UCONN

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to
- Describe type 2 diabetes diagnostic criteria and glycemic targets
- Identify the components of diabetes self-management education and support
- Recognize the importance of an individualized treatment program
- List treatment recommendations for type 2 diabetes in the setting of common comorbidities

After completing the continuing education activity, pharmacy technicians will be able to
- Describe type 2 diabetes diagnostic criteria and glycemic targets
- Identify the components of diabetes self-management education and support
- Recognize the importance of an individualized treatment program
- List common comorbidities in type 2 diabetes

You Asked for It! CE

Management of Adults with Type 2 Diabetes: A Patient-Focused Approach

TARGET AUDIENCE: Pharmacists and pharmacy technicians interested in management of type 2 diabetes.

ABSTRACT: The diabetes epidemic is growing globally. Knowledge of current standards of care is essential for healthcare professionals. Understanding the importance of lifestyle recommendations and current pharmacologic therapies based on comorbidities is integral to improving diabetic patient outcomes. This continuing education activity follows a format similar to the Standards of Medical Care in Diabetes, focusing on the non-pregnant adult with T2DM. The current standards stress the importance of assessing each patient as an individual and emphasize a team care approach with patient involvement in monitoring diet, weight, physical exercise, and glycemic targets. This continuing education activity reviews the treatment of comorbid conditions, including obesity, hyperlipidemia, hypertension, heart disease, and chronic kidney disease, in addition to glycemic care. Using glucose-lowering therapy that decreases weight and slows cardiovascular disease progression is the new standard of care. Current medication therapy highlights incorporation of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 agonists into therapeutic treatment plans.

FACULTY: Gretchen De Nike Irion, PharmD, retired from Sequoia Hospital, a member of Dignity Health in Redwood City, CA, in October 2023. She is a graduate of the UConn Medical Writing Certificate Program.

FACULTY DISCLOSURE: Dr. Irion has no financial relationships with an ineligible company.

DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

Many years ago, I dined with a large man who looked as if he had lost a substantial amount of weight. He ordered meat and vegetables and explained to me that he had eliminated most carbohydrates from his diet. As a result of dietary changes, he was able to discontinue his diabetes medication. As a pharmacist, this concept of treating a disease with lifestyle changes, rather than medication, left a profound impact.

Globally, diabetes mellites is the ninth major cause of death. This epidemic has quadrupled in the past 30 years, affecting about one in 11 adults.[1] Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of diabetes mellitus diagnoses.[1] Traditionally, treatment goals focused on hemoglobin A1C (HbA1c) and blood glucose levels to treat T2DM. However, the incidence of diabetes and diabetic complications continues to rise despite the many hypoglycemic medications on the market.[2,3] Many older hypoglycemics can lead to weight gain, conflicting with the treatment goal of decreasing body mass.[4] Optimizing diet, nutrition, and physical exercise are important treatment components, but patients may find this challenging. The healthcare team can supply the necessary support to optimize therapy. If lifestyle modifications and traditional treatments are ineffective, newer T2DM medications offer novel treatment approaches that potentially improve overall patient outcomes.

Prevalence and Risk Factors

The global adult prevalence of diabetes is significant and varies by several factors[5]:

- Overall, approximately 6.1%
- Males 6.5%
- Females 5.8%
- Older adults between the ages of 65 and 95 years, over 20%
- Adults in their late 70's (75 to 79 years) 24.4%

In 76.5% of those with T2DM, research found risk factors were present, with high body mass index (BMI) being the primary risk factor for T2DM worldwide. Other risk factors included dietary risks, environmental or occupational risks, tobacco use, low physical activity, and alcohol use.[5]

According to the Centers for Disease Control and Prevention (CDC) National Diabetes Statistics Report (2023), in the United States in 2019, 8.7% of the population had diagnosed diabetes. Its prevalence also varied by ethnicity[6]:

- Native Americans and Alaska Natives 14.5%
- Non-Hispanic blacks 12.1%
- Hispanics 11.8%
- Non-Hispanic Asians 9.5%
- Non-Hispanic whites 7.4%.

People with less than a high school education were more likely to have diabetes (13.4%) than those with a high school education (9.2%) and those with more than a high school education (7.1%). Below the federal poverty level, the prevalence was 13.7% for men and 14.4% for women. The percentages vary depending on affected individuals' eating and exercise habits, age, ethnicity, culture, location, education level, and economic status.[6]

Diagnosis

According to the American Diabetes Association (ADA) Professional Practice Committee Classification and Diagnosis of Diabe-

tes, clinicians diagnose T2DM according to one of the following criteria[7]:

1. A fasting plasma glucose level of 126 mg/dL (7 mmol/L) or higher
2. A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-gram oral glucose tolerance test
3. A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
4. A HbA1c level of 6.5% (48 mmol/mol) or higher.

Glycemic Goals

Clinicians in all walks of practice use guidelines to monitor glycemic status in patients with diabetes. Assessing glycemic status at least two times annually in patients who have stable glycemic control is sufficient. Assessment of glycemic status involves one or more of the following[8]:

- Monitoring HbA1c status
- Employing a continuous glucose monitoring device with time in range monitoring
- Using a device containing a glucose management indicator.

The ADA recommends quarterly HbA1c monitoring for those with less stable glycemic control.[8,9] The HbA1c goal for most nonpregnant adults is 7% if the patient experiences no significant hypoglycemia. If the patient uses ambulatory glucose management, a target goal of 6.5% may be suitable. Less stringent HbA1c goals of up to 8% may be appropriate for patients with limited life expectancy or if treatment harm outweighs its benefits. When patients experience unexplained hypoglycemia, providing prompt hypoglycemia avoidance education or raising the glycemic targets are essential interventions, especially in patients with low cognition or declining cognition.[9]

COMMON COMORBIDITIES

Frequently, patients with T2DM have comorbidities. A review study analyzed patients with T2DM at varying times from diagnosis to identify the dominant multimorbidity cluster types. It found that three condition clusters appeared consistently[10-13]:

1. Cardiometabolic precursor conditions are common at diagnosis of T2DM
    a. Disorders of lipid metabolism (hyperlipidemia)
    b. Obesity
    c. Hypertension

2. Vascular conditions are usually associated with later stage T2DM
    a. Coronary artery disease (which can lead to heart failure)
    b. Chronic kidney disease
    c. Peripheral vascular disease (including peripheral arterial disease)
    d. Stroke (a manifestation of cerebrovascular disease)
    e. Atrial fibrillation

3. Mental health conditions occur regardless of diabetes duration
    a. Depression (the second most common condition in females after hypertension)
    b. Severe mental illness

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Diabetes Self-Management Education and Support (DSMES) is an essential component of diabetes treatment. Support from the healthcare professional team augments patients' necessary knowledge and skills. The four critical times to evaluate the need for DSMES are[14]:
- at diagnosis
- annually and/or when not meeting treatment targets
- when compelling factors develop
- when transitions in life or care occur.

