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DCRM 2.0: Multispecialty practice recommendations for the management of diabetes, cardiorenal, and metabolic diseases

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A B S T R A C T

The spectrum of cardiorenal and metabolic diseases comprises many disorders, including obesity, type 2 diabetes (T2D), chronic kidney disease (CKD), atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), dyslipidemias, hypertension, and associated comorbidities such as pulmonary diseases and metabolism dysfunction–associated steatotic liver disease and metabolism dysfunction–associated steatohepatitis (MASLD and MASH, respectively, formerly known as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis [NAFLD and NASH]). Because cardiorenal and metabolic diseases share pathophysiologic pathways, two or more are often present in the same individual. Findings from recent outcome trials have demonstrated benefits of various treatments across a range of conditions, suggesting a need for practice recommendations that will guide clinicians to better manage complex conditions involving diabetes, cardiorenal, and/or metabolic (DCRM) diseases. To meet this need, we formed an international volunteer task force comprising leading cardiologists, nephrologists, endocrinologists, and primary care physicians to develop the DCRM 2.0 Practice Recommendations, an updated and expanded revision of a previously published multispecialty consensus on the comprehensive management of persons living with DCRM. The recommendations are presented as 22 separate graphics covering the essentials of management to improve general health, control cardiorenal risk factors, and manage cardiorenal and metabolic comorbidities, leading to improved patient outcomes.

1. Introduction

Worldwide, the prevalence of obesity has risen steadily, such that the proportion of the global population with excess body weight (43 % with overweight or obesity) now exceeds the underweight proportion [1]. In parallel, global rates of diabetes, cardiovascular disease (CVD), chronic kidney disease (CKD), and associated comorbidities have also increased, leading to significant increases in morbidity, mortality, and healthcare costs [2–7].

Along with obesity, hypertension, hyperglycemia, hyperlipidemia, and inflammation are implicated in the development of a range of cardiorenal and metabolic diseases such as prediabetes, type 2 diabetes (T2D), CKD, atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as nonalcoholic fatty liver disease [NAFLD]) and metabolic dysfunction–associated steatohepatitis (MASH, formerly known as nonalcoholic steatohepatitis [NASH]). These comorbidities share pathophysiologic pathways and thus frequently occur together, and as risk factors accrue and progress in an individual, health outcomes become worse [5–7].

Traditionally, practice recommendations from individual medical societies are designed to guide the management of conditions specific to those disciplines. However, the frequent co-occurrence and pathophysiologic overlap of cardiorenal and metabolic diseases calls for a holistic approach to prevention and treatment that transcends traditional approaches that segment care according to medical specialty. In contrast, practice recommendations that are not constrained by a single discipline may help clinicians better manage persons with complex conditions involving diabetes, cardiorenal, and/or metabolic (DCRM) diseases. As most if not all medical societies are restricted by a single specialty, to meet this need, a volunteer task force comprising U.S.-based experts in cardiology, nephrology, endocrinology, and primary care medicine developed the DCRM Multispecialty Practice Recommendations, published in 2022 [8]. Here, we present the DCRM Practice Recommendations 2.0, an updated and expanded revision developed by a multispecialty, international consensus group of DCRM experts from North America and Europe. The present document aims to provide recommendations based on evidence and expert consensus that is clinically relevant and feasible to implement, with the aim of improving the health of individuals with cardiorenal and metabolic risk factors and diseases. The recommendations consist of 22 separate slides organized into 3 sections (slide set downloadable at https://www.dcrmi.com/dcrmi-2-0-2024):

Section I. General health

1. Lifestyle therapy
2. Patient education
3. Technology and digital care
4. Clinical tests
5. Cognitive function
6. Vaccinations

Section II. Cardiorenal risk

7. Obesity: a heterogeneous chronic disease
8. Prediabetes
9. Lipid disorders
10. Hypertension
11. Inflammation
12. Antihyperglycemic therapy in type 2 diabetes
13. Hypoglycemia
14. Antiplatelet and anticoagulation therapy

Section III. Cardiorenal and metabolic comorbidities

15. Pulmonary disease
16. MASLD/MASH (*NAFLD/NASH*) prevention and management
17. ASCVD prevention and management
18. Heart failure prevention and management
19. CKD prevention and management
20. Comorbid heart failure and CKD

Section IV. Implications for management

21. Summary of medications

2. DCRM multispecialty practice recommendations

2.1. Section I. General health

2.1.1. Lifestyle therapy

Optimizing lifestyle can improve the quality and quantity of life, even in persons with multiple risk factors and comorbidities.

Good mental health is the cornerstone of a healthy lifestyle. Mood disturbances, substance abuse, prior personal traumas, and psychosocial limitations should be addressed, and the person should be referred to specialized care as necessary. Encourage positive practices such as mindfulness and engagement with social activities.

Nutrition is of paramount importance for health. A healthy diet comprises a balanced intake of nutrients; consumption of fruits, vegetables, whole grains, lean poultry, fish and legumes should be encouraged, while processed foods and those with excess saturated fat, salt, and sugar should be discouraged [9,10]. Many healthy diet plans are available, but proper nutrition management must be personalized. It is important to emphasize that healthy eating is a life-long endeavor, and short-term diets will not be a solution. Caloric restriction may lead to short-term weight reduction but does not target the mechanisms of obesity (see Section 2.2.1. Obesity) [11]. Even in persons taking anti-obesity medication, appropriate nutrition is important to optimize health outcomes. In persons with diabetes, short-term continuous glucose monitoring (CGM) may help understand the impact of food and exercise on blood glucose [12,13].

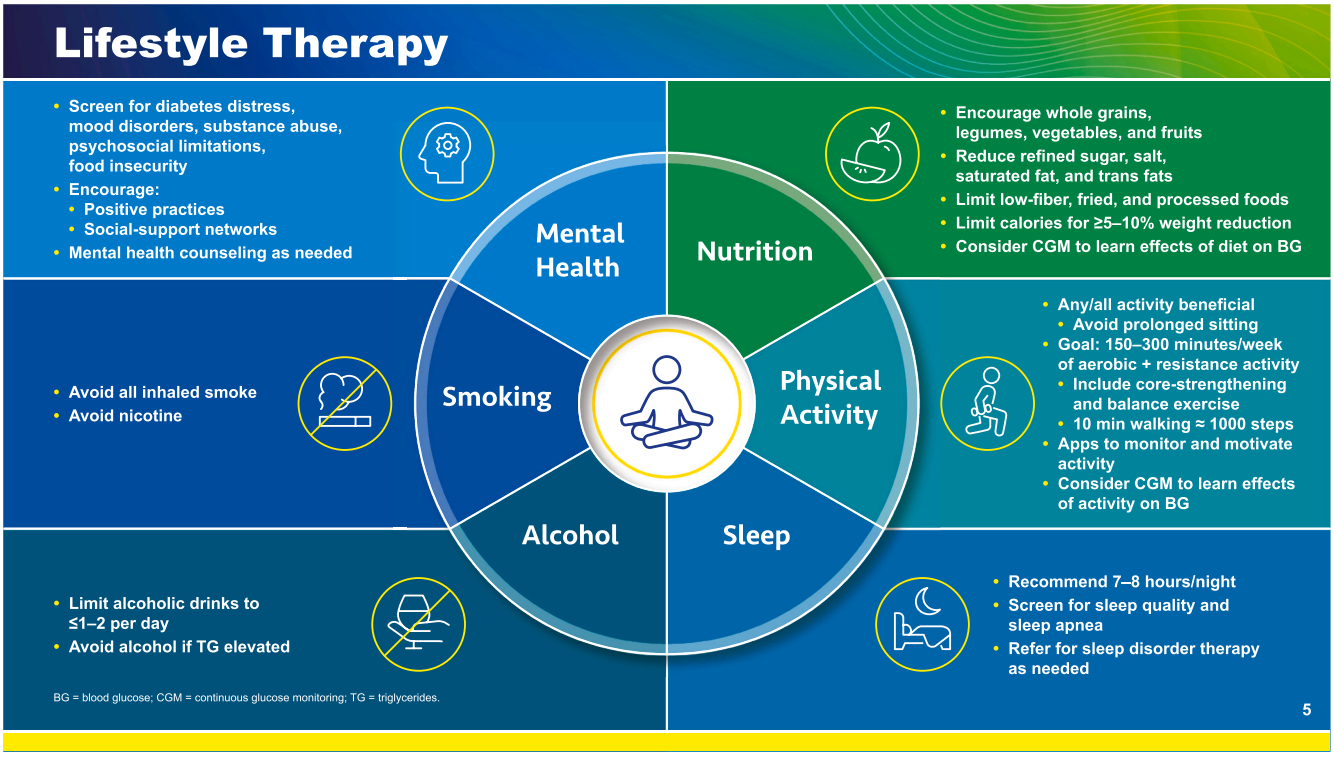
For most persons, at least 150 min per week of moderate-intensity aerobic plus resistance activity is recommended. However, any type or amount of physical activity is useful, especially that which can be done as a part of usual daily activities (e.g., an extra 5–10 min of walking per day). Encourage the use of apps and devices to motivate and monitor activity.

Sleep deprivation worsens insulin resistance, hypertension, hyperglycemia, and dyslipidemia and increases inflammatory cytokines. Adequate sleep (usually 7–9 h) on a nightly basis may decrease these risks [14]. Appropriate preventive measures can help improve the quality of life and comorbidities in persons with sleep disturbances [15]. Pharmacotherapy is generally not effective for obstructive sleep apnea and can cause serious adverse effects.

Smoking cessation is the single most important component of lifestyle therapy, and a clinician's encouragement is cited as a frequent motivator to quit smoking [16]. Excess alcohol intake can contribute to weight gain, hypertension, cardiomyopathy, and atrial fibrillation, as well as peripheral neuropathy, fatty liver, and dementia—all issues in persons with cardiorenal and metabolic disease. Individuals should consume no more than 1–2 daily drinks per day (women, ≤1 drink per day; men, ≤2 drinks per day of 12 oz [350 mL] of beer, 5 oz [150 mL] of wine, or 1.5 oz [50 mL] of distilled spirits) [17].

2.1.2. Patient education

The purpose of patient self-management education is to empower individuals to manage their chronic medical conditions by increasing their knowledge and understanding. Self-management education improves psychological, clinical, and lifestyle outcomes [18]. All individuals with cardiorenal or metabolic diseases should receive



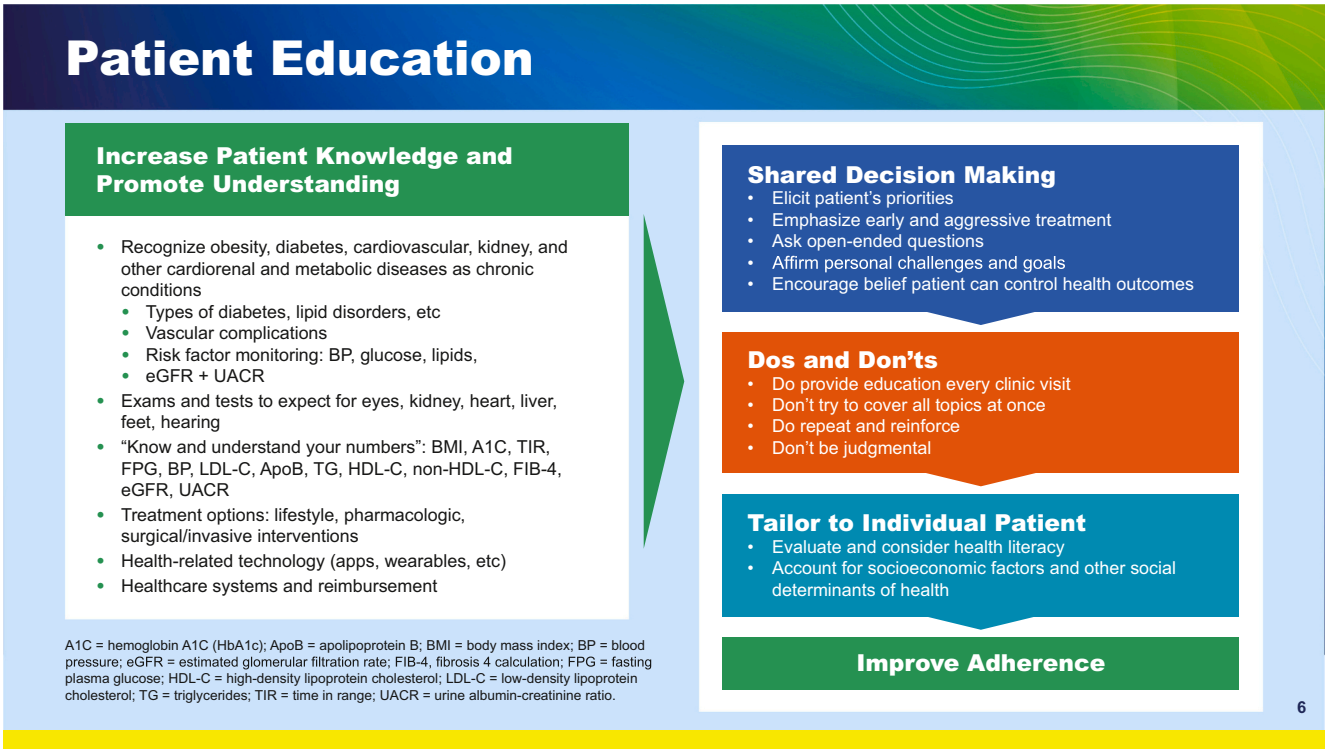


Table 1
"Know your numbers" suggested plain-language communication points to patients.

Parameter	What it tells us	What's normal	What's risky	The direction we want it to go[a]
General health (all patients)				
BMI	Whether your weight puts you at risk for other diseases. BMI is your weight (in kilograms) divided by your height (in meters)	18 to 25	30 or more	Lower
Waist circumference	A way of measuring how much fat you have around your stomach area; too much puts you at risk for other diseases	Women ≤88 cm (35 in); men ≤102 cm (40 in)	More than these	Lower
BP	The amount of pressure your blood puts against the walls of your blood vessels (like the water in a hose)	Less than 120 over 80	More than 140 over 90	Lower
HDL-C	How much "good" cholesterol you have, which helps keep the blood flowing in your body	More than 50	Less than 40	Higher
Triglycerides	How much fat is in your blood	Less than 100	More than 135	Lower
LDL-C	How much "bad" cholesterol you have; too much can clog up your blood vessels	Less than 100	More than 55, 70, or 100[b]	Lower
Non-HDL-C	Total cholesterol minus HDL-C ("good" cholesterol)	Less than 130	More than 85, 100, or 130[b]	Lower
Diabetes				
A1C	How well your diabetes is controlled overall	Less than 5.7	More than 6.5 or 7 or 7.5[c]	Lower
FPG	How much sugar is in your blood when you haven't eaten for 8 h, such as in the morning before breakfast	More than 70 and less than 100	Less than 70 and more than 140	Stay between 70 and 140
TIR	The percentage of time each day your blood sugar is well controlled	100 %	Less than 70 %	Longer (more time)
Diabetes and CKD				
eGFR	How well your kidneys are working	More than 90	Less than 60	Higher (or at least stay the same)
UACR	How much protein is in your urine, which tells us if your kidneys are damaged	Less than 30	More than 300	Lower (or at least stay the same)

Abbreviations: A1C, hemoglobin A1C; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TIR, time in range; UACR, urine albumin-creatinine ratio.

[a] Assumes patient's levels are abnormal.

[b] Depends on the patient's individual comorbidities; see Section 2.2.3. Lipid disorders.

[c] Depends on patient's individual characteristics; see Section 2.2.6. Antihyperglycemic therapy in type 2 diabetes.

education about their condition from reliable sources to improve adherence to therapeutic interventions—both lifestyle *and* medications—and to reduce associated risks. Persons with diabetes should be referred to diabetes care and education specialists (CDCES), if available, for disease-specific training.

