline-directed treatments and targets (see VA/DoD CPG for CKD).
- Monitor urine microalbumin/creatinine ratio at least annually.
- Consider ACEi/ARB use in patients with HTN, moderately increased albuminuria (i.e., microalbuminuria), or CKD.
- Consider SGLT-2 inhibitor or GLP-1 RA use in patients with diabetic nephropathy.
- Avoid nephrotoxic medications (e.g., NSAIDs).

Abbreviations: ACEi: ACE inhibitor; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; CPG: clinical practice guideline; GLP-1 RA: glucagon-like peptide-1 receptor agonist; NSAID: non-steroidal anti-inflammatory drug; SGLT-2 inhibitor: sodium-glucose cotransporter 2 inhibitor

Sidebar 4: Comorbidities

- Consider guideline-directed treatments and targets (see VA/DoD CPGs for hypertension, dyslipidemia, obesity, CKD).
- Consider VA/DoD DM guideline-directed therapy for ASCVD and heart failure.

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CPG: clinical practice guideline

Sidebar 5: Basic Education and Survival Skills, as Needed

- Healthy eating
- Use of prescribed medication
- Ways to recognize and treat hypoglycemia and hyperglycemia
- Use of a glucose meter
- Management of glucose on sick days and knowing when to call the provider

Sidebar 6: Comprehensive DSMES

- Assessment, including food insecurity and diabetes distress
- T2DM disease overview
- Monitoring (e.g., home glucose, HbA1c, BP, lipids, eGFR, moderately increased albuminuria [i.e., microalbuminuria])
- Nutrition and healthy eating
- Comprehensive assessment and education on 8 topics
  1. Diabetes physiology
  2. Monitoring
  3. Healthy coping
  4. Taking medications
  5. Healthy eating
  6. Being active
  7. Reducing risk
  8. Problem solving
- Individualized approach based on shared decision making

Abbreviation: BP: blood pressure; DSMES: diabetes self-management education and support; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; T2DM: type 2 diabetes mellitus

Sidebar 7: Medical Nutrition Therapy
• Assessment (including food insecurity) • Nutrition diagnosis and intervention • Monitoring and reevaluation

Sidebar 8: DSMES Ongoing Support
• Reassess and reeducate patient and family, support person, or both, as necessary. ♦ Change of treatment regimen or care team ♦ Change in health/cognitive/emotional/social status • Maintain self-management gains by leveraging patient's community and primary care to reinforce education.

IX. Recommendations

The evidence-based clinical practice recommendations listed in Table 5 were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences and other implications (e.g., resource use, equity, acceptability).

Table 5. Evidence-Based Clinical Practice Recommendations with Strength and Category

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Prediabetes	*Exercise/ Nutrition*	1.	In adults with prediabetes, we suggest aerobic exercise (such as walking 8–9 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.	Weak for	Reviewed, New-added
	Pharmacotherapy	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 (e.g., 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	Reviewed, New-added
Telehealth		3.	In adults with type 2 diabetes mellitus, we suggest offering health care delivered through telehealth interventions to improve outcomes.	Weak for	Not Reviewed, Amended

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of Type 2 Diabetes Mellitus	*Screening for Comorbidities*	4.	There is insufficient evidence to recommend for or against routine screening or using a specific tool to screen for or diagnose diabetes distress.	Neither for nor against	Reviewed, New-added
		5.	In adults with type 2 diabetes mellitus and co-occurring non-alcoholic fatty liver disease, we suggest clinicians should assess for fibrosis using a non-invasive tool (e.g., Fibrosis-4).	Weak for	Reviewed, New-added
		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	Reviewed, New-added
	Diabetes Self-Management Education and Support	7.	In adults with type 2 diabetes mellitus, we recommend diabetes self-management education and support.	Strong for	Not Reviewed, Amended
	Glycemic Management	8.	For adults with type 2 diabetes mellitus, we suggest using high glycemic variability over time (e.g., fluctuation in HbA1c or fasting blood glucose) as a prognostic indicator for risk of hypoglycemia, morbidity, and mortality.	Weak for	Reviewed, New-replaced
		9.	We suggest setting an individualized HbA1c 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	Not reviewed, Amended
		10.	We suggest an HbA1c range of 7.0–8.5% for most patients, if it can be safely achieved.	Weak for	Not reviewed, Amended
		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 improve HbA1c.	Weak for	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Non-pharmacotherapy	*Medical Nutrition Therapy*	12.	For adults with type 2 diabetes mellitus, we suggest a Mediterranean style diet to improve glycemic control, body weight, and hypertension.	Weak for	Reviewed, New-replaced
		13.	For adults with type 2 diabetes mellitus, we suggest a nutrition intervention strategy providing 13–50% of their total daily caloric intake from carbohydrates for diabetes management.	Weak for	Reviewed, New-replaced
		14.	For adults with type 2 diabetes mellitus, we suggest a vegetarian dietary pattern for glycemic control and weight loss.	Weak for	Reviewed, New-added
		15.	For adults with type 2 diabetes mellitus, we suggest against intermittent fasting.	Weak against	Reviewed, New-added
	Exercise	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, or tai chi.	Weak for	Reviewed, New-added
	Stress	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	Reviewed, New-added
		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	Reviewed, New-added
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	Reviewed, New-added
		20.	For adults with type 2 diabetes mellitus at high risk of atherosclerotic cardiovascular disease (i.e., 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	Reviewed, New-added
		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	Reviewed, New-added
		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	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
		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	Reviewed, New-added
		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 their individualized target range for glycemic control.	Weak for	Reviewed, New-added
		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	Reviewed, New-added
		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	Reviewed, New-added

[a] For additional information, see Determining Recommendation Strength and Direction.

[b] For additional information, see Recommendation Categorization and Appendix E.

A. Prediabetes

Recommendation

1. In adults with prediabetes, we suggest aerobic exercise (such as walking 8-9 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.
   (Weak for | Reviewed, New-added)

Discussion

The systematic evidence review returned two articles that addressed findings associated with prediabetes.(34, 35) In an RCT by Mora-Rodriguez et al. (2020), the authors studied patients with prediabetes and metabolic syndrome. They compared treatment with aerobic exercise versus no exercise, with both groups receiving nutritional education and weight assessments. The exercise group did 43 minutes of interval training three times weekly. After 16 weeks, the exercise group demonstrated greater reductions in fasting blood glucose. Although no significant difference in weight loss between the study groups was found, patients who achieved a >3% body weight loss had significant improvement in insulin sensitivity.

Another RCT by Stentz et al. (2016) referenced the CDC DPP (2010), which had established lifestyle interventions—weight loss, diet, and exercise—as the “gold

standard" for the prevention of T2DM.(35) The authors designed the study to separate the exercise component from the diet and weight loss in preventing the progression to T2DM. The patients were randomized into four groups for the interventions: (1) low amount/moderate intensity exercise, (2) high amount/moderate intensity exercise, (3) high amount vigorous intensity, and (4) a group that mimicked the DPP standards of diet and weight loss education and low amount/moderate exercise. Stentz et al. (2016) defined moderate intensity exercise as 50% of VO2 reserve, and vigorous exercise as 75% of VO2 reserve. The VO2 reserve is the difference between resting VO2 and peak VO2.(34)

Lasting 6 months, the study compared baseline and post-intervention metabolic blood values, with the primary focus on improvements in glucose homeostasis. The authors found no significant difference between the intervention groups in FPG or weight loss. However, they saw significant improvement in the FPG in the DPP-like control group.

The authors also looked at OGTT testing, comparing results from before and after exercise interventions in all four groups. The OGTT was performed after a 10-hour overnight fast, with a 75-gram glucose bolus and samples drawn at 0, 30, 60 90, and 120 minutes. The authors found significant reduction in Glucose AUC (area under the curve) values in the OGTT in two groups: the high amount/moderate intensity exercise group (6.4%) and the DPP-like control group (8.2%). Counterintuitively, the high amount/vigorous exercise group did not significantly improve Glucose AUC after the intervention, with only a 1.2% reduction.

Lastly, the authors reviewed the Matsuda index, a calculated composite of the values of glucose and insulin (both fasting and AUC) from the 2-hour OGTT. In all the groups, the post intervention index scores were improved from the baseline. However, the DPP-like control group had a 188–269% greater improvement than the three intervention groups.

The authors determined that the high amount/moderate intensity exercise was comparable to 13.8 miles per week walking. This group averaged 5.3 hours weekly for women and 4.1 hours weekly for men of moderate exercise.(35) However, the DPP-like control group's approach of changes in diet, weight loss, and low amount/moderate exercise would require only about 8.6 miles per week of walking. This pace corresponded to a weekly average of 2.7 hours for men and 3.1 hours for women.(35)

The Work Group recommended future research to clarify the benefits of different types of physical activity and specific times, intervals, and intensity. In addition, a study to elucidate why certain individuals succeed in changes in lifestyle—whether physical activity, weight loss, or diet—might help patients in self-managing prediabetes.

The Work Group systematically reviewed evidence related to this recommendation. (34, 35) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and a high dropout rate for the exercise

interventions. The evidence GRADE rating for the outcomes of FBG and weight loss were very low. The benefits of moderate aerobic exercise combined with healthy eating for reduction in body fat, weight loss, and improvement in fasting blood glucose slightly outweighed the potential harm from injury and challenges, such as financial burdens and safety in using a gym or, if outdoors, weather. Patient values and preferences varied somewhat because some patients prefer alternative treatments, such as exercise and diet, but others might prefer medication or no treatment for prediabetes. Thus, the Work Group made the following recommendation: In adults with prediabetes, we suggest aerobic exercise (such as walking 8–9 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.

Recommendation

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 (e.g., 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 | Reviewed, New-added)

Discussion

The systematic evidence review retrieved four RCTs from four SRs that assessed the efficacy of pharmacotherapy in preventing the progression to T2DM in patients with prediabetes. The studies looked at the effectiveness of different drug classes compared with placebo, diet and exercise, no intervention, direct drug-to-drug comparisons, or any combination of the foregoing.(36–43) The quality of evidence for drug-to-drug comparison ranged from low to very low. However, when evaluating the efficacy of medications compared with placebo, along with additional comparators, the quality of evidence was insufficient to moderate. Evidence suggests metformin reduces the risk of progression of prediabetes to T2DM.(39) Madsen et al. (2019) found that treatment with metformin significantly reduced rates of progression (relative risk [RR]: 0.50; 95% confidence interval [CI]: 0.41–3.01) compared with placebo or standard care with diet and exercise over a 1- to 5-year time period.(39) This SR also compared metformin to thiazolidinediones, acarbose, and intensive exercise and diet. It found no difference between metformin and any of these three groups; however, these studies included either smaller sample sizes or were of lower evidence quality than the placebo-controlled trials with metformin. In comparing pioglitazone to placebo, Ipsen et al. (2020) demonstrated that treatment was associated with high glucose-lowering efficacy with decreased incidence of progression to T2DM during the treatment period, from 6 months to 36 months (RR: 0.40; 95% CI: 0.17–0.95).(36) And, although not part of the systematic evidence review, Fernando et al. (2017) showed benefit with pioglitazone in patients with non-alcoholic steatohepatitis; however, the side effects of weight gain, fluid

retention, and exacerbation of congestive heart failure would likely worsen in patients at increased risk.(44) Acarbose was found to be superior to placebo in preventing progression to T2DM (RR: 0.82; 95% CI: 0.75–0.89) in the SR by Moelands et al. (2018). The same was found for liraglutide versus placebo in Hemminsen et al. (2017) (RR: 0.28; 95% CI: 0.18–0.45). In these instances, the quality of evidence was moderate for decreased incidence of progression to T2DM. When comparing dipeptidyl-peptidase-4 inhibitors, the critical outcome of progression to T2DM was evaluated only in the case of vildagliptin versus placebo, which was inconclusive and very low-quality evidence.

When looking at the drug-to-drug comparison, no difference was found between pioglitazone versus acarbose, metformin versus acarbose, and pioglitazone versus metformin in the progression to T2DM.(36, 39) However, although the evidence favored pioglitazone versus placebo, as previously mentioned, careful consideration should be given to patient specific characteristics before recommending medications with proven adverse events, as in the case of pioglitazone and history of heart failure (HF). Furthermore, most adults age 75 and older appear to experience no harms from prediabetes, suggesting prediabetes might be less clinically relevant in this patient population.(45) (Rooney et al. 2021).

There is likely a large variation in patient preferences with these pharmaceutical interventions based on risk versus benefit, delivery method, dosing schedules, and medication side effect profile. For instance, patients might be reluctant to take a daily injection versus a pill. In addition, medication side effect profile for these drug classes—for example, gastrointestinal (acarbose and glucagon-like peptide-1 receptor agonist [GLP-1 RA]), weight gain, fluid retention, visual changes (pioglitazone)—might be more problematic for some patients based on their characteristics or might be beyond a patient's comfort level. The side effects of each medication should be reviewed with the patient. Furthermore, patients' personal beliefs might favor lifestyle interventions versus medication for prediabetes.

The use of medication beyond metformin in the treatment of individuals with prediabetes is an area of active research and without current consensus. Several recent studies, unavailable at the time of the literature search or not included in our evidence base because of exclusion and inclusion criteria, offer compelling arguments for the consideration of additional classes of medications in the management of prediabetes. In their meta-analysis of 5,655 adults with prediabetes and HF or CKD, Mori et al. (2023) found a 20% reduction in progression to new-onset T2DM in the group treated with sodium-glucose transporter 2 (SGLT-2) inhibitors versus placebo.(46) Similarly, The STEP trial demonstrated improvement in HbA1C, fasting glucose, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in patients with prediabetes when treated with once-weekly semaglutide versus placebo.(47) Furthermore, changing formularies and pricing might influence preferences for specific medications based on

patient characteristics. We recommend that clinicians continue monitoring the most up-to-date research for evidence-based changes in practice management related to prediabetes.

The Work Group systematically reviewed evidence related to this recommendation. (36-43) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The evidence had some limitations, including the fact that adverse events were being poorly reported in the SR or in some of the individual RCTs. Overall, the sample size in some studies was low, and follow-up varied from 6.0 months to 3.5 years. In patients who are poor candidates for metformin, the benefits of using an alternative medication to prevent progression of prediabetes to T2DM slightly outweighed the potential harm of side effects, such as nausea and diarrhea. Patient values and preferences varied largely because of varying dosing and delivery options and personal beliefs. Thus, the Work Group made the following recommendation: 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 (e.g., 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.

B. Telehealth

Recommendation

3. In adults with type 2 diabetes mellitus, we suggest offering health care delivered through telehealth interventions to improve outcomes.
   (Weak for | Not reviewed, Amended)

Discussion

Evidence suggests that delivering care via telehealth is an option in treating patients with T2DM. However, telehealth studies in patients with T2DM are limited and heterogeneous. Tildesley et al. (2011) conducted a study (n=46) in which participants were randomized to an internet-based blood glucose monitoring system (IBGMS) uploaded every 2 weeks to a secure, commercially available website plus conventional care with endocrinology or to conventional care with endocrinology only. A statistically significant decrease occurred in HbA1c for the IBGMS group (adjusted HbA1c difference -1.3%) compared with the control group (adjusted HbA1c difference -0.1%) for up to 6 months of follow-up. However, patients returned to conventional care after 6 months, and the effect was unsustainable at the 12-month mark.(48) Shea et al. (2009) (n=1,665) evaluated registered nurse (RN) case management telehealth versus treatment as usual (TAU) in patients age ≥55 years. 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 5 years of follow-up, but the difference in HbA1c

reduction was not clinically significant (telemedicine: mean 7.09 ± 0.06 versus TAU: mean 7.38 ±0.06; treatment effect: 0.29; 95% CI: 0.12–0.46).(49)

Two other studies involved primary care providers (PCP) using telehealth.(50, 51) Holbrook et al. (n=511) evaluated a web-based diabetes tracker shared between patients and their PCPs.(50) A statistically significant improvement in HbA1c, but not in quality of life, was found in the intervention group compared with 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.(51) Transmitted data were reviewed by the clinic registered nurse (RN), and if issues were identified they were shared with the provider. No significant difference was found in changes in HbA1c from baseline to 6 months of follow-up. Pacaud et al. (2012) compared three models of education and communication support in patients newly diagnosed with T2DM (n=68): (1) web static (virtual appointments using asynchronous communication) versus (2) web interactive (electronic communication and virtual appointments using synchronous and asynchronous communication) versus (3) a control group (face-to-face education, both synchronous and asynchronous).(52) No overall significant differences were found among the three groups.

The systematic evidence review from the 2017 VA/DoD DM CPG focused on the comparative effectiveness of various telehealth modalities requiring physician interaction or supervision versus standard patient management in improving T2DM-related outcomes. Only three of the five studies identified involved physician interaction and the quality of this research was graded as low. One study evaluated patient education only via telehealth.(52) Another study, graded as moderate quality, used an RN for case management.(53) The Work Group anticipates that how telehealth interventions are provided will continue to expand with technological innovations.

The Work Group considered the assessment of the evidence put forth in the 2017 VA/DoD DM CPG related to this recommendation.(48, 50–53) Therefore, it is categorized as *Not Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small sample size, confounding variables, and the heterogeneity of the telehealth interventions. Notably, no single study reported harm associated with the telehealth intervention, and outcomes ranged from neutral to moderately beneficial.(48, 50) The Work Group anticipates that although some patients might prefer telehealth care delivery methods to improve access to care and decrease wait time, others might find the technology challenging, the environment impersonal, and the provider-patient relationship diminished. Thus, the Work Group made the following recommendation: In adults with type 2 diabetes mellitus, we suggest offering health care delivered through telehealth interventions to improve outcomes.

C. Diabetes Mellitus

Recommendation

4. There is insufficient evidence to recommend for or against routine screening or using a specific tool to screen for or diagnose diabetes distress.
   (Neither for nor against | Reviewed, New-added)

Discussion

The Work Group found no evidence in the systematic evidence review related to this recommendation for screening for diabetes distress or using a specific tool for such screening.

Diabetes distress is a term used to describe multiple negative emotions related to having diabetes.(54) Some emotions might be guilt, anger, sadness, or a sense of helplessness. Therefore, identifying patients who might have diabetes distress and assisting them with tools for lifestyle balance and self-management of their disease is important.

The Work Group rendered no opinion on confidence in the quality of the evidence because no evidence was available.

The Work Group systematically searched for evidence and did not identify any studies that met inclusion criteria regarding routine screening for diabetes distress or assessing the diagnostic accuracy of specific screening tools used to screen for or diagnose diabetes distress. Therefore, this recommendation is categorized as *Reviewed, New-added*. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against routine screening or using a specific tool to screen for or diagnose diabetes distress.

Recommendation

5. In adults with type 2 diabetes mellitus and co-occurring non-alcoholic fatty liver disease, we suggest clinicians should assess for fibrosis using a non-invasive tool (e.g., Fibrosis-4).
   (Weak for | Reviewed, New-added)

Discussion

Non-alcoholic fatty liver disease (NAFLD) is generally defined as hepatic steatosis not attributable to alcohol consumption or other secondary causes of fatty liver. In addition to obesity, T2DM is one of the leading risk factors for NAFLD. Patients with T2DM are at two-fold higher risk of NAFLD compared with the general population. Estimates indicate that approximately 50–70% of patients with T2DM have NAFLD, many of whom have early disease characterized by steatosis in isolation, without attendant hepatocyte injury or significant fibrosis.(55–57) The absence of hepatocellular injury and fibrosis indicates lower risk for complications of NAFLD, such as decompensated cirrhosis, hepatocellular carcinoma, and liver-related death. Patients with T2DM are also at increased risk for

progressive disease such as non-alcoholic steatohepatitis (NASH), a more severe form of fatty liver disease associated with a greater risk of advanced fibrosis and cirrhosis. Approximately 70% of patients with T2DM and NAFLD are diagnosed with biopsy-proven NASH, which is two to three times the incidence in the general population.(57) The fact that all-cause and liver-related mortality and morbidity are tightly correlated with advanced fibrosis and cirrhosis raises concern that patients with T2DM are a population uniquely predisposed to progressive liver disease and, consequently, poorer outcomes.(58)

The clinical utility of screening patients with T2DM for NAFLD is determined by various factors, including disease prevalence, accuracy of diagnostic tools, and availability of effective treatment. 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. Alternatively, the diagnostic accuracy of a given test (e.g., sensitivity, specificity, predictive values) illuminates one element of the screening framework by informing decisions to choose between diagnostic tests based on differences in reliability, if screening is pursued. As such, the Work Group deemed it important and relevant for clinical practice to concurrently assess the literature for both the clinical utility of screening and the diagnostic accuracy of various testing methods for NAFLD.

Given the considerable consequences of NAFLD, the Work Group felt that recognizing that some organizations have advocated screening for NAFLD based on biological plausibility is important.(59, 60) However, our systematic evidence review found no studies evaluating the clinical utility of screening for NAFLD in patients with T2DM. Although T2DM is a risk enhancer for NAFLD and disease progression, prospective trials to bolster the claims that screening improves clinical outcomes are lacking. Furthermore, concerns about potential harms from unnecessary testing and treatments accompanying false positives and incidental findings are amplified when the benefit of screening is predicated on presumption rather than evidence. The potential benefits are promising, but additional studies are needed to clarify the effects on patient-oriented outcomes and any potential unintended consequences associated with screening for NAFLD.

In patients with T2DM and co-occurring NAFLD, assessing for advanced fibrosis has important implications for staging and prognosis. Although liver biopsy remains the gold standard for diagnosing advanced fibrosis, various noninvasive methods might be prioritized to avoid the procedural complications associated with biopsy. Magnetic resonance elastography and transient elastography with ultrasound are examples of imaging modalities that may be used to noninvasively diagnose advanced liver fibrosis. Although the evidence to support these technologies is more robust in the general population, our systematic evidence review found no studies evaluating their diagnostic accuracy in patients with T2DM. Consequently, we were unable to make a statement about their diagnostic fidelity, either individually or comparatively, in patients with T2DM. The Work Group recognizes that evidence supporting the accuracy of imaging in the

general population might be extrapolated to patients with T2DM and used as justification for their application in clinical practice.

Other noninvasive methods that require no imaging may be used to assess advanced liver fibrosis in patients with T2DM and co-occurring NAFLD. These methods include calculators based on clinical prediction modeling, such as the FIB-4, non-alcoholic fibrosis score (NFS), AST-to-platelet ratio index, and aspartate aminotransferase/ alanine aminotransferase (AST/ALT) ratio. These calculators use routinely available demographic information and laboratory data to classify patients according to the probability of having advanced liver fibrosis, often defined as F3 and F4 by histopathological criteria. Although evidence supports reasonable diagnostic accuracy, these tests perform modestly in patients with T2DM and NAFLD. For example, although they have demonstrated some degree of discriminative ability, the c-statistics from receiver operating curves have all fallen short of generally accepted thresholds for clearly useful discrimination.(61) The FIB-4 test has consistently performed favorably compared with other prediction models when studied in patients with T2DM.(61, 62) This test is the only one with evidence demonstrating likelihood ratios reaching clinical usefulness. The lesser diagnostic accuracy of other noninvasive tests in patients with T2DM might be explained by the risk factors that constitute the modeling. For example, T2DM is included as a covariate in the NFS, which might bias the results toward overestimating the risk of advanced liver fibrosis in populations exclusively with T2DM. Despite its greater accuracy in patients with T2DM, the FIB-4 score has limitations that should be noted. If a threshold of 2.67 is used to predict a high likelihood of advanced fibrosis, the test is more specific than it is sensitive and is, therefore, better at ruling in rather than ruling out significant fibrosis. This fact raises concerns for false negatives, which should be a consideration when interpreting scores to guide further testing. Furthermore, the FIB-4 has been validated in patients under age 65, so caution should be exercised when interpreting results in older adults. It is also Highlighting that all the fibrosis prediction models evaluated in our review, including the FIB-4, underperform in patients with diabetes compared with the general population is also important.(61–63) The literature did not address direct harms, but the downstream consequences of inaccurate predictions, such as delayed diagnosis or unnecessary testing and treatments, should be counterbalanced with any potential benefits. Furthermore, the current evidence informing this topic is generally of low quality, comprising studies with various methodologic limitations, such as uncertain validity of reference standards, retrospective study designs, and unrepresentative study populations.

Some variation in patient preference might be expected when deciding to screen for NAFLD or using noninvasive testing to predict advanced liver fibrosis. The ease and availability of noninvasive clinical prediction calculators are more acceptable for patients who prioritize complete but efficient care. At the same time, imaging-based tests might be preferred by those valuing comprehensive evaluations. Patients motivated by preventative health are likely to be interested in screening, although others might be

inclined to reserve testing until signs and symptoms appear. Other considerations, such as acceptability and feasibility, are unlikely to have a significant impact.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, it is categorized as *Reviewed, New-added*.(61–63) The Work Group's confidence in the quality of the evidence was low. The body of evidence had significant limitations based on the methodologic shortcomings previously mentioned. (61–63) If a clinician chooses to assess a patient with T2DM for advanced liver fibrosis, the benefits of using a non-invasive prediction calculator, such as the FIB-4 test, to determine whether further diagnostic testing is warranted slightly outweigh the undesirable effects associated with inaccuracy. Patient values and preferences are likely to vary somewhat based on differences in the value placed on efficient versus comprehensive care. Thus, the Work Group made the following recommendation: In adults with type 2 diabetes mellitus and co-occurring non-alcoholic fatty liver disease, we suggest clinicians should assess for fibrosis using a non-invasive tool (e.g., Fibrosis-4).

Recommendation

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 | Reviewed, New-added)

Discussion

Adult patients with T2DM commonly have comorbidities that with the potential to impact quality of life or life expectancy significantly. For example, a vascular disease associated with T2DM can lead to peripheral neuropathy, retinopathy, and vascular dementia, which can lead to an increased risk of falls. In older adults, falls represent a significant cause of injury-related mortality and morbidity, with an estimated 30–40% of elderly patients experiencing at least one fall.(64) Similarly, cognitive impairment in older adults is associated with increased mortality.(65) As a result, several tools are available to screen for falls and cognitive impairment in this population. Although there have been recommendations from the American Geriatrics Society and the CDC to screen adults over age 65, the literature supporting routine screening for the cognitive decline has been less clear.(66) An SR of evidence did not inform whether any clinical utility in screening for fall risk and cognitive impairment in adults with T2DM was found. Therefore, ample opportunity exists for future research on this population.

There is some variation in patient preferences regarding additional screening. Patients have come to expect more screening and involvement in care, including shared decision making in their care plan, even though screening for cognitive impairment is potentially more sensitive than screening for fall risk. Responses from the patient focus group support more comprehensive interactions with clinicians, and patient empowerment is increasing. In addition, screening patients in areas with limited access or providers (e.g., rural, housebound) is challenging. Further, additional screening can

be burdensome for providers with limited time. Most screening tools were developed to target older patients, so their accuracy in younger patients is unclear.

The Work Group systematically searched for evidence and did not identify any studies that met inclusion criteria regarding routine screening for fall risks and cognitive decline in adult patients with T2DM. Therefore, this recommendation is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was inapplicable; no evidence was retrieved. The Work Group held that despite a lack of published evidence, the possible benefits of screening for these conditions in this population would outweigh any harm. Although the potential for harm of overdiagnosis exists, screening causes no direct harm to the patient, and identifying risks earlier in the disease process, albeit relatively minor, is a potential benefit. Thus, the Work Group made the following recommendation: 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.