Collaboration between patients and the healthcare team provides patient-centered DSMES. Thorough DSMES includes counselling on nutrition, physical activity, and psychosocial issues. Digital coaching and self-management interventions can be the means to deliver education and support.[14]

Diabetes self-management training (DSMT) is the reimbursable component of DSMES. A health care professional who is a certified Diabetes Care and Education Specialist (CDCES)—generally a dietitian, nurse or pharmacist—administers the DSMT. DSMT covers blood glucose monitoring, physical activity, healthy eating, medication, coping, problem solving.[15]

PAUSE AND PONDER: What lifestyle behaviors are fueling the diabetes epidemic?

Nutritional Therapy

Compelling evidence supports nutrition therapy's efficacy and cost-effectiveness as a component of the medical management of T2DM.[16] According to the CDC, a registered dietitian or nutritional professional provides medical nutrition therapy (MNT). MNT focuses solely on diet. Education should encompass in-depth, individualized nutritional assessment and follow-up with repeated reinforcement to aid with behavior change.[17] MNT encourages a diet rich in non-starchy vegetables, whole foods, and limited added sugars and refined grains. Increasing dietary fiber intake is beneficial, as diets high in fiber may lower HbA1c moderately. Minimizing carbohydrate intake improves glycemia. Diets higher in unsaturated fats than carbohydrates improve glycemia, triglycerides, HDL-C, and LDL-C in patients with cardiovascular disease and kidney disease.[16]

Caloric goals with an overall energy deficit (calories in are less then calories expended) promoting 5% weight loss have shown clinical benefit in reducing HbA1C. The goal for optimal outcomes in T2DM is to reduce body weight by 15%.[16] Dietary intervention can lead to disease remission, defined as sustained HbA1c levels below 6.5% for three months. Those diagnosed with type 2 diabetes for four years or fewer are more likely to achieve remission through diet. However, interventions accompanied by other lifestyle changes can be more effective than diet alone.[18]

Physical Activity

The World Health Organization (WHO) recommends adults engage in at least 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity physical activity, or a combination of both, per week. Additionally, the WHO recommends reducing sedentary behaviors across all age groups and abilities.[19]

According to the CDC, moderate-intensity physical activity includes brisk walking, light yard work, light snow shoveling, biking, or playing with children. Ideally, patients' heart rates will be 64% to 76% of their maximum. (To calculate actual beats per minute, patients subtract their age from 220, then multiply by 0.64 for the lower limit and by 0.76 for the upper limit.) Vigorous-intensity (high-intensity) exercise is jogging, swimming, rollerblading, cross country skiing, competitive sports, or jumping rope. Ideally, patients' heart rate will be 77% to 93% of their maximum heart rate. (Calculation of the beats per minute is the same as above using 0.77 and 0.93 as the multipliers.)[20]

Physical exercise has a positive effect on glycemic control. One study compared baseline glycemic levels with those measured after 30 minutes of moderate exercise before breakfast for three consecutive days. The study found that blood glucose levels were less variable throughout the day after morning exercise.[21] In patients with impaired fasting glucose, progression to diabetes is slower in those who chose leisure time physical activity over sedentary tasks.[22] High intensity exercise improves HbA1c more than moderate- or mild-intensity exercise.[23]

Researchers conducted an 8-year study of 30 patients with T2DM in which participants engaged in three 90-minute sessions of aerobic exercise per week. The exercise program included a 15-minute warm up and cool down period. During the aerobic period, participants' exercise intensity gradual increased from 50% to 80% maximum heart rate. Study participants had significantly reduced HbA1c and BMI. Participants also had significantly improved oxygen utilization. The researchers reported a HbA1c significant decrease of 1.39% among the experiment group.[24]

Physical activity may be the most underutilized tool in T2DM management. Physical activity improves cardiorespiratory fitness, reduces insulin resistance and insulin levels, improves lipid profiles, reduces visceral adipose tissue, and lowers blood pressure, decreasing cardiovascular risk.[25] Due to exercise's overwhelming benefit, developing a structured exercise plan for patients diagnosed with T2DM is a key responsibility for healthcare teams. Ideally, the healthcare care team would include an exercise physiologist.[25]

PAUSE AND PONDER: What self-care behaviors contribute to effective T2DM self-management?

Psychosocial Support
Up to 19% of patients with diabetes experience mental health symptoms. Depression is common, especially in women. Early detection and treatment of mental health comorbidities can reduce their impact on health outcomes. Mortality risk is higher in patients with mental health comorbidities, especially in those with substance use disorder and schizophrenia. Mental health comorbidities also increase the likelihood of all-cause hospitalization.[26]

Experts agree that collaborative patient-centered approaches to psychosocial care are best; such approaches include assessing patients for depression, anxiety, disordered eating, and cognitive capacities. Psychosocial screening and follow-up may include attitudes about diabetes, expectations for medical management, and outcomes.[8]

The Association of Diabetes Care and Education Specialists has identified seven self-care behaviors that contribute to effective self-management of diabetes and related conditions through improved behavior[27]:
- being active
- healthy coping
- healthy eating
- monitoring
- problem solving
- reducing risk
- taking medication

Well-educated patients can contribute to their diabetes management with self-care behaviors. Monitoring health metrics like blood glucose, blood pressure, physical activity, diet, weight, medication adherence, mood, and sleep empower diabetes patients and improve outcomes.[27] Higher medication adherence, as would be expected, is associated with improved glycemic control, fewer emergency department visits, decreased hospitalizations, and lower medical costs.[28] Patients sharing data with the healthcare team can fuel discussion to find solutions, reduce risk, and improve personalized therapy plans.[27]

PHARMACOLOGIC THERAPY
First line therapy for T2DM depends on comorbidities, patient-centered treatment factors, and management needs. It frequently includes metformin and comprehensive lifestyle modification. If the patient has atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD) then appropriate initial medical therapy may include glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose

cotransporter-2 (SGLT-2) inhibitors with or without metformin. Prescribers may continue metformin upon initiation of insulin therapy for ongoing glycemic and metabolic benefits.[8]
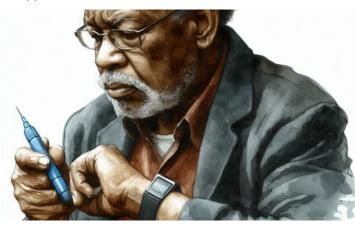
Metformin

Apothecaries have used metformin medicinally for centuries. It is a guanidine derivative found in *Galega officinalis*, a plant called goat's rue. Metformin was isolated and introduced in Europe in the 1950s and the United States in the 1990s.[29] Metformin decreases hepatic glucose production, decreases intestinal glucose absorption, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not cause hypoglycemia and patients generally tolerate it well. The most common adverse effect is diarrhea, resulting in 6% of patients discontinuing therapy. Other common adverse effects include nausea/vomiting, flatulence, asthenia, indigestion, and abdominal discomfort. Precautions include the potential for lactic acidosis, especially in patients with the following risk factors[30]:

- Renal impairment
- Hepatic impairment
- Heart failure
- Hypoxic states
- Excessive alcohol intake
- Radioactive dye studies
- Restricted food and fluid intake

Metformin may interfere with vitamin B_{12} absorption. Approximately 7% of patients become deficient. Supplementation with vitamin B_{12} is appropriate if deficits develop.[30]

Metformin can reduce HbA1c by 1.8% and lower the amount of insulin required to achieve glycemic targets by 19%.[31] Initial dosing is 500 mg twice daily, or 850 mg daily, increasing as tolerated by 500 mg weekly to a maintenance dose of 1000 mg twice daily in patients with normal renal function. The maximum recommended dose is 2,550 mg per day. Monitoring fasting plasma glucose during initiation and dose titration aids in determining therapeutic response. Maintenance measurement of HbA1c levels should occur every three months.[30] Renal function is an important factor in metformin use. The recommended eGFR threshold for initiation of metformin is 45 mL/min. If, during therapy, the eGFR falls below 45 mL/min, the team needs to as-

sess the benefit of continued therapy. Use is contraindicated in patients with an eGFR below 30 mL/min.[30]

INSULIN THERAPY

ADA Standards of Care recommend early introduction of insulin if clinicians see evidence of ongoing weight loss, symptoms of hyperglycemia, HbA1c levels exceeding 10%, or blood glucose levels of 300 mg/dL or higher. The potential for over-basalization (titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets) exists with insulin therapy. Signs of over-basalization may include a basal dose exceeding 0.5 units/kg/day, high bedtime-morning or post-prandial glucose differential, hypoglycemia, and high glycemic variability.[8]

When caring for hospitalized patients with diabetes, basal insulin or a basal plus bolus correction insulin is the preferred treatment for noncritically ill patients with poor oral intake. The standards prefer an insulin regimen with basal, prandial, and correctional components in patients with good nutritional intake. In many hospital settings, the basal and prandial doses are weight-based, and a correctional scale is added to scheduled mealtime doses to correct for pre-meal hyperglycemia.

It's critical to initiate insulin therapy for persistent hyperglycemia at a threshold of 180 mg/dL or more, confirmed on two occasions. After initiating insulin, the current Standards of Care recommend a target glucose range of 140 to 180 mg/dL for most patients. More stringent goals, such as 110 to 140 mg/dL, may be appropriate for select patients if they do not exhibit significant hypoglycemia. The ADA defines hyperglycemia as blood glucose levels over 140 mg/dL in the hospital, and hypoglycemia as blood glucose below 70 mg/dL. Monitoring glucose every four to six hours or every two hours for an insulin infusion is best. Each hospital or hospital system should implement hypoglycemic management protocols.[8]

TREATMENT RECOMMENDATIONS IN COMMON COMORBIDITIES
Obesity

High BMI is the primary risk factor for T2DM.[5] Diabetes was the second leading cause of BMI-related deaths in 2015 globally.[32] The DIRECT trial showed a T2DM remission rate of 36% after 24 months in patients receiving structured support for initial weight loss and weight loss maintenance.[33] The 2022 ADA Standards of Medical Care in Diabetes categorize obesity treatment options based on BMI[8]:

- Nonpharmacologic strategies may be sufficient for those with BMI 25 to 26.9
- Providers should consider adding pharmacotherapy for those with a BMI of 27 to 29.9
- For those with a BMI exceeding 30 (or for Asian Americans with BMI 27.5 and over), patients and their treatment teams might consider metabolic surgery

Table 1. Landmark Trials for SGLT-2 Inhibitors Evaluating T2DM with Cardiovascular Disease[47-50]		
Trial	**Drug**	**Outcome**
EMPA-REG OUTCOME	Empagliflozin 10-25 mg daily	Reduction in major adverse cardiovascular events; Reduction in hospitalization for heart failure
CANVAS	Canagliflozin 300 mg daily goal	Reduction in major adverse cardiovascular events; Reduced hospitalization for heart failure and cardiovascular death
DECLARE-TIMI 58	Dapagliflozin 10 mg daily	Reduction in heart failure-related death and hospitalization; Reduction in renal events

The Standards of Care in Diabetes stress a minimum of 5% weight loss for most people with T2DM. It is important to include counseling with two to three monthly sessions focusing on dietary changes, physical activity, and behavioral strategies to achieve a 500 to 750 kcal/day energy deficit. Person-centered, nonjudgmental language, specifically "person with obesity" rather than "obese person," fosters collaboration between patients and providers. Consideration of the medication's effect on weight gain is important.[8] Metformin, SGLT-2 inhibitors, GLP-1 receptor agonists, alpha-glucosidase inhibitors, and amylin mimetics promote weight loss.[34]

As of November 2023, three FDA-approved obesity medications also have FDA approval for treating T2DM. These are the GLP-1 agonists liraglutide, semaglutide, and tirzepatide.[35,36] Dosages are as follows[37-39]:

- Liraglutide (Saxenda) has an initial dose of 0.6 mg/day with a maintenance dose of 3 mg/day
- Semaglutide (Wegovy) has an initial dose of 0.25 mg/week with a maintenance dose of 2.4 mg/week
- Tirzepatide (Zepbound) has an initial dose of 2.5 mg/week with a maintenance dose of 5 to 15 mg/week

The FDA has approved these medications for weight loss in patients with a BMI of 30 or above or BMI of 27 or above with a comorbidity including hypertension, T2DM, or dyslipidemia.[37-39] These drugs lower glucose by stimulating insulin secretion from pancreatic islets in response to oral glucose load, like the natural hormone incretin. They delay gastric emptying, suppress appetite, increase satiety, decrease inappropriate glucagon secretion, and promote beta cell proliferation.[40,41]

Clinical data for the GLP-1 medications in weight loss is impressive. The SCALE trial has shown that the absolute weight loss with liraglutide 3 mg daily in patients with T2DM is 5.6 kg (12.3 lbs) over 56 weeks.[42] The absolute weight loss associated with semaglutide 2.4 mg weekly in patients who are obese or overweight patients with at least one risk factor is 12.7 kg (28 lbs) over 68 weeks.[43] Diabetic patients treated with tirzepatide 5, 10 or 15 mg weekly for 72 weeks lost an average of 12% body weight compared to placebo.[39] These medications contain warnings and precautions for thyroid C-cell tumors, acute pancreatitis, acute gallbladder disease, hypoglycemia with some T2DM medications, kidney injury, hypersensitivity reactions, and suicidal ideation.[37-39] The labeling for semaglutide and tirzepatide carries a precaution for diabetic retinopathy.[38,39] A precaution for heart rate increase is included in the labeling for liraglutide and semaglutide.[37,38] Most patients find these drugs have overwhelming benefits with effects primarily gastrointestinal adverse effects.[36-38]