Clinicians should explain—in plain language—all the different examinations and tests individuals with DCRM might undergo. A goal for all individuals is that they "know their numbers" for risk factors and goals and have a basic understanding of what each means for their health (Table 1). The components of a healthy lifestyle should be explained and applicable technology options discussed. Each individual should fully understand their medication regimen, including what each medication does, when they should take it, what side effects may occur, and what to do if a side effect is serious or extremely bothersome. Medication reconciliation helps drive discussions about treatment adherence—a frequent problem in clinical practice. Offering support and information on navigating the healthcare system can help address healthcare disparities and improve health outcomes. Telehealth may allow clinicians to provide education to multiple persons in a group setting.

All management decisions should be made using shared decision making based on the individual's personal priorities as well as medical needs. This strategy is highly effective at improving health metrics [19–21]. Clinicians should provide ongoing education and reinforcement at every visit but should not try to cover all topics at once. Risk factor control and medication adherence should be assessed at each encounter, but clinicians should avoid judgmental language.

2.1.3. *Technology and digital care*

Persons with cardiorenal and metabolic diseases should be encouraged to use validated apps (for smart phones, tablets, and/or computers) to help track components of lifestyle therapy, which have been shown to improve activity levels, dietary quality, sleep, weight, and blood pressure (BP) control [22,23]. Arrhythmia detector apps may be helpful for persons at risk of atrial fibrillation, and wearable fitness trackers may increase the frequency and duration of physical activity [24,25].

Ambulatory and home BP monitoring can help distinguish between normotension and masked hypertension and between white coat and sustained hypertension. Individuals with suspected hypertension should be encouraged to take blood pressure at home and bring those results to their medical appointments. Out of office BP readings more accurately predict morbidity and mortality than in-office readings [26,27].

In addition to technologies used to track general health measures, various devices for glucose monitoring and insulin delivery can help improve glycemic control in persons with diabetes. Recent diabetes management guidelines have thoroughly reviewed the evidence supporting these devices [28,29].

CGM is increasingly becoming a mainstay of diabetes management, allowing patients and clinicians to track time in range and hyper- and hypoglycemic excursions to more closely tailor glucose-lowering drug regimens. CGM is also an important tool for individuals at risk from severe hypoglycemia due to nondiabetic causes (e.g., insulinoma, nesidioblastosis, postbariatric hypoglycemia, etc.). These devices may be owned and used continuously by patients (*personal* CGM) or owned by the clinical practice and used intermittently to identify glycemic patterns that are undetectable with A1C monitoring (*professional* or *diagnostic* CGM). Models that include hyper- and hypoglycemic alarms and remote monitoring provide important safeguards for patients. CGM data represent important motivational and educational tools to help patients understand the impact of lifestyle choices on their glucose. In some regions, CGM sensors may be available without a prescription.

For persons without access to CGM who take insulin, sulfonylureas, or glinides, structured self-monitoring of blood glucose (SMBG) with traditional fingerstick blood glucose monitors should be used. *Structured* refers to SMBG regimens comprising a predefined testing schedule and interpretation of the data with the patient to inform clinical decision making [30].

Automated insulin delivery (AID) devices, with appropriate training, may be preferred for many patients treated with intensive insulin regimens (basal insulin plus prandial insulin for ≥2 meals per day)—primarily patients with type 1 diabetes (T1D) and some with T2D—because

Technology and Digital Care

	Technology	Recommendation
General	Validated apps, wearables	Track weight, calorie intake, nutritional quality, physical activity, BP, heart rate, sleep quality, etc
	Arrhythmia detector app	Persons at risk of atrial fibrillation
	Fitness tracker	All persons wishing to monitor cardiometabolic fitness
	Ambulatory BP monitor	Patients with known or suspected hypertension
Diabetes	CGM	All persons on insulin[a] Consider for persons using SUs Persons with hypoglycemia regardless of etiology[a] Consider: • Episodic CGM as an audit of glycemic patterns in any person with diabetes taking any antihyperglycemic medication • Episodic or ongoing CGM for persons desiring information on impact of diet and physical activity
	Structured[b] SMBG	All persons using insulin or oral agents who lack access to CGM
	AID	All patients on intensive insulin regimens
	Smart pens	All persons on intensive insulin regimens based on personal preference or lack of access to AID

[a] Ongoing CGM preferred over episodic CGM.

[b] SMBG that is recorded and used for clinical decision making.

AID = automated insulin delivery; BP = blood pressure; CGM = continuous glucose monitor; SMBG = self-monitored blood glucose; SU = sulfonylurea.

7

Clinical Tests

	Assessments for all persons: medical history, symptoms, physical examination, BP, lipids, glycemia			
	Test	**Condition**	**Purpose / Population**	**Frequency**
Imaging	ECG	AF, ACS	Diagnostic / most adults	Annually
	Echocardiogram	AF, HF	Diagnostic / symptomatic or suspected AF or HF	If needed
	CAC score	ASCVD	CAC risk stratification / high risk for ASCVD or CAD • 0 = low risk, even in diabetes • 1–99 = moderate to high risk depending on percentile for age and gender • ≥100 or 75th percentile for age and gender = very high risk • >300 = secondary prevention equivalent	Every 5 years
	CTA	ASCVD	Diagnostic / angina or very high risk for ASCVD or very high CAC	If needed
	Treadmill and/or pharmacologic stress test, with or without imaging	ASCVD	Diagnostic / symptomatic CVD or very high CAC	If needed
	Carotid plaque by US (if symptoms) / PWV	Atherosclerosis	Early assessment / younger high-risk persons	Once; repeat if symptoms
	Retinal imaging with fundus camera	Diabetes	Diagnostic and assessment / diabetes	Every 1–2 years
	ABI	PAD	Diagnostic / claudication or suspected claudication	If needed
Biomarkers	Lp(a)	ASCVD	Diagnostic / all adults	Once, at initial screening
	ApoB, non-HDL-C, or LDL particle number	ASCVD	Assessment of atherosclerotic risk / high ASCVD risk	Annually
	Albuminuria	ASCVD, CKD, Diabetes, Obesity	Diagnostic and ongoing assessment / at-risk or existing CKD, diabetes, or HF • UACR ≥30 mg/g / ≥3 mg/mmol = high CVD risk • UACR ≥300 mg/g / ≥30 mg/mmol = CKD progression + very high CVD and HF risk	Annually
	eGFR	CKD	Diagnostic / all adults	Annually
	Natriuretic peptide (NTproBNP or BNP)	HF	Diagnostic and ongoing assessment / at-risk or existing HF	If needed
	hs-Troponin	HF	Diagnostic and ongoing assessment / myocardial injury or existing HF	If needed
Other	Foot exam with 10-g microfilament	Diabetes	Diagnostic and ongoing assessment / diabetes, at-risk or with neuropathy	Every visit

ABI = ankle brachial index; ACS = acute coronary syndrome; AF = atrial fibrillation; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BNP = B-type natriuretic peptide; BP = blood pressure; CAC = coronary artery calcium; CAD = coronary artery disease; CKD = chronic kidney disease; CTA = computed tomography angiography; CVD = cardiovascular disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; hs = high sensitivity; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); NTproBNP = N-terminal pro-B-type natriuretic peptide; PAD = peripheral artery disease; PWV = pulse wave velocity; UACR = urine albumin-creatinine ratio; US = ultrasound. 8

of documented improvements in glycemic control and diabetes outcomes relative to those using multiple daily injections (MDI) [28,29].

"Smart" insulin pens, which capture data on insulin dosing and incorporate this information with glucose excursion data from glucose monitors and connect wirelessly to diabetes management software, are suitable for individuals taking insulin injections.

2.1.4. *Clinical tests*

The guidance lists the most commonly performed clinical assessments beyond the standard tests for BP, lipids, and glucose; others may be necessary for the individual patient. Clinicians should explain the purpose of all clinical examinations to patients (see Section 2.1.2. Patient education).

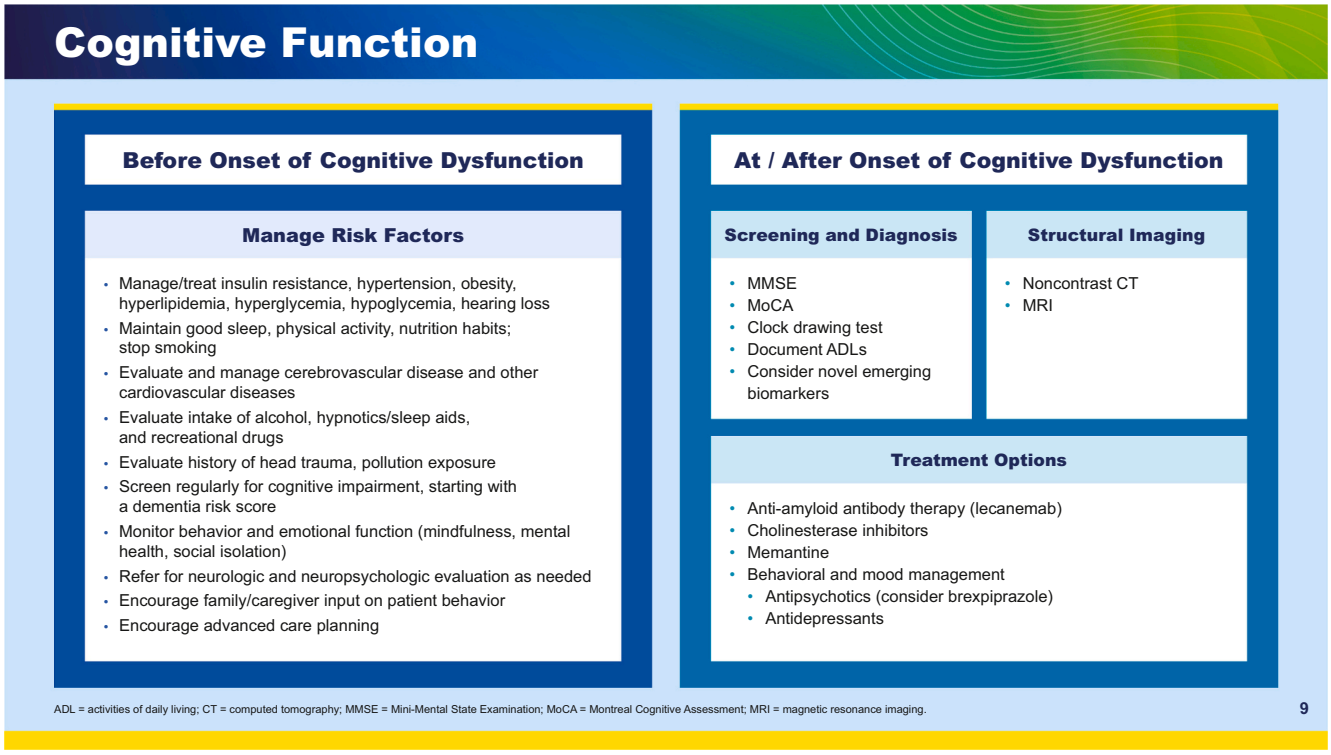
Electrocardiograms (ECG) should be performed annually on most patients to screen for atrial fibrillation (AF), conduction abnormalities, and structural abnormalities. When acute chest pain symptoms are present, ECGs are performed to evaluate for acute coronary syndrome (ACS). Echocardiography may be used in persons with symptomatic or suspected AF or HF or in those with risk factors for these conditions. The coronary artery calcium (CAC) score uses computed tomography (CT) to stratify ASCVD risk based on the amount of calcium in arterial walls, which is a surrogate marker for the total atherosclerotic plaque burden. The CAC score may be useful tool in low to intermediate risk patients and may be repeated every ~5 years in persons with very low or normal CAC [31]. Computed tomography angiography (CTA) can help diagnose coronary artery disease (CAD), or a treadmill test, with or without imaging, or pharmacological stress testing with imaging may also be used to help diagnose CAD [32,33]. Additional imaging tests used primarily for diagnosis include ultrasound of carotid plaque and the ankle brachial index (ABI) [34,35]. The Task Force does not recommend measurement of carotid intima media thickness (IMT) in clinical practice or use of the stress testing, 6-min walking test, or ABI for routine screening.

Albuminuria and estimated glomerular filtration rate (eGFR) are used to diagnose and monitor CKD in persons with or at risk of CKD as well as those with diabetes (see Section 2.3.5. CKD). Experts no longer recommend classifying urinary albumin levels as *microalbuminuria* and *macroalbuminuria*. Any level of persistent albuminuria (i.e., urine albumin-creatinine ratio [UACR] ≥30 mg/g [≥3 mg/mmol] for >3 months) suggests at least a moderate risk of CKD progression as well as an increased risk of ASCVD. Individuals with UACR ≥300 mg/g (≥30 mg/mmol) are at high risk of CKD progression, as are persons with eGFR ≤44 mL/min/1.73 m^2 [36,37].

Lipid parameters are important in predicting cardiovascular risk (see Section 2.2.3. Lipid disorders). Routine lipid panel measurement provides low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non-HDL-C). Defined as total cholesterol minus HDL-C, non-HDL-C is an estimate of atherogenic lipoproteins that is important in persons with hypertriglyceridemia. Other important measures are apolipoprotein B (apoB; a measurement of all circulating atherogenic particles) and LDL particle number. Elevated lipoprotein (a) [Lp(a)] suggests enhanced ASCVD risk in persons with a family history of premature ASCVD or personal history of ASCVD not explained by major risk factors.

In persons with or at risk of HF (see Section 2.3.4. Heart failure), both natriuretic peptides (N-terminal [NT]-pro-B-type natriuretic peptide [NT-proBNP] or BNP) and high-sensitivity troponin T or I (hs-TnT or hs-TnI) are useful biomarkers of the presence and severity of HF. Natriuretic peptides may be particularly useful in the diagnosis of HF when the cause of dyspnea, edema, or fatigue is unclear. Elevated troponin indicates myocyte injury or necrosis in persons with myocardial injury or diagnosed HF [38,39].

In individuals with diabetes and prediabetes, annual screening for diabetic retinopathy should be done by an ophthalmologist or by retinal imaging. Retinal images should be interpreted by trained eye care providers and, if positive, should be referred to an ophthalmologist immediately [40]. Albuminuria and eGFR should also be checked annually to monitor for CKD onset or progression. Individuals with diabetes and evidence of sensory loss or a history of ulceration or amputation should have their bare feet examined at every office visit. In other persons with diabetes and prediabetes, a comprehensive foot examination should be performed annually [40]. Assessment of sudomotor dysfunction can aid in early detection of peripheral neuropathy [41].



2.1.5. *Cognitive function*

Cognitive dysfunction refers to various forms of major neurocognitive disorder (also known as dementia), characterized by a decrease from previous level of performance in one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) [42]. All forms of cognitive dysfunction including the most common forms (Alzheimer's disease [AD] and vascular dementia) are strongly associated with diabetes and obesity and may be considered complications of diabetes and/or cardiovascular disease.

Age is the primary risk factor for cognitive dysfunction [43]. All vascular risk factors and lifestyle factors such as physical inactivity, dietary fat intake, alcohol intake, and smoking at midlife are associated with the risk of dementia and AD, especially among apoE-epsilon4 carriers, who may be more vulnerable to environmental factors. Thus, lifestyle interventions may greatly modify dementia risk, particularly among genetically susceptible individuals [44]. Vascular dementia may have a sudden onset and progress in a stepwise fashion, whereas AD usually has a more gradual onset and progression; both frequently co-occur in the same individual [45]. Diabetes more than doubles the risk of AD and vascular dementia, and atrial fibrillation and HF more than double the risk of dementia [46–48]. Recurrent, severe hypoglycemia and hearing loss also increase cognitive impairment risk [49,50]. Insulin resistance has been associated with cognitive decline [51]. To date, intensive glycemic control has not shown an impact on cognition, but post-hoc analyses of controlled trials have demonstrated some benefit of improved BP control on cognition [52].

Screening (Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], Clock Drawing Test) and diagnosis of cognitive dysfunction can be done in the primary care office and should be part of the regular screening for progression, with referral as needed. Personal history with caregiver or family input is critical and structural imaging is useful to identify vascular dementia–related brain injuries [45]. Plasma biomarkers (e.g., total tau, phosphorylated tau 181; amyloid-beta-42 [$A\beta_{42}$], etc.) are now available that predict magnetic resonance imaging (MRI) findings of AD, although their value in the setting of metabolic disorders is yet to be established [53].