Recommendation

7. In adults with type 2 diabetes mellitus, we recommend diabetes self-management education and support.
   (Strong for | Not reviewed, Amended)

Discussion

Diabetes self-management education and support (DSMES) is described in the literature as a dynamic process that provides knowledge and self-management skill-building activities based on individual needs, attitudes, beliefs, and ever-changing life situations.(67–69) DSMES content consists of eight or more topics; the eight core topics are diabetes physiology, monitoring, healthy coping, taking medications, healthy eating, being active, reducing risk, and problem solving. During a needs assessment visit, using shared decision making, topic choices and sequence are prioritized as the DSMES treatment plan is devised and monitored.

Evidence suggests DSMES training improves outcomes for glycemic control, BP, disease knowledge, and self-care behaviors in patients with T2DM.(67, 68). Findings from multiple studies conducted in various patient populations endorse DSMES as empowering those with T2DM or prediabetes to navigate self-management skills and behaviors.(69)

The workgroup identified an additional SR by Chrvala, Sherr, and Lipman published after the 2016 evidence review.(69) This study evaluated 118 RCTs to evaluate DSMES in adults with T2DM and assessed the effect that different methods, providers, duration, and contact time had on glycemic control. The average HbA1c reduction for DSMES participants from all 118 trials was 0.74 compared with 0.017 for controls. DSMES with 10 or more hours of engagement was associated with a greater proportion of participants manifesting a clinically meaningful improvement in HbA1c.

The Work Group considered the assessment of the evidence put forth in the 2017 VA/DoD DM CPG. Therefore, it is categorized as *Not reviewed, Amended*.([70–72]) The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including inability to blind participants or DSMES providers as well as attrition. The benefits of DSMES include improved HbA1c, glycemic control, BP, knowledge, and self-care behaviors. The Work Group acknowledged that DSMES is time consuming and labor intensive, but the benefits outweighed the burdens. Patient values and preferences were similar, and the patient focus group members stated that they value diabetes self-management education. Participants in the patient focus group emphasized the importance of DSMES and that understanding diabetes is an important component for disease self-management. Participants from the focus group felt that DSMES should be available to all patients, including those with medical credentials and their family members and support system via various modalities. Thus, the Work Group made the following recommendation: In adults with type 2 diabetes mellitus, we recommend diabetes self-management education and support.

Recommendation

8. For adults with type 2 diabetes mellitus, we suggest using high glycemic variability over time (e.g., fluctuation in HbA1c or fasting blood glucose) as a prognostic indicator for risk of hypoglycemia, morbidity, and mortality. **(Weak for | Reviewed, New-replaced)**

Discussion

Glycemic variability refers to variation (i.e., coefficient of variation [CV] or standard deviation [SD]) in glucose or HbA1c values over time. It can be used as another measure of glucose control in addition to average or cumulative values of these measures. The determinants of glycemic variability differ and might include factors such as glucose-lowering medication regimens, medication adherence, level of HbA1c, comorbidities, engagement with self-care, food insecurity, and financial and social support. Although variability can be determined over many time intervals (e.g., within-day, between-day, between-visit), the studies identified in the systematic evidence review focused on variability of between-day fasting glucose or between-visit fasting glucose or HbA1c. Different variability measures were used, although they commonly included SD (i.e., how much values differ from the group mean) and CV (i.e., ratio of SD to the mean). Estimates of glycemic variability were typically calculated over months to years using data from longitudinal studies or RCTs.

An SR evaluating five studies of fasting glucose and nine independent studies found associations between increased fasting glucose and HbA1c variability and risk for all-cause mortality in T2DM.([73–82]) Although the data were most robust for all-cause mortality, increased fasting glucose and HbA1c variability were also associated with various composite CVD outcomes. Variability in fasting glucose, and to a lesser extent HbA1c, was also associated with an increased risk of significant hypoglycemia

events.(75, 76, 83) The increased risk for hypoglycemia events in the setting of higher variability generally ranged from 50–300%. Notably, the median duration of follow-up ranged from 8 months to nearly 9 years, so the number of measures of fasting glucose or HbA1c differed substantially across studies. Additionally, studies varied in assessing whether glycemic variability was predictive of outcomes independent of mean or cumulative measures of fasting glucose or HbA1c. Most studies included individuals using both insulin and oral medications, so discerning whether insulin use was a major determinant of the above relationships is difficult.

Based on the available evidence, diabetes health care providers should consider high glycemic variability over time as an indicator of risk for major adverse outcomes. Additional steps may include screening for hypoglycemia, assessing medication and diet adherence, reviewing self-monitoring glucose profiles, or referring patients to diabetes specialists, to identify potential sources of glycemic variability that might be remediable.

The studies showed that glycemic variability over time is an independent predictor of adverse health outcomes and that risks tended to increase linearly as variability increased. However, no concurrence exists on a preferred glycemic variability measure or thresholds of glycemic variability to optimally stratify risk. Whether glycemic variability has a causal effect on adverse events and whether prospectively reducing fasting blood glucose or HbA1c variability will favorably impact outcomes are also unknown.

The Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2017 VA/DoD DM CPG. (74-77, 83) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including reliance on observational and retrospective studies, risk for bias because of a smaller number of studies, differences in the choice of glycemic variation metrics, methods of analysis, and varying outcomes and follow-up periods.(73–82) The benefits of using glycemic variability as a prognostic factor for all-cause mortality, composite CVD, and hypoglycemia slightly outweighed the potential harm because no harms of determining glycemic variability from past data were perceived. Patient values and preferences varied somewhat because calculating glycemic variability could be performed with existing data and would not require additional testing. Feedback from the patient focus group indicates an interest in having more information about optimizing diabetes management and treatment. Implications exist for resource use and feasibility related to having systems in place to obtain data and calculate the degree of glycemic variability. Thus, the Work Group made the following recommendation: For adults with type 2 diabetes mellitus, we suggest using high glycemic variability over time (e.g., fluctuation in HbA1c or fasting blood glucose) as a prognostic indicator for risk of hypoglycemia, morbidity, and mortality.

Further research is required to determine (1) the preferred measures of glycemic variability that convey risk information and practical means to communicate them to clinicians and patients, (2) whether a dose-response relationship occurs between the magnitude of exposure to glycemic variability and adverse outcomes, and (3) whether interventions to reduce glycemic variability affect outcomes.

Recommendation

9. We suggest setting an individualized HbA1c 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 | Not reviewed, Amended)

Discussion

Patients, providers, and even health care systems often focus on therapies that reduce HbA1c levels to reduce complications. Yet, appropriate shared decision making requires a more nuanced approach. For example, presenting the benefits and harms of an intervention as an estimate of absolute, rather than relative, the risk might be more meaningful to the patient. Further, the magnitude of the benefits, which accrue over more extended periods of time, also depends on the initial degree of glycemic control and stage of disease.

As a clinical example of how framing of trial results differs, we consider the results from the United Kingdom Prospective Diabetes Study 33 (UKPDS, 1998).(84) This study showed that the major benefit of lowering HbA1c from 7.9% (average) to 7.0% (average) over 10 years in those with recent onset disease was the reduction in the risk of advanced microvascular complications, as demonstrated by the need for laser photocoagulation (absolute risk reduction [ARR] was 3.1/100 persons treated for 10 years).(84) The ARR of any microvascular complication was 5.0/100 and number needed to treat (NNT) was 19.6. The relative risk reduction was a 37% decrease in risk for microvascular complications and was continuous and without a threshold. 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.(84) Understandably, the lower the level of HbA1c (i.e., greater than 6.5% but strict control of less than 7.0%) did not lessen microvascular complications.

Three major trials conducted in the 2000s tested the hypothesis that intensive glycemic control (target goal <7%) improved cardiovascular (CV) outcomes in patients with T2DM.(85–87) The Action to Control Cardiovascular Risk in Diabetes (ACCORD, 1999), Veteran Affairs Diabetes Trial (VADT, 2009), and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE, 2008) trials were to test this hypothesis of the macrovascular benefit of intensive control in patients with diabetes of longer duration.

Throughout the randomized phases of the studies, no CV benefit of intensive glucose monitoring in ADVANCE or VADT was found and increased mortality occurred in the intensive glycemic control (target A1c <6%) compared with standard control (target HbA1c 7.0–7.9%) in ACCORD, leading to early termination of the latter study.(85–87) After 10 years of follow-up, patients in VADT had 8.6 fewer major CV events per 1,000 person-years but no survival benefit.(86) No CV benefit in the long-term follow-up of subjects in ADVANCE was found; however, a microvascular benefit was observed during the follow-up period.(87) 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) seen in ADVANCE, persisted after 10 years of overall follow-up (29 versus 53 events, HR: 0.54, p <0.01).(87) These benefits were greater in those with lower stage CKD (p=0.04) and with lower baseline systolic BP levels (p=0.01). The effects of glucose-lowering on the risks of death, CV death, or major CV events did not differ by levels of kidney function (p=0.28).

These studies have established that the microvascular benefit of intensive control in older patients with a longer duration of diabetes was less than in the UKPDS. However, macrovascular benefits were not observed in these patients with more advanced disease. These studies clarify that intensive control in an older population with established disease should not be routinely implemented.

The above findings highlight that in recommending a target HbA1c goal for an individual patient, the clinician should consider the patient's diabetes status (e.g., new onset, intermediate duration, long-standing diabetes), diabetes complications, comorbidities, and an estimate of the patient's life expectancy. We suggest clinicians consider the magnitude of expected benefit using principles of ARR or NNT, not relative risk. The studies above can provide an order of magnitude of expected benefit, especially in older adults.

The Work Group appreciates the challenge to clinicians when working with patients to establish an individualized, therapeutic diabetes treatment goal. Assessing the risk-benefit ratio requires a thorough understanding of patient characteristics, which include demographics, behavioral factors, cultural factors, and other social determinants that contribute to disparity in adult diabetes care and outcomes in the U.S. population. Understanding the individual patient's characteristics will mitigate the negative impact social determinants of health can have on diabetes outcomes. Similarly, considering the presence of end–organ injury from chronic diabetes or other comorbidities is important. Although challenging to quantify, life expectancy weighs the relative risk of death when comparing mortality rates among populations. Still, when viewed as a function of age, comorbidity, and disability, frailty, or both, it can be a valuable concept to consider when developing a treatment plan. The presence of these complications, comorbidities, or reduced life expectancies supports a more relaxed HbA1c target range and offers the clinician flexibility to establish expectations and to choose how to safely improve clinical outcomes.

There is a slight variation in patient preferences regarding this treatment because most patients value an individualized approach to their HbA1c target goals. The patient focus group noted the challenges of managing their T2DM considering the impact that testing and medication schedules had on their QoL, especially in co-occurring conditions. They also noted the importance of shared decision making in their diabetes management. No further concerns arose regarding resource use, equity, acceptability, feasibility, or subgroup considerations concerning this recommendation.

The Work Group considered the assessment of the evidence put forth in the 2017 VA/DoD DM CPG.(84–86) Therefore, it is categorized as *Not Reviewed, Amended.* The Work Group reviewed the outcomes in the three major trials referenced—ACCORD, VADT, and ADVANCE—and the UKPDS and follow-on studies. A Cochran review of 20 trials (n=29,986) was reviewed and reported no significant difference between intensive and conventional glucose control for all-cause mortality but showed a reduced risk of amputation and microvascular diseases, including retinopathy and nephropathy in the intensive treatment arm.(88) The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including low-quality evidence from the 2017 VA/DoD DM CPG resources. The benefits of this recommendation outweighed the potential harm because setting an HbA1c value range should be associated with fewer episodes of hypoglycemia than setting a rigid HbA1c treatment goal. Patient values and preferences were similar because patients would value an individualized approach to their care plan that included shared decision making and sought to limit injury. Thus, the Work Group made the following recommendation: We suggest setting an individualized HbA1c target range based on the clinician's appraisal of the risk benefit ratio, patient characteristics, presence or absence of T2DM, comorbidities, and life expectancy.

Recommendation

10. We suggest an HbA1c range of 7.0–8.5% for most patients, if it can be safely achieved.
    (Weak for | Not reviewed, Amended)

Discussion

VA/DoD CPGs for managing T2DM have consistently recommended distinct HbA1c target ranges based on differences in risks and benefits for each individual and when determined in the context of shared decision making. VA/DoD and external guideline development groups have proposed various HbA1c targets, including target ranges generally held as representing intensive control, such as HbA1c <7.0%. More recently, a consensus has trended toward individualizing glycemic targets, with consideration for less intensive glycemic control in patients with complex medical conditions or shortened life-expectancy. However, determining which patients might benefit from lower HbA1c target ranges while maintaining relatively acceptable risks of hypoglycemia and other

harms is challenging, especially when guided by clinical trials enrolling different populations and reporting mixed results.

Various patient factors, such as life expectancy, age, presence and severity of microvascular complications, self-management difficulties, and presence or absence of comorbid illnesses, have been proposed as considerations when tailoring HbA1c target ranges to patients with T2DM. These factors and the long-held belief that lower HbA1c is better are extrapolations and inferences derived primarily from four RCTs comparing intensive glycemic management to conventional strategies: UKPDS, ADVANCE, ACCORD, and VADT.(84, 89–91) In 2017, the VA/DoD DM CPG Work Group concluded the body of evidence was sufficient to substantiate unique HbA1c ranges for specific groups of patients.(88) For example, an HbA1c range of 6–7% was suggested for patients with a life expectancy greater than 10–15 years and absent or mild microvascular complications, if it could be safely achieved. Alternatively, an HbA1c range of 7–8.5% was recommended for patients with established microvascular or macrovascular disease, comorbid conditions, or a life expectancy of 5–10 years. The recommendations for individualized HbA1c target ranges with specified upper and lower bounds were an attempt to resolve the clinical equipoise ensuing from evidence suggesting a delicate balance between both benefits and substantial harms with intensive glucose lowering. For example, the Work Group concluded that intensively lowering HbA1c will reduce microvascular complications (i.e., nephropathy, neuropathy, retinopathy) but not other important clinical outcomes, such as non-fatal CV events, CV mortality, and all-cause mortality. Additionally, any microvascular benefits are counterbalanced by an increased risk of hypoglycemia, weight gain, and, in one trial, all-cause mortality.

Although the evidence base for this topic has not changed, standards in guideline development have. We reviewed the existing body of evidence captured by the 2017 Work Group and applied current, more rigorous guideline development processes. As a result, some of the conclusions from the evidence base have changed. First, although multiple RCTs have compared "more intensive" to "less intensive" glycemic targets, the achieved HbA1c ranges varied considerably in the intensive group across trials. Notably, only ACCORD and ADVANCE reached and sustained HbA1c levels between 6–7% in the intensive therapy group through the end of the study (e.g., average HbA1c 6.5%; interquartile range 6.0–6.8%).(85, 87, 89, 90) The UKPDS initially lowered HbA1c below 7%, but values steadily increased to approximately 7% after 6 years and subsequently remained between 7–8% through completion.(84) Consequently, the results from ADVANCE and ACCORD should be weighted more heavily when interpreting the relative benefits and risks of intensive glucose lowering, if defined as HbA1c <7%.

Both ADVANCE and ACCORD showed intensive glucose lowering diminishes the risk of microvascular complications from T2DM.(85, 90) These findings justify considering low HbA1c target ranges in patients with T2DM to lower risk of undesirable complications, such as ESRD. For example, intensive therapy in ADVANCE(90)

reduced the risk of a renal composite outcome by 21% that included ESRD, which was also reduced in long-term follow-up.(85, 87, 89, 90) However, these benefits come at a cost. In both trials, rates of hypoglycemia and weight gain were higher with intensive therapy than with conventional therapy. More concerning, in the ACCORD study, death from any cause was more common in the intensive group. For example, low HbA1c nearly doubled the rate of hypoglycemia and increased the risk of death from any cause by 22%. In more absolute terms, the number needed to harm for all-cause mortality over 3.5 years was 100. That most of these events were vascular deaths is noteworthy, bearing in mind other clinical trials have failed to show CV benefits with intensive therapy. As a consequence of these tradeoffs, elucidating which patient characteristics or subgroups define the populations most likely to benefit and those most vulnerable to the potentially catastrophic harms associated with intensive glucose lowering would be helpful. Data from various patient populations would be needed to identify these patient groups and validate claims of individualized net benefit. Some of the trials under consideration might be considered sufficient evidence to make definitive conclusions because comparatively disparate patient populations were studied. However, differences between subgroups were not found in individual studies. Furthermore, studies that enrolled similar patient populations often had discordant results. For example, trials of older patients with longer durations of diabetes, such as ADVANCE and VADT, did not show an increased risk of all-cause mortality with lower HbA1c targets(86, 90, 91), despite being similar to the patients enrolled in ACCORD, where death from any cause was more common in those treated intensively. Many explanations for these inconsistencies have been proposed, but definitive conclusions have not been derived from subsequent studies. Consequently, the evidence is unclear regarding which patient characteristics define those individuals at most risk of major harms with lower HbA1c target ranges. In conclusion, intensive therapy improves some clinical outcomes in patients with T2DM at the expense of risk for adverse events, but the patient populations that stand to benefit or suffer potentially catastrophic harms are poorly defined by the evidence.

Despite these uncertainties, achieving and sustaining HbA1c levels between 7–8.5% clearly reduces significantly the risk of microvascular complications and possibly non-fatal CV events when compared with higher HbA1c levels. Participants in the VADT study sustained a median HbA1c of 6.9% in the intensive treatment group when compared with 8.5% in the conventional treatment group through 5.6 years.(91) This difference reduced the risk of proteinuria during the treatment period and reduced non-fatal CV events by 17% at 10 years of follow-up.(86, 91) In the UKPDS, although the average HbA1c was 7% in the intensively treated group, the time-to-event analysis showed that microvascular benefits associated with intensive therapy emerged when the group's average HbA1c had risen to 7–8% as compared with 8–9% in the conventional treatment group.(84)

After carefully reviewing the evidence, the Work Group determined that an HbA1c range of 7–8.5% is appropriate for most patients, if it can be safely achieved. This target range leverages the potential for meaningful benefits while reducing risks of catastrophic harms associated with lower HbA1c targets. Consequently, both deprescribing and augmentation of pharmacotherapy are reasonable considerations when individualizing management to achieve the suggested HbA1c range.

Whether unique characteristics exist to define a patient population that will accrue greater benefits than harms with lower HbA1c target ranges remains unclear. Ample reason exists, however, to speculate that preferred use of medications associated with a lower risk of hypoglycemia will mitigate potential harms from lower HbA1c targets. For example, drugs now established to improve clinical outcomes without the attendant risk of hypoglycemia, such as SGLT-2 inhibitors and GLP-1 RAs, were mostly unavailable when the clinical trials investigating the effects of intensive glycemic management were conducted. Consequently, the effect these agents might bear on the relative trade-offs of lower HbA1c targets is unknown. Therefore, caution should be exercised given the absence of definitive evidence about the patient characteristics predisposed to major adverse events when intensive glycemic targets are reached and the uncertain mitigative effects of currently available drugs.

There is likely some variation in patient preferences regarding glycemic targets. Patients more comfortable with uncertainty and risk but given to maximizing benefits might prefer more intensive management, although patients who are risk averse might choose more relaxed glycemic management.

The Work Group systematically reviewed the assessment of the evidence put forth in the 2017 VA/DoD DM CPG related to this recommendation.(84–91) Therefore, it is categorized as *Not reviewed, Amended*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including variability in drug classes to achieve HbA1c goals, possible confounding from overlapping treatments for BP targets within studies, inconsistency in results, absence of blinding, and inclusion of older studies that used disease definitions and drug classes that might be considered obsolete by current standards.(84–91) The benefits on microvascular complications and possibly non-fatal CV events likely outweigh the potential harms of hypoglycemia and other drug-associated adverse effects for virtually all patients if an HbA1c range of 7–8.5% is targeted as opposed to other ranges. Thus, the Work Group made the following recommendation: We suggest an HbA1c range of 7.0–8.5% for most patients, if it can be safely achieved.

Recommendation

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 improve HbA1c.
    (Weak for | Reviewed, New-added)

Discussion

Although evidence is increasing that continuous glucose monitoring (CGM) can improve glucose control and might reduce hypoglycemia in T1DM patients, whether CGM improves outcomes in patients with T2DM is unclear. However, the systematic evidence review found that results differed depending on the type of CGM.

For real-time CGM (rtCGM) (i.e., glucose readings automatically and continuously pushed to the user's receiver or smartphone), we found moderate quality evidence that rtCGM use led to decreased time in hypoglycemia and decreased HbA1c in T2DM. One SR published in 2019 identified three RCTs of fair to poor methodologic quality, suggesting that rtCGM decreased HbA1c by 0.45% compared with self-monitoring of blood glucose (SMBG).(92) Subsequently, two of three RCTs of fair to good methodologic quality published from 2021–22 reported that the use of rtCGM led to decreased time in hypoglycemia (<70 mg/dL) compared with SMBG.(93–95)

The systematic evidence review found low-quality evidence showing little or no difference in time in hyperglycemia between patients using rtCGM and SMBG. Two RCTs found that rtCGM leads to reduced hyperglycemia time (>180 mg/dL).(93, 94) However, a third study of higher methodologic quality found no difference in time in hyperglycemia between rtCGM and SMBG.(95)

For intermittently scanned continuous glucose monitoring (isCGM) or flash continuous glucose monitoring (fCGM) without alarms (i.e., requires users to scan the device to obtain glucose data), we found minimal evidence to suggest that these CGM modalities improve glycemic outcomes. Two RCTs of very low-quality evidence found no difference in hypoglycemia (defined as events requiring medical assistance or time in hypoglycemia) between those randomized to isCGM and fCGM without alarms compared with those randomized to SMBG.(96, 97) One low-quality RCT found that time in hyperglycemia decreased with the use of isCGM and fCGM.(97) However, given the low to very low confidence in the evidence base for isCGM and fCGM, we focused our recommendation on rtCGM.

Several important contextual factors must be considered when interpreting this recommendation. First, most of the evidence base focused on patients who were not at goal and on insulin. Thus, our recommendation is most relevant for these patients; whether rtCGM would provide any benefits for 1) patients not receiving insulin and 2) for patients already at goal is currently unclear. Future studies of rtCGM are needed in patients not receiving insulin and in patients who are already at goal before these recommendations can be broadened to those populations.

Second, whether CGM-identified (subclinical) hypoglycemia leads to the same risks as clinically-identified hypoglycemia is unclear. Specifically, the literature showing the adverse effects of hypoglycemia relied almost solely on symptomatic hypoglycemia. CGM allows us to identify many more episodes of hypoglycemia that do not cause

symptoms. Whether CGM-identified (subclinical) hypoglycemia is associated with subsequent adverse effects in the same way clinically-identified hypoglycemia is associated with adverse effects is unclear. Future research must explore the long-term outcomes related to CGM-identified subclinical hypoglycemia.

Third, CGM technology is rapidly evolving, and research must continue to evaluate new CGM technologies so patients and clinicians can determine whether newer technologies are, in fact, superior to established technologies.

Our review found little data on patient satisfaction and QoL outcomes with rtCGM use, limiting our ability to incorporate these important outcomes into our recommendation.

Numerous priority areas for future research exist. First, more rigorous studies on longer-term clinical outcomes, such as hospitalizations, vascular complications, and mortality, are needed.(98) Second, additional studies on patient-centered outcomes, such as quality of life, anxiety, and diabetes distress, are required. Additionally, studies directly comparing rtCGM and isCGM with alarms analyzing efficacy and cost are warranted. And third, additional studies are needed focusing on specific patient subgroups to guide clinicians on which patients with T2DM are most (and least) likely to benefit from rtCGM.

The Work Group systematically reviewed evidence related to CGM and outcomes for this recommendation.(92, 95–97) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including a small sample size spread among relatively few studies.(92–95) We found moderate evidence that rtCGM led to decreased hypoglycemia (<70 mg/dL) and HbA1c. However, important uncertainties arise, including the unclear clinical importance of CGM-identified hypoglycemia and the effects of rtCGM on patient-centered outcomes. The benefits of rtCGM on decreased time in hypoglycemia and decreased HbA1c slightly outweighed the potential harm of patient burden. Thus, the Work Group made the following recommendation: 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 improve HbA1c.

D. Non-Pharmacotherapy

Recommendation

12. For adults with type 2 diabetes mellitus, we suggest a Mediterranean style diet to improve glycemic control, body weight, and hypertension.
    (Weak for | Reviewed, New-replaced)

Discussion

Recent studies show that several diet interventions positively impact glycemic control, weight, and CV risk factors.(99–103) Healthy eating using the Diabetes Plate method and limited alcohol use is recommended for all patients with T2DM and

prediabetes.(101) When available, a referral to a registered dietitian nutritionist (RDN) should occur for medical nutrition therapy (MNT) to support dietary changes.(104)

MNT is a nutrition-based therapeutic approach to managing chronic health conditions, reducing symptoms, and preventing further complications. It is a crucial component of diabetes education and management of T2DM. The MNT process consists of distinct, interrelated steps.

- **Nutrition Assessment** – The RDN collects and documents 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 selecting 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 and Evaluation** – The final step of the process is monitoring and evaluation, which the RDN uses to determine whether the patient/client has achieved or is making progress toward the planned goals.

Limited evidence exists on the optimal dietary strategy to improve outcomes for individuals with T2DM. Evidence comparing several nutrition intervention strategies shows that the Mediterranean style diet improves glycemic control, BP, and weight.(99) Despite known variation in the cuisine of Mediterranean countries, certain features are commonly used to describe a traditional Mediterranean style diet: high intake of vegetables, legumes, fruits, nuts, seeds, 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, low-fat dairy, and sweets. The Mediterranean style diet focuses on natural foods that might be attractive to some but might create a hindrance for others.

In a large network meta-analysis of 54 RCTs (n=4937 individuals with T2DM) Schwingshackl et al. (2018) compared nine different dietary approaches; vegetarian, Mediterranean style, high protein, moderate carbohydrate, low carbohydrate, low glycemic index/glycemic load, paleolithic, low fat, and control diet (minimal or no intervention).(99) The Mediterranean style was the most effective dietary approach to improve glycemic control in patients with T2DM.(99, 100) In addition, both the Mediterranean style diet approach and the low carbohydrate diet were more effective lowering HbA1c than the low-fat diet.(99)

A 12-week RCT (n=60) conducted by Jin et al. (2020) compared an East Asian diet based on the Mediterranean style diet–Dietary Approaches to Stop Hypertension (DASH) diet, an Asian Food Exchange Diet, and a plant-based diet.(100) All study participants received medical nutrition therapy for T2DM. To assure compliance, the Mediterranean style–DASH dietary approach and Asian Food Exchange diet groups

received two prepared packaged meals per day. The food in the Mediterranean style–DASH group replaced the typical East Asian diet with food equivalent to macronutrients in the Mediterranean style–DASH dietary approach. Starches were decreased and fiber content was increased. Twenty percent of the total calories were from fat, of that about two-thirds were monounsaturated fat. The sodium content per day was approximated at 2,300 mg. The Mediterranean style–DASH dietary approach demonstrated a reduced HbA1c, fasting glucose, and body weight; moreover, it showed an improvement in low-density lipoproteins, high-density lipoproteins, and TGs compared with the Asian Food Exchange diet and the plant-based diet in patients with T2DM.

There is some variation in patient preferences regarding the Mediterranean style dietary approach. Some individuals might find this plan time intensive and expensive because of the expectation to avoid processed foods and the need for meal preparation. Adhering to the Mediterranean style dietary approach might be difficult for individuals when entertaining because of cultural differences, cognitive impairments, homelessness, availability or affordability of fresh food or both, and during deployment. Some might think of the Mediterranean diet as the “red wine diet,” though wine is not an essential part of the Mediterranean diet. Therefore, patients should be assessed and provided with education and guidance on alcohol use.