Providers may consider metabolic surgery for T2DM treatment in adults with a BMI of 30 and over (or for Asian Americans with a BMI of 27.5 and greater). Metabolic surgery refers to surgical organ modification; bariatric surgery, for example, is metabolic surgery for treatment of obesity (commonly called a gastric bypass). A high-volume surgical center with experienced multidisciplinary teams knowledgeable about obesity management, diabetes, and gastrointestinal surgery is the best choice. Access to long-term medical, nutritional, and behavioral support after the procedure optimizes recovery. Patients may benefit from continuous glucose monitoring as an important adjunct, especially for those with episodes of hypoglycemia. After surgery, the clinical team should provide patient support, including mental health services.[44]

Bariatric surgery is an effective treatment option in T2DM patients with obesity. In a recent study, after a median follow-up of 19 months post-surgery, 68 of 105 obese patients achieved diabetes remission. Study participants had a median BMI of 42.4 and a diagnosis of T2DM before the procedure. Patients taking multiple glucose-lowering medications or dependent on insulin or SGLT2 inhibitors were less likely to undergo complete remission. A longer duration of T2DM pre-operatively was a negative predictor of remission.[45]

PAUSE AND PONDER: Which classes of diabetes medications are best for patients with ASCVD?

Cardiovascular Disease

All diabetic patients require yearly assessment of HF and ASCVD (coronary artery disease, cerebrovascular disease, or peripheral

arterial disease). Hypertension, dyslipidemia, and diabetes are risk factors for ASCVD. Controlling cardiovascular risk factors can prevent or slow ASCVD in people with diabetes.[46]

Prescribers should consider the presence of coronary artery disease in patients exhibiting atypical cardiac symptoms, signs of vascular disease, or electrocardiogram abnormalities. Atypical cardiac symptoms include unexplained dyspnea or chest discomfort. Carotid artery stenosis, transient ischemic attack, stroke, and peripheral arterial disease are indicators of ASCVD.[46]

In T2DM patients with established ASCVD or kidney disease, current ADA Standards of Medical Care suggest an SGLT-2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit (see **Table 1** on the previous page and **Table 2** below). A quick review of FDA indications and landmark trials ensures the correct medication and dose have been chosen as newer agents continue to emerge with indications that may encompass weight loss and treatment of T2DM. To reduce the risk of adverse cardiovascular and kidney events, patients with T2DM and established ASCVD may benefit from combined therapy with an SGLT-2 inhibitor and a GLP-1 receptor agonist with demonstrated cardiovascular benefit.[46]

The SGLT-2 inhibitors' primary mechanism of action is reduction of renal tubular glucose reabsorption at the proximal tubule resulting in glucosuria.[51] The SGLT-2 inhibitors' glucose-lowering efficacy decreases with increasing renal impairment.[52] Most patients tolerate these medications well, with mild adverse effects. The proposed cardiovascular benefits include improved, blood pressure reduction, inflammation reduction, diuresis, inhibition of nervous system, and prevention of cardiac remodeling (physical changes to heart).[47] Their adverse effects include genitourinary infections, intravascular volume depletion, increased risk of diabetic ketoacidosis, and potentially an increased risk of lower limb amputations.[52] Prescribers need to hold SGLT-2 inhibitors during acute illness (hospitalization), when fluid intake is inadequate, or if acute kidney injury occurs.[47]

Pancreatic hormones and incretin hormones regulate glycemic homeostasis. GLP-1 is an incretin hormone that increases pancreatic insulin release and decreases glucagon release.[41] The

GLP-1 receptors are located in the renal proximal convoluted tubular cells and preglomerular vascular smooth muscle cells in the kidneys.[53] The GLP-1 receptor agonists lower HbA1c, weight, and blood pressure.[54]

GLP-1 receptor agonists promote natriuresis (increased sodium in the urine), lowering blood pressure.[55] GLP-1 receptor agonists also reduce reactive oxygen production, thereby reducing platelet activation, macrophages, and monocytes in the vascular wall. Stabilization of the endothelial cells occurs with less plaque hemorrhage and rupture.[56] Overall, GLP-1 enhancement results in a slower progression of atherosclerosis.[57]

In T2DM patients with a history of ASCVD, aspirin 75 mg to 162 mg daily is a secondary prevention strategy. In patients with documented aspirin allergies, clopidogrel 75 mg daily is an alternative. Patients with stable coronary and or peripheral artery disease and a low bleeding risk should take dual antiplatelet therapy for at least one year following acute coronary syndrome. Aspirin and low dose rivaroxaban can prevent major adverse limb and cardiovascular events.[61]

Hypertension

Hypertension exacerbates cardiovascular disease, which is the major cause of morbidity and mortality in diabetes.[62] In 2023, the ADA updated the hypertension criteria. According to the 2023 Standards of Care in Diabetes recommendations, patients are hypertensive if they exhibit a sustained blood pressure of 130/80 mm Hg or more, or a single level of 180/110 or more. The target goal is 130/80 mm Hg or less. Blood pressure targets below 120/80 mmHg are associated with hypotensive adverse events (such as falls). Patients with diabetes who are hypertensive should monitor their blood pressure at home. Patients with blood pressures exceeding 120/80 should implement lifestyle interventions including diet changes and weight loss, reduced sodium and increased potassium intake, moderation of alcohol, and increased physical activity.[61] Treatment of hypertension reduces cardiovascular events and microvascular complications.[63,64]

In patients with persistently elevated blood pressure, pharmacologic therapy in addition to lifestyle modifications improves outcomes. First-line pharmacologic therapy includes use of an

Table 2. Landmark Trials for GLP-1 Agonists: Evaluating T2DM with Cardiovascular Disease[57-60]

Trial	Drug	Outcome
REWIND	Dulaglutide 1.5 mg once a week	Reductions in major adverse cardiovascular events
SUSTAIN-6	Semaglutide 0.5 or 1 mg once a week	Relative risk reduction in major adverse cardiovascular events
LEADER	Liraglutide 1.8 mg (or max dose tolerated) daily	Relative risk reduction in major adverse cardiac events and cardiovascular death

Table 3. Once daily: High-intensity and Moderate-intensity Statin Therapy[61]	
Moderate-intensity statin therapy	**High-intensity statin therapy**
Atorvastatin 10–20 mg	Atorvastatin 40–80 mg
Rosuvastatin 5–10 mg	Rosuvastatin 20–40 mg
Simvastatin 20–40 mg	
Pravastatin 40–80 mg	
Lovastatin 40 mg	
Fluvastatin (extended release) 80 mg	
Pitavastatin 1–4 mg	

angiotensin-converting enzyme inhibitor (ACEi), or an angiotensin receptor blocker (ARB). Clinical trials assessing these drugs demonstrate a reduction of cardiovascular events in T2DM patients with coronary artery disease. Prescribers should maximize doses for patients with a urine-to-creatinine ratio greater than 30 mg/g creatinine, as this is a sign of kidney damage. If the patient does not tolerate one drug class, the prescriber may switch to the other; however, the prescriber should not use them together. Annual monitoring of glomerular filtration rate (GFR) and serum potassium are needed.[61]