The pathophysiology of AD is not well understood, and pharmacological agents have not yet shown conclusive benefits. Lecanemab, an anti-amyloid antibody therapy, reduces beta-amyloid plaque and slowed declines in cognition and function at 18 months, but treatment led to amyloid-related imaging abnormalities with edema or effusions in 13 % of trial participants [54]. Other agents approved for AD (cholinesterase inhibitors and memantine) do not address the underlying etiology but rather may stall symptomatic decline. Brexpiprazole has been approved for the treatment of agitation in persons with AD [55]. Currently, no agents are approved to treat cognitive deficits caused by vascular dementia. Multidomain lifestyle and vascular risk factor management have been shown to prevent cognitive decline in high-risk individuals and persons with diabetes [56,57].

2.1.6. *Vaccinations*

The Centers for Disease Control and Prevention (CDC) has designated individuals with diabetes, cardiovascular, kidney, and other chronic metabolic diseases as priority groups for vaccination because they are at high risk of complications from infections—especially from the influenza virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus 2019 (COVID-19) [58]. These respiratory infections may worsen or even cause long-term cardiovascular and renal complications, and vaccination can reduce these outcomes [59–62].

The vaccinations listed in the slide were compiled based on CDC recommendations and apply to all adults with diabetes, CVD, or CKD [58]. If the vaccination status is unknown, it is advisable to administer the vaccine in question, because the benefits of protection far outweigh the negligible risks of an extra dose.

Vaccinations

Must Have	
Influenza	All persons
COVID-19	All persons
Hepatitis B	All persons
HPV	Persons aged ≤26 years
PCV20	Persons aged ≥65 years whose most recent pneumococcal pneumonia vaccine was >5 years previously
Tdap	All persons; booster every 10 years
Zoster (shingles)	Adults aged ≥50 years

May Need Based on Risk Factors
Hepatitis A
Hib
HPV (persons aged >26 years)
MMR
MenACWY
MenB
RSV (persons aged ≥60 years; pregnant persons at 32–36 weeks gestation)
Varicella

COVID-19 = coronavirus 2019; Hib = Hemophilus influenzae type b; HPV = human papilloma virus; MenACWY = meningococcal strains A, C, W, Y; MenB = meningococcal strain B; MMR = measles, mumps, rubella; PCV20 = 20-valent pneumococcal conjugate vaccine; RSV, respiratory syncytial virus; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

10

Obesity: A Heterogeneous Chronic Disease

Clinical Assessment

General medical evaluation:
- BMI, BP, pulse, CMP[a], eGFR, plasma lipids, A1C

Obesity-focused assessment:
- Obesity-related disease risk factors and diseases
- Physical function
- Quality of life
- Mental health and eating disorders
- Lifestyle: diet, eating behaviors, daily physical activities, sleep, work factors, family/social support
- Weight history: age of obesity onset, max weight, weight loss/gain history and contributors, family history of obesity
- Barriers to lifestyle change and weight loss therapy
- Personal weight/health goals and reasons for goals

Develop Treatment Goals

Overall goals:
- Improve health, obesity-related diseases, physical function, and quality of life and decrease risk of developing obesity-related complications

Specific treatment goals based on clinical assessment and shared decision making with the patient:
- Define progressive clinical targets and general timelines for achieving each goal
- Define estimated weight reduction needed to achieve targets

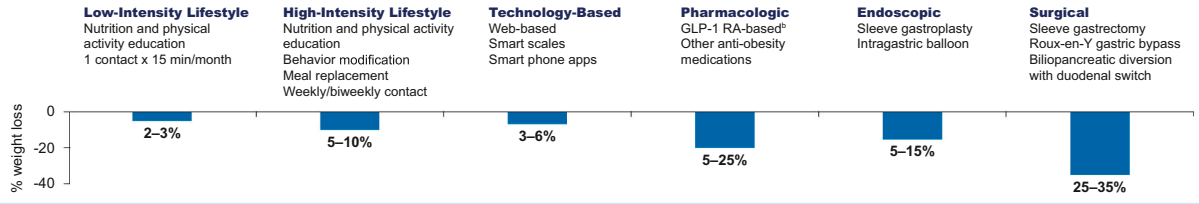
Determine Treatment

Choose initial therapy based on:
- Treatment goals
- Individualized lifestyle changes
- Access and cost of therapy (availability, insurance coverage, affordability)
- Potential adverse effects
- Medical contraindications
- Patient preference

Monitor Response to Therapy

- Monitor weight reduction, clinical response, and acceptability of/adherence to therapy
- Adjust goals and treatment as needed

Mean 1-Year Percent Weight Loss of Specific Therapies



[a] Glucose, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, calcium, ALP, ALT, AST, bilirubin, albumin, total protein.
[b] GIP/GLP-1 RA or GLP-1 RA; 1.5-year weight loss.

A1C = hemoglobin A1C (HbA1c); ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CMP = comprehensive metabolic panel; eGFR = estimated glomerular filtration rate; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 RA = glucagon-like peptide 1 receptor agonist.

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2.2. Section II. Cardiorenal risk

2.2.1. Obesity: A heterogeneous chronic disease

Obesity is a heterogeneous chronic disease with adverse effects on all organ system in the body. Because intentional weight reduction can prevent and treat obesity complications and related diseases, obesity treatment should begin early after diagnosis. The clinical benefits of obesity treatment often correlate directly with percent weight lost [63]. However, the percent weight reduction with any specific therapy and the therapeutic effect of a given amount of weight reduction vary among individuals.

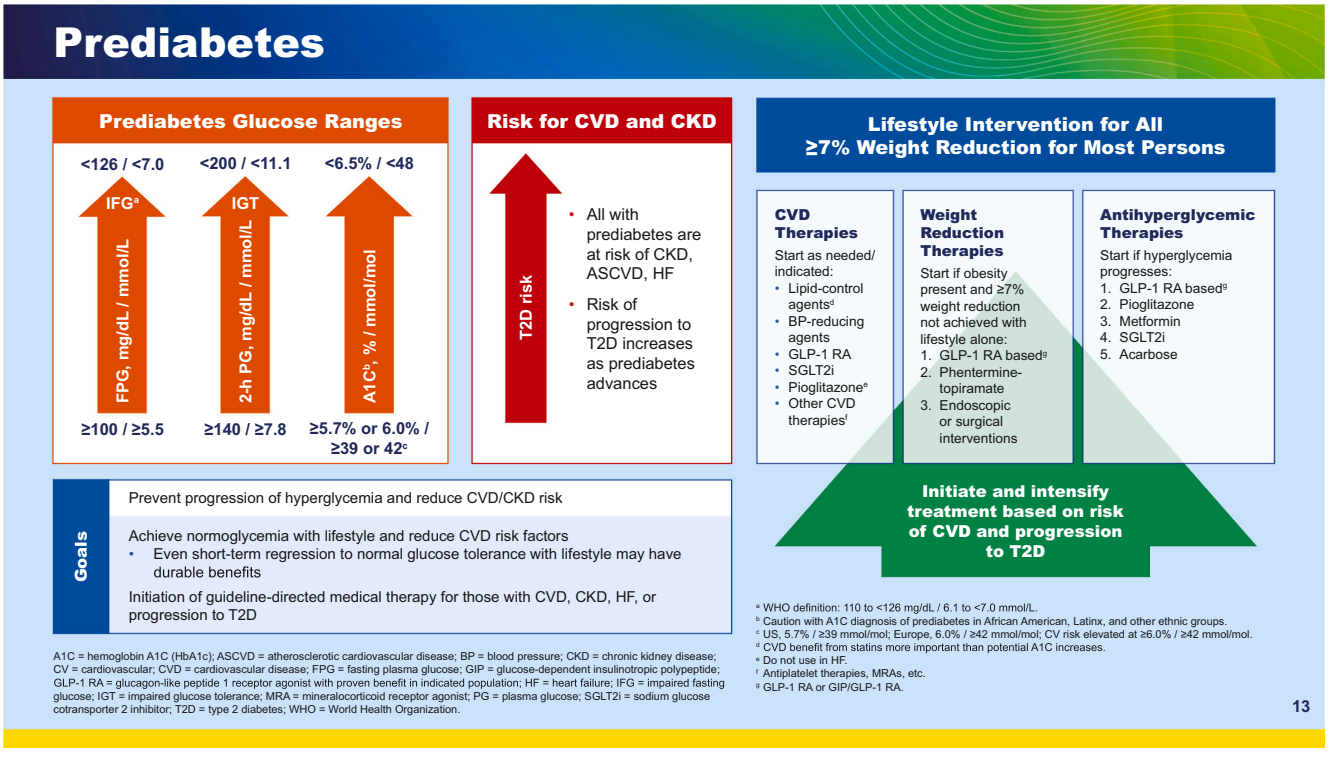
An obesity assessment should be conducted in addition to a general medical evaluation to help guide therapeutic decisions. Person-first language should always be used (e.g., *person with obesity*). The goal of therapy is to achieve and sustain sufficient weight reduction to prevent and treat obesity complications and related diseases and enhance quality-of-life, although percentage weight reduction varies widely depending on the intervention [64–67]. While lifestyle therapy (i.e., diet and physical activity) should be the foundation of all weight reduction efforts to optimize health, when used alone it often results in only moderate weight reduction and a high likelihood of weight regain. The development of glucagon-like peptide 1 (GLP-1)–based anti-obesity medications has revolutionized obesity therapy because of their ability to achieve marked (15–25 %) weight reduction and improve clinical outcomes, including a reduction of cardiovascular events in persons with obesity and established CVD [68]. The specific treatment approach should involve shared decision making between the clinician and patient, based on assessment of: 1) goals of therapy (percent weight reduction and clinical outcomes); 2) individualized lifestyle changes; 3) availability and cost of therapy; and 4) contraindications and adverse effects of specific treatments. It is critical to monitor clinical efficacy and side-effects of therapy and adjust treatment as needed.

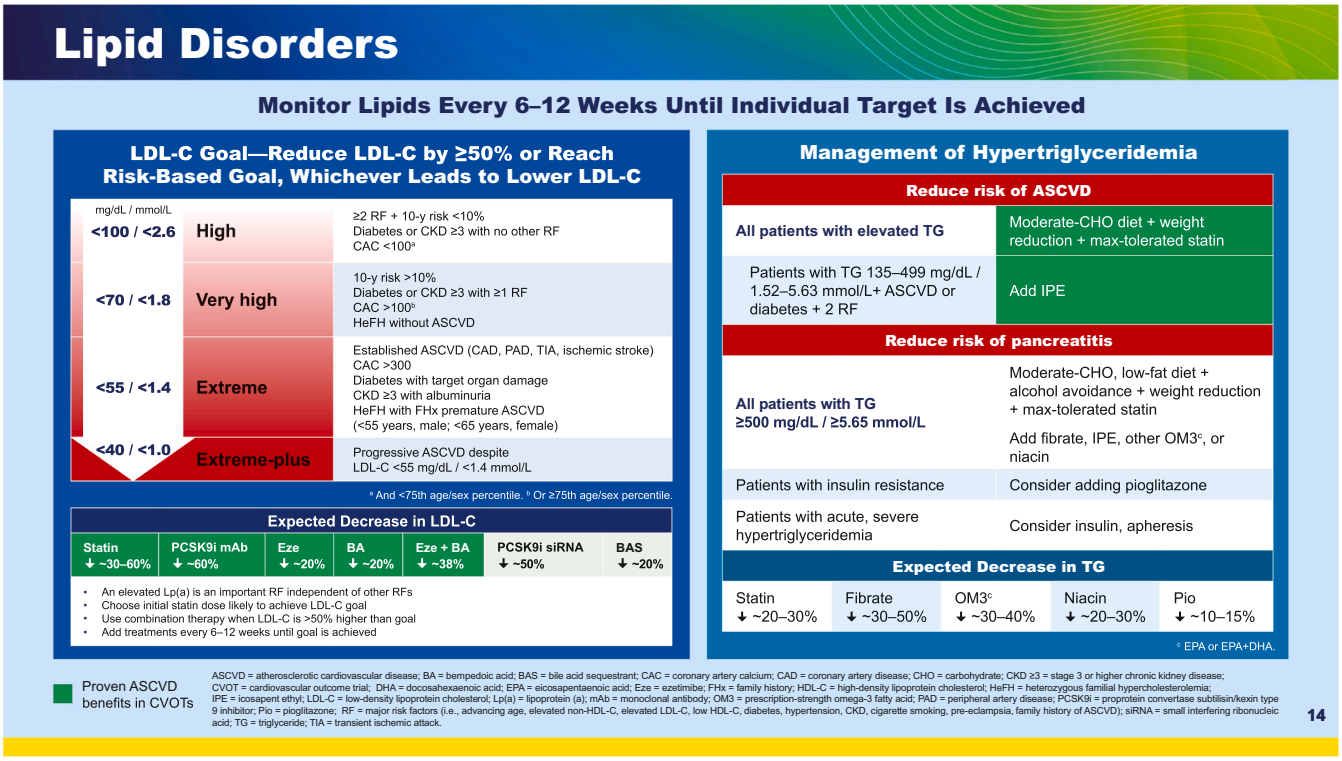
2.2.2. Prediabetes

Prediabetes (also called intermediate hyperglycemia) is a continuum of metabolic abnormalities that extends from high normal glucose to just below the diagnostic thresholds for T2D and includes impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), determined on a 75-g oral glucose tolerance test (OGTT). Persons with prediabetes have increased risks of CKD, ASCVD, HF, and mortality relative to those with normoglycemia [69,70]. It is therefore essential to optimally control weight, glucose, BP, lipids, and all other CVD risk factors (see Section 2.2).

Progression from normoglycemia to overt T2D results from progressive loss of beta-cell function in the setting of insulin resistance, which is often exacerbated by concomitant obesity [71]. Individuals with prediabetes have a high but variable rate of progression to overt diabetes ranging from 8 % to 11 % annually. T2D eventually develops in at least half of at-risk persons. Evidence suggests that intervening early, when dysglycemia is less severe, may prevent progression to T2D or even foster reversion to normoglycemia [72]. Prediabetes management is therefore focused on identifying and educating the person at risk, emphasizing lifestyle modification, weight management, control of CVD risk factors, and efforts to revert to normoglycemia.

Sustained weight reduction increases the likelihood of achieving normoglycemia [72]. If a weight loss of at least 7 % cannot be achieved with lifestyle interventions alone, pharmacological and surgical intervention should be considered depending on the underlying comorbidities and body mass index (BMI) [73]. Although lifestyle intervention is effective in delaying or preventing T2D onset in persons with prediabetes, long-term adherence can be challenging for many. Pharmacological therapy with GLP-1 receptor agonists (GLP-1 RAs), pioglitazone, metformin, acarbose, and orlistat has been shown to decrease the risk of T2D in persons with prediabetes for the duration of the medication's use [74,75]. In persons with obesity without diabetes, GLP-1 RAs and a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA improved A1C levels [76,77]. Sodium glucose cotransporter 2 (SGLT2)





inhibitors have been shown to improve glycemia and decrease the development of T2D in persons with HF [78].

2.2.3. *Lipid disorders*

Lipid management should include lipid-lowering medications in addition to health behavioral modifications. The goals and targets of treatment should be based on patients' comorbidities, which, along with their baseline lipid levels, inform their level of risk. A wealth of data from outcomes trials with statins, ezetimibe, bempedoic acid, and pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have shown that for persons with elevated LDL-C, there appears to be no threshold of benefit for LDL-C level—in other words, lower is always better [79–83]. It is therefore recommended to reduce LDL-C levels by at least 50 % from baseline or reach the individual's risk-based goal, whichever is lower. Achieving these levels often requires combination therapy.