The Work Group acknowledges the importance of shared decisions when recommending the best dietary approach for T2DM. For example, an RDN can work with a patient to tailor dietary recommendations to values and preferences, to include ethnic values and preferences.

The Work Group systematically reviewed the evidence related to this recommendation (99, 100) and considered evidence put forth in the 2017 VA/DoD DM CPG. Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group’s confidence in the quality of the evidence for this recommendation is very low. The benefits of the Mediterranean style dietary approach outweigh the potential harm. Patient values and preferences varied somewhat because of expense, time intensity, deployment, and availability of fresh food in some areas. Thus, the Work Group made the following recommendation: For adults with type 2 diabetes mellitus, we suggest a Mediterranean style diet to improve glycemic control, body weight, and hypertension.

Recommendation

13. For adults with type 2 diabetes mellitus, we suggest a nutrition intervention strategy providing 13–50% of their total daily caloric intake from carbohydrates for diabetes management.
    (Weak for | Reviewed, New-replaced)

Discussion

Evidence suggests a nutrition intervention strategy provided by an RDN that reduces energy intake from carbohydrates to 13–50% improves HbA1c, BP, and body weight in

individuals with healthy kidneys and prediabetes or T2DM of 5 years' duration or fewer.(100, 102, 105, 106)

Gram-Kampmann et al. (2022) found patients randomized to a nutrition intervention strategy that limited total daily carbohydrate intake to <20% of energy without energy restriction and approximately 60% energy from fat without restricting the type of dietary fat compared with those randomized to a diet with 50–60% nutrients from carbohydrate, 20-30% fat and 20-30% protein had clinically significant ($p < 0.001$) improvements in HbA1c at 3 months and 6 months.(102) Patients randomized to the low carbohydrate diet also experienced statistically significant weight loss as compared with those randomized to the traditional diet without caloric restriction. Surrogate CV risk markers, including LDL and HDL, demonstrated improvement in HDL values for patients randomized to the low carbohydrate nutrition intervention. HOMA-IR, a reflection of the degree of insulin resistance, measurements showed statistically significant improvements for patients randomized to the low-carb diet intervention at 6 months.(102)

Jin et al. (100, 102, 105, 106) evaluated three nutrition intervention strategies in Asian individuals with T2DM and BMI values of 18.5–30. A 12-week, open-label randomized nutrition intervention trial was carried out among 60 Korean adults with T2DM. Participants were randomized to one of three nutrition intervention arms: Group A is an Asian Food Exchange Diet; Group B is an Asian Mediterranean style–DASH diet; and Group C is a healthy eating Diabetes Plate diet. All participants received an initial one-on-one visit with a research dietitian where energy and protein requirements were calculated using the Harris-Benedict equation. Participants randomized to Groups A and B maintained weekly food logs periodically assessed for energy intake and regimen adherence. Participants randomized to Groups A or B were also provided with two meals per day prepared in a metabolic kitchen, so participants would need only to heat them before consumption. At 12 weeks, Groups A and B were compared with Group C. The Asian Food Exchange diet, with 27% of energy from net carbohydrates, or the Asian Mediterranean style–DASH diet was associated with improvements in HbA1c, BP, and HOMA-IR as compared with recommendations for a healthy eating Diabetes Plate diet (45–65% carbohydrates). Whether the nutrition strategy or the meal delivery impacted the primary outcome is inconclusive. Whether the nutrition intervention strategy or the meal delivery impacted the primary outcome is inconclusive.

Evidence from studies lasting 12 weeks to 6 months, using an RDN to individually calculate participant energy requirements, monitoring energy intake using structured nutrient analysis software and altering macronutrient distribution from less than 20% of daily energy requirements from carbohydrates to 60% of daily energy requirements from carbohydrates, demonstrated that patients randomized to the lower percentage of dietary carbohydrates experienced the most significant improvement in HbA1c and fasting plasma glucose. Studies assessing the ability to implement and sustain a low carbohydrate nutrition intervention strategy found that patients randomized to a low

carbohydrate diet (defined as 10–25% energy from carbohydrates) rarely achieved an intake of <20% energy from carbohydrates.(102)

Weight loss in patients with prediabetes and T2DM is often sought. A non-caloric restricted low carbohydrate diet (maximum 20% energy from carbohydrates) was found to reduce body weight at both 3 months and 6 months with concurrent reductions in HbA1c and fasting glucose and body weight at both 3 months and 6 months compared with a control diet (carbohydrate 50–60% energy) in patients with T2DM and receiving two or fewer antihyperglycemic medications.(102) Thomsen et al. (2022) demonstrated body weight improvement when comparing a hypocaloric diet with 30% energy from carbohydrate as compared with 50%, and both groups experienced very similar weight loss at 6 weeks.(107) Weight loss appears to improve when dietary carbohydrate is limited.

The overall strength of evidence for macronutrient distribution in individuals with prediabetes or T2DM based on the duration of the disease is weak. Yet, the evidence does support the benefits of limiting dietary carbohydrates to 13–50% of energy. Longer duration trials that evaluate baseline energy requirements and varying macronutrient distribution from carbohydrate, protein, fat, and alcohol measuring HbA1c, FPG, time in range (TIR), HOMA-IR, and Homeostasis Model Assessment of β-cell Function (HOMA-B) are warranted.

The Work Group systematically reviewed evidence related to this recommendation (100, 103, 105–108) and considered the assessment of the evidence put forth in the 2017 VA/DoD DM CPG. Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was very low. The lack of evidence had some limitations, including short study duration and lack of data safety monitoring board to evaluate serious adverse events.(100–102, 105–107, 109, 110) The benefits of reducing the percentage of energy intake from carbohydrates to 13–50% of energy intake to improve HbA1c, glucose, BMI, and HOMA-IR outweighed the potential harm of infrequent hypoglycemia or very rare unrelated dyspnea.(34) Patient food preferences are highly variable. Food intake varies based on various factors gathered during the nutrition assessment process. Thus, the Work Group made the following recommendation: For adults with type 2 diabetes mellitus, we suggest a nutrition intervention strategy providing 13–50% of their total daily caloric intake from carbohydrates for diabetes management.

Recommendation

14. For adults with type 2 diabetes mellitus, we suggest a vegetarian dietary pattern for glycemic control and weight loss.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests that for individuals with T2DM a vegetarian dietary pattern (including vegan to lacto-ovo-vegetarian) improves glycemic control and weight loss compared with non-vegetarian diets. An SR by Viguiliouk et al. (2019) evaluated 9 trials of ≥3 weeks duration with a median follow-up duration of 12 weeks (range: 4–74 weeks) and including n= 369 participants with T2DM (mean duration of 7–9 years).(103) The median age was 56 years and median BMI of 34 kg/m^2. The median daily carbohydrate micronutrient intake value across the trials was 60%. The authors found a significant reduction in HbA1c compared with control diets, suggesting some glycemic benefit for a relatively short intervention involving a healthy vegetarian eating pattern.

Additional benefits to the vegetarian dietary patterns study included a significant reduction of fasting glucose in six trials (n=313) of participants with T2DM. Body weight was significantly reduced by 2.15 kg. No significant effect was noted on BP. However, the benefits of a vegetarian dietary intervention slightly outweigh the burdens and potential harms.

There is a large variation in patient preferences regarding this treatment. Some individuals might want to avoid trying a vegetarian diet and might be circumspect regarding what it entails. However, others might find it aligns with ethical, religious, and environmental values of low environmental impact on the planet. Restaurants or fast-food venues might have no vegetarian option, making dining out challenging. This nutrition intervention strategy might incur nutritional health burdens of adequately maintaining sufficient proteins and balancing essential amino acids, iron, and B-12 levels in the diet. Vegan diets are associated with reduced bone mineral density and increased fracture risk. However, a thoughtfully planned vegetarian diet can adequately provide essential caloric needs, even in younger or more athletic individuals who require higher calorie intake to meet higher energy demands. Finally, some individuals might believe that a vegetarian diet is a “salad diet” exclusively and, therefore, poses the risk of a potential disordered eating pattern.

The Work Group suggests a referral to an RDN whenever possible for individuals who choose this vegetarian style diet to ensure all potential harms are mitigated. Additional considerations exist for the incurred likely higher cost of vegetarian diets and limited availability in certain food desert areas, thus having more impact on low-income individuals.

The Work Group systematically reviewed evidence related to this recommendation. (103) Therefore, it is categorized as *Reviewed, New-added*. The Work Group’s confidence in the quality of the evidence was moderate based on the lowest GRADE rating for critical outcomes of glycemic control and weight loss. The body of evidence was limited to one SR of nine RCTs. Furthermore, the dietary intervention duration was variable within the individual RCTs and, in some instances, limited to a duration as low as 4 weeks with a median of 12 weeks and an extended range of 74 weeks. The

benefits of a vegetarian style diet slightly outweighed the harms and burdens. Patient values and preferences varied primarily because of socioeconomic, personal lifestyle habits, perceptions, religious beliefs, and cultural values. Thus, the Work Group made the following recommendation: For adults with type 2 diabetes mellitus, we suggest a vegetarian dietary pattern for glycemic control and weight loss.

Recommendation

15. For adults with type 2 diabetes mellitus, we suggest against intermittent fasting. **(Weak against | Reviewed, New-added)**

Discussion

Intermittent fasting (IF) has gained popularity as a weight-loss strategy, a goal of importance to many patients with T2DM and coincident obesity. Common IF interventions include 24-hour complete fasting, intermittently restricted energy intake (25% total caloric intake), time-restricted feeding (examples include 16/8 IF, limiting the intake of foods and calorie-containing beverages to a set window of 8 hours per day and abstaining for the remaining 16 hours, and 14/10 IF, eating for 10 hours of the day and fasting for 14 hours), alternate-day fasting (fasting or modified fasting every other day), the twice-a-week or 5:2 method (normal eating 5 days of the week and restricted, 500-calorie intake on the remaining 2 days), the Warrior Diet (small servings of fruit and vegetables during the day with a large meal at night), and the Eat Stop Eat method (a 24-hour fast once or twice per week).

A 2021 SR of seven RCTs by Borgundvaag et al. (2021) (n=338) suggested that effects on HbA1c, lipid profile, waist circumference, fasting glucose, and BP were equivalent in obese patients with T2DM assigned to IF versus those assigned a standard diet.(111) The median follow-up was 24 weeks. Weight loss favored IF by 1.89 kg (95% CI: -2.91 to -0.86 kg) compared with a standard diet. Hence, patients with T2DM focused on weight reduction could find IF appealing.

However, a small RCT of short duration by Corley et al. (2018) suggested that patients taking medication with the potential to cause hypoglycemia should exercise caution(112). The authors provided education about hypoglycemia and, for patients taking sulfonylureas or insulin, medication dosages were reduced for some time proximate to fasting. Despite these measures, the risk of having a hypoglycemic event was twofold greater during periods of IF.

Patient values and preferences regarding IF were somewhat varied. For example, the patient focus group noted that interventions related to dietary restriction interrupted or prevented participation in social activities.

The Work Group systematically reviewed evidence related to this recommendation. (111, 112) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of evidence was very low. The body of the evidence had

limitations, including lack of blinding of patients, small sample size, and imprecision. The harms of IF in adults with T2DM, which include hypoglycemia (despite education and medication reduction), dehydration, and the potential to reinforce the maladaptive behaviors characteristic of some eating disorders, slightly outweighed the benefit of a 1.89 kg weight loss when compared with a standard diet. IF conferred no additional reduction in HbA1c when compared with a standard diet. IF was not associated with other positive effects on lipid profile, waist circumference, fasting glucose, or BP compared with a standard diet. Patient values and preferences varied because some patients reported that any diet could adversely impact social interactions. The Work Group posited that modifying the dose or timing of medication administration on a fasting day could prove difficult for some patients. Thus, the Work Group made the following recommendation: For adults with type 2 diabetes mellitus, we suggest against intermittent fasting. The Work Group noted that there were no studies comparing the glycemic profile (e.g., as measured by continuous glucose monitoring) in patients who restrict various macronutrients but do not fast versus those who limit macronutrient intake though fasting. Further study of this issue, as well as the overall safety and efficacy of IF for patients with T2DM, is needed.

Recommendation

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, or tai chi.
    (Weak for | Reviewed, New-added)

Discussion

Shah et al. (2021) found that general exercise was associated with improved blood glucose, glycemic control, and weight loss in patients with T2DM.(113) Zhu et al. (2022) found that supervised aerobic exercise training improved metabolic outcomes by reductions in body weight, total body fat, HbA1c, and FPG.(114) Bock et al. (2022) found that yoga reduced HbA1c in adults with T2DM.(115).

According to Acosta-Manzano et al. (2019), resistance training is an effective first-line intervention for managing T2DM. Hypertrophy training (HT) and muscular endurance training (MERT) were two types of resistance training highlighted in the study. Combined HT and MERT were associated with improved HbA1c, glucose levels, fat mass, muscle strength, and BMI. Liu et al. (2019) found that patients diagnosed with T2DM had larger reductions in HbA1c from high-intensity resistance exercise than low to moderate-intensity exercise. Yang et al. (2017) found that the combination of resistance training and aerobic exercise training for 6 months improved glycemic control.

Wang et al. (2022) found that tai chi improved glucose in older patients. Loss of balance and anticipating falling are major concerns in the older population. The study identified

improved additional benefits, including QoL as well as balance, which was demonstrated in the single limb standing test.

There is some variation in patient preferences regarding physical activity. The patient focus group noted that physical activity could be burdensome because some patients dislike exercising. Additionally, high costs can be associated with equipment needed to complete or participate in some types of physical activity (e.g., yoga mat, walking shoes, gym memberships, classes, and access to electronic devices). The patient might need accountability assistance to participate in physical activity. For example, patients who reside in certain geographical areas might have no access to walking trails or sidewalks. Finally, some patients might live in a geographic region where they must consider personal safety. For patients geographically distant from facilities, without access to safe places to exercise, or other challenges, virtual care provision of complementary and integrative health services, such as tai chi and yoga, might be considered.

The Work Group systematically reviewed evidence related to this recommendation. (113–115) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and small number of studies.(113, 114, 116) The benefits of physical activity improved glycemic control and slightly outweighed the potential harms, which include the potential for injury. As stated above, patient values and preferences varied somewhat because some patients prefer not to take part in physical activity. Although it was not included as a part of our evidence base, we know the benefits of physical activity during the DPP study (2010) (see Recommendation 1). The DPP provides evidence that lifestyle intervention, including exercise, decreases the risk of progression from prediabetes to T2DM. Further research is needed to assess the optimal activity prescription to improve control for patients with T2DM. Thus, the Work Group made the following recommendation: 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, or tai chi.

Recommendation

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 | Reviewed, New-added)

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 | Reviewed, New-added)

Discussion

Diabetes distress related to the burden of diabetes self-care is an independent predictor of diabetes outcomes.(117) In addition, the Work Group investigated whether complementary integrated health interventions improve outcomes in patients with T2DM and stress.

In the systematic evidence review, two SRs and one RCT were found that addressed mindfulness-based interventions for stress reduction.(117–119) The multiple component studies of the RCTs involved differing techniques that integrated mindfulness practices, such as meditation and breathing exercises, with psychotherapy or diabetes self-management and education. Specifically, the mindfulness interventions assessed in the studies used the following approaches: group-based mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy, acceptance and commitment therapy, and individualized mindfulness programs.

The studies showed benefit for mindfulness-based interventions across the four critical outcomes of QoL, adherence to diet, HbA1c, and diabetes distress; however, the benefit was shown only in the shorter term of 2–3 months. Longer-term follow-up, in most interventions, showed no difference versus control.

An RCT by DiNardo et al. (2022) showed improvement in adherence to diet with MBSR at 12 weeks compared with TAU.(117) In one RCT from one SR by Ni et al. (2020), an improvement in a QoL scale for the mental health component occurred, but not the physical health component, compared with TAU in adults with T2DM at 8 weeks.(119) In three RCTs from one SR by Ngan et al. (2021), the results favored mindfulness for HbA1c improvement through 8 weeks, but no benefit was seen in longer timeframes (i.e., up to 6 months).(117, 118)

Evidence from four of the RCTs, in the two SRs, demonstrated that mindfulness-based interventions improved the symptoms of diabetes distress compared with TAU or diabetes education at 8 weeks in adults with T2DM.(117, 118) The Work Group acknowledged and agreed with the decision by Ngan et al. (2021) to drop one of the RCTs for this outcome. In reviewing the SR, a consensus was reached that the high imprecision of the one RCT by Pearson et al. (2018) led to its being considered an outlier.(120) This RCT was the only one where the intervention was a self-directed, home-based process that relied on the patients to report completing a program on a compact disc. The decreased reliability and inaccurate reporting on compliance with self-taught behavioral interventions led to the decision to omit the findings from this study for this recommendation.

The Work Group determined that the evidence was low to very low quality. The benefits only slightly outweighed the harms because the positive effects all occurred in the shorter term; however, no harm was noted in using mindfulness strategies and stress reduction. There will be some variations in patient preferences and values. On the

negative side, the interventions require significant time commitment, and some patients will still associate behavioral health interventions with a negative stigma. On the positive side, some patients will prefer interventions that avoid pharmacotherapy.

Other implications for recommending mindfulness-based interventions for stress reduction are the resources and availability. For example, in DoD treatment facilities, the ability to run a mindfulness program might be difficult in smaller and more remote sites, especially with challenges in staffing. In addition, VA has already established a program, and ease of access exists with self-referral and general acceptability by the patients and care providers.

The Work Group systematically reviewed evidence related to this recommendation. (117–119) Because no previous recommendation on stress reduction was made, this recommendation is categorized as *Reviewed, New-added*. The confidence in the quality of evidence is very low because of imprecision and small sample sizes for the studies. The body of evidence had some limitations, including concerns about the applicability of Chinese population findings for U.S. patients and the difficulty of comparing the significant variability in the definition and execution of what is called a mindfulness program. The limited short-term benefits of mindfulness-based interventions slightly outweigh any harm, Patient values and preferences are varied because patients might view the time commitment as a burden, and some are averse to the stigma of using behavioral health interventions. In contrast, some patients might prefer behavioral health interventions over pharmacotherapy. The availability within VA also increases the applicability in older populations. Thus, the Work Group made the following recommendation: In adults with stress related to type 2 diabetes mellitus, we suggest offering a mindfulness-based stress reduction program for short-term improvement.

The Work Group systematically searched for evidence and did not identify any studies that met inclusion criteria regarding explicitly named interventions commonly used in behavioral health and holistic treatment plans, which include acupuncture, biofeedback, hypnosis, guided imagery, massage therapy, yoga, and tai chi. The literature review returned no RCTs nor SRs that met the qualifications for review. These treatments have broad appeal to many patients and are limited in harm. Moreover, they are gaining acceptance and understanding and are more frequently recommended by care providers. However, the lack of research means the Work Group could not make a recommendation for or against these interventions. This recommendation is categorized as *Reviewed, New added*. Thus, the Work Group made the following recommendation: 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.

With both of these recommendations, the Work Group noted the need for more evidence for complementary health interventions for stress in T2DM patients. Future research into a broader subset of these interventions is recommended. Furthermore, because T2DM

tends to be a chronic, lifelong condition, the need for more longitudinal studies to find interventions that will affect more than the acute/subacute period after initiation would be helpful to patients. In addition, the Work Group suggested that comparative studies of the many interventions and self-guided treatments and digital and virtual interventions would help expand care for diabetes stress.

E. Pharmacotherapy

Recommendation

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 | Reviewed, New-added)

20. For adults with type 2 diabetes mellitus at high risk of atherosclerotic cardiovascular disease (i.e., 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 | Reviewed, New-added)

Discussion

Since 2008, the Food and Drug Administration has required that CV outcome trials be conducted for all new agents approved for glycemic management to ensure CV safety. Select agents from two drug classes, the GLP-1 RAs and SGLT-2 inhibitors, have been shown to significantly reduce 3-point major adverse CV outcomes (3-point MACE, i.e., CV death, non-fatal myocardial infarction [MI], and non-fatal stroke) in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD).

Several SRs evaluated these drug classes. Kristensen et al. (2019) found a 12% reduction in 3-point MACE with GLP-1 RA use (strength of evidence [SOE] high).(121) Of drugs available on the U.S. market today, liraglutide, dulaglutide, and injectable semaglutide were associated with significant CV benefit (see Table C-2).(121) Giugliano et al. (2020) and Sattar et al. (2021) reported similar effects.(122, 123) Bellastella et al. found that these agents reduced fatal and non-fatal stroke, with the most significant benefit seen with dulaglutide and semaglutide.(124) Giugliano et al. (2020) found that improved glycemic control might have contributed to the decrease in non-fatal stroke with GLP-1 RAs, but change in glycemia did not impact MI or mortality.(122) SGLT-2 inhibitor use similarly has resulted in a reduction in 3-point MACE as shown by McGuire et al. (2021) (SOE high); specific drugs available in the U.S. that have CV benefit include canagliflozin and empagliflozin.(125–127) Once again, please refer to the table for individual drug efficacy and adverse effects (Table C-2). Most of the included randomized trials were rated as very high quality, leading to SRs that were deemed

good quality, except for Tian et al., which was rated as fair.(127) This guideline reviewed no evidence on the combination use of GLP-1 RAs with SGLT-2 inhibitors.

Most of the above trials included a majority of patients with established ASCVD (CV, cerebrovascular, or peripheral vascular disease), New York Heart Association class II or III HF, or CKD stage 3 or higher. Additionally, all the trials except EMPA-REG OUTCOME had some patients with high CV risk, which was variably defined including age >50–60 years, plus albuminuria or proteinuria, hypertension with left ventricular hypertrophy, or ankle/brachial index <0.9. Although the data supporting reduction of 3-point MACE in patients with known ASCVD is robust, data supporting major adverse CV events (MACE) benefit in patients at high risk of ASCVD is less strong. The REWIND trial included the greatest proportion of patients at high CV risk. In addition to the previous criteria, patients age 60 years or older with at least two of the following were included: tobacco use, dyslipidemia, hypertension, or abdominal obesity. Overall support for benefit in patients with high CV risk comes largely from smaller proportions of those in trials including both patients with and without known CVD (see details in Table C-2) and two SRs (Kristensen et al. 2019; Giugliano et al. 2020). The strongest support for use of GLP-1 RA in patients with high risk of ASCVD is based on the REWIND trial, which included more than 9,000 patients, of whom greater than two-thirds had no known ASCVD but instead were at high risk.(128)

Whether these classes of drugs should be used as first-line therapy for T2DM or as add-on therapy to metformin in patients with ASCVD is unclear. The large randomized CV outcome trials looking at all these agents included 71–82% of patients on metformin as baseline therapy (see Table C-2). Whether future trials will be done to assess this question is unclear. What is clear is that for adults with T2DM and ASCVD, a GLP-1 RA or SGLT-2 inhibitor with proven CV benefits should be a part of the treatment regimen, regardless of HbA1C, to decrease the risk of MACE.

Both classes of agents have notable side effects as well as associated adverse events. Use of GLP-1 RAs is associated with significant gastrointestinal side effects, including nausea, vomiting, and diarrhea, but these often are mild and resolve over time; additionally, they can be modulated by appropriate patient selection (i.e., avoiding those with gastroparesis). A risk of cholelithiasis and acute cholecystitis increases slightly with dose and duration of treatment.(129) No increased risk of pancreatitis, pancreatic cancer, or hypoglycemia with GLP-1 RA use was noted.(121, 123) However, injectable semaglutide use is associated with a slightly increased risk of progression of diabetic eye complications because of, it is theorized, rapid improvement in glycemic control and is not a direct effect of the drug.(123) SGLT-2 inhibitor use has been associated with an increased risk of mycotic genital infections, but these are typically mild and easily treated.(125, 126) A slightly increased risk of diabetic ketoacidosis occurs, which can largely be mitigated with appropriate patient selection and education not to take when oral intake is diminished, the patient is feeling unwell, during acute illness, before surgery, or any combination of the foregoing.(125, 126) Silverii et al. (2019) found no

increased risk of Fournier's gangrene with SGLT-2 inhibitor use,(109) although this finding does not rule out the possibility of this rare adverse event. Amputation risk does not appear to be increased for this class overall,(126) although a review of canagliflozin randomized trials(127) indicates that this specific agent might, indeed, be associated with increased risk and that perhaps that risk was mitigated in subsequent SGLT-2 inhibitor trials by avoiding these agents in patients with diabetic foot complications. Overall, for both drug classes, it appears that glycemic and CV benefits outweigh the risks, with the latter mitigated by appropriate patient selection.

There is some variation in patient preferences regarding this treatment. Although most patients respond favorably to the benefits of these medications, which include weight loss, BP reduction, and CV and renal protection, some patients might be less enthusiastic about using them because of side effects, such as urinary frequency with SGLT-2 inhibitors or nausea or the need to administer an injection with the GLP-1 RAs. Additional factors might impact use, including high cost of GLP-1 RAs and PCP discomfort with these newer therapies. Additionally, one would need to consider discrete patient characteristics to make the best choice between these drug classes. For patients with morbid obesity, difficulty emptying their bladder, incontinence or who are male and uncircumcised, a GLP-1 RA might be a better choice. In contrast, for patients at current high risk for pancreatitis or personal or family history of medullary thyroid carcinoma or with concerns over cold chain storage, including patients experiencing homelessness or those who are actively deployed, an oral therapy such as an SGLT-2 inhibitor would be preferred. Neither agent would be optimal in patients with absolute insulin deficiency or patients who are already underweight and aiming to avoid weight loss.

The Work Group systematically reviewed evidence related to these recommendations. (109, 121–127) Therefore, they are categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was high. The body of evidence was robust, including SRs of large, high-quality RCTs. The major limitation noted was that patients without high CV risk were not included. Hence, we cannot apply this data for the primary prevention of CV disease in lower-risk patients with T2DM. Additionally, most of the patients in the GLP-1 RA and SGLT-2 inhibitor CV outcome studies had known ASCVD. The strength of evidence for benefit in high CV risk populations is not as strong as in patients with established vascular disease, making our confidence in the evidence for these patients less robust. The benefits of reduction in 3-point MACE outweighed the potential harms, including increased risk of diabetic ketoacidosis, genital yeast infection, polyuria, progression of retinopathy, and gastrointestinal side effects, which were felt to be relatively uncommon or transient. Patient values and preferences varied somewhat because many patients will respond favorably to therapy that enhances weight loss or mitigates CV events. Still, some patients might prefer non-injectable therapies or therapies not associated with urinary frequency. Thus, the Work Group made the following recommendations: 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. For adults with type 2 diabetes mellitus at high risk of atherosclerotic cardiovascular disease (i.e., 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.