Prescribers should start their patients on two medications if they have a confirmed office blood pressure of 160/100 mm Hg or more.[61] Common therapies include thiazide-like diuretics and dihydropyridine calcium channel blocker.[65] Patients on triple antihypertensive therapy including a diuretic with unmet blood pressure goals may require a mineralocorticoid receptor antagonist, such as spironolactone.[66] Adding a mineralocorticoid receptor antagonist may increase the risk of hyperkalemia. Regular monitoring of serum creatinine and potassium is prudent.[46]

In the absence of albuminuria, ACEi and ARBs may not provide superior cardio-protection over thiazide-like diuretics or dihydropyridine calcium channel blockers.[67] Patients who have had a prior myocardial infarction, active angina, or HF with reduced ejection fraction (HFrEF) should be treated with a beta blocker. However, beta blockers do not reduce mortality when used as antihypertensives in the absence of these conditions.[54,68]

Hyperlipidemia

Reduction of lipids and cholesterol is important because hyperlipidemia is a risk factor and common comorbidity for T2DM. Lifestyle modification focusing on weight loss is the first step of lipid management. Trained nutritionists can educate patients to eat a diet low in saturated fat and trans-fat. The goal is a diet that increases dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols. Physical activity also helps improve lipid profiles. The importance of lifestyle therapy and glycemic optimization for triglycerides of 150 mg/dL or greater and/or HDL equal to or less than 40 mg/dL for men and 50 mg/dL for women cannot be understated. Lipid profiles at the time of diabetes diagnosis, at initiation of statin therapy or dose change, and annually thereafter are useful to monitor disease progression.[61]

Statin therapy has documented beneficial outcomes in patients with ASCVD.[69,70] The intensity of dosing is outlined below (see **Table 3** above) [61]:

- Patients with diabetes aged 40 to 75 without ASCVD should begin moderate-intensity statin therapy in addition to lifestyle therapy.
- Patients with diabetes aged 40 to 75 years and multiple ASCVD risk factors should take high intensity statin therapy to reduce LDL cholesterol by at least 50% of baseline for an LDL target of less than 70 mg/dL.
- Patients with diabetes and ASCVD should take high-intensity statin therapy. Prescribers may add ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, such as alirocumab or evolocumab, to achieve a goal of LDL below 55 mg/dL and an LDL reduction of 50% or more.

Heart Failure

HF is a major cause of morbidity and mortality from cardiovascular disease. Recent studies indicate that people with diabetes have twice the risk of hospitalization due to HF compared to those without, after adjusting for age and sex.[71,72] Patients with established T2DM have a 33% greater risk of hospitalization for HF.[71]

HF is staged as A to D. Stage A HF indicates risk for developing HF. All patients with established diabetes are in the stage A category and at heightened risk for progression to later stages of HF. Stage B HF is asymptomatic with structural heart disease, abnormal cardiac function, or elevated cardiac biomarkers. Prescribers should monitor biomarkers, natriuretic peptide (BNP), or high sensitivity cardiac troponin yearly to detect subclinical HF in individuals with diabetes. Monitoring helps identify those in stage A or B HF who are at the highest risk of progressing to symptomat-

ic HF. Useful cutoff values for these indicators are a BNP of 50 pg/mL and a NT-proBNP of 125 pg/mL.[73]

Individuals considered to be at stages C and D have had or are experiencing symptomatic HF. Common symptoms are exertional dyspnea (shortness of breath), fatigue and edema that reflect fluid retention, congestion, and low cardiac output. Laboratory evaluations for patients with HF include natriuretic peptide, complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function, and thyroid stimulating hormone. Additionally, prescribers should order a chest x-ray and 12 lead electrocardiogram.[73]

In stage A or B HF patients with diabetes and hypertension, medical therapy includes an ACEi or ARB. Clinical trials have found that treatment with a thiazide-type diuretic or an ACEi is more effective than treatment with a calcium channel blocker in preventing progression to symptomatic HF. Patients with diabetes and diabetic kidney disease (DKD) without symptomatic HF may benefit from finerenone, a nonsteroidal mineralocorticoid receptor antagonist.[73]

Standards of Care recommendations for those with HFrEF and diabetes include an angiotensin receptor/neprilysin inhibitor (ARNI) or ACEi or ARB, beta blockers, mineralocorticoid receptor antagonist, and SGLT-2 inhibitor. In individuals with diabetes and HFrEF, including an ARNI (sacubitril/valsartan) instead of ACEi or ARBs is prudent. It is reasonable to consider treatment with spironolactone among individuals with heart failure with preserved ejection fraction (HFpEF) as well. Clinical trials have shown that treatment with an SGLT-2 inhibitor reduces HF hospitalizations.[72] Individuals with high cardiovascular risk, including those with stage B HF and those with symptomatic HF, should take an SGLT-2 inhibitor. Prescribers may consider statins based on age and background risk factors. Treatment for patients requiring additional glycemic control may include a GLP-1 agonist, metformin, or both, or insulin. Current Standards of Care do not recommend the use of dipeptidyl peptidase-4 (DPP) inhibitors or thiazolidinediones in T2DM patients with stage B, C or D HF.[73]

In addition to drug therapy, participation in cardiac rehabilitation is associated with improved patient outcomes. Cardiac rehabili-

tation involves exercise training, education, and emotional support. Key counseling points for patient with diabetes and HF are to minimize alcohol intake and avoid smoking. Weight loss improves cardiometabolic risk factors. Metabolic surgery can improve risk factors for HF in obese patients.[73]

Chronic Kidney Disease

Diabetes is the leading cause of kidney disease in the developed world.[74] The presence of CKD markedly increases cardiovascular risk and health care costs.[75] Practitioners diagnose CKD primarily by sustained elevation of urinary albumin excretion and low estimated glomerular filtration rate (eGFR).[76]

Recommendations include yearly assessment of eGFR and urinary albumin in all T2DM patients. In patients with established DKD, monitoring up to four times yearly may be necessary.[76] Consistent eGFR values less than 60 mL/min, in conjunction with a urinary albumin value over 30 mg/g creatinine defines an abnormal eGFR.[77] The definition of stage 1 and 2 CKD is high albuminuria with eGFR 60 mL/min or above. CKD stages 3-5 have progressively lower eGFR ranges.[78] At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease, CVD progression, and mortality.[75]

Current ADA Standards of Care emphasize optimization of blood pressure and blood glucose to reduce the risk of and slow CKD progression.[76] ACEi or ARBs are the preferred first-line agents for blood pressure treatment in T2DM patients with hypertension and decreased eGFR.[79,80] The healthcare team needs to continue renin-angiotensin system blockade for increases in serum creatinine of 30% or less in the absence of volume depletion. In addition, it needs to monitor serum potassium levels when patients take ACE inhibitors, ARBs, or diuretics.[76]