Risk-based goals shown in the slide are based on guideline recommendations from the American College of Cardiology (ACC) and American Heart Association (AHA), the American Association of Clinical Endocrinologists (AACE), and the European Society of Cardiology (ESC) and the European Atherosclerotic Society (EAS) (Table S1) [31,79,84–86]. In addition, some experts recommend targeting apoB levels of <90 mg/dL (<1.8 μmol/L) for high, <80 mg/dL (<1.6 μmol/L) for very high, <70 mg/dL (<1.4 μmol/L) for extreme, and <60 mg/dL (<1.2 μmol/L) for extreme-plus risk and/or non-HDL-C levels of <130 mg/dL (<3.4 mmol/L), <100 mg/dL (<2.6 mmol/L), <80 mg/dL (<2.1 mmol/L), and <65 mg/dL (<1.7 mmol/L) for the same respective risk categories [87].

The *extreme plus* goal (<40 mg/dL [<104 mmol/L]) is for persons who have an extreme risk and continue to have cardiovascular events despite an achieved LDL-C <55 mg/dL (<1.42 mmol/L) [84]. Ten-year risk, which refers to the risk of a hard ASCVD event (myocardial infarction [MI], coronary heart disease death, non-fatal or fatal stroke) within 10 years, can be calculated using a validated risk calculator chosen based on the person's characteristics (Table S2) [88–95].

Major risk factors include those that increase atherosclerotic risk, including advancing age, elevated LDL-C or non-HDL-C, diabetes, obesity, inflammation, albuminuria, hypertension, CKD, MASLD, smoking, and family history of ASCVD. An elevated Lp(a) increases the risk of ASCVD independent of other major risk factors, including LDL-C.

Drug classes that lower LDL-C and are highlighted in green have proven benefits in cardiovascular outcome trials (CVOTs) [80–83]. All persons at elevated ASCVD risk should receive a statin at the maximally tolerated dose unless there is a contraindication. If the baseline LDL-C is >50 % above the goal, initial combination therapy with a statin plus ezetimibe, bempedoic acid, or a PCSK9 inhibitor (either monoclonal antibody or small interfering RNA) should be instituted. The choice of the second or third agent to add to statin therapy is based on how much additional LDL-C lowering is required to reach the LDL-C goal. Whether treatment begins with a statin alone or in combination with another agent, therapy should be intensified every 6–12 weeks until the LDL-C goal is achieved.

Persons with homozygous familial hypercholesterolemia should be referred to a lipid specialist. In these individuals, adding the monoclonal antibody evinacumab, an inhibitor of angiopoietin-like 3 (ANGPTL3) and/or lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, to other lipid-lowering therapy reduces LDL-C levels by a further ~50 % [96].

The generally accepted therapeutic goal for triglycerides of <150 mg/dL (<1.7 mmol/L) was defined in 2001 by the NCEP ATP III [97], although studies suggest that optimal triglyceride levels may be lower [98]. Elevated triglycerides (>150 but <500 mg/dL [>1.7 but <5.7 mmol/L]) should be managed with maximum tolerated statin therapy and a heart healthy, moderate-carbohydrate diet with restricted simple sugar and alcohol intake in addition to other lifestyle approaches (see Section 2.1.1. Lifestyle therapy). Based on evidence from the Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial (REDUCE-IT) trial, adding icosapent ethyl (IPE), a highly purified, non-oxidized formulation of the omega-3 fatty acid eicosapentaenoic acid (EPA), to statin therapy further reduces the risk of ASCVD events in persons with triglycerides between

135 and 500 mg/dL (1.5–5.7 mmol/L) who have ASCVD or diabetes plus two major ASCVD risk factors. The use of fish oil supplements is not recommended.

With the exception of the Helsinki Heart Study and the pre-statin era Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) with gemfibrozil, CVOTs involving triglyceride-reducing agents, including fenofibrate, pemafibrate, omega-3 fatty acids other than IPE, and niacin, have not demonstrated reductions in ASCVD [87,99]. However, subgroup analyses from several trials showed a trend toward benefit in persons with triglycerides ≥200 mg/dL (≥2.3 mmol/L) and HDL-C ≤40 mg/dL (≤1.0 mmol/L) who received fenofibrate [100–103]. Future CVOTs with novel triglyceride-lowering agents will clarify whether triglyceride reduction decreases cardiovascular risk.

Persons with severely elevated triglycerides (>500 mg/dL [5.7 mmol/L]) are at risk of pancreatitis. They should be prescribed dietary restriction and other lifestyle therapeutic approaches along with a fibrate, omega-3 fatty acid, or niacin, which may possibly reduce pancreatitis risk. Glycemic control should be optimized in persons with T2D (see Section 2.2.6. Antihyperglycemic therapy in T2D).

Fibrates, which reduce triglycerides by up to 50 %, are considered the most potent triglyceride-lowering agents [79,104]. Because of increased risk of myopathy, fibrates should be used with caution in combination with certain statins (e.g., simvastatin). Prescription-grade omega-3 fatty acids reduce triglycerides by up to 40 % [79,105]. Niacin, or nicotinic acid, reduces triglycerides by up to 30 %; however, niacin should be used with caution based on new data suggesting it may increase the risk of ASCVD [106]. Depending on the severity of triglyceride elevations, more than one of these agents may be needed. Pioglitazone may also be useful in persons with insulin resistance. Those with acute, severe hypertriglyceridemia and hyperglycemia may benefit from extreme reduction of fat intake, insulin infusion, and in some cases apheresis [79,107].

2.2.4. *Hypertension*

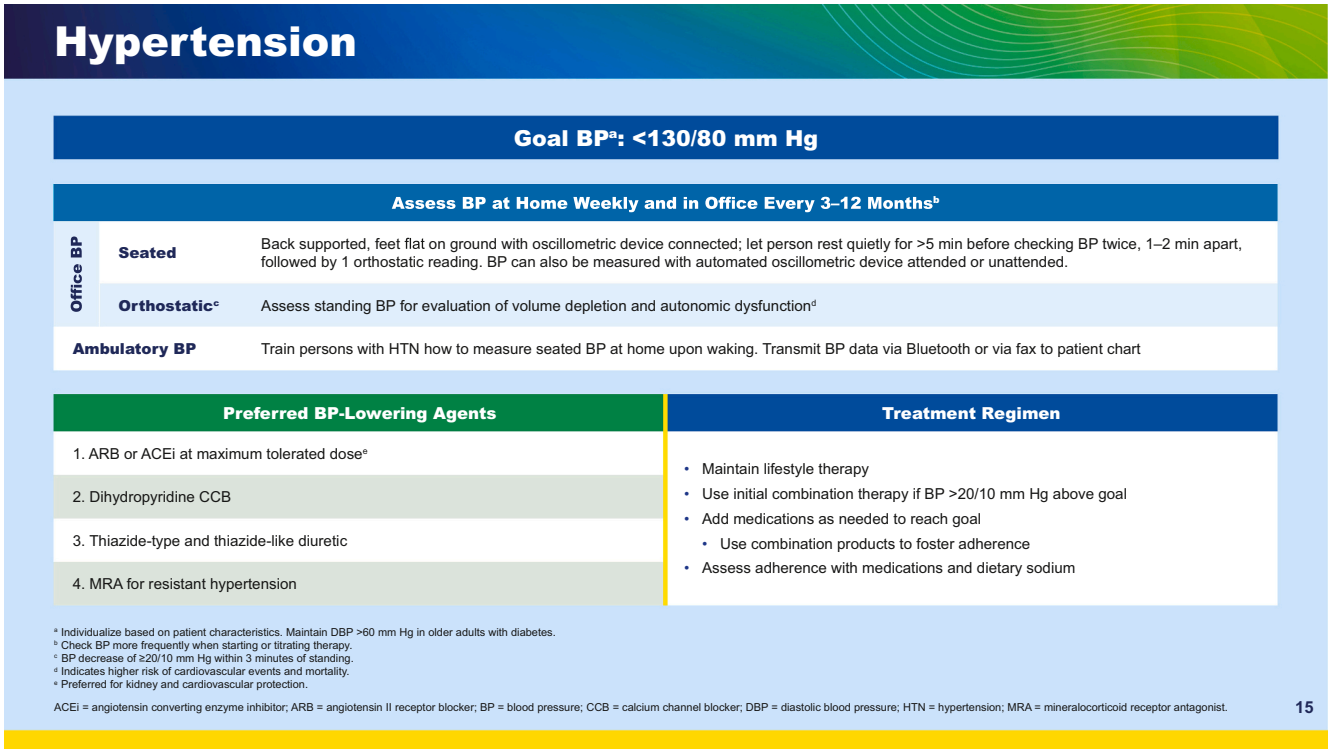
Overall, most current guidelines recommend a BP <130/80 mmHg to reduce cardiorenal risk in persons with hypertension [108,109]. The response to BP lowering drug treatment varies among individuals, but achieving good BP control with combination therapy, if necessary, should be the goal. For most persons with resistant hypertension or stage 3 CKD, three BP lowering drugs are usually needed to achieve a SBP <130 mmHg. For any person with albuminuria and hypertension, the BP-lowering regimen should include a renin-angiotensin system (RAS) inhibitor at maximal dose, a calcium channel blocker (CCB), and a thiazide-type diuretic such as chlorthalidone or indapamide [108–111]. Chlorthalidone or indapamide are preferred over hydrochlorothiazide (HCTZ) because they have a longer half-life and reduce mortality compared to HCTZ [110,112].

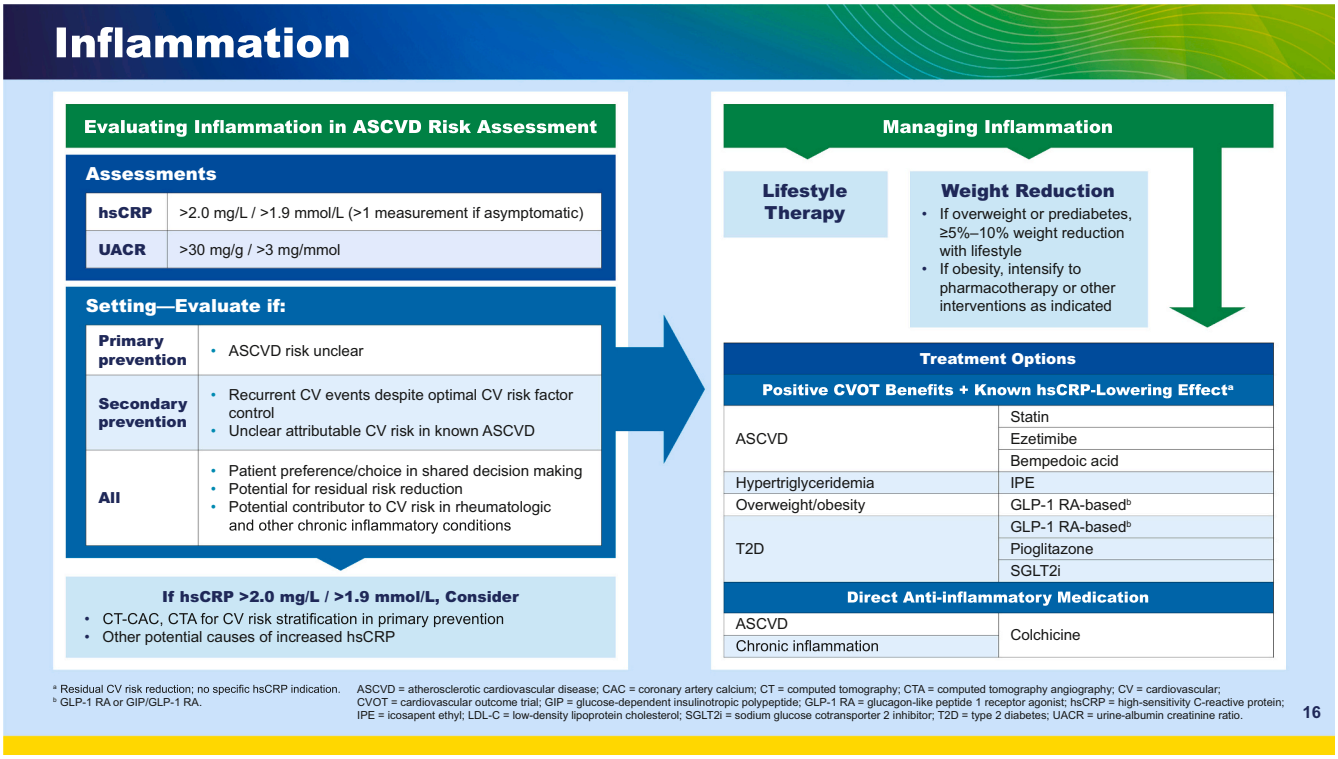
Increases in creatinine in response to BP-lowering treatment should not be concerning unless hyperkalemia develops or creatinine rises >30 % over baseline levels.

Out-of-office assessment of BP is very important because white coat and especially masked hypertension (i.e., higher BP elevations outside than inside the clinic) are common and may affect BP lowering treatment. These conditions must be diagnosed with home BP monitoring and the measurements compared with office BP readings. Ambulatory 24-h BP monitoring can also be a useful tool if there are significant discrepancies between home and office BP readings. Ambulatory blood pressure monitoring has the added benefit of assessing blood pressure during sleeping hours. Cardiovascular mortality may be increased in persons with white coat or masked hypertension [26,113]. For many of these individuals, pharmacologic and/or behavioral therapies to prevent anxiety and other stress-related disorders may be needed.

2.2.5. *Inflammation*

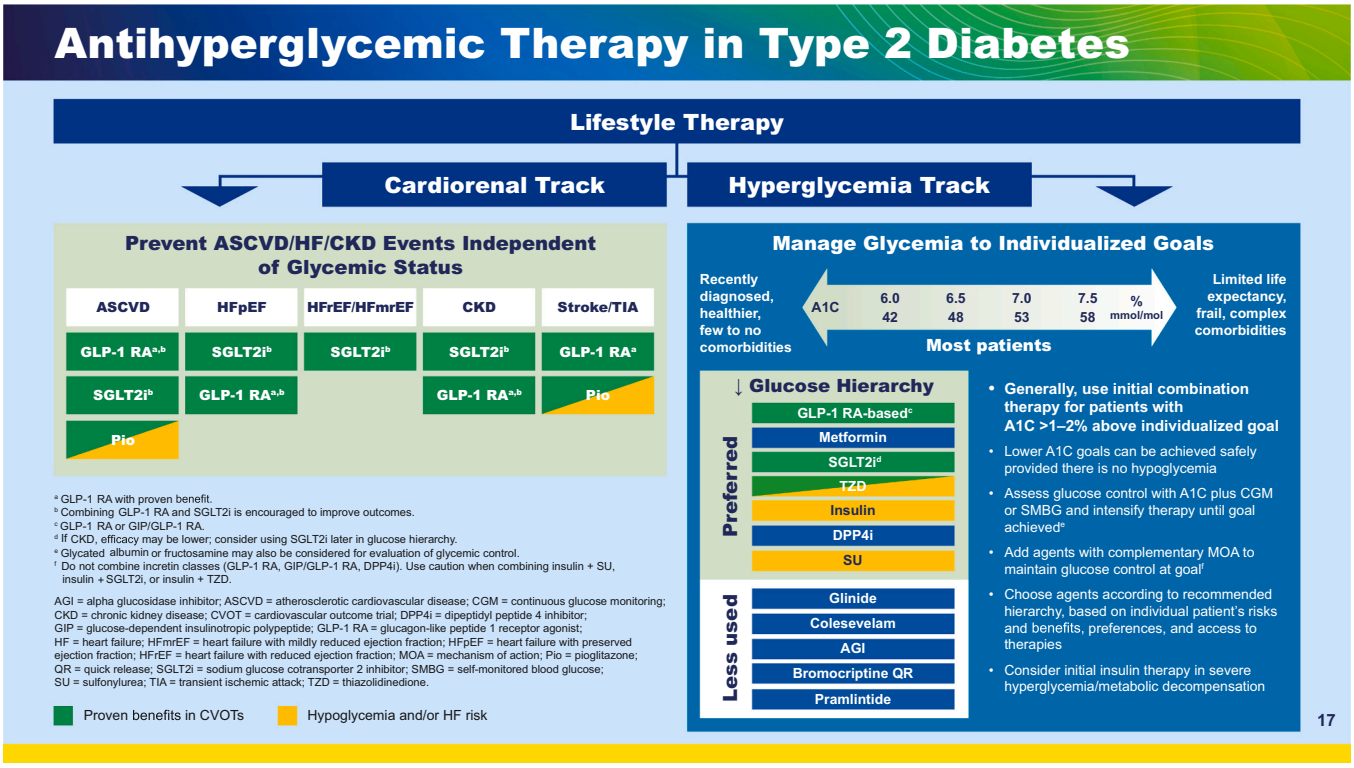
Inflammation independently contributes to ASCVD risk, including in persons with relatively low LDL-C [114–120]. Inflammatory biomarkers include high-sensitivity C-reactive protein (hsCRP) and urinary albumin creatinine ratio (UACR), which should be evaluated in persons whose ASCVD risk is unclear, including individuals with borderline or intermediate 10-year risk or individuals who have diagnosed ASCVD or have





had ASCVD events despite optimal lipid and blood pressure control. UACR or hsCRP may also be measured in anyone who wishes to have a deeper understanding of their personal risk of ASCVD events, as part of shared decision-making. If hsCRP is >2.0 mg/L, additional coronary imaging tests can be considered for further risk stratification when appropriate, i.e., for primary prevention in the absence of conditions associated with ASCVD risk, such as T2D.