Recommendation

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 | Reviewed, New-added)

Discussion

Evidence suggests that treatment of patients with T2DM and HF with SGLT-2 inhibitors reduces hospitalizations for HF (HHF).(130, 131) Several SRs compiled evidence from RCTs and demonstrated a consistent benefit for SGLT-2 inhibitors in reducing HHF. McGuire et al. (2021) examined the effect of SGLT-2 inhibitors on HHF from EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, and VERTIS CV trials and found an overall HR of 0.68 (95% CI: 0.61–0.76) for HHF with SGLT-2 inhibitors compared with placebo.(125) This effect was consistent among patients with established ASCVD (HR: -0.70; 95% CI: 0.62–0.78) and without established ASCVD (HR: 0.63; 95% CI: 0.5–0.80). Salah et al. (2021) analyzed similar trials as well as DAPA-HF and EMPEROR-Reduced and reported an overall HR of 0.69 (95% CI: 0.64–0.74) for HHF with SGLT-2 inhibitors versus placebo. A similar effect was seen when considering only patients with a prior diagnosis of HF (HR: 0.71; 95% CI: 0.61–0.83).(126) Guigliano et al. (2020) found a similar reduction in HR (HR: 0.88; 95% CI: 0.79–0.98) and further found no association between the degree of HbA1c reduction and HR for HHF, suggesting this benefit was independent of the impacts of SGLT-2 inhibitors on glycemic control.(122)

The evidence for the benefit of SGLT-2 inhibitors in reducing HHF is fairly consistent across all the high-quality studies reviewed by the Work Group without significant heterogeneity (see Table C-2). Evidence also indicates some risk of harm. Salah et al. (2021) found substantial increases in diabetic ketoacidosis (DKA) (HR: 2.86; 95% CI: 1.39–5.86) and genital infection (HR: 3.95; 95% CI: 3.01–5.18) but not hypoglycemia or amputation. The event rates for DKA and genital infections were overall low in the SGLT-2 inhibitor-treated patients compared with placebo-treated patients (DKA: 0.08% versus ~0.23% and genital mycotic infections: 0.67% versus 3.44%, for control and treatment groups, respectively). Silverii et al. (2020) analyzed similar RCTs to examine whether using SGLT-2 inhibitors increased the risk of Fournier's gangrene.(108) They

did not detect a significantly increased risk for Fournier's gangrene with using SGLT-2 inhibitors. However, the event rate was low, and the confidence interval was wide.

There is likely some variation in patient preferences regarding this treatment. The increase in urinary frequency can be bothersome, especially in patients with coexisting bladder or prostate conditions. A history of recurrent or severe genitourinary infections is likely to give patients and providers pause before initiating SGLT-2 inhibitors; however, the marked reduction in HHF is likely to be perceived as a worthwhile benefit. Older patients on other antihypertensives or diuretics, those with systolic HF, or both might experience symptomatic hypotension or volume depletion, which might require de-escalation or discontinuation of SGLT-2 inhibitor or other therapy.

Cardiology guidelines recommend SLGT-2 inhibitors for HF.(132) Guideline-directed medical therapy includes SGLT-2 inhibitors as part of an initial "four pillar" approach for patients with HF, along with angiotensin receptor–neprilysin inhibitors, beta blockers, and mineralocorticoid receptor antagonists.(133) In some cases, confusion might occur regarding which service is responsible for initiating SGLT-2 inhibitors and following patients (e.g., Primary Care, Cardiology, Nephrology, Endocrinology). Adding an SGLT-2 inhibitor to a regimen in a patient already achieving glycemic goals might require de-escalation of other medications to allow patients the benefit of the SGLT-2 inhibition to limit the risk of hypoglycemia. Although empagliflozin has been shown effective in patients with reduced and preserved ejection fraction, evidence of similar efficacy for other SGLT-2 inhibitors is emerging as of this CPG update.(134, 135) Dapagliflozin similarly reduced the rate of HF outcomes in patients with reduced or preserved ejection fraction. Although some SRs suggest that GLP-1 RAs might also reduce HHF, the effects appear to be largely driven by the HARMONY Outcomes trial, which studied albiglutide. This agent is no longer marketed in the U.S.(136, 137) Without this agent, the overall impact of GLP-1 RAs on HHF is likely minimal (see Table C-2).(122, 123)

The Work Group systematically reviewed evidence related to this recommendation. (109, 123, 126, 138) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was high. The benefits of SGLT-2 inhibitors in reducing HHF for patients with T2DM and HF outweighed the potential harm (e.g., uncomplicated genitourinary tract infections, euglycemic DKA). Patient values and preferences varied somewhat due to the side effects of these medications (e.g., urinary frequency, hypotension). Thus, the Work Group made the following recommendation: 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.

Recommendation

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 | Reviewed, New-added)

Discussion

Evidence from two large SRs suggests that SGLT-2 inhibitors reduce the cumulative incidence of adverse kidney events (i.e., reduction in estimated glomerular filtration rate [eGFR] or doubling of serum creatinine level, ESRD, and kidney related mortality) compared with placebo by 38% (HR: 0.62; 95% CI: 0.56–0.70).(125, 126) Results were consistent across subgroups stratified by presence or absence of baseline ASCVD, albuminuria, HF, T2DM, and CKD.(125, 126) In the included trials, the majority (>80%) of patients were concurrently prescribed an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) at baseline. SGLT-2 inhibitors decreased the risk of the composite kidney outcome in patients with CKD (eGFR less than 60 mL/min/1.73m^2; HR: 0.68; 95% CI: 0.77–0.94) and without CKD (HR: 0.53; 95% CI: 0.44–0.64).(126) Findings from multiple other studies conducted in various patient populations have been consistent with these results. In individual large, RCTs, empagliflozin, canagliflozin, and dapagliflozin were each associated with significantly improved kidney outcomes versus placebo, although no statistically significant benefit was seen with ertugliflozin.(125) Across the CV outcomes trials demonstrating renal benefit, most patients (74% or more) had an eGFR of at least 60 mL/min/173m^2, and 7-11% had macroalbuminuria at baseline. Canagliflozin reduced the risk of the composite renal endpoint of ESRD or renal mortality in a pooled analysis of the CANVAS and CREDENCE programs (HR: 0.64; 95% CI: 0.54–0.75).(127) In the DAPA-CKD trial, dapagliflozin reduced the primary composite outcome (sustained decline in eGFR ≥50%, ESRD, or renal or CV death) compared with placebo in patients with CKD [eGFR 25–75 mL/min/1.73m^2 and urine albumin to creatinine ratio (UACR) 200–5000 mg/g] with or without T2DM (HR: 0.61; 95% CI: 0.51–0.72).(126, 127) Empagliflozin reduced a similar composite outcome compared with placebo in patients with CKD (eGFR 20–45 mL/min/1.73m^2 or eGFR 45-90 with UACR ≥200) with or without T2DM in the EMPA-KIDNEY trial (HR: 0.72; 95% CI: 0.64–0.82).(139) The evidence base demonstrates that select SGLT-2 inhibitors improve renal outcomes in patients with T2DM, with and without CKD.

The renal protection conferred by SGLT-2 inhibitors is independent of glycemic control, although the underlying mechanisms are not fully elucidated. Small between-group HbA1c differences were seen in patient populations without T2DM.(125) An SR of trials achieving a between-group HbA1c difference with various interventions found no proportional relationship between HbA1c lowering and reduction in the composite renal outcome before or after adjustment for confounders.(138) Thus, select SGLT-2

inhibitors are recommended to improve renal outcomes regardless of whether glycemic targets are already met.

In an SR (n=59,747) including eight trials, SGLT-2 inhibitor use was not associated with an increased risk of hypoglycemia (OR: 0.92; 95% CI: 0.84–1.01) or amputation (OR: 1.25; 95% CI: 0.97–1.62).(126) CANVAS was the only trial in which a statistically significant increase in amputation risk was seen with canagliflozin versus placebo. The risk of diabetic ketoacidosis events was increased with SGLT-2 inhibitor use compared with placebo (2.3% versus 0.8%; OR: 2.86; 95% CI: 1.39–5.86), as was the risk of genital infections (3.3% versus 0.67%; OR: 3.95; 95% CI: 3.01–5.18). A meta-analysis found no significant difference between SGLT-2 inhibitors and comparators in the risk of Fournier's gangrene.(109)

Patient preferences are similar regarding this treatment. The patient focus group noted that medication and blood glucose monitoring (BGM) adherence could be burdensome, so an oral medication taken once daily without regard to food and without frequent BGM requirements might be preferable over other options. Taking a single medication for multiple benefits (i.e., glucose lowering, cardiorenal protection, BP lowering, weight loss) is anticipated to be viewed favorably by most patients. However, some patients might experience intolerable polyuria or recurrent genitourinary infections, possibly leading to treatment discontinuation.

Patients at increased risk of adverse effects from SGLT-2 inhibitors include those at baseline increased risk for genitourinary infections (i.e., history of frequent or severe urinary tract infections or genital mycotic infections, uncircumcised males, indwelling catheters, known increased post-void residual, immunosuppression) or diabetic ketoacidosis (i.e., pancreatic insulin deficiency, extreme caloric or carbohydrate restriction, alcohol abuse, acute illness, or severe infection). Additionally, SGLT-2 inhibitors should be held for at least 3 days before surgery to decrease the risk of diabetic ketoacidosis. SGLT-2 inhibitors might increase the risk of hypotension and dehydration; antihypertensive or diuretic medications or both might require adjustment. A reversible decrease in eGFR after initiation of a SGLT-2 inhibitor might occur, but therapy can be continued unless the decline is significant and persistent. Appropriate patient selection, shared decision making, and counseling are necessary to minimize the risk of harm.

The glucose-lowering effect of SGLT-2 inhibitors is attenuated in patients with lower eGFR (less than 45 mL/min/1.73m^2); however, they should still be used for renal protective benefits, which are retained with lower eGFR (evidence supports safety if eGFR is at least 20 mL/min/1.73m^2). Select SGLT-2 inhibitors are indicated for T2DM, CKD, and HF; thus, primary and specialty care providers (i.e., endocrinology, nephrology, cardiology) are all empowered to prescribe these agents for appropriate patients.

The Work Group systematically reviewed evidence related to this recommendation. (109, 125–127, 138) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was high. The body of evidence had some limitations, including limited studies reporting results based on eGFR/CKD status or baseline albuminuria, under-representation of racial and ethnic minorities in trials, and limited trial duration.(125, 126) The benefits of select SGLT-2 inhibitors to improve renal outcomes outweighed the potential harm of genitourinary infections and diabetic ketoacidosis events, the absolute risk of which were minor. The risk of these adverse events can be further decreased by careful patient selection to avoid those at high risk at baseline. Patient values and preferences were similar for these medications, which are easy to administer and have multiple benefits. Thus, the Work Group made the following recommendation: 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.

Recommendation

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 | Reviewed, New-added)

Discussion

Findings from the systematic evidence review suggest that GLP-1 RA treatment improves the composite kidney outcome (including the development of macroalbuminuria, doubling of serum creatinine or at least 40% decline in eGFR, renal replacement therapy, or death because of kidney disease) compared with placebo in patients with T2DM (HR: 0.79; 95% CI: 0.73–0.87).(123) This improvement was driven by the reduction in new onset macroalbuminuria, a finding that was statistically significant in individual trials for liraglutide, semaglutide, dulaglutide, and efpeglenatide.(121, 123) In contrast, GLP-1 RA use did not significantly improve worsening renal function (as indicated by doubling of serum creatinine or at least 40% decline in eGFR) compared with placebo (HR: 0.86; 95% CI: 0.72–1.02).(123) The PIONEER-6 trial with oral semaglutide did not report renal outcomes.(140) Outcomes for renal replacement therapy and death because of kidney disease were reported in five and two trials, respectively; no significant differences between GLP-1 RA and placebo were found. Baseline kidney function was similar across trials (median/mean estimated eGFR ranged from 72–80 mL/min/1.73m^2), and subgroup analysis based on eGFR was unavailable for renal outcomes. A SR of trials achieving a between-group HbA1c difference with various interventions found no proportional relationship between HbA1c lowering and reduction in the composite renal outcome before or after adjustment for confounders.(138)

No head-to-head studies compared the effects of GLP-1 RAs and SGLT-2 inhibitors on renal outcomes in the systematic evidence review. A network meta-analysis found SGLT-2 inhibitors were associated with significantly lower renal risk compared with GLP-1 RAs in both patients with and without albuminuria (RR [95% CI]; 0.75 [0.63–0.89] and 0.59 [0.44–0.79], respectively).(141) Based on available evidence, the Work Group recommends prioritizing select SGLT-2 inhibitors to improve renal outcomes, if appropriate.

Overall, GLP-1 RA use was not associated with an increased risk of severe hypoglycemia (OR: 0.90; 95% CI: 0.74–1.10), retinopathy (OR: 1.07; 95% CI: 0.92–1.25), pancreatitis (OR: 1.02; 95% CI: 0.77–1.36), or pancreatic cancer (OR: 0.98; 95% CI: 0.56–1.70) compared with placebo.(123) Semaglutide was associated with a significant increase in retinopathy complications in the SUSTAIN-6 trial (OR: 1.75; 95% CI: 1.10–2.78) and some other agents demonstrated a nonsignificant trend toward increased risk, possibly because of rapid glucose lowering.(142)

There is some variation in patient preferences regarding this treatment. The patient focus group noted that adhering to medication schedules can be burdensome, so agents administered once weekly might be preferred. However, some patients might prefer to avoid injectable medication. Some might have difficulty with administration because of dexterity, vision, or confusion or might be unable to store the medication properly. Although semaglutide is available in an oral formulation, it lacks the proven cardiorenal benefits associated with injectable semaglutide and some other agents in the class. Taking a single medication for multiple benefits (i.e., glucose lowering, cardiorenal protection, weight loss) is anticipated to be viewed favorably by most patients. However, some patients might experience intolerable gastrointestinal side effects, possibly leading to treatment discontinuation. Additionally, GLP-1 RAs are among the more expensive diabetes medications.

Patients with multiple endocrine neoplasia syndrome type 2, gastroparesis, and personal or family history of medullary thyroid carcinoma should not be prescribed a GLP-1 RA. Patients at current increased risk of pancreatitis (because of history of idiopathic pancreatitis, TGs greater than 1,000 mg/dL, gallbladder disease, or alcohol use disorder) and those with advanced diabetic retinopathy might be at increased risk of adverse effects from GLP-1 RAs. It is prudent to de-escalate medications known to cause hypoglycemia (such as insulin, sulfonylureas, and meglitinides) when initiating GLP-1 RAs in patients at risk of hypoglycemia. Appropriate patient selection, shared decision making, and counseling are necessary to minimize the risk of harm.

The Work Group systematically reviewed evidence related to this recommendation. (121, 123, 138, 141) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was high. The body of evidence had some limitations, including no studies reporting results based on eGFR/CKD status or baseline albuminuria, no studies with primary renal endpoints or enrollment of an all

CKD population, under-representation of racial and ethnic minorities in trials, and limited trial duration.(121, 123) The benefit of select GLP-1 RAs to improve incident macroalbuminuria outweighed the potential harm of gastrointestinal or other less common adverse events. The risk of these adverse events can be further decreased by careful patient selection to avoid those at high risk at baseline. Patient values and preferences varied somewhat because patients might favor the potential for once-weekly administration and multiple health benefits but disapprove of the need for injection and storage requirements. Thus, the Work Group made the following recommendation: 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.

Recommendation

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 their individualized target range for glycemic control.

    (Weak for | Reviewed, New-added)

Discussion

Evidence from meta-regression analyses suggests that select medications reduced the risk of specific ASCVD and renal disease outcomes independently of changes in glucose control. Giugliano et al. (2020) assessed data from 15 RCTs using either SGLT-2 inhibitors, GLP-1 RAs, or DPP4 inhibitors and compared the achieved HbA1c to MACE, including non-fatal stroke, non-fatal MI, and CV death.(122) Although all outcomes were generally reduced by SGLT-2 inhibitor or GLP1-RA, the improvement in MACE, non-fatal MI, and CV death appeared to be independent of the HbA1c reduction. In contrast, the reduction in non-fatal stroke was related to the degree of HbA1c reduction. Chalmouka et al. (2022) performed a similar analysis of clinical trials of glucose lowering agents, including new trials with SLGT-2 inhibitors and GLP-1 RAs, examining 27 trials ranging from the Kumamoto study (1995) and the UKPDS (1998) through more recent studies.(138) The development of a composite renal endpoint (which included a doubling in serum creatinine, a decrease in eGFR by 30% or more, renal death, end-stage renal disease, renal transplantation, or dialysis) was not directly associated with HbA1c. In contrast, the development of macroalbuminuria was positively related to HbA1c, suggesting that improved glucose control decreased this specific renal endpoint. Of note, only the SGLT-2 inhibitors decreased the risk of worsening kidney function, although GLP-1 RAs and SLGT-2 inhibitors decreased the risk of macroalbuminuria. DPP4i's impacted neither outcome.

The evidence for these two analyses is drawn from high-quality studies. However, as with any secondary data analysis, some limitations limit the generalizability of these results. Further, we need an underlying mechanistic understanding of why some outcomes are directly related to lower glycemia. In contrast, improvement in other outcomes appears to be independent of glycemic levels. Nonetheless, these data do raise the possibility that adding an agent with proven CV and renal benefits could still be useful for some patients, even if they have already achieved their target level of glycemic control.

There is likely large variation in patient preferences regarding this recommendation. This recommendation is most applicable to patients who attain adequate glycemic control with monotherapy (i.e., metformin) or combination therapy with agents other than an SGLT-2 inhibitor or a GLP-1 RA (e.g., sulfonylurea). Though the addition or substitution of an SGLT-2 inhibitor or a GLP-1 RA could improve CV and renal outcomes and could provide additional benefits (e.g., weight loss, lower BP, decreased hypoglycemia risk, or any combination of the foregoing), this maneuver might pose an extra medication burden on the patient. Further, GLP-1 RAs and SGLT-2 inhibitors both have discrete adverse event profiles. However, high-risk patients might opt for the addition or substitution of these agents into their regimen to decrease the risk of high-stakes major CVD or renal outcomes, like CV death or worsening of renal function. Shared decision making regarding starting a new medication is needed to arrive at an appropriate treatment plan.

The Work Group systematically reviewed evidence related to this recommendation. (122, 138) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, namely the small number of meta-regression analyses that support this recommendation. Further, whether stratifying patients at high risk for certain outcomes (e.g., patients who have previously had an ASCVD event) would provide additional insights into the efficacy of GLP-1 RAs and SGLT-2 inhibitors to reduce outcomes is unclear. Thus, the Work Group made the following recommendation: 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 their individualized target range for glycemic control.

More research is needed into the underlying mechanisms by which GLP-1 RAs and SGLT-2 inhibitors might improve clinical outcomes independently of glucose control.

Recommendation

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 | Reviewed, New-added)

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 not against | Reviewed, New-added)

Discussion

Older adults with T2DM represent a large and varied group of individuals, with some experiencing healthy aging and others having comorbidities, frailty, and limited life expectancy. It is accepted that lower HbA1c over time confers a reduced risk of microvascular complications, but these benefits are often realized over many years. Thus, glycemic management plans should consider the risks and benefits of diabetes treatments in the setting of an individual's unique characteristics and goals of care. In addition, older adults with concomitant conditions that limit life expectancy should be evaluated for polypharmacy, hypoglycemia, hospitalization, and fall risks.

Averting adverse outcomes that result from potential overtreatment is particularly important in older adults with cognitive impairment, dementia, or risk of falls. Treatment strategies to control hyperglycemia and minimize hypoglycemia have direct and tangible benefits for such patients. Therefore, we sought evidence on effective and safe glucose-lowering strategies in adults with T2DM and cognitive impairment or at risk of falls. The systematic evidence review, however, did not locate reports in which investigators recruited patients with T2DM and these higher-risk features. Eighteen studies were identified that evaluated diabetes treatments in patients with T2DM, age ≥65 years, or who were overweight or obese but without age-related conditions such as cognitive impairment or risk of falls. There were seven SRs and 11 randomized controlled trials. Many pharmacologic agents were studied in direct comparisons, including monotherapies and combinations of agents.

To overcome the absence of studies among the target populations, we found that predictive modeling suggested that factors such as older age, overweight, or obesity increase the risk of cognitive impairment or falls. Being overweight increases the risk of falls in women with T2DM by at least three-fold,(143) and each decade of age increases the risk of cognitive impairment by two-fold.(144) Other factors that can increase fall risk were considered, including impaired balance, reduced gait speed, peripheral neuropathy, multiple comorbid conditions, and lower extremity pain, but studies with these factors were also not identified to address the interventions of interest. Accordingly, the systematic evidence review focused on treatment strategies among

patients with older age and overweight or obesity as surrogates for the risk of cognitive impairment and falls. Because no reports were identified to inform the specific question about safe and effective treatments for glucose lowering in patients with cognitive impairment or risk of falls, the Work Group noted that evidence was insufficient to guide treatment strategies in such patients. This area is fertile ground for future research efforts. Indeed, some newer findings suggest that SGLT-2 inhibitors, DPP4i, and GLP-1 RAs have similar fracture risks, which might be a surrogate for the adverse consequences of falls.(145)

Clear evidence regarding diabetes treatment strategies and the risk of hypoglycemia exists. Insulin and sulfonylureas were noted to increase the risk of hypoglycemia in older adults.(146–151) In direct comparisons, medications such as metformin, DPP4i, GLP-1 RAs, and SGLT-2 inhibitors were all associated with a lower risk of hypoglycemia when compared with insulin or sulfonylureas.(146–149) These data were both consistent and compelling. Thus, the Work Group recommends that clinicians who treat older adults with T2DM should prioritize agents other than insulin or sulfonylureas to minimize the risk of hypoglycemia, when possible. Such a treatment strategy does not exclude the use of insulin or sulfonylureas when needed to achieve appropriate glycemic targets, such as in patients with marked hyperglycemia or contraindications to other medications. The overall strength of evidence was rated as very low, although the individual studies were rated from very low to high.

Hypoglycemia was considered a critical outcome of interest given its direct impact on patients and its potential role as a mediator of adverse outcomes, including falls and hospitalizations. In addition, medications such as GLP-1 RAs and SGLT-2 inhibitors are associated with lower hypoglycemia risk and might confer added benefits in patients with CVD, HF, and chronic kidney disease. GLP-1 RA medications are frequently associated with weight loss. Potential limitations to the application of this recommendation are that many medications with lower hypoglycemia risk are proprietary and might be subject to restricted use in specific subsets of patients because of costs. This limitation might legitimately affect their broader use among older adults with T2DM at risk of hypoglycemia.

Research priorities were also identified to inform this topic area. Additional studies are needed on these drug classes and others and their combinations regarding safety and effectiveness in patients with cognitive impairment or fall risk. Because hypoglycemia risk might vary based on demographic and clinical factors (i.e., age, race, obesity, comorbidities), studies should investigate whether the safety and effectiveness of diabetes medications differ based on patient characteristics.

The Work Group systematically reviewed evidence related to Recommendation 25. (146–151) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations, including studies that did not report measures of dispersion, had low event

rates, or lacked appropriate blinding. Other studies were relevant and associated with outcomes of interest and contributed to the confidence in the quality of evidence. (146-151) The benefits of prioritizing treatments to minimize the risk of hypoglycemia outweighed the potential harm. Patient values and preferences were similar because it was felt that most patients would want to avoid hypoglycemia. Thus, the Work Group made the following recommendation: 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.

The Work Group systematically searched for evidence and did not identify any studies that met inclusion criteria regarding the use of specific treatment strategies for glucose lowering to reduce the risk of harms in patients with co-occurring cognitive impairment or risk of falls. Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was inapplicable because no evidence was retrieved. The body of evidence had significant limitations because no studies were identified that focused on the topic nor the populations of interest. The Work Group was unable to judge the balance of desirable and undesirable outcomes because no specific intervention is being evaluated. The potential benefits of offering specific treatments to patients with cognitive impairment or at risk of falls should be considered against the potential harms that might result in overtreatment or undertreatment or exposure to other drug-related adverse events. The Work Group was unable to make a judgment on patient values and preferences because no specific intervention was being evaluated. Thus, the Work Group made the following recommendation: 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.

X. Research Priorities

During the development of the 2023 Type 2 DM CPG, the Work Group identified topics needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPGs. In addition, the Work Group recognized the need to complement these recommendations with participatory action research that would engage individuals with T2DM and their families in reviewing these guidelines, identifying gaps in the recommendations and in current care as well as in dialog to translate recognition of gaps into areas for research.

In reviewing the available evidence and using it to formulate recommendations or suggestions, the Work Group raised a substantial number of questions that could not be answered with the available evidence. These questions concerned the following.

A. Complementary and Integrative Health

- In reviewing complementary and integrative care for diabetes distress, the Work Group recommended that further research across a broader subset of interventions (e.g., acupuncture, biofeedback, hypnosis, guided imagery, massage therapy, yoga, tai chi) is needed. Because T2DM tends to be a chronic, lifelong condition, the need for more longitudinal studies to find interventions that will impact more than the acute/subacute period would be helpful to patients. In addition, the Work Group suggested that comparative studies of the diverse interventions, self-guided treatments, and digital and virtual interventions would help expand care options for diabetes stress. To accomplish this effort, longitudinal or longer-term studies or both (including RCTs) are needed to assess better the effectiveness and impact of complementary and integrative care on critical outcomes.
- In considering our unique VA/DoD populations, studies that incorporate management of stress related to combat and other social determinants of health (e.g., poverty, homelessness, substance use disorders) would also be helpful.

B. Pharmacological Management of Prediabetes

- With the increasing recognition of prediabetes as a risk factor for future morbidity, research into the pharmacological management of prediabetes should also include agents that often lead to weight loss.
- In addition, studies that help identify specific patient populations or characteristics that might benefit most from medications to prevent progression from prediabetes to T2DM (based on age, BMI, history of GDM, glucometrics within the range of prediabetes, etc.) are of interest.
- Metformin has been shown to decrease the risk for progression from prediabetes to T2DM, but the effect is relatively modest and varies with baseline characteristics. With the development of newer medications that have the potential to achieve substantial weight loss, including agents with significant glucose-lowering activity, an urgent need exists to know whether these medications are more effective in slowing the progression to T2DM. Thus, studies comparing these newer agents with metformin will help determine their relative ability to protect against the development of T2DM. Moreover, these studies will provide further insight into the relative importance and extent of weight loss needed to slow the progression of T2DM.

C. Pharmacological Management of T2DM

A gap in the evidence exists in evaluating for the efficacy and safety of various pharmacologic treatment options that lower glucose levels in adults with T2DM and memory loss or cognitive impairment or those at increased risk of falls. Additionally, more studies comparing insulin and sulfonylurea class of glycemic control medications with other available drug classes and/or a combination of SGLT2 inhibitor and GLP-1

RA would be beneficial in selecting the safest and most effective treatment options. A gap exists in identifying whether some medications positively affect slowing cognitive decline. Particular interest in evaluating the risk of hypoglycemia across various subgroups (e.g., age, sex race or ethnicity or both, obese versus not obese) would help further understanding of pharmacologic choices and expected outcomes.

D. Glycemic Variability

Recent studies have highlighted the potential value of assessing glycemic variability (i.e., glucose or HbA1c fluctuation) in predicting important diabetes adverse outcomes. However, many important questions must be answered before estimates of glycemic variability can be effectively translated into appropriate clinical actions. For example, what are the preferred metrics of glycemic variability to use for risk stratification, and do the metrics vary depending on the outcome? Will the CV or SD (or other available metrics of variation) of visit-to-visit fasting glucose or HbA1c provide better estimates of future macrovascular complications, or would they be most helpful in predicting renal outcomes or hypoglycemia? Moreover, with the increasing use of CGM and the ability to calculate both within and between day variation over short- and long-term scales, we can obtain more granular assessments and even new metrics of glycemic variability that might provide even better assessments of risk for adverse outcomes. Finally, we need to understand better what type of interventions might reduce glycemic variation and, most importantly, whether reductions in variability translate into improved outcomes. This knowledge will likely require careful study of large observational cohorts and eventually randomized controlled trials of promising and practical interventions.

E. Glycemic Management – HbA1C Targets

Whether unique characteristics identify a patient population that will accrue greater microvascular and macrovascular benefits than harms with lower HbA1c target ranges remains unclear. Valid reasons exist to speculate greater net benefit in populations who are younger, are newly diagnosed with T2DM, have minimal or no complications from T2DM, have longer life expectancy, or are taking medications with low risk of hypoglycemia. Although clinical trials of intensive glycemic management have been informative, limitations in their study design, conduct, and patient demographics have hindered definitive conclusions about relative tradeoffs within specific patient subgroups. Additional research is needed, therefore, to determine whether specific subsets of patients will achieve a favorable balance of benefits and harms by targeting lower HbA1c ranges.