Recent trials show SGLT-2 inhibitor therapy reduces CKD progression and cardiovascular events in patients with CKD, T2DM, and an eGFR of 20 mL/min/1.73m^2 or greater.[76] SGLT-2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, albuminuria, and slow GFR loss through mechanisms that are independent of glycemia.[81] To minimize cardiovascular events, addition of a GLP-1 agonist may help, or a nonsteroidal mineralocorticoid receptor antagonist (nsMRA) if eGFR is 20 mL/min/1.73m^2. For patients with urinary albumin of 300 mg/g or greater, reduction of at least 30% slows

Table 4. Landmark Trials for SGLT-2 inhibitors in renal disease[47,83,84,86]		
Trial	Drug	Outcome
CREDENCE	Canagliflozin 100 mg daily	Cardiovascular and renal protection
DAPA-CKD	Dapagliflozin 10 mg daily	Reduction of eGFR decline; Reduction of ESRD; Reduction of renal mortality
EMPA-KIDNEY	Empagliflozin 10 mg daily	Reduced progression of kidney disease; Reduced cardiovascular death

Table 5. Landmark Trials for GLP-1 Receptor Agonists in T2DM and Renal Disease[57,58,87,88]

Trial	Drug	Outcome
AWARD-7	Dulaglutide 0.75 -1.5 mg once a week	Slower decline in eGFR. No change in urine albumin-creatine ratio
LEADER	Liraglutide 1.8 mg (or max dose tolerated) daily	Reduced the development and progression of diabetic kidney disease
REWIND (analysis)	Dulaglutide 1.5 mg once a week	Relative risk reduction in composite renal outcome

CKD progression.[76] Suggested daily protein intake in CKD stage 3 (non-dialysis) patients is 0.8 g/kg body weight per day. Higher levels of protein have been associated with increased albuminuria and more rapid kidney function loss.[82] If the eGFR falls below 30, a nephrologist referral is needed.[76]

Tables 4 (on the previous page) and 5 (above) list recent trials that support current ADA Standards of Care regarding treatment of diabetes in the presence of CKD.[76] In the CREDENCE trial, canagliflozin therapy reduced the development of ESRD by 32% in patients with CKD.[83] The DAPA-CKD trial studied dapagliflozin in CKD. Two thirds of the patients had a diabetes comorbidity. There was significant benefit for a decline in eGFR, ESRD or death from cardiovascular or renal causes.[84] The FIDELIO-DKD trial studied the nonsteroidal mineralocorticoid receptor antagonist, finerenone. The trial identified a significant reduction in DKD progression and cardiovascular events in people with advanced kidney disease. Participants took finerenone 10 to 20 mg daily. Evaluation after a mean of 3.4 years demonstrated a 23% reduction in the composite kidney outcome consisting of sustained decrease in eGFR of at least 57%.[85]

CONCLUSION

T2DM is indeed a growing epidemic fueled by an unhealthy diet and a sedentary lifestyle.[1] A prescription is only a partial answer to a multifactorial problem. This is why the ADA Standards of Care for diabetes incorporate a multidisciplinary approach focusing on individuals, their current disease states, and preventive measures for disease progression. Recommendations emphasize the importance of self-management, education, and support. Nutritional therapy, physical activity, and psychological support are key elements. Effective weight management is a powerful tool for managing or even reversing T2DM. Current therapy recommendations also incorporate the use of cardiovascular protective medications with demonstrated efficacy for ASCVD.[8]

Due to the high prevalence of comorbid conditions associated with T2DM, it is fortunate that the SGLT-2 inhibitors and GLP-1 receptor agonists are a resource for patients with T2DM comorbidities. These agents improve cardiovascular function and are compatible with guideline-based preventive recommendations for blood pressure, lipids, glycemia, and antiplatelet therapy.[51,89]

Diabetes treatment has entered a new era of understanding. The overwhelming data favors addressing the whole patient including lifestyle, education, weight loss options, and cardiovascular related comorbidities. The new ADA Standards of Medical Care provide clinicians with the knowledge and tools to treat the growing diabetic epidemic.

Figure 1 (next page) summarizes action points to remember.

Figure 1. Addressing Common Comorbidites in Type 2 Diabetes

Best

❶ **Be COMMUNITY CHAMPIONS** and whenever possible, attend community events and state hearings about diabetes care and accessibility to medication and supplies

❷ **Encourage discussion** with patients about exercise, nutritional requirements, and adherence

❸ **Talk about potential and actual comorbidities,** and involve caregivers if the patient could benefit from increased assistance or supervision

Better

❶ **Post information about T2DM on bulletin boards in patient waiting areas** using patient-friendly language

❷ **Ask patients about adverse events related to any therapy for diabetes** to determine is adverse events are contributing to nonadherence

❸ **Remind patients to read labels carefully** and monitor for hyperglycemia and hypoglycemia routinely

Good

❶ **Be familiar with possible cardiometabolic, vascular, and mental health concerns** in people with T2DM

❷ **Identify your patients who have T2DM** and aks about risk factors

❸ **Understand that many people who have T2DM need ongoing support and counseling** to reach their goals

© Can Stock Photo / ymgerman

REFERENCES

1. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88-98. doi: 10.1038/nrendo.2017.151

2. Fang M, Wang D, Coresh J, Selvin E. Trends in Diabetes Treatment and Control in US Adults, 1998-2019. N Eng J Med 2021; 384(23):2219-2228 doi: 10.1056/NEJMsa2032271

3. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence and estimates for 2023 and 2045. Results from the International Diabetes Atlas 9th Edition. Diabetes Res Clin Pract 2019;157:107843 doi: 10.1016/j.diabres.2019.107843

4. Provilus A, Abdallah M, Mcfarlans S. Weight gain associated with antidiabetic medication. Therapy 2011;8(2):113-120

5. Ong KL, Stafford LK, McLaughlin SA. Et al: GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2023;402(10397):203-234. https//doi:10.1016/S0140-6736(23)01301-6

6. Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report website. Accessed October 14, 2023. https://www.cdc.gov/diabetes/data/statistics-report/index.html

7. American Diabetes Association Professional Practice Committee. 2.Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022;45(Suppl 1):S17–S38. https://doi.org/10.2337/dc22-S002

8. American Diabetes Association. Standards of Medical Care in Diabetes-2022 Abridged for Primary Care Providers. *Clin Diabetes* 2022;40(1):10–38. https://doi.org/10.2337/cd22-as01

9. American Diabetes Association. 6.Glycemic Targets: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021;44(Suppl 1):S73–S84 https://doi.org/10.2337/dc21-S006

10. Cicek M, Buckley J, Pearson-Stuttard J, et al. Characterizing Multimorbidity from Type 2 Diabetes. *Endocrinol Metab Clin North Am*. 2021; 50(3): 531–558. doi: 10.1016/j.ecl.2021.05.012

11 Iglay K, Hannachi H, Howie JP. Prevalence and co-prevalence of co-morbidities among patients with type 2 diabetes mellitus. *Curr Med Res Opin.* 2016;32(7):1243–1252. doi: 10.1185/03007995.2016.1168291