Increasing attention on CKD and its connection to ASCVD has



highlighted inflammation as a contributor to pathogenesis. Given the connections between CKD and ASCVD, the presence of CKD without known ASCVD may also prompt consideration of inflammation as a contributor to cardiovascular risk.

Lifestyle therapy, including a healthy diet and regular physical activity, as well as weight reduction in persons with overweight, obesity, or prediabetes are foundational approaches to improving cardiovascular outcomes and may also help reduce inflammation. Smoking avoidance is particularly important. Considerable attention has been directed toward therapies that may reduce cardiovascular risk by decreasing chronic, low grade inflammation, a rapidly evolving field. A conservative approach is taken here, focusing on treatments that have demonstrated a reduction in major adverse cardiovascular events (MACE) in CVOTs and also have an established, significant effect on reducing hsCRP. In such cases, the reduction in inflammation may have contributed to the cardiovascular benefit, even if the mechanism is not definitively known. Treatment options that may indirectly reduce inflammation include statins, ezetimibe, or bempedoic acid in persons with or at risk for ASCVD; IPE in those with triglycerides >135 mg/dL who have diabetes or ASCVD; GLP-1 RAs and dual GIP/GLP-1 RA in obesity; and GLP-1 RAs and pioglitazone in T2D [68,76,105,116,117,121–127]. In higher risk individuals, therapeutic intervention targeting inflammation concomitant with lifestyle efforts may be warranted, given evidence, for example, of significant cardiovascular event reduction with a GLP1-RA in persons with overweight/obesity and ASCVD but not diabetes [68]. Colchicine, a known anti-inflammatory agent, directly lowers hsCRP and has also been shown to reduce ASCVD risk; as a result, colchicine 0.5 mg is now indicated to reduce the risk of MI, stroke, coronary revascularization, and cardiovascular death in adults with established atherosclerotic disease or with multiple risk factors for cardiovascular disease [118].

2.2.6. Antihyperglycemic therapy in type 2 diabetes

The emergence of antihyperglycemic therapies with extra-glycemic benefits permits a two-pronged approach to managing T2D. In addition to lifestyle therapy, GLP-1 RAs and/or SGLT2 inhibitors should be prescribed to individuals with T2D who have established or are at high risk for ASCVD, CKD and/or HF [128,129]. Combining agents from these classes will be beneficial in many people. The consensus includes the thiazolidinedione (TZD) pioglitazone as another agent with possible cardiovascular benefits, especially in individuals with or at high risk for stroke, with appropriate cautions about HF [126,130,131]. Once the CVD, CKD, or HF have been addressed, antihyperglycemic regimens should be directed toward meeting glycemic goals for the individual.

Classes with proven benefits are listed beneath each comorbidity according to the strength of CVOT evidence of benefit. The GLP-1 RAs dulaglutide, liraglutide, and injectable semaglutide reduce the risk of MACE, including cardiovascular deaths, nonfatal MI, and nonfatal strokes independent of glucose control [128]. CVOT findings suggested improvement in kidney function, which may be confirmed when results of a kidney outcomes trial are published [128]. In persons without diabetes who had symptomatic HF with preserved ejection fraction (HFpEF) and obesity, injectable semaglutide improved HF symptoms, so semaglutide may be considered for persons with T2D and HFpEF [132]. CVOTs support cardiovascular safety of lixisenatide, exenatide, oral semaglutide, and tirzepatide, which are currently recommended for glycemic control but not ASCVD or CKD risk reduction [133–135]. Of note, there are ongoing CVOTs with tirzepatide and oral semaglutide.

In outcome studies, SGLT2 inhibitors reduced the risk of HF, kidney disease progression, and other cardiovascular endpoints [129,136–138]. Recent studies with dapagliflozin, empagliflozin, and sotagliflozin (a dual SGLT2/1 inhibitor) have also demonstrated that these agents improve outcomes in persons with HF with reduced and with preserved ejection fraction (HFrEF and HFpEF, respectively), including those who do not have T2D (dapagliflozin, empagliflozin) [78,137,139–141]. Canagliflozin, dapagliflozin, and empagliflozin improved CKD and reduced ASCVD and HF events in persons with moderate to severe CKD and T2D, and dapagliflozin and empagliflozin showed similar effects in individuals without diabetes in the same trials [129].

Glycemic control efforts should be tailored to individualized goals for A1C. The American Diabetes Association (ADA) and the AACE recommend an A1C goal between 6.5 % and 7.0 % for most persons with T2D. Younger, healthier individuals at lower cardiovascular risk may benefit from A1C goals closer to normal (<6.0 %), whereas higher A1C goals (~7.5 % or higher) may be appropriate for older adults with more complex disease complicated by multiple comorbidities. In general, glycemic control regimens should aim to achieve and maintain the lowest A1C possible without hypoglycemia or other unacceptable side effects [107,142,143].

Combination therapy generally should be instituted for persons whose A1C is >1–2 % above their individualized goal, even in newly diagnosed T2D. Combination therapy should involve agents with complementary mechanisms of action; do not combine agents from the incretin classes (GIP/GLP-1 RAs, GLP-1 RAs, and dipeptidyl peptidase 4 [DPP4] inhibitors) with each other or combine sulfonylureas with glinides. The Task Force recommends choosing agents according to the top-down hierarchy shown, although the individual's characteristics, preferences, and access to therapies should be considered. In the list of *Preferred* classes, the GLP-1 RAs (including GIP/GLP-1 RAs) are positioned above metformin because they are the most potent non-insulin antihyperglycemic class in addition to reducing weight and BP and providing cardiovascular benefits. Metformin is placed ahead of SGLT2 inhibitors due to glycemic potency, although it should be noted that SGLT2 inhibitors also reduce weight and BP modestly and have additional kidney and cardiovascular benefits. To achieve glucose goals, many individuals will need combination therapy with either or both the GLP-1 RAs and SGLT2 inhibitors as well as metformin, although some experts recommend other medications such as a TZD or insulin. The sequence should be individualized [144]. Many persons with T2D will require insulin as an important component of their glycemic control regimen. Insulin is associated with weight gain and the risk of hypoglycemia; nevertheless, insulin should not be withheld from individuals who cannot meet their glucose goals. Finally, sulfonylureas carry an increased risk of hypoglycemia and weight gain with little benefit beyond rapid and relatively potent, albeit short-term, glycemic reductions. The *Less used* classes—glinides, colesevelam, alpha glucosidase inhibitors (AGIs), bromocriptine quick release (QR), and pramlintide—may be appropriate for individuals in specific circumstances [107,142,143].

Glycemic control should be evaluated on an ongoing basis. A1C reflects the average glucose level over 3 months and is the gold standard glycemic measure, although it has significant limitations. Other glycemic indices, such as TIR and glucose management indicator (GMI) data from patients' CGM or SMBG devices, glycated albumin, or fructosamine, provide valuable information [107,142,143,145,146].

2.2.7. Hypoglycemia

Prevention and treatment of hypoglycemia are essential for the safety and cardiometabolic management of persons with diabetes and other conditions such as refractory insulinoma, nesidioblastosis, or postbariatric hypoglycemia. All individuals susceptible to hypoglycemia and their family members and caregivers should be given education on the causes of hypoglycemia and how to prevent, detect, and treat it. Mild, acute hypoglycemia can cause cognitive impairment or result in accidents or falls, while the long-term risk of sudden death, autonomic neuropathy, cardiac arrhythmia, cardio- and cerebrovascular disorders, and other adverse outcomes are associated with recurrent and/or severe hypoglycemia [147,148]. Fear of hypoglycemia poses a significant barrier to glycemic control in diabetes and contributes to under-

Hypoglycemia

Define	• Level 1: BG <70 mg/dL / <3.9 mmol/L • Level 2: BG <54 mg/dL / <3.0 mmol/L • Level 3/severe: characterized by altered mental or physical function requiring external assistance for recovery
Identify risks	• Use of insulin or SU, older age (≥65 years), previous severe hypoglycemia, long duration of diabetes, hypoglycemia unawareness, CKD, liver disease, frailty, and/or high comorbidity burden
Prevent	• Delay use of medications associated with hypoglycemia (insulin, SU) until other options have been exhausted • For patients already using insulin or an SU, consider switching to a nonhypoglycemic regimen and/or de-intensify regimen
Detect	• Recommend CGM over SMBG in patients using insulin; consider CGM for SU users • Ask patients about any hypoglycemia incidents at every visit
Treat	• Oral glucose (3 glucose tablets or gels, sugar-rich food or drink; avoid treating with high-fat foods) • Prescribe glucagon to every patient on insulin (any regimen) • Consider prescribing glucagon to patients taking SUs who meet at-risk criteria for hypoglycemia • Consider stopping SU in those with documented hypoglycemia
Educate	• Causes, signs and symptoms, and management of hypoglycemia • Use of glucagon for patient's close associates (e.g., family members, coworkers, teachers, friends) • Refer to CDCES and online resources (e.g., International Hypoglycaemia Study Group)

BG = blood glucose; CDCES = certified diabetes care and education specialist; CGM = continuous glucose monitor; CKD = chronic kidney disease; SMBG = self-monitored blood glucose; SU = sulfonylurea.

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treatment of the disease [149,150].

Hypoglycemia is categorized as level 1 (blood glucose <70 mg/dL [<3.9 mmol/L]), level 2 (blood glucose <54 mg/dL [<3.0 mmol/L]), and level 3 (severe hypoglycemia) involving an altered mental state requiring assistance from another person [143].

To prevent hypoglycemia, antihyperglycemic classes that generally do not induce hypoglycemia should be used in preference to insulin, sulfonylureas, and glinides, unless individualized glycemic targets

Antiplatelet and Anticoagulation Therapy

	Condition	Risk Consideration	Recommended Medication
Primary Prevention	No known ASCVD but ≥2 RF	Low bleeding risk	• Aspirin 75–100 mg daily
	CAC ≥100	Low bleeding risk	• Aspirin 75–100 mg daily
Secondary prevention	ACS, within 1 year of event		• Aspirin 75–100 mg + P2Y12i
	Stable CAD with history of PCI or >12 months after ACS	High ischemic risk AND Low bleeding risk	• Aspirin 75–100 mg + ticagrelor 60 mg BID • Rivaroxaban 2.5 mg BID + aspirin 75–100 mg • Aspirin 75–100 mg + clopidogrel 75 mg
		Low ischemic risk OR High bleeding risk	• Clopidogrel 75 mg daily • Aspirin 75–100 mg daily
	Stable CAD, no PCI	High ischemic risk AND Low bleeding risk	• Rivaroxaban 2.5 mg BID + aspirin 75–100 mg
		Low ischemic risk OR High bleeding risk	• Clopidogrel 75 mg daily • Aspirin 75–100 mg daily
	PAD	Without limb revascularization	• Rivaroxaban 2.5 mg BID + aspirin 75–100 mg • Clopidogrel 75 mg daily
		After limb revascularization	• Rivaroxaban 2.5 mg BID + aspirin 75–100 mg

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BID = twice daily; CAC = coronary artery calcium score; CAD = coronary artery disease; CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral artery disease; P2Y12i = P2Y12 inhibitor; PCI = percutaneous coronary intervention; RF = major risk factors (i.e., advanced age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD).

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cannot be met otherwise (see Section 2.2.6. Antihyperglycemic therapy and Section 2.4.1. Summary of medications). In high risk individuals already taking a sulfonylurea or glinide, consider switching to a non-hypoglycemic class, while for those who require insulin, their regimen should ideally include insulin analogs (rather than human insulins) to minimize hypoglycemia risk [142].

Utilizing CGM systems that alert patients of downward trends in glucose concentrations may help prevent hypoglycemia. CGM data are also useful in identifying glycemic trends and guiding the adjustment of insulin and other therapies to reduce the risk of hypoglycemia [28]. Persons without access to CGM but who use therapies likely to induce hypoglycemia should test their blood glucose frequently using a structured SMBG regimen.

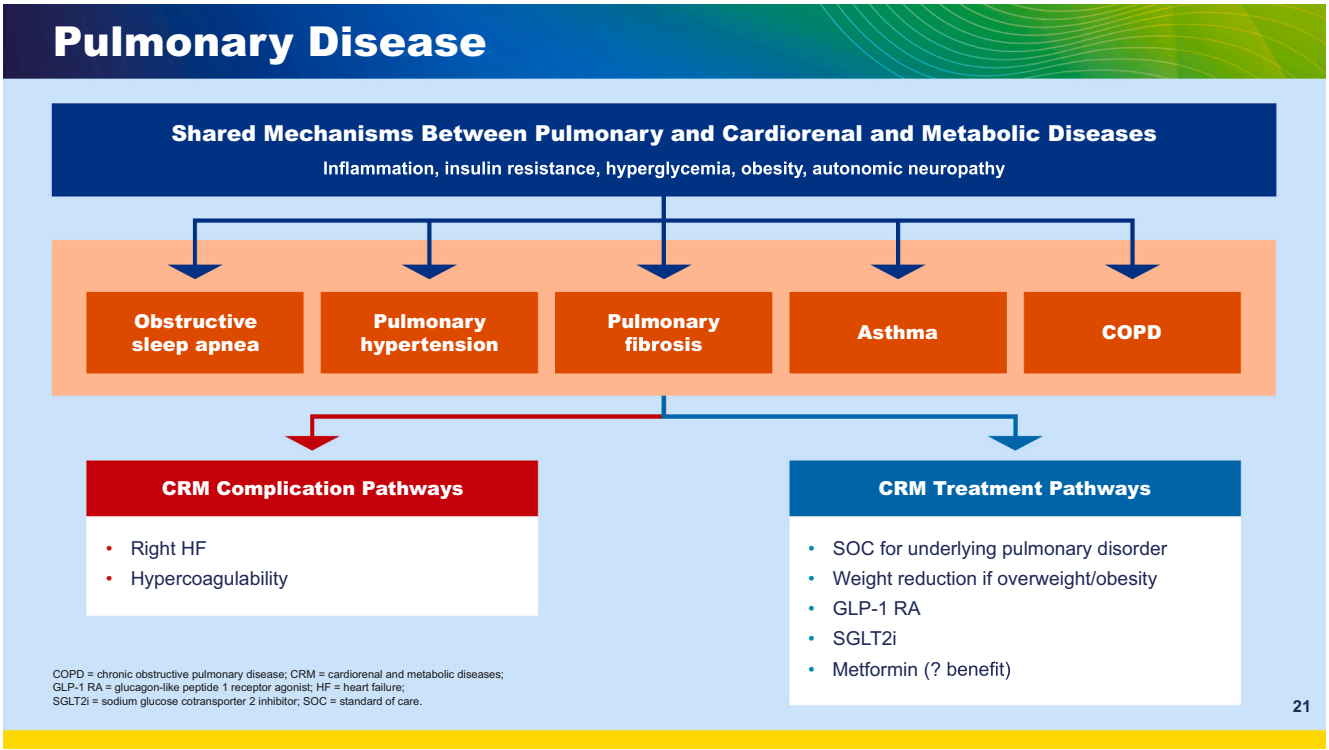
Individuals experiencing hypoglycemia should treat it by consuming 15 g of carbohydrate in the form of glucose tablets or gels or drink but avoid high-fat foods such as ice cream, which may slow glucose absorption. If hypoglycemia is not resolved within 15 min (i.e., glucose remains <70 mg/dL [<3.9 mmol/L]), a 15-g carbohydrate load should be repeated. Every person taking insulin—even basal-only regimens—should be prescribed glucagon to treat severe hypoglycemia, and glucagon may also be considered for persons taking sulfonylureas who meet criteria for high hypoglycemia risk—or the sulfonylurea should be stopped in such persons. Family members and close associates of persons using insulin should be trained in how to administer glucagon to prevent unnecessarily prolonged episodes of severe hypoglycemia [151]. Newer glucagon formulations, including nasal glucagon, single-dose auto-injector glucagon, or dasiglucagon pens, are easier to use than traditional glucagon kits, which can facilitate training [152].