F. SGLT-2 Inhibitors and GLP-1 Receptor Agonists

- In determining the benefit of SGLT-2 inhibitors or GLP-1 RAs, the Work Group had many recommendations for future investigation. Foremost, does evidence exist that the cardiac and renal benefits are also seen in other ethnic or racial groups or both, as well as for females because much of the studied population were predominantly middle-aged males of European descent?

- Do these agents have a role in primary prevention for ASCVD in patients with T2DM?
- Also, the Work Group recommended further research into the pharmaceutical effectiveness in reducing other known diabetic comorbidities. For example, does the use of SGLT-2 inhibitors or GLP-1 RA impact the risk of retinopathy?
- The ADA no longer recommends metformin as the first line in patients with ASCVD, CKD, and HF. Therefore, a direct comparison of initial therapy with metformin versus SGLT-2 inhibitor or GLP-1 RA, or a combination therapy on cardiorenal and other outcomes in all T2DM patients, might allow for more broad use.

G. Continuous Glucose Monitoring

Comparative effectiveness of telehealth and CGM for making home monitoring available to health care team members is another area of interest. The use of CGMs is expanding rapidly in T2DM patients, but our understanding of the full benefits of these devices remains limited. Although recent studies have highlighted their ability to reduce HbA1c, improve TIR for daily glucose levels, and reduce hypoglycemia, we need more information about their effects on outcomes such as hospitalizations and microvascular and macrovascular complications. Additionally, that the benefits of CGM might vary greatly is anticipated, depending on patient-level factors, such as hypoglycemia risk, glycemic control, and patterns of CGM use. More detailed studies of these and other subgroups of CGM users are needed to help providers make more informed decisions about who should start or continue using CGM or both. Moreover, maintaining these devices is relatively expensive, not just in terms of direct device and supply costs but also for the personnel to offer all the health care services and education needed to support these newer technology efforts. Thus, as the various beneficial short-term and long-term effects of using CGM become more apparent, detailed studies of the expenditures and potential savings are needed to help inform health care facilities on how to deploy these devices and programs most appropriately.

H. Diabetes Self-Management Education and Support

- Comparative effectiveness of in-person versus virtual DSMES to mitigate access and digital divide issues
- Comparative effectiveness of health coaches and peer support
- Examination of additional outcomes beyond A1c, such as hospitalization, ED visits, and hypoglycemia reduction
- Comparative effectiveness of DSMES during patient periods of transition of care
- Expansion to evaluate this approach to persons with prediabetes

I. Nutritional Interventions

- Comparative effectiveness of optimal daily energy (e.g., carbohydrate, protein, fat, alcohol, including 0 percent)
- Comparative effectiveness of optimal daily energy (e.g., carbohydrate, protein, fat, alcohol) distribution based on the duration of disease
- Comparative effectiveness of the impact of various eating patterns on within-day glycemic variability using CGM
- Comparative effectiveness of the impact of a vegetarian dietary pattern with various energy combinations (with and without alcohol) using CGM
- Comparative effectiveness of fiber supplements and vegetarian dietary patterns
- Comparative effectiveness of diets with red meat consumption and inflammation
- Comparative effectiveness of IF for individuals not on antihyperglycemic agents
- Comparative effectiveness of various energy distribution using CGM in individuals who use IF strategies

Although a Mediterranean style diet is recommended to improve glucose control and other metabolic features of diabetes, concern exists that this diet might not be universally applicable to, or generally accepted by, all populations. Further studies are needed to determine the impact of food deserts (i.e., areas where high-quality fresh food is unavailable or unaffordable) and whether this diet or others can be applied in certain urban areas where components of the Mediterranean style diet are less available.

- Evaluation of the impact of food deserts and accessibility of a Mediterranean style diet to individuals in low-income urban areas
- Comparative effectiveness of the Mediterranean style–DASH dietary approach in individuals with T2DM on HOMA-IR and HOMA-B in racial and ethnic groups based on the duration of diabetes
- Evaluation of adherence, impact, and effectiveness of boxed or premade Mediterranean style diet meals provided through a delivery service

J. Telehealth

- Evaluation of the impact and effectiveness of telehealth hubs and Centers of Excellence on efficiency and equity

K. Physical Activity

A key area for future research is the relationship between exercise and glucose control. Studies are needed that include more detailed comparisons between the types and extent of physical activity and related changes in glucose metabolism. For example, does high-intensity interval training lead to more significant declines in fasting or post-

prandial glucose levels than less intensive training? More careful studies of less traditional types of exercise are also needed.

- Comparative effectiveness of various exercise modalities (e.g., strength, endurance, flexibility) in individuals with newly diagnosed T2DM on insulin resistance and insulin secretion
- Comparative effectiveness of various exercise modalities (e.g., strength, endurance, flexibility) in individuals with T2DM for more than 10 years on insulin resistance and insulin secretion

L. Screening and Diagnostic Testing

- Further research or prospective studies evaluating the validity and efficacy of various tools to screen for or diagnose diabetes distress or both would be helpful in formulating recommendations regarding the use of specific tools in clinical practice.
- Research, specifically RCTs, that evaluates the effects of screening for NAFLD is needed. Evidence is lacking for assessing the impact of this screening on clinical outcomes, such as mortality, liver cirrhosis, or liver transplantation. This data will enable better clinical decision making in developing the plan of care for patients with T2DM.
- Prospective RCTs are needed to determine whether screening tools for fall risk and cognitive impairment affect clinical outcomes in patients with T2DM.
- A key area of future research includes identifying methods with greater diagnostic accuracy, including non-invasive risk calculators of non-alcoholic fatty liver disease in patients with T2DM. This could be enhanced by identifying novel biomarkers that bolster existing prediction models. Studies are also needed to refine imaging techniques further to improve the characterization of fibrotic liver disease in patients with T2DM versus those without diabetes.

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 key questions (KQ) on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 lists and describes the PICOTS elements.

Table A-1. PICOTS (152)

PICOTS Element	Description
Population or Patients	Patients of interest. It includes the condition or conditions, populations or subpopulations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic /screening test used with the patient or population.
Comparator	Treatment or treatments (e.g., placebo, different drugs) or approach or approaches (e.g., different dose, different frequency, standard of care) being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing and setting; QoL: quality of life

Because of resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1–9 scale (7–9, critical for decision making; 4–6, important, but not critical, for decision making; and 1–3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Determining Recommendation Strength and Direction).

a. Populations

- All Key Questions, except Key Question 6
    - Including: Nonpregnant community-dwelling adults, Veterans, deployed and non-deployed active duty Service members age ≥18 years diagnosed with T2DM

- *Excluding*: Studies limited to individuals with T1DM or gestational diabetes, pregnant individuals, individuals with other health conditions managed exclusively outside primary care (e.g., hospitalized)

- Key Questions 4, 5
  - Including: Studies with the above-described population or with prediabetes
- Key Question 9
  - Including: Studies with the above-described population with unknown risk for falls or cognitive impairment
- Key Question 10
  - Including: Studies with the above-described population with cognitive impairment, memory loss, or risk of falls
- Key Questions 11,12
  - Including: Studies with the above-described population and without known diabetes distress, renal disease, NASH/NAFLD
- Key Question 6
  - Including*:* Nonpregnant community-dwelling adults, Veterans, deployed and non-deployed active duty Service members age ≥18 years with known prediabetes
  - Excluding: Exclusion criteria from the above with an addition—exclude studies with persons already diagnosed with T2DM

b. Interventions

- Key Question 1
  - One level of long- or short-term glycemic variability (GV) is measured as, but not limited to the following
    - Short-term GV
      - Average Daily Risk Range (ADRR)
      - Average Glucose Profile (AGP)
      - Coefficient of Variation (CV)
      - Continuous Overlapping Net Glycemic Action (CONGA)
      - Interquartile Ranges (IQR)
      - Mean Absolute Glucose (MAG)
      - Mean Amplitude of Glycemic Excursions (MAGE)
      - Mean of Daily Differences (MODD)
      - Standard Deviation (SD)

            - Time in Range (TIR)
        - Long-term GV
            - SD or CV of HbA1c
            - Fasting Plasma Glucose (FPG)
            - Postprandial Glucose (PPG)
- Key Question 2
    - Continuous glucose monitoring
- Key Question 3
    - Complementary integrative health interventions
        - Acupuncture
        - Biofeedback
        - Clinical hypnosis
        - Guided imagery
        - Massage therapy
        - Meditation
        - Mindfulness-based stress reduction
        - Tai chi or qigong
        - Yoga
- Key Question 4
    - One or more nutrition interventions, including
        - Carbohydrate counting diet (e.g., South Beach, Whole 30)
        - Dietary Approaches to Stop Hypertension (DASH)
        - Intermittent fasting (IF)
        - Ketogenic diet (e.g., Atkins diet)
        - Mediterranean style diet
        - Paleo diet
        - Vegan or vegetarian diet
- Key Question 5
    - Physical activity modalities
        - Aerobic exercise (e.g., walking, swimming, water aerobics)
        - Interval training (e.g., high-intensity interval training)
        - Pilates

        - Qigong
        - Strength training
        - Tai chi
        - Yoga
    - Exercise modality with one dose, duration, or intensity
- Key Question 6
    - Metformin (biguanide)
    - Alpha glucosidase inhibitors (acarbose, miglitol)
    - Dipeptidyl peptidase 4 inhibitors (DPP4i) (sitagliptin, saxagliptin, linagliptin, alogliptin)
    - GLP-1 agonists (dulaglutide [Trulicity], exenatide [Byetta, extended release; Bydtypes of insulinureon], liraglutide [Victoza], lixisenatide [Adlyxin], semaglutide [Ozempic, Rybelsus])
    - SGLT-2 (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin)
    - TZDs (pioglitazone)
- Key Question 7
    - SGLT-2 inhibitors or GLP-1 receptor agonists
- Key Question 8
    - De-intensified T2DM management, defined as discontinuation or dosage decrease of at least one glycemic medication without the addition of, or an increase in the dose of, another glycemic medication

      OR
    - Intensified glucose-lowering treatment, defined as an addition of any glycemic medication for persons with controlled T2DM
- Key Question 9
    - Screening strategies for the following
        - Risk factors for falls
            - Morse Fall Scale (MFS), Five Times Sit to Stand (5X STS), Single Leg Stance (SLS), Time Up and Go (TUG)
            - Autonomic insufficiency
        - Cognitive impairment
            - Montreal Cognitive Assessment (MoCA)
            - Mini-Cog
            - Mini mental state examination (MMSE)

- St Louis University Mental Status (SLUMS)

- Key Question 10
  - Pharmacologic treatment
    - Sulfonylureas (glipizide, glimepiride, glyburide)
    - Meglitinides (nateglinide, repaglinide)
    - Amylin analog (pramlintide)
    - Insulin
    - Biguanide (metformin [Glucophage, Glucophage XR])
    - Alpha glucosidase inhibitors (acarbose, miglitol)
    - Dipeptidyl peptidase 4 inhibitors (DPP4i) (sitagliptin, saxagliptin, linagliptin, alogliptin)
    - GLP-1 agonists (dulaglutide [Trulicity], exenatide [Byetta, extended release; Bydureon], liraglutide [Victoza], lixisenatide [Adlyxin], semaglutide [Ozempic, Rybelsus])
    - SGLT-2 (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin)
    - TZDs (pioglitazone)
    - Dopamine-2 agonists (e.g., bromocriptine)
  - Nutrition assessment
    - Weight history (percentage of weight loss)
    - Vitamin D status
    - Anemia
    - Hypoglycemia
    - Hydration status
    - Degree of malnutrition (mild, moderate, severe)
    - Caloric insufficiency
    - Sodium intake
- Key Question 11
  - Screening tools and strategies for established diabetes-related complications
    - Renal disease
      - MRI
      - Renal ultrasound
      - Serum creatinine, eGFR, urine microalbumin/creatinine ratio

- NAFLD/NASH
  - Fibroscan (transient elastography)
  - MRI elastography
  - Routine ultrasound (right upper quadrant or “hepatic”) and liver enzymes (Aspartate transaminase [AST]/Alanine transaminase [ALT]/Alkaline phosphatase AP/Total Bilirubin)
- Diabetes distress
  - Diabetes Distress Scale with Screener – the two-question screener
  - T1-Diabetes Distress Scale (DDS) – can be used with adults with T1DM to inform clinical interventions
  - Diabetes Distress Scale – Original 17 – can be used with adults with T1DM or T2DM
  - T2-Diabetes Distress Assessment System (T2-DDAS) – can be used with insulin-using and non-insulin-using adults with T2DM
  - PAID Questionnaire (Problem Areas in Diabetes) – can be helpful to hone in on a specific problem with a patient

- Key Question 12
  - Same as KQ 11

c. Comparators

- Key Question 1
  - Another level of GV
- Key Question 2
  - Conventional self-monitoring
- Key Question 3
  - Sham interventions, non-active interventions, other complementary integrative health interventions (listed or not listed in intervention column)
- Key Question 4
  - No dietary intervention, usual diet (including “healthy eating” unrelated to specific dietary plan), other dietary intervention (listed or not listed in intervention column)
- Key Question 5
  - No physical activity or other physical activity modalities from the intervention column

    - Same exercise modality with different intensity (e.g., dose, duration, frequency)
- Key Question 6
    - Placebo, TAU, or another single pharmacotherapy listed
- Key Question 7
    - TAU (i.e., without SGLT-2 or GLP-1) or placebo
- Key Question 8
    - Different patient characteristics (e.g., hypoglycemia, polypharmacy, age [>65], cognitive impairment/decline, multiple comorbidities)
- Key Question 9
    - No screening
- Key Question 10
    - Another pharmacologic treatment from the intervention column
    - Another nutrition assessment from the intervention column
- Key Question 11
    - Reference test
- Key Question 12
    - No screening

d. Outcomes

- Key Question 1
    - Critical outcomes
        - Mortality: all-cause or diabetes-related
        - Hypoglycemia and hyperglycemia
    - Important outcomes
        - Cardiovascular (CV) outcomes: congestive heart failure, atherosclerotic cardiovascular disease (CVD), stroke, myocardial infarction (MI), peripheral vascular disease
        - Diabetes-related microvascular complications: diabetic neuropathy, diabetic retinopathy, neuropathy
        - Falls (secondary to hypoglycemia, neuropathy, or both, including end stage renal disease [ESRD])
        - HbA1c
        - Quality of life (QoL)

- Key Question 2
  - Critical outcomes
    - Hypoglycemia and hyperglycemia
  - Important outcomes
    - CV outcomes: congestive heart failure, atherosclerotic CVD, stroke, MI, peripheral vascular disease
    - Diabetes distress
    - HbA1c
    - Hospitalizations
    - Patient satisfaction
    - QoL
- Key Question 3
  - Critical outcomes
    - Adherence to diabetes treatment (including adherence to self-monitoring, diet (i.e., portion size, disordered eating), exercise, medications)
    - Diabetes distress
    - HbA1c
    - QoL
  - Important outcomes
    - Glycemic variability
    - Number of medications used
- Key Question 4
  - Critical outcomes
    - Glycemic control
    - Progression from prediabetes to T2DM
  - Important outcomes
    - Blood glucose
    - Hypertension
    - Weight loss
- Key Question 5
  - Critical outcomes
    - Progression from prediabetes to T2DM

- Important outcomes
  - Blood glucose
  - Glycemic control (A1c)
  - Hypertension
  - Weight loss
- Key Question 6
  - Critical outcomes
    - Progression to diabetes (HOMA-IR and HOMA-B, HbA1c, diagnosis of DM via HbA1c, FPG, OGGT)
  - Important outcomes
    - CV outcomes: congestive heart failure, atherosclerotic CV disease, stroke, MI, peripheral vascular disease
    - Diabetes-related microvascular complications: diabetic neuropathy, diabetic retinopathy, neuropathy
    - Harms: episode of hospitalization with hyperglycemia or coma
    - Medication adverse effects
    - Weight loss or gain
- Key Question 7
  - Critical outcomes
    - Cardio-renal outcomes, for example,
      - CVD outcomes: cardio-vascular death, non-fatal myocardial infarction, non-fatal stroke, HF
      - Renal outcomes: dialysis, need for renal-replacement therapy, kidney transplant, renal death, doubling of SCr, macroalbuminuria, sustained decline in eGFR of at least 30–50%
      - Medication adverse effects (e.g., genitourinary infections, pyelonephritis, urosepsis, Fournier's gangrene, hypotension/dehydration, diabetic ketoacidosis, gastrointestinal intolerance, pancreatitis, gallbladder disease, retinopathy complications, lower limb amputation.)
  - Important outcomes
    - Hypoglycemia

- Key Question 8
  - Critical outcomes
    - Falls
    - Hospitalization
    - Mortality
  - Important outcomes
    - CVD
    - Days of lost productivity
    - QoL
- Key Question 9
  - Critical outcomes
    - Hypoglycemia
    - Falls (secondary to hypoglycemia and/or neuropathy)
  - Important outcomes
    - CV outcomes: congestive heart failure, atherosclerotic CV disease, stroke, myocardial infarction, peripheral vascular disease
    - Diabetes-related microvascular complications: diabetic neuropathy, diabetic retinopathy, neuropathy
    - Function (IADLs and ADLs)
    - Mortality: all-cause or diabetes-related
    - QoL
- Key Question 10
  - Critical outcomes
    - Hypoglycemia
    - Falls (secondary to hypoglycemia, neuropathy, or both)
    - Hospitalization
  - Important outcomes
    - HbA1c
    - Medication side effects (i.e., hypotension and changes in blood pressure [BP])
    - QoL

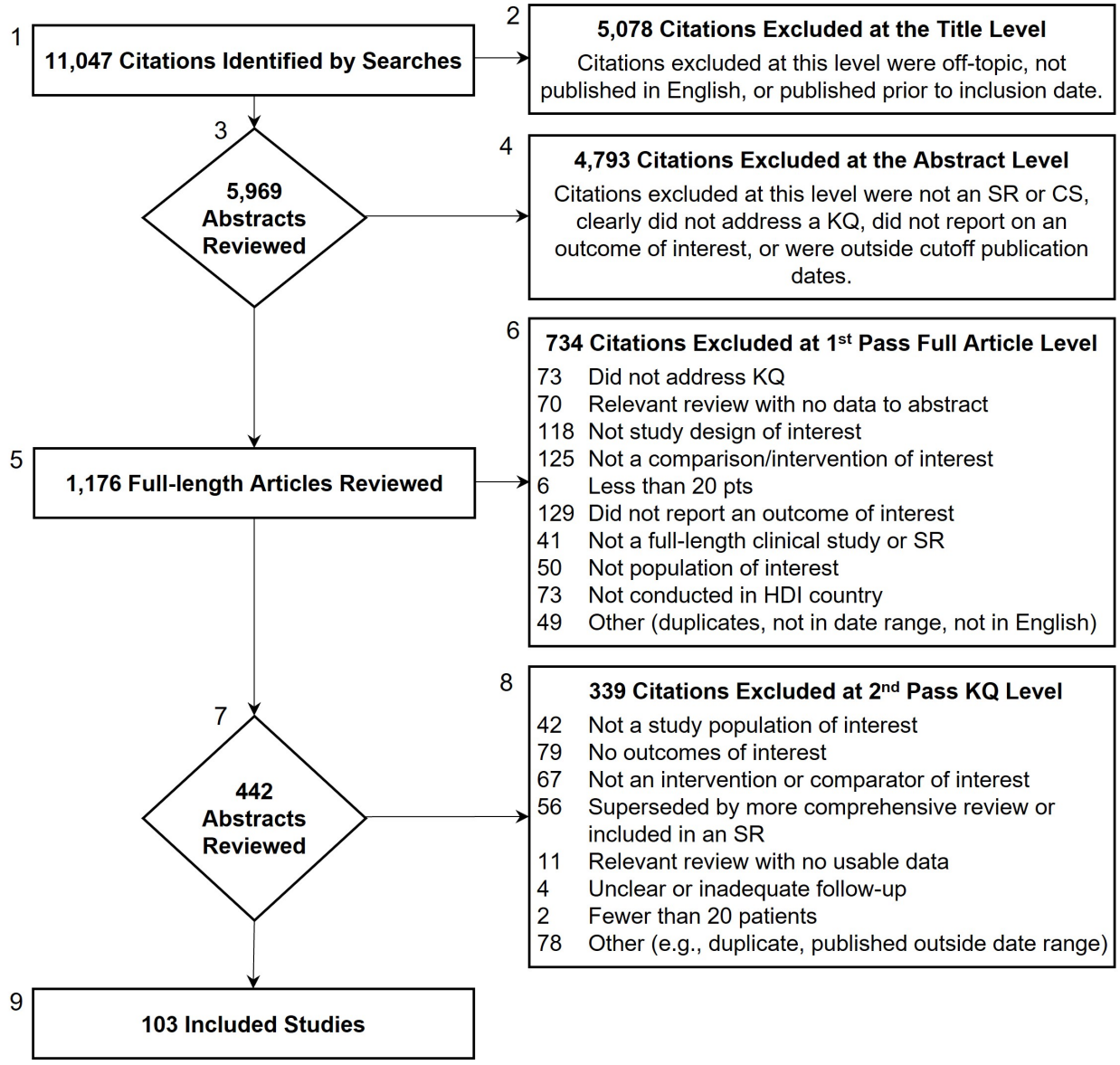
- Key Question 11
  - Critical outcomes
    - Accuracy outcomes: sensitivity, specificity, positive and negative predictive values of the screening tools
  - Important outcomes
    - NA
- Key Question 12
  - Critical outcomes
    - NA
  - Important outcomes
    - Blood glucose
    - CV outcomes: congestive heart failure, atherosclerotic CV disease, stroke, myocardial infarction, peripheral vascular disease
    - Other complications directly related to T2DM: non-alcoholic steatohepatitis (NAFLD/NASH), cirrhosis, and HCC
    - QoL
    - Stress measures (i.e., diabetes distress)
    - Renal disease outcomes – decline in eGFR, progression to ESRD

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review and Key Question Specific Criteria). In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; HDI: human development index; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 11,047 Citations Identified by Searches
    a. Right to Box 2: 5,069 citations excluded at the title level
        i. Citations excluded at this level were off topic, not published in English, or published prior to the inclusion date.
    b. Down to Box 3
2. Box 3: 5,969 Abstracts Reviewed
    a. Right to Box 4: 4,793 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or CS, clearly did not address a KQ, did not report an outcome of interest, or were outside cutoff publication dates.
    b. Down to Box 5
3. Box 5: 1,176 Full-Length Articles Reviewed
    a. Right to Box 6: 734 citations excluded at 1st pass full article level
        i. 73 did not address a KQ
        ii. 70 relevant review with no data to abstract
        iii. 118 not a study design of interest
        iv. 125 not a comparison/intervention of interest
        v. 6 fewer than 20 pts
        vi. 129 did not report an outcome of interest
        vii. 41 not a full-length clinical study or SR
        viii. 50 not a population of interest
        ix. 73 not conducted in an HDI country
        x. 49 other (duplicates, not in date range, not in English)
    b. Down to Box 7
4. Box 7: 442 Articles Reviewed
    a. Right to Box 8: 339 citations excluded at 2nd pass KQ level
        i. 41 not a study population of interest
        ii. 77 no outcomes of interest
        iii. 65 not an intervention or a comparator of interest
        iv. 53 superseded by a more comprehensive review or included in an SR
        v. 9 relevant review with no usable data
        vi. 1 unclear or inadequate follow-up

vii. 1 fewer than 20 patients

viii. 78 other (e.g., duplicate, published outside date range)

b. Down to Box 9

5. Box 9: 103 Included Studies

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	In adults with T2DM, what impact does glycemic variability (short-term and long-term) have on outcomes?	SR: 1 Other: 7 post-hoc studies
2	In adults with T2DM, what is the impact of CGM on outcomes? In adults with T2DM, does CGM compared to SMBG improve adherence to glucose-lowering medication or diet/exercise or improve patient-reported outcomes such as diabetes distress or quality of life?	RCTs: 8 (10 publications) SR: 1
3	In adults with T2DM and diabetes distress, which complementary integrative health interventions for diabetes distress improve glycemic control and adherence?	RCTs: 1 SR: 2
4	In adults with T2DM or prediabetes, what is the effectiveness and comparative effectiveness of nutrition intervention strategies?	RCTs: 10 SR: 4
5	In adults with T2DM or prediabetes, what is the effectiveness or comparative effectiveness of different physical activity modalities on diabetes outcomes? How do outcomes differ based on frequency, duration, and intensity?	RCTs: 12 SR: 8
6	For adults with prediabetes, what is the effectiveness and comparative effectiveness of pharmacotherapy in preventing progression to diabetes?	RCTs: 4 SR: 4
7	In adults with T2DM, what are the risks and benefits of treatment with either SGLT-2 inhibitors or GLP-1 receptor agonists on cardiovascular or renal outcomes? Is the effect of these medications on cardio-renal outcomes independent of their impact on glycemic control?	SRs: 9
8	What are the indications for de-intensification of T2DM care?	SR: 2 Other: 3 post-hoc studies
9	In adults with T2DM, what is the clinical utility of screening for fall risk and cognitive impairment?	0 studies
10	What treatment strategies are most effective and safe for glucose lowering in adults with T2DM and memory loss or cognitive impairment or at-risk of falls?	RCTs: 11 SR: 7

KQ Number	KQ	Number and Study Type
11	In patients with T2DM, what is the accuracy of screening strategies for diabetes distress, renal disease, and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis?	SR: 1 Other: 5 diagnostic accuracy studies
12	In patients with T2DM, what is the clinical utility of screening for diabetes distress, renal disease, and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis?	Other: 1 retrospective comparative trial
	Total Evidence Base	103 studies

Abbreviations: CGM: continuous glucose monitoring; GLP-1: glucagon-like peptide 1; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter-2 inhibitor; SMBG: self-monitoring of blood glucose; SR: systematic review; T2DM: type 2 diabetes mellitus.

a. General Criteria for Inclusion in Systematic Evidence Review

Randomized controlled trials (RCT) or systematic reviews (SR) were published January 1, 2016, through April 11, 2022, if not otherwise listed in Table A-3. If multiple SRs address a KQ, the most recent or comprehensive review or both are selected. Systematic reviews were supplemented with RCTs published after the SR.

Studies must be published in English.

Publication must be a full clinical study or SR; abstracts alone will not be included. Similarly, letters, editorials, and other publications that are not peer-reviewed, full-length clinical studies will not be included.

Systematic reviews must search at least MEDLINE or EMBASE for eligible publications, perform risk of bias assessment of included studies, and assess the quality of evidence using a rigorous rating system (e.g., GRADE, the Strength of Evidence grading used by the Evidence-based Practice Centers of the Agency for Healthcare Research and Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must be reported in a manner that allows the ECRI team to judge the overall quality, consistency, directness, and precision of evidence. Otherwise, an SR will not be included.

Unless otherwise specified, the study must enroll at least 20 patients (10 per study group for treatment studies). Small sample size is associated with increased risk of bias, and small studies are downgraded in the GRADE domain of precision: one downgrade for imprecision of a single study with <200 patients per study arm.

Studies must enroll at least 80% of patients who meet the study population criteria.

Only full clinical studies or SRs were included; abstracts alone were excluded. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.