12. Roger V. Epidemiology of heart failure: A Contemporary Perspective. Circ Res 2021;128(10):1421-1434 https://doi.org/10.1161/CIRCRESAHA.121.318172

13. Nowakowska M., Zghebi S.S., Ashcroft D.M. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. *BMC Med.* 2019;17(1):145. doi: 10.1186/s12916-019-1373-y

14. American Diabetes Association Professional Practice Committee. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S60-S82. doi:10.2337/dc22-S005b

15. Davies J, Fischi A, Beck J, et al. National Standards for Diabetes Self Management and Support. Diabetes Care 2022; 45(2): 484-492 doi: 10.2337/dc21-2396

16. Evert AB, Dennison M, Gardner CD, et al. Nutrition Therapy for Adults with Diabetes or Prediabetes: A Consensus Report. *Diabetes Care.* 2019;42(5):731–754. https://doi.org/10.2337/dci19-0014

17. Centers for Disease Control and Prevention (CDC). Diabetes Self-Management Education and Support (DSMES) Toolkit: Medical Nutrition Therapy. https://www.cdc.gov/diabetes/dsmes-toolkit/reimbursement/medical-nutrition-therapy.html Accessed October 14, 2023

18. Rosenfeld RM, Kelly JH, Agarwal M, et al. Dietary Interventions to Treat Type 2 Diabetes in Adults with a Goal of Remission: An Expert Consensus Statement from the American College of Lifestyle Medicine.

Am J Lifestyle Med. 2022;16(3):342-362. https//doi:10.1177/15598276221087624

19. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behavior. *Br J of Sports Med*. 2020;54(24):1451-1462. doi:10.1136/bisports-2020-102955

20. Centers for Disease Control and Prevention (CDC). Physical Activity. Measuring Physical Activity Intensity. https://www.cdc.gov/physicalactivity/basics/measuring/index.html Accessed March 1, 2024

21 Zheng X, Qi Y, Bi L, et al. Effects of Exercise on Blood Glucose and Glycemic Variability in Type 2 Diabetic Patients with Dawn Phenomenon. *Biomed Res Int.* 2020; 2020: 6408724. https//doi:10.1155/2020/6408724

22. Lao XQ, Deng HB, Liu X, et al. Increased leisure-time physical activity associated with lower onset of diabetes in 44 828 adults with impaired fasting glucose: a population-based prospective cohort study. *Br J Sports Med*. 2019 Jul;53(14):895-900. doi: 10.1136/bjsports-2017-098199

23. Liu Y, Ye W, Chen Q, et al. Resistance Exercise Intensity is Correlated with Attenuation of HbA1c and Insulin in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2019;16(1):140. doi: 10.3390/ijerph16010140.

24. Najafipour F, Mobasseri M, Yavari A, et al. Effect of regular exercise training on changes in HbA1c, BMI and VO2 max among patients with type 2 diabetes in an 8 year trial. BJM Open Diabetes Res Care 2017;5(1): e000414 doi: 10.1136/bmjdrc-2017-000414

25. Wake AD. Antidiabetic Effects of Physical Activity: How It Helps to Control Type 2 Diabetes. *Diabetes Metab Syndr Obes.* 2020;13: 2909–2923. https//doi:10.2147/DMSO.S262289

26. De Alba IGF, Gimeno-Miguel A, Poblador-Plou B, et al. Association between mental health comorbidity and health outcomes in type 2 diabetes mellitus patients. *Sci Rep. 2020;10*(1):*19583*. doi: 10.1038/s41598-020-76546-9

27. Kolb L, Association of Diabetes Care and Education Specialists. An Effective Model of Diabetes Care and Education: The ADCES7 Self-Care Behaviors.™ *Diabetes Self Manag Care*. 2021;47(1):30-53. doi: 10.1177/0145721720978154.

28.Capoccia K, Odegard PS, Letassy N. Medication Adherence with Diabetes Medication: A Systematic Review of the Literature. *Diabetes Educ*. 2016;42(1):34-71. doi: 10.1177/0145721715619038.

29. Bailey, CJ. Metformin: historical overview. *Diabetologia* 2017;60(9):1566-1576. doi: 10.1007/s00125-017-4318-z

30. Glucophage. Prescribing information. Bristol-Myers Squibb Co.; 2017. Accessed September 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020357s037s039,021202s021s023lbl.pdf

31. Sivitz WI, Phillips LS, Wexler DJ, et al. Optimization of Metformin in the GRADE Cohort: Effect on Glycemia and Body Weight. *Diabetes Care*. 2020;43(5):940-947. doi: 10.2337/dc19-1769

32. Afshin A, Forouzanfar MH, Reitsma MB, et al. GBD (Global Burdon of Disease) 2015 Obesity Collaborators; Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. 2017;377(1):13-27. doi: 10.1056/NEJMoa1614362.

33. Lean MEJ, Wilma S Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomized trial. *Lancet Diabetes Endocrinol*. 2019;7(5):344-355. doi: 10.1016/S2213-8587(19)30068-3

34. Apovian CM, Okemah J, O'Neil PM. Body Weight Considerations in the Management of Type 2 Diabetes. *Adv Ther.* 2019;36(1):44-58. doi: 10.1007/s12325-018-0824-8

35. Chakhtoura M, Haber R, Ghezzawi M, et al. Pharmacotherapy of obesity: an update on the available medications and drugs under inves-

tigation. *EClinicalMedicine.* 2023;58:101882. doi: 10.1016/j.eclinm.2023.101882

36. FDA News Release. FDA Approves New Medication for Chronic Weight Management. November 8, 2023. Accessed November 10, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-new-medication-chronic-weight-management

37. Saxenda. Prescribing information. Novo Nordisk 2023. Accessed September 15, 2023. https://www.novo-pi.com/saxenda.pdf

38. Wegovy. Prescribing information. Novo Nordisk 2021. Accessed September 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf

39. Zepbound. Prescribing information. Eli Lilly 2023. Accessed November 12, 2023. https://uspl.lilly.com/zepbound/zepbound.html#pi

40. Latif W, Lambrinos KJ, Rodriguez R. Compare and Contrast the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs) Treasure Island (FL): StatPearls Publishing;Last Update: March 27, 2023. Accessed Sept 20, 2023. https://www.ncbi.nlm.nih.gov/books/NBK572151/

41. Lee YS, Jun HS. Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. *Metabolism*. 2014;63(1):9-19. doi: 10.1016/j.metabol.2013.09.010

42. Pi-Sunyer X, Astrup A, Ken Fujioka, M.D., et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med*. 2015; 373(1):11-22. doi: 10.1056/NEJMoa1411892

43. Wilding JP, Batterham RL, Calanna Sl, et al. Once Weekly Semaglutide in in Adults with Overweight or Obesity. *N Engl J Med.* 2021;384(1):989-1002. doi: 10.1056/NEJMoa2032183

44. America Diabetes Association Professional Practice Committee. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S113–S124. https://doi.org/10.2337/dc22-S008