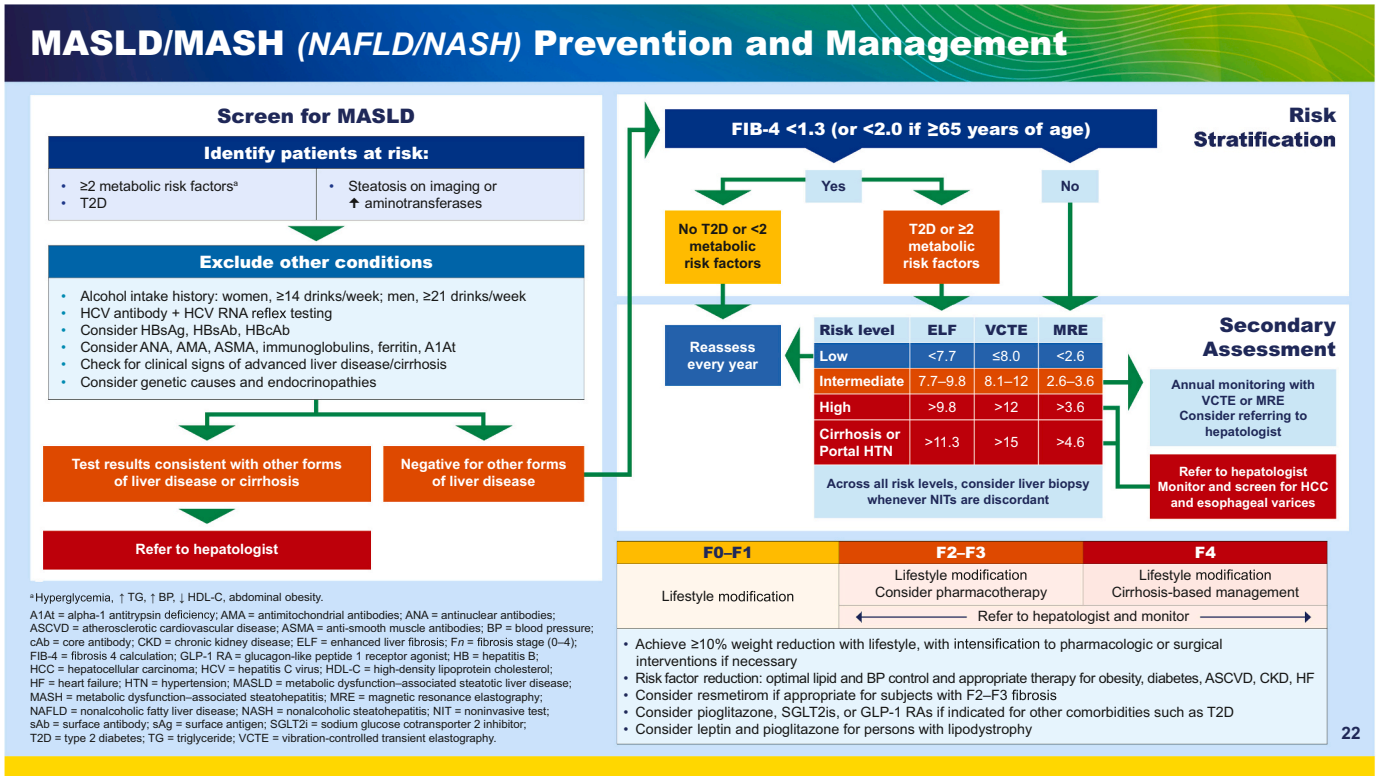
2.2.8. *Antiplatelet and anticoagulation therapy*

Determination of the optimal antithrombotic therapy is complex. For individuals without a history of ASCVD or other risk factors, the use of aspirin is not generally recommended. However, A Study of Cardiovascular Events in Diabetes (ASCEND) demonstrated a modest reduction in ischemic events for persons with diabetes but without ASCVD, although an increased risk of bleeding was similar in magnitude to the benefit [153]. The Task Force believes prescribing aspirin for persons with two or more cardiovascular risk factors (i.e., elevated non-HDL-C, elevated LDL-C, elevated Lp(a), low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD, elevated CAC score >100) may be beneficial, but there is an increased risk of bleeding, which should be carefully addressed and monitored.

The use of antithrombotic therapy in persons with atherosclerosis has been studied in various clinical trials. In the setting of an acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT) consisting of aspirin with a P2Y12 inhibitor for at least 12 months has been found to reduce the incidence of MI and death [154–156]. In ACS treated with percutaneous coronary intervention (PCI), prasugrel is superior to clopidogrel [155]. Prasugrel should be avoided in persons with history of transient ischemic attack (TIA) or stroke. Ticagrelor has demonstrated superiority compared with clopidogrel in ACS managed medically or with revascularization [155,156]. As many as 5 % of patients prescribed ticagrelor stopped the medication because of shortness of breath [157]. In persons who have not had any bleeding but remain at high ischemic risk, durations of DAPT longer than 12 months are recommended. Bleeding risk should be periodically reassessed.

Individuals with stable CAD undergoing PCI should be treated with DAPT for at least 6 months if there are no bleeding complications. Shorter duration DAPT can also be considered in persons at high risk for bleeding complications. Thereafter, continued DAPT is reasonable if there has been no bleeding and they remain at high ischemic risk, although de-escalation to either clopidogrel or aspirin monotherapy may be considered if the bleeding risk is not low. In persons with a more remote history of PCI who are not receiving DAPT but are still at high ischemic risk and at low bleeding risk, either aspirin plus ticagrelor 60 mg twice daily or dual pathway inhibition (DPI), which consists of rivaroxaban 2.5 mg twice daily plus aspirin 75–100 mg, should be considered [158–161]. For high-risk persons with stable CAD and no prior PCI, either DPI or clopidogrel alone is acceptable; either clopidogrel or low-dose aspirin may be used for those at moderate risk. For individuals with PAD, DPI is recommended after revascularization, and DPI or clopidogrel alone is acceptable in the setting of PAD without





revascularization [162,163].

Persons with diabetes are at higher risk of stroke from atrial fibrillation. If a person has atrial fibrillation, therapeutic anticoagulation with a non–vitamin K oral anticoagulant (NOAC) should be used if there are no contraindications. Care should be taken if combined with an antiplatelet, as concomitant use will raise bleeding risk. In persons who develop an indication for antiplatelet therapy such as ACS or PCI, the duration of combination antithrombotic therapy should be limited [164].

2.3. Cardiorenal and metabolic comorbidities

2.3.1. Pulmonary disease

There are numerous associations between cardiorenal and metabolic diseases and pulmonary disorders. Inflammation, insulin resistance, obesity, hyperglycemia, and autonomic neuropathy may contribute to the pathophysiologic mechanisms underlying chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, and pulmonary hypertension [165–168]. Obesity and diabetes are also strongly associated with the sleep-related breathing disorder obstructive sleep apnea (OSA). The complications of OSA include hypertension, atherosclerosis, HF, arrhythmia, stroke, and increased mortality [15,169,170]. Several OSA screening tools are available; diagnosis is by polysomnography or alternatively by respiratory polygraphy [15,171].

Cardiorenal and metabolic therapies that reduce weight (bariatric surgery, GLP-1 RAs, SGLT2 inhibitors) have shown positive effects in OSA, and metformin, SGLT2 inhibitors, and GLP-1 RAs have also shown benefits in COPD and other pulmonary conditions [15,165]. SGLT2 inhibitors have been shown to improve pulmonary hypertension in individuals with HF, and treatment with either SGLT2 inhibitors or GLP-1 RAs reduced COPD exacerbations in an epidemiologic study of persons with T2D and COPD [172]. Of potentially greatest benefit is the effect of GLP-1 RAs in reducing the severity of pulmonary conditions associated with obesity and diabetes [165,173].

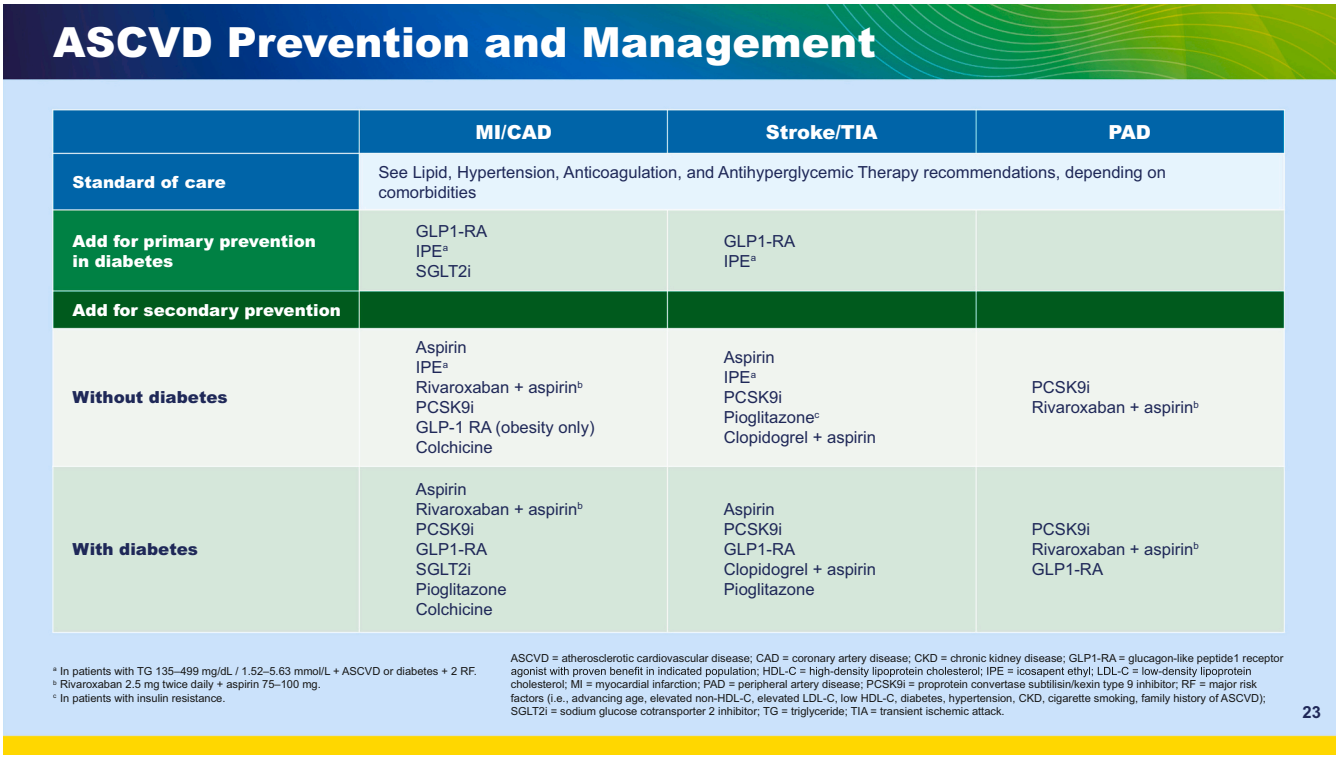
2.3.2. MASLD/MASH (NAFLD/NASH) prevention and management

MASLD is characterized by evidence of hepatic steatosis in the presence of at least one of the following: overweight/obesity, T2D, or evidence of metabolic dysregulation (Table S3) [174,175]. Persons with MASLD should optimally be identified before their condition progresses to MASH.

Screening for liver disease should be conducted annually among individuals with two or more metabolic risk factors, including hyperglycemia, hypertension, dyslipidemia (high triglycerides, low HDL-C), obesity (especially abdominal obesity), and hypothyroidism [176–178]. Measurement of alanine transaminase (ALT) and aspartate transaminase (AST) is recommended, with the caveat that these tests may not be elevated in advanced stages of the disease and may lack sensitivity in detecting early fatty liver disease. Fatty liver disease may be present even if liver enzymes are normal, especially in individuals with insulin resistance [175].

To diagnose MASLD, the clinician should evaluate for other (or additional) potential etiologies of hepatic disease, including infectious hepatitis, hemochromatosis, drug-related hepatotoxicity, and endocrinopathies (e.g., hypothyroidism and Cushing's syndrome) [178]. Persons with or at high risk for fibrosis should be referred to a hepatologist [176,177,179].

Among noninvasive tests (NITs), the fibrosis 4 calculation (FIB-4; calculated based on platelets, ALT, AST, and age) is useful in estimating the risk of hepatic fibrosis that may be associated with MASLD [179]. Persons with FIB-4 scores <1.3 (<2.0 if ≥65 years of age) without T2D or with <2 risk factors should be rescreened annually. Those with higher FIB-4 scores and/or T2D or ≥2 risk factors should be further evaluated with an enhanced liver fibrosis (ELF) test and elastography (either vibration-controlled transient elastography [VCTE] or magnetic resonance elastography [MRE]) to determine the degree of hepatic fibrosis.



ASCVD Prevention and Management

	MI/CAD	Stroke/TIA	PAD
Standard of care	See Lipid, Hypertension, Anticoagulation, and Antihyperglycemic Therapy recommendations, depending on comorbidities		
Add for primary prevention in diabetes	GLP1-RA IPE[a] SGLT2i	GLP1-RA IPE[a]	
Add for secondary prevention			
Without diabetes	Aspirin IPE[a] Rivaroxaban + aspirin[b] PCSK9i GLP-1 RA (obesity only) Colchicine	Aspirin IPE[a] PCSK9i Pioglitazone[c] Clopidogrel + aspirin	PCSK9i Rivaroxaban + aspirin[b]
With diabetes	Aspirin Rivaroxaban + aspirin[b] PCSK9i GLP1-RA SGLT2i Pioglitazone Colchicine	Aspirin PCSK9i GLP1-RA Clopidogrel + aspirin Pioglitazone	PCSK9i Rivaroxaban + aspirin[b] GLP1-RA

[a] In patients with TG 135–499 mg/dL / 1.52–5.63 mmol/L + ASCVD or diabetes + 2 RF.
[b] Rivaroxaban 2.5 mg twice daily + aspirin 75–100 mg.
[c] In patients with insulin resistance.

ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CKD = chronic kidney disease; GLP1-RA = glucagon-like peptide1 receptor agonist with proven benefit in indicated population; HDL-C = high-density lipoprotein cholesterol; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; RF = major risk factors (i.e., advancing age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD); SGLT2i = sodium glucose cotransporter 2 inhibitor; TG = triglyceride; TIA = transient ischemic attack.

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The field of NITs is evolving rapidly [180,181]. Individuals with abnormally high ranges in these tests should be referred to a hepatologist. Liver biopsy is the gold standard means of determining the presence of MASH and should be considered, especially when NIT results are discordant.

Management of persons with MASLD who do not have MASH or significant fibrosis involves primarily lifestyle modification—including smoking cessation—and management of other cardiovascular and renal risks as appropriate. Persons with overweight or obesity should be targeted for weight reduction of ≥10 % using lifestyle modification and obesity medications or bariatric surgery as needed. Follow up (at least annually) should include regular reassessment for progression to more severe liver disease.