Study must have reported at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

Table A-3. Study Design

Key Question	Study Designs
1, 8	• SRs • RCTs Large (≥200) cohort or nonrandomized studies with contemporaneous control
2–6, 10	• SRs • RCTs
7	• SRs
9, 12	• SRs • RCTs • Cohort or nonrandomized studies with contemporaneous control
11	• Cohort studies, cross-sectional studies focused on assessing diagnostic accuracy

Abbreviations: RCT: randomized controlled trial; SR: systematic review

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-4. See Appendix H for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-4. Bibliographic Database Information

Name		Date Limits	Platform or Provider
Bibliographic Databases	EMBASE (Excerpta Medica) and MEDLINE	January 1, 2016, through April 11, 2022	Elsevier
	PsycINFO (for selected KQs)	January 1, 2016, through April 11, 2022	Ovid
	PubMed (In-process and Publisher records)	January 1, 2016, through April 11, 2022	National Library of Medicine
Grey Literature	Agency for Healthcare Research and Quality (AHRQ)	Searched on April 19, 2022	AHRQ
	U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program	Searched on April 19, 2022	VA

d. Rating the Quality of Individual Studies and the Body of Evidence

The Lewin Team assessed the methodological risk of bias of individual diagnostic, observational and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(153)

Next, the Lewin Team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations),

consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very Low*.

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, Defense Health Agency, the Lewin Team convened a 4-day virtual recommendation development meeting from August 8–11, 2022, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (see Determining Recommendation Strength and Direction).

a. Determining Recommendation Strength and Direction

Per GRADE, each recommendation's strength and direction is determined by the following four domains:(20) Information on each domain, questions to consider, and the resulting judgment can be found in Table A-5.

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the body of evidence supporting a recommendation (see Rating the Quality of Individual Studies and the Body of Evidence). The options for this domain include *High*, *Moderate*, *Low*, or *Very low*. These four ratings are a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2, 22)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very Low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(20)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include *benefits outweigh harms/burdens*, *benefits slightly outweigh harms/burdens*, *benefits*

and harms/burdens are balanced, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most providers will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they might apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include *similar values*, *some variation*, and *large variation*. For instance, there might be *some variation* in patient values and preferences for a recommendation on the use of acupuncture because some patients might dislike needles. When patient values seem homogeneous, this domain might increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain might decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix D).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain, for example, include resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population might be geographically remote from an intervention (e.g., complex radiological equipment); a drug might be contraindicated in a subgroup of patients.

Table A-5. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	• Among the designated critical outcomes, what is the lowest quality of relevant evidence? • How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very low
Balance of desirable and undesirable outcomes	• What is the magnitude of the anticipated desirable outcomes? • What is the magnitude of the anticipated undesirable outcomes? • Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	• Benefits outweigh harms/burdens • Benefits slightly outweigh harms/ burdens • Benefits and harms/burdens are balanced • Harms/burdens slightly outweigh benefits • Harms/burdens outweigh benefits

Decision Domain	Questions to Consider	Judgment
Patient values and preferences	• What are the patients' values and preferences? • Are values and preferences similar across the target population? • Are you confident about typical values and preferences?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• What are the costs per resource unit? • Is this intervention generally available? • What is the variability in resource requirements across the target population and settings? • Are the resources worth the expected net benefit from the recommendation? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 4.

1. Categorizing Recommendations with an Updated Review of the Evidence

Reviewed refers to recommendations on topics included in this CPG's systematic evidence review. *Reviewed*, *New-added* recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

Reviewed, *New-replaced* recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations might have clinically relevant edits. *Reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change, llowing for the recommendation language to reflect GRADE approach and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of evidence included in the current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

Reviewed, *Deleted* refers to recommendations from the previous CPG that were deleted after a review of the evidence. This action might occur if the evidence supporting the recommendation is outdated (e.g., a basis to recommend use of an intervention no longer exists, new evidence suggests a shift in care), rendering the recommendation obsolete.

2. 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 CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update was unable to cover all available evidence on T2DM; therefore, its KQs focused on new or updated research or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was, thus, also carried forward from the previous 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 were carried forward from the previous CPG unchanged. *Not reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. *Not reviewed*, *Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation might be irrelevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the Recommendations. The recommendation categories from the 2017 VA/DoD DM CPG are noted in Appendix F.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the VA/DoD EBPWG for approval. The Work Group considered the VA/DoD EBPWG's feedback and revised the CPG, as appropriate, to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, quick reference guide, and patient summary. The VA/DoD EBPWG approved the final CPG and toolkit products in May 2023.

Appendix B: Glycemic Control Targets and Monitoring

Setting an HbA1c target range is an important treatment strategy in the management of Type 2 Diabetes Mellitus. Table B-1 provides general guidance for setting HbA1c target ranges based on patients' comorbidities, life expectancy, and extent of microvascular complications. Other factors might also be considered, and these are addressed in several footnotes. Setting target ranges with upper and lower bounds highlights the importance of considering the risks associated with both hyper- and hypoglycemia. These guiding principles are intended to complement Recommendations 9 and 10 and to help in creating individualized treatment strategies using shared-decision making.

Table B-1: Determination of HbA1c target ranges [a, b, c, d, e, f]

Major Comorbidity[g] or Physiologic Age	Microvascular Complications		
	Absent or Mild [h]	Moderate [i]	Advanced [j]
Absent [k] >10–15 years of life expectancy	6.0–7.0% [l]	7.0–8.0%	7.5–8.5% [m]
Present [n] 5–10 years of life expectancy	7.0–8.0% [l]	7.5–8.5%	7.5–8.5% [m]
Marked [o] <5 years of life expectancy	8.0–9.0% [m]	8.0–9.0% [m]	8.0–9.0% [m]

HbA1c Laboratory Considerations

[a] HbA1c assays should be based on the NGSP reference standard. Clinicians should obtain information regarding the coefficient of variation (CV) from the methodology used at their site. As an example, an HbA1c of 8.0% from a laboratory with a CV of 3% would be measured in a 7.8–8.2% range 13 out of 20 times (1 standard deviation) and would be between a 7.58.5% range 19 out of 20 times (2 standard deviations).

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

[c] We discourage medication changes in response to a single HbA1c test that falls slightly outside target ranges, especially if it is discordant with self-monitoring of blood glucose (SMBG) results.

[d] African Americans, on average, have HbA1c levels about 0.4% higher than Whites and this difference cannot be explained by measured differences in glycemia. Caution is recommended when changing medications based on HbA1c results that slightly exceed target ranges, especially for patients on insulin therapy, without considering SMBG results.

[e] The VA/DoD DM CPG does not recommend the use of estimated average glucose derived from HbA1c levels.

Social Determinant Considerations

[f] Social determinants of health and factors such as social support, ability to self-monitor glucose, food insecurity, and cognitive impairment should be considered. Additionally, side effects of medications and patient preferences must be considered in a process of shared decision making.

Comorbid Illness Considerations

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

[h] Mild microvascular disease is defined by early background retinopathy, moderately increased albuminuria, mild neuropathy, or any combination of the foregoing.

[i] Moderate microvascular disease is defined by pre-proliferative (without severe hemorrhage, intraretinal microvascular anomalies [IRMA], or venous bleeding) retinopathy oseverely increased albuminuria, demonstrable peripheral neuropathy (sensory loss), or any combination of the foregoing.

[j] Advanced microvascular disease is defined by severe non-proliferative (with severe hemorrhage, IRMA, or venous bleeding) or proliferative retinopathy, renal insufficiency (serum creatinine level >2.0 mg/dL), insensate extremities, autonomic neuropathy (e.g., gastroparesis, impaired sweating, orthostatic hypotension), or any combination of the foregoing.

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

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

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

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

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

Appendix C: Pharmacotherapy

Table C-1: Pharmacotherapy for Type 2 Diabetes Mellitus

Drug Class	Average A1c Reduction	Hypo-glycemia (as mono-therapy)	Cardio-vascular Effects	Renal Effects	Weight Change	Contraindications or Precautions	Adverse Effects	Dosing and Administration
Biguanide (Metformin)	1–1.5%	No	Potential ASCVD benefit	Neutral	Neutral/ mild loss	• Contraindicated eGFR <30; may continue at reduced dose, but do not initiate if eGFR <45 • Increased risk of lactic acidosis (especially in setting of acute HF, dehydration, excessive alcohol intake, renal impairment, sepsis)	• GI (diarrhea, nausea) • Vitamin B12 deficiency; rarely associated with anemia	• Slow titration, taking with food, and using SA formulation improve GI tolerability. • Hold temporarily for radiologic studies with contrast and other procedures.

Drug Class	Average A1c Reduction	Hypo-glycemia (as mono-therapy)	Cardio-vascular Effects	Renal Effects	Weight Change	Contraindications or Precautions	Adverse Effects	Dosing and Administration
SGLT-2 inhibitor	0.5–1%	No	ASCVD benefit (empagliflozin, canagliflozin)	Benefit (empagliflozin, canagliflozin, dapagliflozin)	Moderate loss	• eGFR <20–30 (see labeling) • Increased risk for DKA • Increased risk for frequent or serious genitourinary infections • Pregnancy/ breastfeeding	• Genitourinary infections • DKA (might be euglycemic) • Volume depletion/ hypotension • Initial reversible increase in serum creatinine; long-term improvement • Bone fractures (canagliflozin) • Lower limb amputations were increased with canagliflozin versus placebo in one trial (CANVAS).	• Taken orally without regard to food • Hold at least 3 days before surgery. • Cardiorenal benefits are realized at initial doses. • Glucose-lowering efficacy is reduced at lower eGFR, but other benefits are retained.

Drug Class	Average A1c Reduction	Hypo-glycemia (as mono-therapy)	Cardio-vascular Effects	Renal Effects	Weight Change	Contraindications or Precautions	Adverse Effects	Dosing and Administration
GLP-1 receptor agonist	1–2%	No	ASCVD benefit (liraglutide, dulaglutide, semaglutide injectable)	Benefit (primarily reduced albuminuria; liraglutide, dulaglutide, semaglutide injectable)	Moderate - very high loss (Efficacy depends on agent and dose.)	• Personal or family history of medullary thyroid carcinoma • Multiple endocrine neoplasia syndrome 2 • Gastroparesis • At high risk of pancreatitis • Current gallbladder disease • CrCl <15 (lixisenatide) <30 (exenatide) • Pregnancy • Proliferative Diabetic Retinopathy (semaglutide): This risk must be balanced against the risk of progressive retinopathy in the setting of persistent poor glycemic control.	• GI (nausea, vomiting, diarrhea, constipation) • Injection site reactions • Possible renal impairment if dehydration from GI side effects occurs • Increased risk of diabetic retinopathy complications in labeling for semaglutide and dulaglutide (significantly increased with semaglutide versus placebo in SUSTAIN-6) • Post-marketing reports of pancreatitis (causality not established)	• All are injected subcutaneously, except oral formulation of semaglutide. • Administer via pens 1–2 times daily or weekly (depending on agent). • Avoid concurrent use with DPP4 inhibitor or GIP/GLP-1 agonist.

Drug Class	Average A1c Reduction	Hypo-glycemia (as mono-therapy)	Cardio-vascular Effects	Renal Effects	Weight Change	Contraindications or Precautions	Adverse Effects	Dosing and Administration
GIP/GLP-1 agonist (Tirzepatide)	2–2.5%	No	Neutral based on available evidence Prospective studies to evaluate ASCVD and HF outcomes are ongoing.	Neutral based on available evidence	Very high loss	• Personal or family history of medullary thyroid carcinoma • Multiple endocrine neoplasia syndrome • Gastroparesis • At high risk of pancreatitis • Current gallbladder disease • Pregnancy	• GI (nausea, vomiting, diarrhea, constipation) • Injection site reactions • Possible renal impairment if dehydration from GI side effects occurs	• Injected subcutaneously once weekly without regard to meals • Supplied as single-dose pens • Might decrease efficacy of OCP, especially 4 weeks after initiation and dose increases (alternative method recommended)
DPP4i	0.5–1%	No	Neutral for ASCVD risk, potential increased risk of HF (saxagliptin)	Neutral	Neutral	• At high risk of pancreatitis • Pregnancy	• Hypersensitivity reactions, including rare anaphylaxis and severe dermatologic reactions (bullous pemphigoid) • Arthralgia • Post-marketing reports of pancreatitis (causality not established) • Incidence of HF hospitalization was increased with saxagliptin versus placebo in the SAVOR TIMI 53 trial	• Taken orally without regard to food • Renally dose adjusted (except linagliptin) • Avoid concurrent use with GLP-1 and GIP/GLP-1 agonists.

Drug Class	Average A1c Reduction	Hypo-glycemia (as mono-therapy)	Cardio-vascular Effects	Renal Effects	Weight Change	Contraindications or Precautions	Adverse Effects	Dosing and Administration
SU	1–1.5%	Yes	Neutral	Neutral	Mild-moderate gain	• Possible cross-sensitivity in patients with sulfonamide allergies • Increased risk for hypoglycemia (elderly, renal or hepatic impairment, poor intake and certain antimicrobials, such as fluoroquinolones, sulfamethoxazole-trimethoprim and others)	• Hypoglycemia • Weight gain • Nausea • Skin reactions • Photosensitivity	• Taken orally with or before a meal, depending on formulation • Do not combine with meglitinide or prandial insulin.
TZD	1–1.5%	No	Potential ASCVD benefit (pioglitazone), increased risk of HF	Neutral	Moderate gain	• HF or evidence of fluid overload • History or high risk of fracture • Active liver disease (liver transaminases >2.5 times above the upper reference limit), unless NASH is known to be the underlying cause of the elevation • Active or history of bladder cancer • Pregnancy • Macular edema	• Weight gain • Fluid retention • HF • Macular edema • Bone fractures • Might increase risk of bladder cancer (pioglitazone)	• Taken orally without regard to meals • Full glycemic effect takes several weeks. • HF risk is increased with concurrent insulin.

Drug Class	Average A1c Reduction	Hypo-glycemia (as mono-therapy)	Cardio-vascular Effects	Renal Effects	Weight Change	Contraindications or Precautions	Adverse Effects	Dosing and Administration
Meglitinide	0.5–1%	Yes (less than SU)	Neutral	Neutral	Mild-moderate gain	• Increased risk for hypoglycemia (elderly, renal or hepatic impairment, poor intake)	• Upper respiratory infection • Flu-like symptoms	• Taken orally three times daily with meals (skip dose if skipped meal) • Do not combine with SU or prandial insulin.
Insulin	Variable (no limit)	Yes	Neutral	Neutral	Moderate gain	• Hypokalemia • Caution with dosing in hepatic and renal disease	• Hypoglycemia • Weight gain • Injection site reaction • Hypersensitivity reactions	• Available as subcutaneous injections or inhaled (rapid-acting only) • Available in a variety of formulations to allow for flexibility for patient-specific treatment • Rapid-acting and regular insulin should be taken before meals. • Preferred in pregnancy

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CrCl: creatinine clearance; DKA: diabetic ketoacidosis; DPP4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; GIP: gastric inhibitory polypeptide; GI: gastrointestinal; GLP-1: glucagon-like peptide-1; HbA1c: hemoglobin A1C; HF: heart failure; NASH: non-alcoholic steatohepatitis; OCP: oral contraceptive pills; SA: sustained action; SGLT2: sodium-glucose cotransporter-2; SU: sulfonylurea; TZD: thiazolidinedione

Table C-2: Pharmacotherapy Supplementary Evidence Table

Comparison Study, Follow-up	CVD-Related Outcomes (Selected)		CKD Composite Outcome
	CVD Composite Outcome Effect, HR; 95% CI SOE	Hospitalizations for Heart Failure Effect, HR; 95% CI SOE	Effect, HR; 95% CI SOE
SGLT-2 inhibitors (combined effect) versus placebo CVD composite: 6 RCTs in 1 SR,(154) n=39,949; follow-up: 3.0 years median HF hospitalizations: 7 RCTs in 1 SR,(155) n=49,108, follow-up: 2.8 years median CKD composite: 7 RCTs in 1 SR,(155) n=44,993, follow-up: 2.5 years median	0.90; 0.85 to 0.95, (I^2=23%), **SOE: High for benefit of SGLT-2 inhibitors**[a]	0.70; 0.63 to 0.77, (I^2=0%), **SOE: High for benefit of SGLT-2 inhibitors**[a]	0.64; 0.57 to 0.72, (I^2=24%), **SOE: High for benefit of SGLT-2 inhibitors**[a]
Canagliflozin versus placebo 3 RCTs (CANVAS, CANVAS R, CREDENCE in 1 SR,(156) n=14,543, follow-up: 2.5 years	0.84; 0.76 to 0.93, (I^2=0%), **SOE: High for benefit of canagliflozin**[a]	0.64; 0.53 to 0.77, (I^2=0%), **SOE: High for benefit of canagliflozin**[a]	0.64; 0.45 to 0.75, (I^2=0%), **SOE: High for benefit of canagliflozin**[a]
Dapagliflozin versus placebo CVD composite: 1 RCT (DECLARE–TIMI 58) in 1 SR,(154) n=17,160, follow-up: 4.2 years HF hospitalizations: 2 RCTs in 1 SR,(155) n=19,281, follow-up: 4.2 and 1.5 years CKD composite: 3 RCTs in 1 SR,(155) n=22,204, follow-up: 4.2, 1.5, and 2.4 years	1 RCT (DECLARE–TIMI 58) in 1 SR,(154) n=17,160, follow-up: 4.2 years 0.93; 0.84 to 1.03, ARD 95% CI: -1.4% to 0.3%, **SOE: High for no difference**	0.73; 0.61 to 0.88 (1 RCT: DECLARE–TIMI 58, n=17,160), favors dapagliflozin 0.76; 0.61 to 0.95 (1 RCT: DAPA-HF, n=2,121), favors dapagliflozin Overall effect: **SOE: High for benefit of dapagliflozin**[a]	0.53; 0.43 to 0.66 (1 RCT: DECLARE–TIMI 58, n=17,160), favors dapagliflozin 0.72; 0.39 to 1.34 (1 RCT: DAPA-HF, n=2,139), no difference 0.64; 0.52 to 0.79 (1 RCT: DAPA-CKD, n=2,905), favors dapagliflozin Overall effect: **SOE: High for benefit of dapagliflozin**[a]
Empagliflozin versus placebo CVD composite: 1 RCT (EMPA-REG OUTCOME) in 1 SR,(154) n=7,020, follow-up: 3.1 years HF hospitalizations and CKD composite: 1 RCT (EMPA-REG OUTCOME) in 1 SR,(155) n=7,020, follow-up: 3.1 years	0.86; 0.74 to 0.99, ARD 95% CI: -3.22% to -0.05%, **SOE: High for benefit of empagliflozin**[a]	0.65; 0.50 to 0.85, ARD 95% CI: -2.3 to -0.5%, **SOE: High for benefit of empagliflozin**[a]	0.54; 0.40 to 0.75, ARD 95% CI: -2.1% to -0.5%, **SOE: High for benefit of empagliflozin**[a]

Comparison Study, Follow-up	CVD-Related Outcomes (Selected)		CKD Composite Outcome
	CVD Composite Outcome Effect, HR; 95% CI SOE	Hospitalizations for Heart Failure Effect, HR; 95% CI SOE	Effect, HR; 95% CI SOE
Ertugliflozin versus placebo CVD composite: 1 RCT (VERTIS CV) in 1 SR,(154) n=8,246, follow-up: 3.0 years HF hospitalizations and CKD composite: 1 RCT (VERTIS CV) in 1 SR,(155) n=8,246, follow-up: 3.0 years	0.99; 0.88 to 1.12, ARD 95% CI: -1.6% to 1.5%, **SOE: Moderate for no difference**	0.70; 0.54 to 0.90, ARD 95% CI: -1.9% to -0.3%, **SOE: High for benefit of ertugliflozin**[a]	0.81; 0.63 to 1.04, ARD 95% CI: -1.6% to 0.1%, **SOE: Moderate for no difference**

[a] Green shading indicates evidence of benefit.

Abbreviations: ARD: absolute risk difference; CKD: chronic kidney disease; CVD: cardiovascular disease; HF: heart failure; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter-2; SOE: strength of evidence; SR: systematic review

Appendix D: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited four participants for the focus group, with support from the Champions and other Work Group members, as needed. Although participant recruitment focused on eliciting a range of perspectives likely relevant and informative in the CPG development process, the patient focus group participants were not intended to be a representative sample of VA and DoD patients. The participants were not incentivized for participation or reimbursed for travel expenses. The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed and the Work Group approved a patient focus group guide covering these topics. The focus group facilitator led the discussion, using the guide to elicit patient perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. Participants found that their diabetes impacted their daily life; some participants expressed challenges in managing the impacts (e.g., managing diabetes alongside co-occurring conditions, adhering to medication schedules).

- Participants shared that managing their diabetes and adhering to testing and medication schedules was time-consuming and required attention and discipline. Some participants indicated this often hindered them from participating in some life activities (e.g., social), while others indicated that this became a part of their normal routine.
- Some participants emphasized that the negative health impacts from other co-occurring conditions could make it difficult to follow prescribed nutrition and exercise plans to manage their diabetes.

b. Participants stated that more available, structured, and/or frequent educational opportunities involving multiple types of clinicians to learn about their diagnosis and treatment plan would better help them to understand and manage their diabetes.

- Participants recognized the importance of educational opportunities to learn about their diagnosis, its impact on their life, and treatment options.
- Some expressed a desire for more options, such as courses on diabetes self-management, nutrition, and exercise.
- Some participants shared that the emotional toll of diabetes could be challenging; structured opportunities to connect with other people with diabetes could help.

c. Participants expressed that social/peer/family support to assist them in the management of their treatment plans would be beneficial.

- Participants generally reported the need to manage their diabetes rather relatively independently, with minimal support from family members or others in their immediate social network. Some participants found this challenging and intimidating, while others expressed greater self-efficacy.
- Participants suggested that having knowledgeable peers and family members involved in their care made managing their diabetes easier.

d. Participants stated more frequent and/or comprehensive interactions with clinicians would be beneficial, including greater involvement in decision-making whewhen determining a treatment plan.

- Participants indicated that they did not have enough opportunities for in-depth interaction and/or time with their clinicians.
- Participants expressed interest in greater involvement in shared decision making; they would have liked to participate more fully in planning their own treatment.

e. Participants recognized the importance of continuity of care and communication between clinicians within and across treatment settings.

- Participants sought medical care from a variety of clinicians, in some cases in various settings, and expressed a desire for more coordinated care.
- Participants worried that important aspects of their medical care were not always clearly communicated between their different clinicians, especially across VA/DoD healthcare systems and the private sector.

Appendix E: Evidence Table

Table E-1: Evidence Table[a,b,c,d]

Recommendation	2017 Strength of Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
1. In adults with prediabetes, we suggest aerobic exercise (such as walking 8–9 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.	Not applicable	(34, 35)	Weak for	Reviewed, New-added
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 (e.g., 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.	Not applicable	(36–43) **Additional References:** (70–72, 157, 158)	Weak for	Reviewed, New-added

[a] 2017 Strength of Recommendation column: The 2017 VA/DoD DM CPG was developed using the GRADE approach to determine the strength of each recommendation. Inclusion of more than one 2017 strength of recommendation indicates that more than one 2017 VA/DoD DM CPG recommendation is covered by the 2023 recommendation. “Not applicable” indicates that the 2023 VA/DoD DM CPG recommendation was a new recommendation, and therefore does not have an associated 2017 strength of recommendation. “Neither for nor against” represents updated language for “N/A” used in the 2017 VA/DoD DM CPG.

[b] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called “Additional References”) includes references that provide additional information related to the recommendation, but which were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[c] 2023 Strength of Recommendation column: The 2023 VA/DoD DM CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Determining Recommendation Strength and Direction section for more information.

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

Recommendation	2017 Strength of Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
3. In adults with type 2 diabetes mellitus, we suggest offering health care delivered through telehealth interventions to improve outcomes.	Weak for	(48, 50–53)	Weak for	Not Reviewed, Amended
4. There is insufficient evidence to recommend for or against routine screening or using a specific tool to screen for or diagnose diabetes distress.	Not applicable	**Additional References:** (159)	Neither for nor against	Reviewed, New-added
5. In adults with type 2 diabetes mellitus and co-occurring non-alcoholic fatty liver disease, we suggest clinicians should assess for fibrosis using a non-invasive tool (e.g., Fibrosis-4).	Not applicable	(61–63) **Additional References:** (55–60)	Weak for	Reviewed, New-added
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.	Not applicable	**Additional References:** (64–66)	Neither for nor against	Reviewed, New-added
7. In adults with type 2 diabetes mellitus, we recommend diabetes self-management education and support.	Strong for	(67, 69, 160, 161) **Additional References:** (68, 162, 163)	Strong for	Not Reviewed, Amended
8. For adults with type 2 diabetes mellitus, we suggest using high glycemic variability over time (e.g., fluctuation in HbA1c or fasting blood glucose) as a prognostic indicator for risk of hypoglycemia, morbidity, and mortality.	Not applicable	(74–77, 83) **Additional References:** (73, 78-82)	Weak for	Reviewed, New-replaced
9. We suggest setting an individualized HbA1c 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.	Strong for	(84-86) **Additional References:** (87, 88)	Weak for	Not reviewed, Amended
10. We suggest an HbA1c range of 7.0–8.5% for most patients, if it can be safely achieved.	Weak for	(84–91)	Weak for	Not reviewed, Amended

Recommendation	2017 Strength of Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
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 improve HbA1c.	Not applicable	(92, 95–97) **Additional References:** (96, 97, 164, 165)	Weak for	Reviewed, New-added
12. For adults with type 2 diabetes mellitus, we suggest a Mediterranean style diet to improve glycemic control, body weight, and hypertension.	Strong for	(99, 100) **Additional References:** (101, 102, 103, 104)	Weak for	Reviewed, New-replaced
13. For adults with type 2 diabetes mellitus, we suggest a nutrition intervention strategy providing 13–50% of their total daily caloric intake from carbohydrates for diabetes management.	Strong for	(100, 103, 105–108) **Additional Reference:** (34)	Weak for	Reviewed, New-replaced
14. For adults with type 2 diabetes mellitus, we suggest a vegetarian dietary pattern for glycemic control and weight loss.	Not applicable	(103)	Weak for	Reviewed, New-added
15. For adults with type 2 diabetes mellitus, we suggest against intermittent fasting.	Not applicable	(111, 112)	Weak against	Reviewed, New-added
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, or tai chi.	Not applicable	(113, 114, 116) **Additional Reference:** (115)	Weak for	Reviewed, New-added
17. In adults with stress related to type 2 diabetes mellitus, we suggest offering a mindfulness-based stress reduction program for short-term improvement.	Not applicable	(117–119) **Additional Reference:** (120)	Weak for	Reviewed, New-added
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.	Not applicable	(117–119) **Additional Reference:** (120)	Neither for nor against	Reviewed, New-added

Recommendation	2017 Strength of Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
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.	Not applicable	(121–127) **Additional References:** (128, 129)	Strong for	Reviewed, New-added
20. For adults with type 2 diabetes mellitus at high risk of atherosclerotic cardiovascular disease (i.e., 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.	Not applicable	(121–127) **Additional References:** (128, 142, 166–168)	Weak for	Reviewed, New-added
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.	Not applicable	(109, 123, 126, 138) **Additional References:** (130–135)	Strong for	Reviewed, New-added
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.	Not applicable	(109, 125-127, 138)	Strong for	Reviewed, New-added
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.	Not applicable	(121, 123, 138, 141) **Additional References:** (140) (142)	Strong for	Reviewed, New-added

Recommendation	2017 Strength of Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
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 their individualized target range for glycemic control.	Not applicable	(122, 138)	Weak for	Reviewed, New-Added
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.	Not applicable	(146–151) **Additional References:** (143–145)	Weak for	Reviewed, New-added
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.	Not applicable	**Additional References:** (143–145)	Neither for nor against	Reviewed, New-added

Appendix F: 2017 CPG Recommendation Categorization Table

Table F-1. 2017 DM CPG Recommendation Categorization Table[a,b,c,d,e,f]

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG Recommendation #
1.	We recommend shared decision-making to enhance patient knowledge and satisfaction.	Strong for	Reviewed, New-added	Deleted	N/A
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	Not reviewed, Amended	7
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	Not reviewed, Amended	3
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	Not reviewed, Amended	9

[a] 2017 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2017 VA/DoD DM CPG.
[b] 2017 CPG Recommendation Text column: This contains the wording of each recommendation from the 2017 VA/DoD DM CPG.
[c] 2017 CPG Strength of Recommendation column: The 2017 VA/DoD DM CPG used the GRADE approach to determine the strength of each recommendation.
[d] 2017 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2017 VA/DoD DM CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2023 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2023 VA/DoD DM CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2023 CPG Recommendation # column: For recommendations that were carried forward to the 2023 VA/DoD DM CPG, this column indicates the new Recommendation(s) to which they correspond.