45. Raja H, Ebrahim S, Mamidanna R, et al. Association between preoperative glucose-lowering medication agents and the status of type 2 diabetes mellitus after bariatric surgery. *Br J Diabetes* 2023;**23**:31-34. doi: https://doi.org/10.15277/bjd.2023.409

46. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022 [published correction appears in *Diabetes Care*. 2022 Mar 07;:] [published correction appears in *Diabetes Care*. 2022 Sep 1;45(9):2178-2181]. *Diabetes Care*. 2022;45(Suppl 1):S144-S174. doi:10.2337/dc22-S010

47. Chan JC. SGLT2 Inhibitors: The Next Blockbuster Multifaceted Drug? *Medicina*. 2023;59(2):388. doi:10.3390/medicina59020388

48. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015; 373(22):2117-2128. doi: 10.1056/NEJMoa1504720

49. Neal, B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017; 377:644-657. doi:10.1056/NEJMoa1611925

50. Wiviott, SD, Raz I, Bonaca MP. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019; 380(4):347-357. doi: 10.1056/NEJMoa1812389

51. Fonseca-Correa JI, Correa-Rotter, R. Sodium-Glucose Cotransporter 2 inhibitors Mechanisms of Action: A Review. *Front Med* (Lausanne). 2021:8:777861. doi: 10.3389/fmed.2021.777861

52. Chesterman T, Thynne TR. Harms and benefits of sodium-glucose co-transporter 2 inhibitors. *Aust Prescr.* 2020:43:168-171. doi: 10.18773/austprescr.2020.049

53. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: Novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014; 155(4):1280–1290. doi: 10.1210/en.2013-1934

54. Sun F, Wu S, Guo S, et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Res. Clin Pract.* 2015;110(1):26-37. doi: 10.1016/j.diabres.2015.07.015

55. Gutzwiller JP, Tschopp S, Bock A., Drewe J, Beglinger C, Sieber CC. Glucagon-like peptide-1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab*. 2004;89(6):3055–3061. doi: 10.1210/jc.2003-031403

56. MA X, Liu Z, Ilyas I, et al. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. *Int J Biol Sci.* 2021;17(8): 2050–2068. doi: 10.7150/ijbs.59965

57. Nachawi N, Rao PR, Makin V. The role of GLP-1 receptor agonists in managing type 2 diabetes. *Clevel Clin J Med*. 2022;89(8) 457-464. doi: https://doi.org/10.3949/ccjm.89a.21110

58. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130. doi: 10.1016/S0140-6736(19)31149-3

59. Maroso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016; 375(19):1834-1844. doi: 10.1056/NEJMoa1607141

60. Maroso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016; 375(4):311-22. doi: 10.1056/NEJMoa1603827

61. ElSayed NA; Aleppo G; Aroda VR; on behalf of the American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. *Diabetes Care.* 2023;46(Suppl 1):S158–S190. https://doi.org/10.2337/dc23-S010

62. Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Can J Cardiol*. 2018;34(5):575-584. doi: 10.1016/j.cjca.2017.12.005American Diabetes

63. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 387(10022):957-967. doi: 10.1016/S0140-6736(15)01225-8

64. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet* 2016; 387(10017):435-443. doi: 10.1016/S0140-6736(15)00805-3

65. De Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40:1273–1284. https://doi.org/10.2337/dci17-0026

66. Iliescu R, Lohmeier TE, Tudorancea I, Laffin L, Bakris GL. Renal denervation for the treatment of resistant hypertension: review and clinical perspective. *Am J Physiol Renal Physiol.* 2015;309(7): F583–F594. doi: 10.1152/ajprenal.00246.2015

67. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ*. 2016;11:352: i438. doi: 10.1136/bmj.i438

68. Murphy SP, Ibrahim NE, Januzzi JL. Heart failure with reduced ejection fraction: a review. *JAMA* 2020;324(5):488–504. doi: 10.1001/jama.2020.10262

69. Mihaylova B, Emberson J, Blackwell L, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials. *Lancet* 2012; 380(9841):581–590. doi: 10.1016/S0140-6736(12)60367-5

70. Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet.* 2005;366(9493):1267–1278. doi: 10.1016/S0140-6736(05)67394-1

71. Cavender MA, Steg PG, Smith SC, Eagle K, Ohman EM, Goto S, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardio-

vascular events, and death. *Circulation*. 2015;132(10):923–31. doi: 10.1161/CIRCULATIONAHA.114.014796

72. McAllister DA, Read SH, Kerssens J, et al. Incidence of Hospitalization for Heart Failure and Case-Fatality Among 3.25 Million People With and Without Diabetes Mellitus. *Circulation*. 2018;138(24):2774–2786. https://doi.org/10.1161/CIRCULATIONAHA.118.034986

73. Pop-Busui R, Januzzi JL, Bruemmer D, et al. Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association. *Diabetes Care*. 2022;45(7):1670–1690. https://doi.org/10.2337/dci22-0014

74. De Boer IH, MD, MS; Rue TC, MS; Hall YN, MD; et al. Temporal Trends in the Prevalence of Diabetic Kidney Disease in the United States. *JAMA.* 2011;305(24):2532-2539. doi:10.1001/jama.2011.861

75. Fox CS, Matsushita K, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012; 380(9854):1662–1673. doi: 10.1016/S0140-6736(12)61350-6

76. ElSayed NH; Aleppo G; Aroda VR; on behalf of the American Diabetes Association. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S191–S202. https://doi.org/10.2337/dc23-S011

77. National Kidney Foundation. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013; 3(1):1–148. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

78. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139(2):137–147. doi: 10.7326/0003-4819-139-2-200307150-00013

79. HOPE Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE sub study. *Lancet* 2000;355(9200):253-9

80. Shaikh A, A Practical Approach to Hypertension Management in Diabetes. *Diabetes Ther*. 2017;8(5):981–989. doi: 10.1007/s13300-017-0310-3

81. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018; 72(15):1845–1855. doi: 10.1016/j.jacc.2018.06.040

82. Klahr S, Levey AS, Beck GJ, et al.; Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med*. 1994; 330(13):877–884. doi: 10.1056/NEJM199403313301301

83. Perkovic V, Jardine MJ, Neal B, et al., for the CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019; 380:2295-2306. doi: 10.1056/NEJMoa1811744

84. Herrspink, HJ, Stefansson, BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2020;383(15):1436-1446. doi: 10.1056/NEJMoa2024816

85. Bakris GL, Agarwal R, Anker SD, et al, for the FIDELIO-DKD Investigators. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med*. 2020; 383:2219-2229. doi: 10.1056/NEJMoa2025845

86. EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388:117-127. doi: 10.1056/NEJMoa2204233

87. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6(8):605-617. doi: 10.1016/S2213-8587(18)30104-9

88. Mann JF, Orsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med.* 2017;377:839-848. doi: 10.1056/NEJMoa1616011

89. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76:1117-1145. doi: 10.1016/j.jacc.2020.05.037