Care of persons with MASH or hepatic fibrosis requires a coordinated, multipronged approach that includes the risk factor recommendations for MASLD as well as pharmacotherapy (regardless of the presence of T2D) to address active steatohepatitis and reduce the risk of progressive fibrosis [176,182]. The oral, liver-directed, thyroid hormone receptor beta–selective agonist resmetirom was recently conditionally approved for the treatment of MASH with stage F2-F3 of fibrosis based on a clinical trial evaluating surrogate markers, with final approval to be granted based on hard outcomes when the trials are concluded [183]. Mitigation of cardiovascular risks as discussed above is vital, including the use of statins and other lipid-lowering agents to meet lipid and BP goals, keeping in mind that upper doses of statins may need to be adjusted down or gemfibrozil may have to be discontinued, if the decision is made for the patient to start taking resmetirom. These individuals may also benefit from pioglitazone, SGLT2 inhibitors, and/or GLP-1 or GIP/GLP-1 RAs.

2.3.3. ASCVD prevention and management

Management of ASCVD, including prevention of the first and all subsequent MI and CAD, stroke or TIA, and PAD events, begins with lifestyle therapy and pharmacotherapy to control lipids, hypertension, hyperglycemia, and obesity as well as implementing antiplatelet/anticoagulation therapy as appropriate for the individual (see Section 2.2). Once traditional risk factors are controlled using standard therapies, additional risk reductions may be achieved with the add-on options shown in the slide.

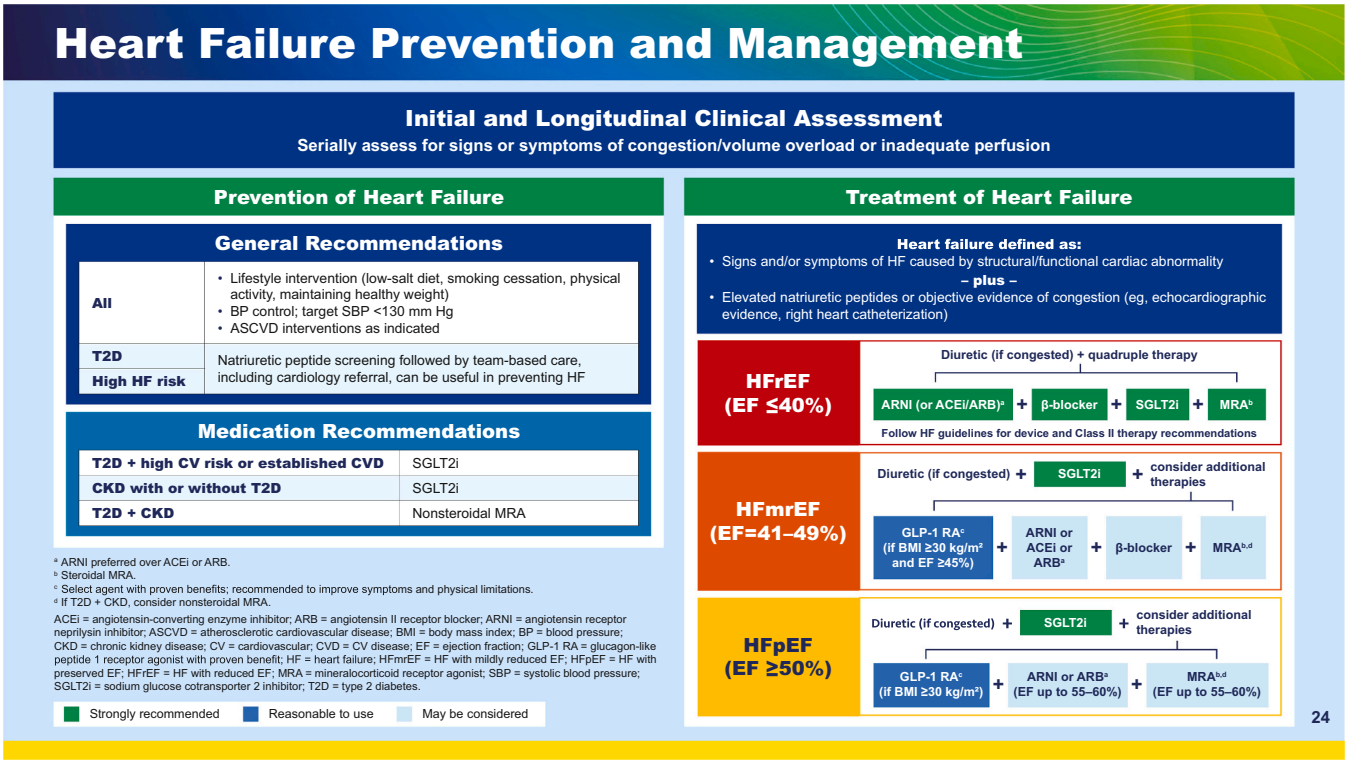
For persons with T2D, treatment with a GLP-1 RA with proven benefits (dulaglutide, liraglutide, or semaglutide) reduces the risk of MACE, and these agents may help prevent strokes in persons with T2D and established ASCVD [128]. High-dose semaglutide has also been shown to reduce the risk of MACE in persons with established ASCVD and obesity without diabetes [68]. The SGLT2 inhibitors have less robust data for MACE prevention but may still be considered to reduce risk of MI and CAD [129]. Both GLP1-RAs and SGLT2 inhibitors may also be considered in persons with T2D and PAD to reduce the risks of cardiovascular events.

Based on findings from the REDUCE-IT trial, which showed significant reductions in cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina in persons with and without diabetes who were given IPE in addition to a statin [105,184], IPE plus a statin is recommended for primary prevention of MI, CAD, or stroke in persons with hypertriglyceridemia, diabetes, and additional risk factors and secondary prevention of these events in persons hypertriglyceridemia with and without diabetes.

Aspirin alone is recommended for secondary prevention of ASCVD events in persons with and without diabetes, but because the risk of bleeding exceeds the benefits of aspirin therapy for persons with diabetes without a prior cardiovascular event, aspirin is generally not recommended for primary prevention in those with diabetes. However, aspirin should be considered in those with high cardiovascular risk [185,186].

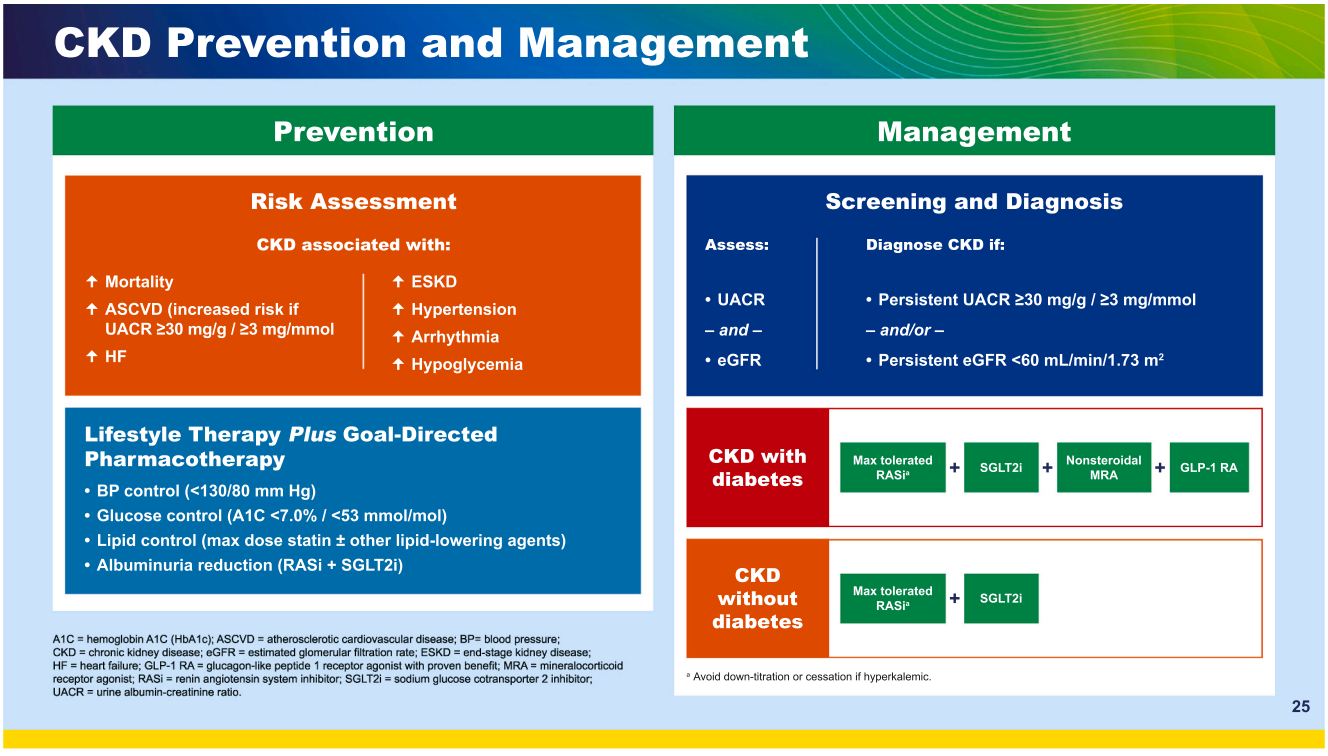
The combination of low dose rivaroxaban plus low-dose aspirin reduces the risk of cardiovascular death, MI, and stroke as well as venous thromboembolism in persons with CAD or PAD with and without T2D [158]. Based on these findings, rivaroxaban 2.5 mg twice daily plus low-dose aspirin is recommended for prevention of MI, stroke, cardiovascular death, and PAD events in those with and without diabetes who have CAD or PAD.

In persons with diabetes and CAD who have not had a prior cardiovascular event, ticagrelor reduces the risk of MI, stroke,



cardiovascular death, and major adverse limb events [160]. Hence, ticagrelor is recommended for secondary prevention of these events in persons with diabetes. In persons with a prior history of MI, ticagrelor treatment for 3 years plus aspirin also reduced risk of MI, stroke, and cardiovascular death but increased the risk of major bleeding [159]. The bleeding risks associated with antiplatelet and/or anticoagulant therapies should be considered before initiating these treatments.

The PCSK9 inhibitors are recommended for secondary prevention of MACE in persons with and without diabetes [80,81]. Colchicine has also been shown to prevent MACE events in persons with CAD [118].



Pioglitazone reduced the risk of a composite of stroke or MI in persons with insulin resistance and a history of stroke or TIA (but not diabetes) and is therefore recommended for secondary prevention of stroke in this setting unless there are prevailing contraindications, such as HF [130]. In persons with T2D, pioglitazone reduced the relative risk of the composite of all-cause mortality, MI, and stroke, although the primary endpoint of the trial (which included peripheral vascular disease outcomes) was not met [126].

2.3.4. *Heart failure prevention and management*

HF diagnosis is based on signs and/or symptoms caused by a structural or functional cardiac abnormality plus elevated natriuretic peptides or objective evidence of congestion. If HF is suspected, a two-dimensional echocardiogram coupled with Doppler flow studies should be conducted to identify abnormalities of the myocardium, heart valves, and pericardium and evaluate left ventricular ejection fraction (LVEF) [38,39]. Approximately 31 % of HF patients meet criteria for HF with reduced ejection fraction (HFrEF; EF ≤40 %); 13 % have mildly reduced ejection fraction (HFmrEF; EF 41–49 %); and 56 % have preserved ejection fraction (HFpEF; EF ≥50 %) [187].

In persons at risk for or diagnosed with HF, clinical assessment should include evaluation for signs or symptoms of congestion or inadequate perfusion, including dyspnea on exertion and decreased exercise tolerance [38,39]. Natriuretic peptides (NT-proBNP and BNP) may be used to identify and stratify persons at risk for HF as well as to determine prognosis in those with manifest HF. It is noteworthy that these peptides may be falsely low in persons with obesity.

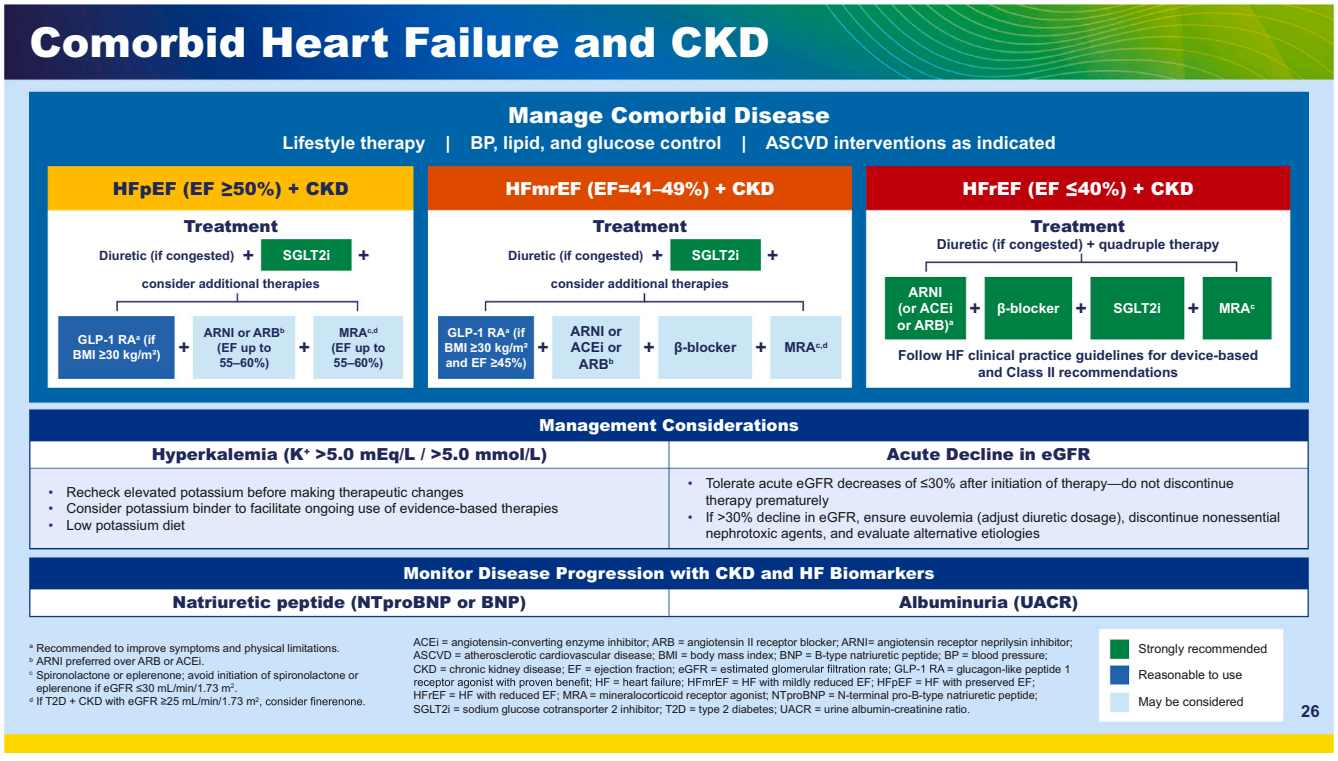
Prevention of HF begins with the same lifestyle interventions and risk factor control measures used for other conditions described in this guidance (see Section 2.1.1. Lifestyle therapy; Section 2.2.4. Hypertension; Section 2.2.6. Antihyperglycemic therapy; Section 2.3.3. ASCVD; Section 2.3.5. CKD). Beyond traditional risk factor control, therapies for prevention of HF include an SGLT2 inhibitor for individuals with T2D at high risk of ASCVD events and for those with CKD. A nonsteroidal mineralocorticoid receptor antagonist (MRA) is recommended for prevention of HF among persons with comorbid T2D and CKD. Individuals with elevated natriuretic peptides, with high clinical risk, and/or those with signs or symptoms of HF should be referred to a cardiologist and/or multidisciplinary disease management program for prevention of HF or its progression. For persons with T2D, validated tools (Machine Learning to Predict the Risk of Incident Heart Failure Hospitalization Among Patients With Diabetes [WATCH-DM] or Thrombolysis in Myocardial Infarction [TIMI] Risk Score for Heart Failure in Diabetes [TRS-HFDM]) are available for predicting risk of new-onset HF [188,189].