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG 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	Deleted	N/A
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	Deleted	N/A
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	Not reviewed, Amended	9
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	Deleted	N/A
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	Not reviewed, Amended	10
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	Deleted	N/A
11.	We suggest that providers be aware that HbA1c variability is a risk factor for microvascular and macrovascular outcomes.	Weak for	Reviewed, New-added	Reviewed, New-replaced	8
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	Deleted	N/A

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG Recommendation #
13.	We recommend a Mediterranean diet if aligned to patient's values and preferences.	Strong for	Reviewed, New-added	Reviewed, Amended	12
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	Reviewed, Amended	13
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	Deleted	N/A
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	Deleted	N/A
17.	We recommend against the use of split mixed insulin regimen for all hospitalized patients with type 2 diabetes.	Strong against	Reviewed, New-added	Deleted	N/A
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	Deleted	N/A
19.	We suggest providing medication education and diabetes survival skills to patients before hospital discharge.	Weak for	Reviewed, Amended	Deleted	N/A
20.	We recommend performing a comprehensive foot risk assessment annually.	Strong for	Not reviewed, Amended	Deleted	N/A
21.	We recommend referring patients with limb-threatening conditions to the appropriate level of care for evaluation and treatment.	Strong for	Not reviewed, Amended	Deleted	N/A
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	Deleted	N/A

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG 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	Deleted	N/A
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	Deleted	N/A
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	Deleted	N/A

Appendix G: Participant List

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Appendix H: Literature Review Search Terms and Strategy

Table H-1. EMBASE and MEDLINE in EMBASE.com Syntax

KQ	Set	Concept	Search Statement
KQ 1	1.	Adults with T2DM	'non insulin dependent diabetes mellitus'/de OR ((‘diabetes mellitus’/exp OR diabet*:ti,ab,kw) AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	2.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	3.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	4.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	5.		#1 OR #2 OR #3 OR #4
	6.	Exclude	#5 NOT 'diabetes insipidus'/exp
	7.	Glycemic variability	'glycemic variability'/de OR ‘glycemic variab*’:ti OR (‘time in range’ AND (glyc* OR hb1a OR glucose))
	8.		((hba 1c OR (fast* NEAR/3 glucose) OR glycem* OR glycaem* OR glycat* OR hypoglycem* OR hypoglycaem*):ti AND ((control* OR episode* OR event* OR fluctuat* OR level* OR variab*):ti OR ‘time in range’)
	9.		(‘fasting blood glucose’/de OR ‘fasting blood glucose level’/de OR 'glucose blood level'/de OR 'hemoglobin A1c'/de OR 'hypoglycemia'/de) AND ((control* OR episode* OR event* OR fluctuat* OR level* OR variab*):ti
	10.		('average daily risk range':ti OR 'adrr':ti OR 'average glucose profile':ti OR 'agp':ti OR 'coefficient of variation':ti OR 'continuous overlapping net glycemic action':ti OR 'conga':ti OR 'interquartile ranges':ti OR 'iqr':ti OR 'mean absolute glucose':ti OR 'mean amplitude of glycemic excursions':ti OR 'mage':ti OR 'mean of daily differences':ti OR 'standard deviation':ti OR 'time in range':ti OR (('standard deviation':ti OR 'coefficient of variation':ti) AND hba1c:ti) OR 'fasting plasma glucose':ti OR 'postprandial glucose':ti)
	11.		#7 OR #8 OR #9 OR #10
	12.	Combine population AND glycemic variability	#6 AND #10
	13.	Remove Animal Studies	#12 NOT (([animals]/lim NOT [humans]/lim) OR ((animal OR animals OR canine* OR dog OR dogs OR feline OR hamster* OR lamb OR lambs OR mice OR monkey OR monkeys OR mouse OR murine OR pig OR piglet* OR pigs OR porcine OR primate* OR rabbit* OR rat OR rats OR rodent* OR sheep* OR swine OR veterinar* OR (vitro NOT vivo)) NOT (human* OR patient*)):ti)

KQ	Set	Concept	Search Statement
KQ 1 (cont.)	14.	Remove Pediatric Population	#13 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR (book OR chapter OR conference OR editorial OR letter):it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR (abstract OR annual OR conference OR congress OR meeting OR proceedings OR sessions OR symposium):nc OR ((book NOT series) OR 'conference proceeding'):pt OR ('case report' OR comment* OR editorial OR letter OR news):ti OR ((protocol AND (study OR trial)) NOT ('therapy protocol*' OR 'treatment protocol*')):ti)
	15.	Remove Unwanted Publication Types	#14 NOT ((adolescen* OR babies OR baby OR boy* OR child* OR girl* OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR nurser* OR paediatric* OR pediatric* OR preschool* OR "school age*" OR schoolchildren* OR teen* OR toddler* OR youth*):ti NOT (adult*:ti,ab OR father*:ti OR matern*:ti,ab OR men:ti,ab OR mother*:ti OR parent*:ti OR patern*:ti,ab OR women:ti,ab))
	16.	Limit to English language publications	#15 AND [english]/lim
	17.	Limit to results published 2016-2022, and added to the database by Mar 1, 2022	#16 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	18.	Limit to systematic reviews and meta-analyses	#17 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR (cochrane* OR metaanaly* OR 'meta analy*' OR (search* AND (cinahl* OR databases OR ebsco* OR embase* OR psychinfo* OR psycinfo* OR 'science direct*' OR sciencedirect* OR scopus* OR systematic* OR 'web of knowledge*' OR 'web of science')) OR (systematic* NEAR/3 review*)):ti,ab) NOT ((protocol NEXT/3 review) OR 'review protocol' OR 'scoping review'):ti
	19.	Limit to randomized controlled trials	#17 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ti,ab OR 'phase iii':ti,ab OR random*:ti,ab OR RCT:ti,ab)
	20.	Non-randomized studies	#17 AND ('cohort analysis'/de OR 'comparative study'/de OR 'cross-sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'between groups':ti,ab OR cohort*:ti,ab OR compar*:ti,ab OR 'cross sectional':ti,ab OR longitudinal:ti,ab OR 'long term':ti,ab)
	21.	Combine	#18 OR#19 OR #20

KQ	Set	Concept	Search Statement
KQ 2	22.	Adults with T2DM	'non insulin dependent diabetes mellitus'/de OR ((‘diabetes mellitus’/exp OR diabet*:ti,ab,kw) AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	23.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	24.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	25.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	26.		#22 OR #23 OR #24 OR #25
	27.	Exclude	#26 NOT 'diabetes insipidus'/exp
	28.	Continuous glucose monitoring	'continuous glucose monitoring'/de OR 'continuous glucose monitoring device'/exp OR 'continuous glucose monitoring system'/exp OR 'glucose monitoring/insulin pump system'/exp OR ('glucose sensor'/exp AND continu*)
	29.		('blood glucose monitoring'/de OR (glucose NEAR/2 monitor*)) AND (continuous OR continual OR 'real time')
	30.		Cgm OR (continu* AND glucose AND monitor*) OR ‘contin* glucose monitor*’ OR fgm OR ‘flash glucose monitor*’
	31.		#28 OR #29 OR #30
	32.	Combine sets	#27 AND #31
	33.		#32 AND [english]/lim
	34.		#33 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	35.	Remove Animal Studies	#34 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	36.	Remove Pediatric Population	#35 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))

KQ	Set	Concept	Search Statement
KQ 2 (cont.)	37.	Remove Unwanted Publication Types	#36 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	38.	Limit to Randomized Controlled Trials	#37 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	39.	Limit to Meta Analyses and Systematic Reviews	#37 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	40.	Combine final sets	#38 OR #39
KQ 3	41.	Adults with T2DM	'non insulin dependent diabetes mellitus'/de OR ((‘diabetes mellitus’/exp OR diabet*:ti,ab,kw) AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	42.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	43.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	44.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	45.		#41 OR #42 OR #43 OR #44
	46.	Exclude	#45 NOT 'diabetes insipidus'/exp
	47.	Condition: Diabetes Stress	(('anxiety disorder'/exp AND diabet*:ti) OR ‘diabet* fatigue’:ti,ab,kw OR 'diabet* stress':ti,ab,kw OR (diabet* NEAR/5 (anxiety OR anxious OR distress* OR fatigue OR stress*))) NOT oxidative
	48.	Acupuncture	'acupuncture'/exp OR acupressure:ti,ab,kw OR acupuncture:ti,ab,kw
	49.	Alternative - general	'alternative medicine'/exp OR 'holistic medicine'/de OR 'integrative medicine'/de OR ((alternative OR complement* OR compliment* OR holistic OR integrative) NEXT/3 (approach* OR medicine OR modalit* OR therap* OR treat*)):ti,ab,kw
	50.		(integrative OR alternative OR complement*) NEXT/3 (approach* OR therap* OR medicine OR treatment* OR program*)

KQ	Set	Concept	Search Statement
KQ 3 (cont.)	51.	Biofeedback	'biofeedback'/exp OR biofeedback OR 'bio feedback' OR neurofeedback OR 'neuro feedback'
	52.	Clinical hypnosis/Guided imagery	'hypnosis'/de OR hypnosis OR hypnother* OR 'guided imagery'/mj OR (guide* NEXT/2 imagery)
	53.	Massage	'massage'/mj OR massage*
	54.	Meditation	'meditation'/exp OR meditat*:ti,ab,kw
	55.	Yoga/Tai chi/Qigong	'qigong'/de OR qigong OR 'qi gong' OR 'tai chi'/de OR 'tai chi':ti,ab,kw OR 't ai chi':ti,ab,kw OR taichi:ti,ab,kw OR 'tai ji':ti,ab,kw OR taiji*:ti,ab,kw OR 'yoga'/exp OR yoga*:ti,ab,kw
	56.	Combine interventions	#48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
	57.	Combine population AND condition AND interventions; Combine condition AND interventions	(#46 OR #47) AND #56
	58.		#57 AND [english]/lim
	59.		#58 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	60.	Remove Animal Studies	#59 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	61.	Remove Pediatric Population	#60 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	62.	Remove Unwanted Publication Types Remove Unwanted Publication Types	#61 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	63.	Limit to Randomized Controlled Trials	#62 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)

KQ	Set	Concept	Search Statement
KQ 3 (cont.)	64.	Limit to Meta Analyses and Systematic Reviews	#62 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	65.	Combine final sets	#63 OR #64
KQ 4	66.	Adults with T2DM	'non insulin dependent diabetes mellitus'/de OR ((‘diabetes mellitus’/exp OR diabet*:ti,ab,kw) AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	67.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	68.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	69.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	70.		#66 OR #67 OR #68 OR #69
	71.	Exclude	#70 NOT 'diabetes insipidus'/exp
	72.	Prediabetes	"impaired glucose tolerance'/mj OR 'impaired glucose tolerance':ti,ab OR ‘impaired fasting glucose’ OR prediabet*:ti,ab,kw OR ‘pre diabet*’:ti,ab,kw
	73.	Nutrition interventions (broad)	(‘diet’/exp/mj OR diet*:ti OR 'nutrition'/mj OR nutritio*:ti)
	74.		('atkins diet'/exp OR 'dash diet'/exp OR 'intermittent fasting'/exp OR 'ketogenic diet'/exp OR 'carbohydrate counting'/de OR 'low carbohydrate diet'/exp OR 'low glycemic index diet'/de OR 'mediterranean diet'/exp OR 'paleolithic diet'/de OR 'vegan diet'/de OR 'vegetarian diet'/exp OR 'very low calorie ketogenic diet'/exp)
	75.		(((atkins* OR carbohydrat* OR dash OR fast OR fasting OR keto* OR 'low calorie*' OR 'low gi' OR 'low gi' OR 'low glycemic' OR 'low glycemic' OR mediterranean* OR paleo* OR ‘plant based’ OR vegan OR vegetable* OR vegetarian*) NEAR/5 (ate OR consum* OR diet* OR eat* OR feed* OR food* OR intake OR nutrition* OR plan* OR program* OR regimen*)):ti,ab,kw) OR (((low* OR minim* OR reduc* OR restrict*) NEAR/2 (calorie* OR carb* OR fat*)):ti,ab,kw) OR 'dietary approaches to stop hypertension' OR 'carbohydrate count*':ti,ab,kw
	76.		#73 OR #74 OR #25
	77.	Combine Prediabetes and interventions	#72 AND #76

KQ	Set	Concept	Search Statement
KQ 4 (cont.)	78.	Nutrition interventions (T2DM)	'atkins diet'/exp OR 'dash diet'/exp OR 'intermittent fasting'/exp OR 'ketogenic diet'/exp OR 'carbohydrate counting'/de OR 'low carbohydrate diet'/exp OR 'low glycemic index diet'/de OR 'mediterranean diet'/exp OR 'paleolithic diet'/de OR 'vegan diet'/de OR 'vegetarian diet'/exp OR 'very low calorie ketogenic diet'/exp
	79.		(((atkins* OR carbohydrat* OR dash OR fast OR fasting OR keto* OR 'low calorie*' OR 'low gi' OR 'low gi' OR 'low glycemic' OR 'low glycemic' OR mediterranean* OR paleo* OR vegan OR vegetarian*) NEAR/5 (ate OR consum* OR diet* OR eat* OR feed* OR food* OR intake OR nutrition* OR plan* OR program* OR regimen*)):ti,ab,kw) OR (((low* OR minim* OR reduc* OR restrict*) NEAR/2 (calorie* OR carb* OR fat*)):ti,ab,kw) OR 'dietary approaches to stop hypertension' OR 'carbohydrate count*':ti,ab,kw
	80.	Diabetes therapy general search	'diabetes mellitus'/exp/dm_pc,dm_th AND ('diet'/exp/mj OR 'nutrition'/mj)
	81.		#78 OR #79 OR #80
	82.	Combine T2DM and interventions	#71 AND #81
	83.	Prediabetes or T2DM final sets	#77 OR #82
	84.		#83 AND [english]/lim
	85.		#84 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	86.	Remove animal studies	#85 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	87.	Remove Pediatric Population	#86 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	88.	Remove Unwanted Publication Types Remove Unwanted Publication Types	#87 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	89.	Limit to Randomized Controlled Trials	#88 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)

KQ	Set	Concept	Search Statement
KQ 4 (cont.)	90.	Limit to Meta Analyses and Systematic Reviews	#88 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	91.	Combine final	#89 OR #90
KQ 5	92.	Adults with T2DM	'non insulin dependent diabetes mellitus'/de OR ((‘diabetes mellitus’/exp OR diabet*:ti,ab,kw) AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	93.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	94.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	95.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	96.		#92 OR #93 OR #94 OR #95
	97.	Exclude	#96 NOT 'diabetes insipidus'/exp
	98.	Prediabetes	'impaired glucose tolerance'/mj OR 'impaired glucose tolerance':ti OR prediabet*:ti,ab,kw OR ‘pre diabet*’:ti,ab,kw
	99.	Exercise intervention: Aerobic	'aerobic exercise'/de OR 'aquatic exercise'/de OR 'exercise'/exp/mj OR 'high intensity exercise'/exp OR 'interval training’/exp OR 'physical activity'/exp/mj OR (aerobic* OR aquatic* OR bicycle* OR exercis* OR (‘high intensity’ NEAR/2 (interval* ORexercise*)) OR (interval NEAR/2 train*) OR jog OR jogging OR ‘physical activit*’ OR racewalk* OR rowing OR running OR steps OR swim OR swimming OR walk* OR workout* OR ‘work out*’):ti
	100.	Exercise intervention: Strength training	'anaerobic exercise'/de OR ‘blood flow restriction training’/de OR 'circuit training'/de OR 'isokinetic exercise'/de OR 'muscle training'/de OR 'plyometrics'/de OR 'resistance training'/exp OR 'weight machine'/exp OR (isometric OR isotonic OR weights OR (weight NEAR/2 (lift* OR machine* OR train* OR workout* OR ‘work out’)):ti) OR (((muscle OR strength) NEAR/2 (exercise* OR train* OR workout* OR ‘work out’)):ti)
	101.	Exercise intervention: Non-aerobic; non-strength training	'pilates'/de OR 'qigong exercise'/de OR 'qigong'/de OR 'stretching exercise'/de OR 'tai chi'/de OR 'yoga'/exp OR (‘chi kung’ OR chigung OR 'martial art*' OR pilates OR qigong OR ‘qi gong’ OR stretch* OR 'tai chi' OR ‘tai ji’ OR ‘taiji quan’ OR taijiquan OR yoga OR yogic):ti

KQ	Set	Concept	Search Statement
KQ 5 (cont.)	102.	Exercise intensity (general)	'exercise intensity'/de OR 'moderate intensity continuous training'/de OR ((exercise*:ti OR 'physical activit*':ti) AND (duration:ti OR frequen*:ti OR intens*:ti OR modalit*:ti)) OR (('exercise'/exp/mj OR 'physical activity'/exp/mj) AND (duration:ti OR frequen*:ti OR intens*:ti OR modalit*:ti))
	103.	Combine interventions	#99 OR #100 OR #101 OR #102
	104.	T2DM AND interventions	#97 AND #103
	105.	Prediabetes AND interventions	#98 AND #104
	106.	Combine	#104 OR #105
	107.		#106 AND [english]/lim
	108.		#107 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	109.	Remove animal studies	#108 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	110.	Remove Pediatric Population	#109 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	111.	Remove Unwanted Publication Types Remove Unwanted Publication Types	#110 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	112.	Limit to Randomized Controlled Trials	#111 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)

KQ	Set	Concept	Search Statement
KQ 5 (cont.)	113.	Limit to Meta Analyses and Systematic Reviews	#111 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	114.	Combine final sets	#112 OR #113
KQ 6	115.	Prediabetes	'impaired glucose tolerance'/mj OR 'impaired glucose tolerance':ti,ab OR ‘impaired fasting glucose’ OR prediabet* OR ‘pre diabet*’ OR (progress* NEAR/3 diabet*):ti,ab,kw
	116.	Broad string	‘pre diabet*’ OR 'impaired glucose tolerance'/exp/dm_dm,dm_dt OR ('impaired glucose tolerance'/exp/dm_pc,dm_th AND (drug* OR prescription* OR medication* OR pharma*))
	117.	Pharma interventions	'antidiabetic agent'/exp OR 'oral antidiabetic agent'/exp OR (drug* OR medication* OR pharma* OR prescription*):ti,ab
	118.	Alpha glucosidase inhibitors	'alpha glucosidase inhibitor'/exp OR 'acarbose'/de OR 'miglitol'/de OR (‘Alpha glucosidase inhibitor*’ OR acarbose OR miglitol):ti,ab,kw,tn
	119.	DPP4i	'dipeptidyl peptidase IV inhibitor'/exp OR ‘dpp4*’ OR (sitagliptin OR saxagliptin OR linagliptin OR alogliptin):ti,ab,kw,tn
	120.	GLP-1 agonists	'glucagon like peptide 1 receptor agonist'/exp OR ‘dulaglutide’/de OR ‘exenatide’/de OR ‘liraglutide’/de OR ‘lixisenatide’/de OR ‘semaglutide’/de OR (‘glp 1 agonist*’ OR ‘glp1ra’ OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide OR adlyxin OR bydureon OR byetta OR ozempic OR rybelsus OR trulicity OR victoza):ti,ab,kw,tn
	121.	Metformin	‘metformin’/de OR metformin:ti,ab,kw,tn
	122.	SGLT-2	'sodium glucose cotransporter 2 inhibitor'/exp OR 'empagliflozin'/de OR 'canagliflozin'/de OR 'dapagliflozin'/de OR 'ertugliflozin'/de OR (‘sglt 2 inhibitor*’ OR empagliflozin OR canagliflozin OR dapagliflozin OR ertugliflozin):ti,ab,kw,tn
	123.	Thiazolidinediones (TZDs)	'2,4 thiazolidinedione derivative'/de OR 'glitazone derivative'/exp OR 'pioglitazone'/de OR 'rosiglitazone'/de OR (pioglitazone OR rosiglitazone OR ‘tzd’ OR thiazolidineodiones):ti,ab,kw,tn
	124.	Combine interventions	#117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123
	125.	Prediabetes AND interventions	#115 AND #124
	126.	Final intervention set	#116 OR #125
	127.		#126 AND [english]/lim
	128.		#127 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)

KQ	Set	Concept	Search Statement
KQ 6 (cont.)	129.	Remove animal studies	#128 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	130.	Remove Pediatric population	#129 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	131.	Remove unwanted publication types	#130 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	132.	Limit to randomized controlled trials	#131 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	133.	Limit to Meta Analyses and Systematic Reviews	#131 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	134.	Combine final	#132 OR #133
KQ 7	135.	Population: Adults T2DM	'non insulin dependent diabetes mellitus'/de OR ((‘diabetes mellitus’/exp OR diabet*:ti,ab,kw) AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	136.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	137.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	138.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	139.		#135 OR #136 OR #137 OR #138
	140.		#139 NOT 'diabetes insipidus'/exp

KQ	Set	Concept	Search Statement
KQ 7 (cont.)	141.	Sodium glucose cotransporter 2 inhibitors	'sodium glucose cotransporter 2 inhibitor'/exp OR (SGLT2 OR SGLT-2 OR 'sodium glucose cotransporter 2' OR 'sodium dependent glucose cotransporter 2'):ti,ab
	142.		(Canagliflozin OR Invokana OR Empagliflozin OR Jardiance OR Dapagliflozin OR Farxiga OR Ertugliflozin OR Steglatro OR OR Zynquista):ti,ab,tn
	143.	Glucagon-like peptide-1 receptor agonists	'glucagon like peptide 1 receptor agonist'/exp OR (GLP-1 OR 'glp 1' OR 'glucagon like peptide 1 agonist' OR 'glucagon like peptide 1 receptor stimulating agent' OR 'long acting GLP 1 agonist' OR 'long acting GLP 1 receptor agonist' OR 'long acting glucagon like peptide 1 agonist' OR 'long acting glucagon like peptide 1 receptor agonist'):ti,ab
	144.		(semaglutide OR Rybelsus OR dulaglutide OR Trulicity OR exenatide OR Byetta OR Bydureon OR liraglutide OR Victoza OR Saxenda OR lixisenatide OR Adlyxin OR Ozempic OR Rybelsus OR Wegovy):ti,ab,tn
	145.	Combine interventions	#141 OR #142 OR #143 OR #144
	146.	Combine population and interventions	#140 AND #145
	147.		#146 AND [english]/lim
	148.		#147 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	149.		#148 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	150.		#149 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))

KQ	Set	Concept	Search Statement
KQ 7 (cont.)	151.		#150 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	152.		#151 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	153.		#151 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	154.		#152 OR #153
KQ 8	155.	Population: Adults T2DM	'non insulin dependent diabetes mellitus'/de OR ((‘diabetes mellitus’/exp OR diabet*:ti,ab,kw) AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	156.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	157.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	158.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	159.		#155 OR #156 OR #157 OR #158
	160.		#159 NOT 'diabetes insipidus'/exp
	161.	Interventions/Drugs general	'antidiabetic agent'/exp OR ‘drug therapy’/exp OR 'non insulin dependent diabetes mellitus'/exp/dm_co,dm_dm,dm_dt,dm_th OR ‘glycemic control’/de OR ((diabet* OR glucose OR glyc*):ti AND (treat* OR therap* OR pharma* OR medicat* OR prescri* OR drug* OR intervention* OR regimen*):ti,ab)
	162.		‘overtreatment’/exp OR ‘polypharmacy’/exp OR (complex* OR intens* OR overtreat* OR tight):ti,ab
	163.	Intensive therapy/overtreatment	‘tight glucose control’ OR ‘intens* glucose control’ OR (intens* NEAR/5 therap*) OR (intens* NEAR/5 treat*)
	164.	T2DM AND interventions AND intensive therapy	#160 AND (#162 OR #163)

KQ	Set	Concept	Search Statement
KQ 8 (cont.)	165.	Deprescribe	('deprescription'/de OR deprescri*:ti OR ((simplify OR reduce OR minimize OR single):ti,ab AND (drug OR drugs OR medication* OR prescription* OR pharma*):ti,ab)) AND (gly* OR gluc* OR hba1* OR hemoglobin OR insulin):ti,ab
	166.	De-intensify	Deintensify OR deintensification OR 'de intens*'
	167.		'tight glycemic control' OR 'tight blood glucose control'
	168.		#165 OR #166 OR #167
	169.	T2DM and deintensify	#160 AND #168
	170.	Final sets	#164 OR #169
	171.	Date limits	#170 AND [english]/lim
	172.		#171 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	173.		#172 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	174.		#173 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	175.		#174 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	176.		#175 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	177.		#175 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)

KQ	Set	Concept	Search Statement
KQ 8 (cont.)	178.		#175 AND (‘case control study’/exp OR ‘cohort analysis’/de OR ‘comparative study’/exp OR ‘cross-sectional study’/de OR ‘longitudinal study’/de OR ‘observational study’/de OR 'prospective study'/de OR ‘retrospective study’/de OR ((‘before and after’ OR ‘pre and post’ OR compar* OR cohort* OR ‘case control’ OR ‘cross sectional’ OR longitudinal OR observational OR prospective OR retrospective OR registry OR registries) NEAR/3 (study OR studies)))
	179.	Final sets	#176 OR #177 OR #178
KQ 9	180.	Standard population	'non insulin dependent diabetes mellitus'/de OR (diabet*:ti,ab,kw AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	181.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	182.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	183.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	184.		#180 OR #181 OR #182 OR #183
	185.		#184 NOT 'diabetes insipidus'/exp
	186.	Fall risk	'fall risk'/de OR 'fall risk assessment'/de OR (‘risk’/exp AND (‘falling’/de OR fall*:ti)) OR (‘risk assessment’/exp AND fall*:ti) OR ‘risk of fall*’:ti
	187.	Fall risk/assessment	'Morse Fall Scale'/de OR 'motor dysfunction assessment'/exp/mj OR 'sit-to-stand test'/de OR 'sit to stand'/de OR 'single leg stance test'/de OR 'single leg stance'/de OR 'timed up and go test'/de OR ‘walk test’/exp OR (‘morse fall scale’ OR (morse NEAR/3 scale) OR ‘motor dysfunction assess*’ OR ‘sit to stand’ OR ‘single leg stan*’ OR ‘timed up and go’ OR ‘walk test*’):ti,ab,kw
	188.		(fall OR falls):ti,ab,kw AND (assess* OR evaluat* OR measur* OR predict* OR scale* OR screen* OR test*):ti
	189.	Combine sets for falls	#186 OR #187 OR #188
	190.	Cognitive impairment	'autonomic instability'/de OR 'cognitive decline'/de OR ‘cognitive defect’/mj OR 'confusion’/exp OR ‘dementia’/exp OR 'frontotemporal dementia'/exp OR ‘mild cognitive impairment’/de OR 'multiinfarct dementia'/de OR ‘senile dementia’/exp OR 'diabetic neuropathy’/exp
	191.		((autonomic OR cognit* OR confus* OR memory) AND (declin* OR defect* OR deficit* OR (diabet* AND neuropath*) OR dysfunction* OR function* OR impair* OR instab* OR insuff*)):ti,ab OR (alzheimer* OR dementia OR frontotemporal OR lewy):ti,ab
	192.		#190 OR #191

KQ	Set	Concept	Search Statement
KQ 9 (cont.)	193.		#192 AND (('risk'/mj OR 'risk assessment'/exp OR assess*:ti OR evaluat*:ti OR measur*:ti OR risk*:ti OR scale*:ti OR screen*:ti OR test:ti OR tests:ti) OR (('Montreal cognitive assessment'/de OR 'mini cog test'/de OR 'Mini Mental State Examination'/exp OR 'mini mental status examination'/de) OR (‘montreal cog* assess*’ OR ‘mini cog test*’ OR ‘mini mental state exam*’ OR ‘mini mental status exam*’):ti,ab,kw))
	194.	Falls or cognitive impairment	#189 OR #193
	195.	T2DM and falls or cognitive impairment	#189 AND #194
	196.		#195 AND [english]/lim
	197.		#196 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	198.		#197 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	199.		#198 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	200.		#199 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	201.		#200 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	202.		#200 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)

KQ	Set	Concept	Search Statement
KQ 9 (cont.)	203.		#200 AND (‘cohort analysis’/de OR ‘comparative study’/de OR 'longitudinal study'/de OR ‘observational study’/de OR ‘prospective study’/de OR ‘retrospective study’/de OR (‘between groups’ OR ‘case control’ OR cohort* OR compar* OR ‘follow up’ OR ‘groups’ OR longitudinal OR (observational NEXT/3 study) OR prospective OR registry OR registries OR retrospective OR ‘non random*’):ti,ab)
	204.		#201 OR #202 OR #203
KQ 10	205.	Standard population	'non insulin dependent diabetes mellitus'/de OR (diabet*:ti,ab,kw AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	206.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	207.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	208.		((late OR adult* OR matur* OR slow OR stabl* OR ‘long stand*’) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	209.		#205 OR #206 OR #207 OR #208
	210.		#209 NOT 'diabetes insipidus'/exp
	211.	Fall risk	'fall risk'/de OR ((‘high risk patient’/de OR ‘risk’/exp) AND fall*) OR ‘risk* of falls’ OR ‘fall risk*’ OR (risk* NEAR/2 fall*) OR ((balance* OR fall* OR (motor NEAR/2 dysfunction*) OR ‘sit to stand’ OR ‘single leg’ OR ‘up and go’) AND (confidence OR deficit OR risk*))
	212.	Cognitive impairment risk	'autonomic instability'/de OR 'cognitive decline'/de OR ‘dementia’/exp/mj OR 'frontotemporal dementia'/exp OR ‘mild cognitive impairment’/de OR 'multiinfarct dementia'/de OR ‘senile dementia’/exp OR 'diabetic neuropathy'/exp OR ‘diabetic neuropath*’
	213.		((autonomic OR cognit*) AND (decline OR defect* OR (diabet* AND neuropath*) OR dysfunction* OR impair* OR instab* OR insuff*)) OR (alzheimer* OR dementia OR frontotemporal OR lewy OR (memory NEAR/3 loss))
	214.		#212 OR #213
	215.	Disease management general	(#211 OR #214) AND ('non insulin dependent diabetes mellitus'/exp/dm_co,dm_dm,dm_dt,dm_th OR (‘non insulin dependent diabetes mellitus’/exp AND ‘drug therapy’/exp))
	216.	T2DM AND falls risk OR cognitive impairment	#210 AND (#211 OR #214)
	217.		#215 OR #216
	218.	Pharmacologic interventions, general	'antidiabetic agent'/exp OR 'oral antidiabetic agent'/exp OR (drug* OR medication* OR pharma* OR prescription*):ti,ab
	219.	Alpha glucosidase inhibitors	'alpha glucosidase inhibitor'/exp OR 'acarbose'/de OR 'miglitol'/de OR (‘Alpha glucosidase inhibitor*’ OR acarbose OR miglitol):ti,ab,kw,tn

KQ	Set	Concept	Search Statement
KQ 10 (cont.)	220.	Amylin Mimetics	'amylin derivative'/exp OR amylin* OR pramlinitide
	221.	DPP4i	'dipeptidyl peptidase IV inhibitor'/exp OR ‘dpp4*’ OR (sitagliptin OR saxagliptinOR linagliptin OR alogliptin):ti,ab,kw,tn
	222.	Dopamine-2 agonists	'dopamine 2 receptor stimulating agent'/de OR ‘dopamine-2 agonists’ OR bromocriptine
	223.	Biguanides	'biguanide'/de OR biguanide*
	224.	Bile acid sequestrant	'bile acid sequestrant'/exp OR colesevelam/de OR colestilan/de OR colestipol/de OR colestyramine/de OR diethylaminoethyldextran/de OR (‘bile acid seq*’ OR colesevelam* OR colestilan* OR colestipol* OR colestyramine* OR diethylaminoethyldextran*):ti,ab
	225.	GLP-1 agonists	'glucagon like peptide 1 receptor agonist'/exp OR ‘dulaglutide’/de OR ‘liraglutide’/de OR ‘lixisenatide’/de OR ‘semaglutide’/de OR (‘glp 1 agonist*’ OR ‘glp1*’ OR dulaglutide OR trulicity OR exenatide OR byetta* OR bydureon OR liraglutide OR victoza OR lixisenatide OR adlyxin OR semaglutide OR ozempic OR rybelsus):ti,ab,kw,tn
	226.	Insulin	'insulin'/de OR insulin
	227.	meglitinides	'meglitinide'/de OR meglitinide* OR nateglinide OR repaglinide
	228.	Metformin	‘metformin’/de OR metformin:ti,ab,kw,tn
	229.	SGLT-2	'sodium glucose cotransporter 2 inhibitor'/exp OR 'empagliflozin'/de OR 'canagliflozin'/de OR 'dapagliflozin'/de OR 'ertugliflozin'/de
	230.		(‘sglt 2 inhibitor*’ OR empagliflozin OR canagliflozin OR dapagliflozin OR ertugliflozin):ti,ab,kw,tn
	231.	Sulfonylureas	'sulfonylurea derivative'/exp OR sulfonylurea* OR glipizide OR glimepiride OR glyburide
	232.	thiazolidinediones (TZDs)	'2,4 thiazolidinedione derivative'/de OR 'glitazone derivative'/exp OR 'pioglitazone'/de OR 'rosiglitazone'/de OR (‘tzd’ OR thiazolidineodiones OR rosiglitazone OR pioglitazone):ti,ab,kw,tn
	233.	Combine pharma interventions	#218 OR #219 OR #220 OR #221 OR #222 OR #223 OR #224 OR #225 OR #226 OR #227 OR #228 OR #229 OR #230 OR #231 OR #232
	234.	Nutrition	'non insulin dependent diabetes mellitus'/exp/dm_dm,dm_th AND (nutrition* OR diet*):ti
	235.		‘nutritional assessment’/de OR ‘nutritional status’/de OR ‘body weight change’/exp OR ‘vitamin d’/exp OR ‘anemia’/exp OR ‘hypoglycemia’/exp OR ‘hydrate’/de OR ‘fluid intake’/exp OR ‘vitamin intake’/exp OR ‘malnutrition’/exp OR ‘calorie intake’/de OR ‘sodium intake’/de
	236.		((nutrition* AND (assess* OR status)):ti,ab OR ((weight OR pounds OR obes*) AND (change* OR improv* OR lose OR lost OR gain*)):ti,ab OR ‘vitamin d’ OR anemi* OR anaemi* OR hypoglyc* OR hydrat* OR water OR vitamin* OR malnutrition OR malnourish* OR calori* OR sodium):ti,ab
	237.		('diabetes mellitus'/exp/dm_pc,dm_th AND ('diet'/exp/mj OR 'nutrition'/mj))

KQ	Set	Concept	Search Statement
KQ 10 (cont.)	238.	Combine diet interventions	#234 OR #235 OR #236 OR #237
	239.	T2DM and Falls or cognitive impairment AND interventions	#217 OR (#217 AND (#233 OR #238))
	240.	Apply limits	#239 AND [english]/lim
	241.		#240 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	242.		#241 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	243.		#242 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	244.		#243 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	245.		#244 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	246.		#244 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	247.	Final sets	#245 OR #246

KQ	Set	Concept	Search Statement
KQ 11	248.	Standard population	'non insulin dependent diabetes mellitus'/de OR (diabet*:ti,ab,kw AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	249.		(‘diabetes mellitus’/exp/mj OR ‘diabetes mellitus’:ti,ab,kw) AND (‘long standing’ OR longstanding OR ‘non insulin dependent*’ OR ‘noninsulin dependent*’ OR ‘insulin independent*’ OR ‘ketosis resistant’):ti,ab,kw
	250.		(NIDDM OR T2DM OR T2D OR ‘dm 2’ OR DM2 OR DM2T OR DMT2):ti,ab,kw
	251.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	252.		#248 OR #249 OR #250 OR #251
	253.		#252 NOT 'diabetes insipidus'/exp
	254.	Diabetes distress/stress/fatigue	‘depression’/exp OR ‘distress syndrome’/de OR anxiety OR depress* OR (diabet* NEAR/2 (fatigue OR distress* OR stress*)) OR (emotional NEAR/3 burden) OR ‘interpersonal distress’ OR (physican NEAR/3 distress) OR (regimen NEAR/3 distress)
	255.	Broad screening strategy	(assess* OR evaluat* OR measur* OR predict* OR question* OR scale* OR screen* OR test*):ti,ab,kw
	256.	Specific screening tools	‘Problem Areas in Diabetes’ OR (paid AND questionnaire) OR ‘diabetes distress scale’ OR ‘dds’ OR ‘T2 Diabetes Distress Assessment System’ OR ‘T2DDAS’ OR ‘dds 17’ OR ‘T1DDS’ OR ‘phq 9’
	257.	Combine diabetes distress	#254 AND (#255 OR #256)
	258.	Renal	‘kidney disease’/exp/dm_di
	259.		'kidney disease'/exp OR kidney*:ti OR renal:ti OR nephro*:ti
	260.		‘diagnostic imaging equipment’/exp OR 'nuclear magnetic resonance imaging'/exp OR 'ultrasound scanner'/exp OR MRI OR ‘magnetic resonance imag*’ OR ultrasound*
	261.	Screening tests	‘creatinine’/exp OR 'creatinine blood level'/exp OR ‘creatinine urine level’/exp OR 'estimated glomerular filtration rate'/exp OR 'glomerulus filtration rate'/exp OR ‘liver enzyme’/exp OR 'microalbuminuria'/exp OR ‘proteinuria’/exp OR (albuminuria OR creatinine OR egfr OR ‘estimated glomerul* filtration’ OR gfr OR glomuerular OR macroalbumin* OR microalbumin* OR (liver AND enzyme*) OR proteinuria):ti,ab,kw
	262.	Combine renal with diagnostics or screening	(#258 OR #259) AND (#260 OR #261)
	263.		'liver disease'/exp/dm_di
	264.		'nonalcoholic fatty liver'/exp OR 'nonalcoholic steatohepatitis'/de OR ((hepatic OR liver) NEAR/3 (fibrosis OR disease)) OR ‘non alcoholic fatty liver disease’ OR ‘nonalcoholic fatty liver disease’ OR ‘NAFLD’ OR ‘non alcoholic steato hepatitis’ OR ‘non alcoholic steatohepatitis’ OR ‘NASH’ OR steatosis

KQ	Set	Concept	Search Statement
KQ 11 (cont.)	265.		'elastograph'/de OR elastograph* OR 'fibro nash' OR fibroscan* OR 'magnetic resonance' OR 'mri' OR ('mr' OR 'mri' NEAR/5 elastograph*) OR 'mri based' OR 'MRI aspartate aminotransferase' OR 'MAST' OR 'NFS' OR 'fib 4' OR (transient NEAR/2 elastograph*) OR OR 'aspartate aminotransferase'/exp OR 'alanine aminotransferase'/exp OR 'alkaline phosphatase'/exp OR 'bilirubin'/exp OR ((aspartate OR alanine) AND transaminase):ti,ab OR 'alkaline phospate:ti,ab OR bilirubin:ti,ab OR (('right upper quadrant' OR hepatic) AND ultrasound*):ti,ab
	266.		'screening'/exp OR (assess* OR detect* OR evaluat* OR measur* OR predict* OR screen* OR test*):ti,ab
	267.	Liver diagnostics or screening	(#263 OR #264) AND (#265 OR #266)
	268.	Distress or renal or liver	#257 OR #262 OR #267
	269.	Diagnostic hedge	'accuracy':de OR (area NEXT/1 under NEXT/3 curve) OR auc OR 'diagnosis'/exp/mj OR diagnos*:ti OR 'diagnostic accuracy' OR 'diagnostic error*' OR 'diagnostic error'/exp OR 'diagnostic test accuracy':de OR 'differential diagnosis'/exp OR ((false OR true) NEAR/1 (positive OR negative)) OR likelihood OR 'maximum likelihood method':de OR ppv OR precision OR 'precision'/exp OR 'prediction and forecasting' OR 'prediction and forecasting'/exp OR 'predictive value'/exp OR 'predictive value' OR 'receiver operating characteristic' OR 'receiver operating characteristic':de OR 'roc curve' OR 'roc curve'/exp OR 'sensitivity and specificity':de OR ('sensitivity' AND 'specficity')
	270.		#268 AND #269
	271.	T2DM and distress or renal or liver	#253 AND #270
	272.		#271 AND [english]/lim
	273.		#272 AND [2016-2022]/py AND ([1-1-2016]/sd NOT [11-04-2021]/sd)
	274.		#273 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	275.		#274 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))

KQ	Set	Concept	Search Statement
KQ 11 (cont.)	276.		#275 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	277.		#276 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	278.		#276 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)
	279.		#276 AND ('cohort analysis'/de OR 'comparative study'/de OR 'cross-sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de OR ('between groups' OR 'case control' OR cohort* OR compar* OR 'cross sectional' OR groups OR longitudinal OR 'post test' OR 'pre test'):ti,ab)
	280.		#277 OR #278 OR #279
KQ 12	281.	Standard population	'non insulin dependent diabetes mellitus'/de OR (diabet*:ti,ab,kw AND ('t2' OR 'type* 2' OR 'type* ii' OR typ*2 OR typ*ii OR 'tii'):ti,ab,kw)
	282.		('diabetes mellitus'/exp/mj OR 'diabetes mellitus':ti,ab,kw) AND ('long standing' OR longstanding OR 'non insulin dependent*' OR 'noninsulin dependent*' OR 'insulin independent*' OR 'ketosis resistant'):ti,ab,kw
	283.		(NIDDM OR T2DM OR T2D OR 'dm 2' OR DM2 OR DM2T OR DMT2):ti,ab,kw
	284.		((late OR adult* OR matur* OR slow OR stabl* OR long-stand*) NEAR/3 onset):ti,ab,kw AND diabet*:ti,ab,kw
	285.		#281 OR #282 OR #283 OR #284
	286.		#285 NOT 'diabetes insipidus'/exp
	287.	Diabetes distress/stress/fatigue	'depression'/exp OR 'distress syndrome'/de OR anxiety OR depress* OR (diabet* NEAR/2 (fatigue OR distress* OR stress*)) OR (emotional NEAR/3 burden) OR 'interpersonal distress' OR (physican NEAR/3 distress) OR (regimen NEAR/3 distress)
	288.	Broad screening strategy	(assess* OR evaluat* OR measur* OR predict* OR question* OR scale* OR screen* OR test*):ti,ab,kw

KQ	Set	Concept	Search Statement
KQ 12 (cont.)	289.	Specific screening tools	'Problem Areas in Diabetes' OR (paid AND questionnaire) OR 'diabetes distress scale' OR 'dds' OR 'T2 Diabetes Distress Assessment System' OR 'T2DDAS' OR 'dds 17' OR 'T1DDS' OR 'phq 9'
	290.	Combine diabetes distress	#287 AND (#288 OR #289)
	291.	Renal	'kidney disease'/exp/dm_di
	292.		'kidney disease'/exp OR kidney*:ti OR renal:ti OR nephro*:ti
	293.		'diagnostic imaging equipment'/exp OR 'nuclear magnetic resonance imaging'/exp OR 'ultrasound scanner'/exp OR MRI OR 'magnetic resonance imag*' OR ultrasound*
	294.	Screening tests	'creatinine'/exp OR 'creatinine blood level'/exp OR 'creatinine urine level'/exp OR 'estimated glomerular filtration rate'/exp OR 'glomerulus filtration rate'/exp OR 'liver enzyme'/exp OR 'microalbuminuria'/exp OR 'proteinuria'/exp OR (albuminuria OR creatinine OR egfr OR 'estimated glomerul* filtration' OR gfr OR glomuerular OR macroalbumin* OR microalbumin* OR (liver AND enzyme*) OR proteinuria):ti,ab,kw
	295.	Combine renal with diagnostics or screening	(#291 OR #292) AND (#293 OR #294)
	296.		'liver disease'/exp/dm_di
	297.		'nonalcoholic fatty liver'/exp OR 'nonalcoholic steatohepatitis'/de OR ((hepatic OR liver) NEAR/3 (fibrosis OR disease)) OR 'non alcoholic fatty liver disease' OR 'nonalcoholic fatty liver disease' OR 'NAFLD' OR 'non alcoholic steato hepatitis' OR 'non alcoholic steatohepatitis' OR 'NASH' OR steatosis
	298.		'elastograph'/de OR elastograph* OR 'fibro nash' OR fibroscan* OR 'magnetic resonance' OR 'mri' OR ('mr' OR 'mri' NEAR/5 elastograph*) OR 'mri based' OR 'MRI aspartate aminotransferase' OR 'MAST' OR 'NFS' OR 'fib 4' OR (transient NEAR/2 elastograph*) OR OR 'aspartate aminotransferase'/exp OR 'alanine aminotransferase'/exp OR 'alkaline phosphatase'/exp OR 'bilirubin'/exp OR ((aspartate OR alanine) AND transaminase):ti,ab OR 'alkaline phospate:ti,ab OR bilirubin:ti,ab OR (('right upper quadrant' OR hepatic) AND ultrasound*):ti,ab
	299.		'screening'/exp OR (assess* OR detect* OR evaluat* OR measur* OR predict* OR screen* OR test*):ti,ab
	300.	Liver diagnostics or screening	(#296 OR #297) AND (#298 OR #299)
	301.	Distress or renal or liver	#290 OR #295 OR #300
	302.	T2DM and distress or renal or liver	#286 AND #301

KQ	Set	Concept	Search Statement
KQ 12 (cont.)	303.	Clinical utility	'clinical practice'/de OR 'decision making'/exp OR ((clinical NEXT/1 (application* OR benefit* OR decision* OR effectiveness OR impact* OR implication* OR management OR outcome* OR practice OR setting* OR use OR utility)):ti,ab) OR 'decision making':ti,ab OR (inform*:ti,ab AND (therapy*:ti,ab OR treat*:ti,ab)) OR actionable:ti OR advantag*:ti OR appropriateness:ti OR benefi*:ti OR decid*:ti OR decision*:ti OR efficac*:ti OR ((guid*:ti OR select*:ti) AND (therap*:ti OR treat*:ti)) OR inform:ti OR informing:ti OR role:ti OR practice:ti OR targeted:ti OR use:ti OR useful*:ti OR utility:ti OR valu*:ti
	304.		#302 AND #303
	305.		#304 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti OR patient*:ti)))
	306.		#305 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
	307.		#306 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR book:it OR chapter:it OR conference:it OR editorial:it OR letter:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR abstract:nc OR annual:nc OR conference:nc OR congress:nc OR meeting:nc OR proceedings:nc OR sessions:nc OR symposium:nc OR book:pt NOT series:pt OR 'conference proceeding':pt OR 'case report':ti OR comment*:ti OR editorial:ti OR letter:ti OR news:ti OR (protocol:ti AND (study:ti OR trial:ti) NOT ('therapy protocol*':ti OR 'treatment protocol*':ti)))
	308.		#307 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR rct:ti,ab)
	309.		#307 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR database*:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab)) NOT (((protocol NEXT/3 review):ti) OR 'review protocol':ti OR 'scoping review':ti)

KQ	Set	Concept	Search Statement
KQ 12 (cont.)	310.		#307 AND (‘cohort analysis’/de OR ‘comparative study’/de OR ‘cross-sectional study’/de OR 'longitudinal study'/de OR ‘observational study’/de OR ‘prospective study’/de OR ‘retrospective study’/de OR (‘between groups’ OR ‘case control’ OR cohort* OR compar* OR ‘cross sectional’ OR groups OR longitudinal OR ‘post test’ OR ‘pre test’):ti,ab)
	311.		#308 OR #309 OR #310
	215.	Combine Results of All KQs	#21 OR #40 OR #65 OR #91 OR #114 OR #134 OR #154 OR #179 OR #204 OR #247 OR #280 OR #311
	216.	Run Retraction Strings	#216 AND ('retraction notice'/de OR retracted:ti OR retraction:ti OR withdrawn:ti)
	217.	Remove Retracted Materials from Final Set	#215 NOT #216

Appendix I: Alternative Text Descriptions of Algorithm

The following outline narratively describes the Management of Type 2 Diabetes Mellitus Algorithm. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

Module A: T2DM Management

1. The algorithm begins with Box 1, in the shape of a rounded rectangle: "Patient with T2DM."
2. Box 1 connects to Box 2, in the shape of a hexagon, which asks, "Does the patient have an urgent or emergent care need (e.g., symptomatic hyperglycemia, severe hypoglycemia, concurrent medical issue)?"
    a. If the answer is "Yes" to Box 2, then Box 3, in the shape of a rectangle: "Treat and/or refer for acute care."
    b. If the answer is "No" to Box 2, then Box 4, in the shape of a rectangle: "Assess barriers to success (e.g., psychosocial needs, navigating health care, health literacy/numeracy, patient/provider inertia, social determinants of health [e.g., transportation, economic or food insecurity])."
3. Box 4 connects to Box 5, in the shape of a rectangle: "Develop an individualized treatment plan. Review non-pharmacologic therapies: Medical Nutrition Therapy (MNT) (including weight management) (see **Module B**); Diabetes Self-Management Education and Support (DSMES) (see **Module B**); Exercise. If pharmacologic therapy is indicated, begin metformin unless contraindicated."
4. Box 5 connects to Box 6, in the shape of a hexagon, which asks, "Does the patient have any of the following: 1. Established ASCVD or high ASCVD risk 2. Diabetic neuropathy 3. Heart failure (see **Sidebar 4**)?"
    a. If the answer is "Yes" to Box 6, then Box 7, in the shape of a rectangle: "Consider GLP-1 RA or SGLT-2 inhibitor if indicated."
    b. If the answer is "No" to Box 6, then Box 8, in the shape of a hexagon, asks, "Has the patient's glycemic target been achieved (A1C 7.0–8.5% for most patients or alternative range based on individualization)?"
        i. If the answer is "No" to Box 8, then Box 10, in the shape of a rectangle: "Consider additional medications until target A1C range is achieved. Select agent based on efficacy and risk-benefit ration. See CPG Appendix B."
        ii. If the answer is "Yes" to Box 8, then Box 9, in the shape of a rectangle: "Review treatment plan to minimize or treat complications and/or comorbidities (see **Sidebars 1, 2, 3, and 4**)."

5. Box 9 connects to Box 11, in the shape of a rectangle: “Review health promotion activities: tobacco cessation; vaccinations, age-related; dental care.”
6. Box 11 connects to Box 12, in the shape of a rectangle: “Follow up as needed.”

Module B: Self-Management Education and Support

1. Module B starts with Box 13, in the shape of a rectangle: “Patients with T2DM should be offered DSMES or MNT at all of the following times: At initial diagnosis; When not meeting treatment goals; Change in health status/barriers to self-management.”
2. Box 13 connects to Box 14, in the shape of a hexagon, which asks, “Is the patient being treated in an acute setting?”
    a. If the answer is “Yes” to Box 14, then Box 15, in the shape of a rectangle: “Train in survival skills (see **Sidebar 5**) and refer for DSMES or MNT following acute care.”
    b. If the answer is “No” to Box 14, then Box 16 in the shape of a rectangle: “Consult/enroll the patient in an outpatient VA/DoD DSMES and MNT program.”
    c. Box 15 also connects to Box 16.
3. Box 16 connects to Box 17, in the shape of a rectangle: “Conduct DSMES assessment (see **Sidebar 6**) and/or MNT screening and assessment (see **Sidebar 7**).”
4. Box 17 connects to Box 18, in the shape of a rectangle: “Conduct comprehensive DSMES (see **Sidebar 6**) or ongoing support (see **Sidebar 8**) and MNT (see **Sidebar 7**).”

Appendix J: Abbreviations

Abbreviation	Definition
3-point MACE	3-point major adverse cardiovascular outcomes
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEi	Ace inhibitor
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blockers
ARR	Absolute risk reduction
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BGM	Blood glucose monitoring
BMI	Body mass index
BP	Blood pressure
CGM	Continuous glucose monitoring
CKD	Chronic kidney disease
COI	Conflict of interest
COPD	Chronic obstructive pulmonary disease
CPG	Clinical practice guideline
CV	Cardiovascular
CV	Coefficient of variation
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DKA	Diabetic ketoacidosis
dL	Deciliter
DM	Diabetes mellitus
DoD	Department of Defense
DPP	Diabetes Prevention Program
DSMES	Diabetes self-management education and support
EBPWG	Evidence-Based Practice Work Group
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
fCGM	Flash continuous glucose monitoring
FPG	Fasting plasma glucose
GDM	Gestational diabetes
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GRADE	Grading of Recommendations Assessment, Development, and Evaluation

Abbreviation	Definition
HbA1c	Hemoglobin A1c
HF	Heart failure
HHF	Hospitalization for heart failure
HOMA-B	Homeostasis Model Assessment of β-cell Function
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR	Hazard ratio
HT	Hypertrophy training
IBGMS	Internet-based glucose monitoring system
IF	Intermittent fasting
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
isCGM	Intermittently scanned continuous glucose monitoring
L	Liter
LDL	Low-density lipoprotein
MACE	Major adverse cardiovascular event
MBSR	Mindfulness-based stress reduction
MERT	Muscular endurance training
mg	Milligram
MHS	Military Health System
MI	Myocardial infarction
mmol	Millimole
MNT	Medical nutrition therapy
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NFS	Non-alcoholic fibrosis score
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
NSAID	Non-steroidal anti-inflammatory drug
OGTT	Oral glucose tolerance test
PCP	Primary care provider
RCT	Randomized controlled trial
RDN	Registered dietitian nutritionist
RN	Registered nurse
RR	Relative risk
rtCGM	Real-time continuous glucose monitoring
SD	Standard deviation
SGLT-2 inhibitor	Sodium-glucose cotransporter 2 inhibitor
SMBG	Self-monitoring of blood glucose

Abbreviation	Definition
SOE	Strength of evidence
SR	Systematic review
SUD	Substance use disorder
TAU	Treatment as usual
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TIR	Time in range
U.S.	United States
UKPDS	United Kingdom Prospective Diabetes Study
USPFTF	United States Preventive Service Task Force
VA	Department of Veterans Affairs
VADT	Veteran Affairs Diabetes Trial
VHA	Veterans Health Administration

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