HF therapy is based on LVEF. Individuals with HFrEF should receive quadruple therapy including angiotensin receptor/neprilysin inhibitor (ARNI) (or ACE inhibitor if ARNI is not feasible), an SGLT2 inhibitor, a beta blocker, and a steroidal MRA, with the addition of a diuretic if congestion is present [38,39]. The regimen should include an SGLT2 inhibitor regardless of the presence of T2D [190]. HF clinical practice guidelines for device-based recommendations should be followed for persons with HFrEF. Individuals with HFmrEF should receive an SGLT2 inhibitor and a diuretic (if congested) and may also be treated with other components of quadruple therapy [38,39].

Persons with HFpEF should receive an SGLT2 inhibitor [38,39,190]. ARNI (or ARB) and steroidal MRA may be appropriate for select individuals with less than normal ejection fraction [38,39,191]. Likewise, a nonsteroidal MRA may be considered for persons with HFpEF, T2D, and CKD (see Section 2.3.6. Comorbid heart failure and CKD). Diuretics may be considered for congestion. Persons with HF, LVEF ≥45 %, and BMI ≥30 kg/m^2 may also benefit from high-dose semaglutide, which has been shown to improve HF symptoms [132].

2.3.5. *CKD diagnosis and treatment*

CKD is defined as persistent eGFR <60 mL/min/1.73 m^2 or UACR ≥30 mg/g (≥3 mg/mmol) [37]. Diabetes and hypertension increase the risk of CKD, whereas CKD itself markedly increases risks of ASCVD, HF, arrhythmia, hypoglycemia, and premature mortality. CKD also exacerbates comorbidities such as hypertension [192,193]. When eGFR is reduced, CKD alters the menu of available medications for multiple cardiorenal and metabolic conditions [194]. Therefore, CKD alters the benefit-risk profiles of many important interventions.



Screening to identify CKD is critical; eGFR *and* albuminuria should be measured at least annually [37]. The new equation estimating GFR from serum creatinine does not include race, and an additional equation that adds serum cystatin C, are more precise than older methods [195,196]. A single-voided ("spot") urine measures albuminuria as UACR.

Lifestyle and goal-directed therapies form the critical foundation to reduce cardiovascular and CKD risk [37]. Sodium restriction is advisable in persons with CKD because sodium excretion is commonly impaired, which could exacerbate hypertension and HF. All persons with CKD should receive the maximum-tolerated dose of a RAS inhibitor and an SGLT2 inhibitor [36,37,197,198]. A decrease in eGFR is expected upon starting either a RAS inhibitor or an SGLT2 inhibitor. In the case of RAS inhibitors, a decrease as large as 30 % is considered acceptable and consistent with beneficial outcomes. Changes in eGFR with SGLT2 inhibitors are more modest (3–10 %). Neither RAS inhibitors nor SGLT2 inhibitors should be discontinued unless serious acute kidney injury is suspected.

SGLT2 inhibitor trials have demonstrated improved kidney outcomes in persons with CKD with and without T2D [129,138,199–201]. These agents can be initiated at eGFRs as low as 20 mL/min/1.73 m^2 [129,199].

Persons with T2D and CKD may be prescribed a GLP-1 RA in addition to a RAS inhibitor and SGLT2 inhibitor to reduce ASCVD events and improve kidney outcomes [128,198,202,203].

When added to standard of care, the non-steroidal MRA finerenone reduced CKD progression and cardiovascular events (predominantly HF) in persons with T2D and albuminuria [198,204–206].

2.3.6. *Comorbid heart failure and CKD*

Persons with comorbid HF and CKD face markedly elevated risks of clinical progression and mortality yet are often inadequately treated with disease-modifying therapies targeting each condition ("a risk-treatment paradox").

Guideline-recommended HF therapies have been studied across a broad range of individuals with comorbid CKD. The SGLT2 inhibitors have been studied and demonstrated to be safe and well-tolerated in persons with HF at eGFRs as low as 20 mL/min/1.73 m^2 [38,39]. Other therapeutic classes, including ACE inhibitors, ARBs, ARNI, and steroidal MRAs (spironolactone and eplerenone) have been mostly studied at eGFR as low as 30 mL/min/1.73 m^2. Although limited evidence exists for use of beta-blockers among those who require kidney-replacement therapy, no overt safety risks have been identified, and their use in those with HF may be considered.

From the novel class of nonsteroidal MRAs, finerenone has been shown to reduce cardiovascular and kidney disease events in persons with T2D and CKD with an eGFR as low as 25 mL/min/1.73 m^2 [204,205]. In persons with comorbid HFmrEF or HFpEF, T2D, and CKD with albuminuria, the use of finerenone as the nonsteroidal MRA of choice appears reasonable. In other individuals with HFrEF, steroidal MRAs (spironolactone or eplerenone) are preferred if tolerated by the individual.

Hyperkalemia can occur with ACE inhibitors, ARBs, and MRAs, especially if eGFR is ≤45 mL/min/1.73 m^2. Hyperkalemia can limit uptitration or use of evidence-based doses of these therapies in HF and CKD [207]. The use of an SGLT2 inhibitor has been shown to lower risks of hyperkalemia related to MRA, and combination use may promote treatment persistence in practice [208]. Likewise, compared with an ACE inhibitor, ARNI carries a lower risk of hyperkalemia among individuals receiving MRA and may lead to less MRA discontinuation [209]. The use of potassium binders such as patiromer and sodium zirconium cyclosilicate may be considered to facilitate use of these therapies among individuals who experience therapy-related hyperkalemia.

Many therapies used in both HF and CKD lower intra-glomerular pressures, and treatment initiation may result in acute eGFR decline, especially if the individual has volume depletion. This eGFR decline is not associated with renal safety signals in clinical trials with or without HF [210,211]. As such, this hemodynamic effect should not prompt treatment discontinuation or de-escalation in most cases. If eGFR declines by >30 % within a week of treatment initiation, and volume

Summary of Medications

	ASCVD	HF	Kidney	GI	Liver	GU	Bone	Eye	Weight	BP	Glucose	Hypoglycemia	DKA	LDL-C	TG	Other
Weight-reducing medications																
GLP-1 RA	++	+	++	↑↑	+				↓↓↓	↓	↓			↓	↓	
GIP/GLP1-RA				↑↑	+				↓↓↓	↓	↓			↓	↓	
Phentermine/ topiramate			↑ Creatinine					Glaucoma	↓↓	↓				↓	↓	↑ Mood/cognition disorders Paresthesia
Naltrexone/ bupropion				↑				↑ Glaucoma	↓						↓	↑ Mental/mood disorders ↑ Seizures
Orlistat				↑↑					↓	↓				↓	↓	
Phentermine								Glaucoma	↓							
Glucose-reducing medications																
Metformin			eGFR <30[a]	↑							↓↓					
GLP-1 RA	++	+	++	↑↑	+				↓↓	↓	↓↓↓			↓	↓	
GIP/GLP-1 RA				↑↑					↓↓	↓	↓↓↓			↓	↓	
SGLT2i	+	++	++ Dialysis[b]			↑ Mycotic infections			↓	↓	↓↓		↑[c]	↑	↓	↓ Hyperkalemia ↓ Uric acid ↑ Mg[c]
TZD	+	↑			++		↑		↑	↓	↓↓				↓	
DPP4i		↑ HF hospitalizations[d]	Dose adjust[e]								↓↓					
Insulin		↑ HF risk[f]	↑↑ Hypoglycemia risk						↑↑		↓↓↓	↑↑↑				
SU			↑ Hypoglycemia risk						↑		↓↓	↑↑				
GLN			↑ Hypoglycemia risk						↑		↓	↑				
AGI				↑↑							↓					
Colesevelam	+			↑							↓			↓	↑	
BCR-QR	+			↑↑							↓					
Pramlintide				↑↑					↓		↓	↑				

++ Strong benefit | + Modest benefit | Mild benefit | ↑ Increased value or incidence | ↓ Decreased value or incidence | Mild risk | Modest risk and/or precaution/warning | Contraindicated

[a] Contraindicated if eGFR <30 mL/min/1.73 m^2 due to increased risk of lactic acidosis.
[b] Contraindicated in hemodialysis.
[c] In metabolically stressful conditions.
[d] Possibly increased HF hospitalizations with saxagliptin and alogliptin.
[e] Except linagliptin.
[f] Due to fluid retention.

AGI = alpha glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; BCR-QR = bromocriptine–quick release; BP = blood pressure; DKA = diabetic ketoacidosis; DPP4i = dipeptidyl peptide 4 inhibitor; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GIP = glucose-dependent insulinotropic polypeptide; GLN = glinide; GLP-1 RA = glucagon-like peptide 1 receptor agonist; GU = genitourinary; HF = heart failure; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; SGLT2i = sodium glucose cotransporter 2 inhibitor; SU = sulfonylurea; TG = triglyceride; TZD = thiazolidinedione.

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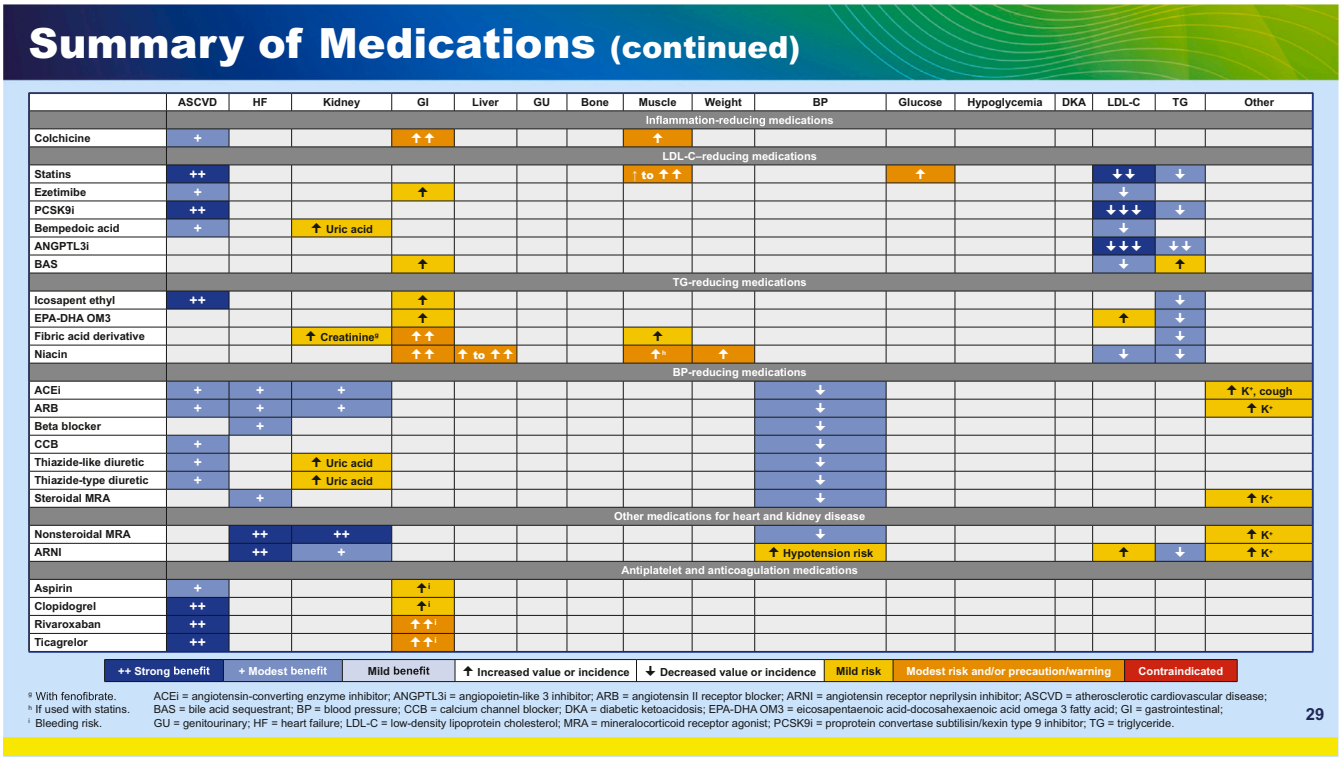

depletion is excluded, alternative etiologies should be evaluated and concomitant diuretic adjustments may be considered.

Monitoring of UACR and natriuretic peptides may be considered to evaluate CKD and HF progression. Declines in these biomarkers with therapy have been associated with improved clinical outcomes [205]. Specifically, a sustained reduction of ≥30 % in albuminuria is considered a surrogate for good renal outcome.

2.4. *Implications for management*

2.4.1. *Summary of medications*

Along with lifestyle recommendations, pharmacotherapy is usually necessary to address cardiorenal and metabolic conditions. The tables provide a brief summary of the most common benefits, concerns, and contraindications for medication classes commonly used for persons with obesity, T2D, hyperlipidemia, hypertension, HF, CKD, or ASCVD (for whom an anti-inflammatory or antiplatelet medication might be prescribed). Treatment decisions should be made based on good clinical judgement, individuals' needs and characteristics, product indications and restrictions, clinical practice guidelines, and other relevant factors.

2.4.1.1. Weight-reducing medications. Recommended anti-obesity medications include GLP-1 RA–based agents and phentermine/topiramate. Naltrexone/bupropion, orlistat, and phentermine are also available, although weight reduction with these agents is not as robust. GI side effects are the most common, usually transient, occurring during dose escalation, and mitigated by slow up-titration of the medications.

GLP-1 RA–based medications indicated for obesity management include once-weekly semaglutide 2.4 mg, liraglutide 3.0 mg, and the dual GIP/GLP-1 RA tirzepatide; the same compounds (at lower doses for semaglutide and liraglutide) are also used for glucose control in T2D. All GLP-1 RA–based medications reduce lipids, BP, and glucose as well as weight [67]. Semaglutide 2.4 mg has demonstrated cardiovascular benefits in persons with obesity [68,132]. Adverse effects are primarily gastrointestinal and transient, occurring during dose escalation; these effects can be minimized with slow titration [67].

Weight reduction with phentermine/topiramate is less robust than that with GLP-1 RA–based agents, although this agent also improves cardiovascular risk factors such as lipids and BP. Increased heart rate and increased risk of mood and sleep disorders and impaired cognitive function, as well as increased creatinine may occur. Phentermine/topiramate is contraindicated in persons with untreated closed-angle glaucoma [67].

Naltrexone/bupropion is associated with increased gastrointestinal effects, suicidal thoughts and behaviors, risk of seizure, and, rarely, BP increases and closed-angle glaucoma [67]. The effects of orlistat on weight are modest, but it was shown to reduce the risk of progression to T2D in a prediabetic population. This agent is associated with significant gastrointestinal adverse effects [67].

2.4.1.2. Glucose-reducing medications. Thorough reviews of the attributes of antihyperglycemic classes can be found elsewhere [142]. Compared with sulfonylureas, metformin is associated with increased cardiovascular safety and more durable antihyperglycemic effects. This agent does not promote hypoglycemia and may induce mild weight loss. It should not be initiated if eGFR is <45 mL/min/1.73 m^2, but established therapy may be continued with stable eGFR ≥30 mL/min/1.73 m^2 [37,212]. Vitamin B12 deficiency can develop, and supplementation may be needed to address associated anemia and/or peripheral neuropathy [213]. Among persons with prediabetes, metformin may delay progression to T2D [214].

GLP-1 RAs and the GIP/GLP-1 RA yield robust glycemic reductions as well as decreases in weight, BP, and lipids and carry a low risk of hypoglycemia. Most GLP-1 RA–based medications are given as injections (daily or weekly); currently one oral formulation is available. Dulaglutide, liraglutide, and injectable semaglutide have been shown to improve cardiovascular outcomes [215–217]. Gastrointestinal side effects can be mitigated by careful, slow dose titration. GLP-1 RAs are contraindicated in persons with a personal or family history of

medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, and caution should be exercised in persons with a history of acute pancreatitis. Exenatide is contraindicated if eGFR is <30 mL/min/1.73 m^2, and renal function should be monitored with all GLP-1 RAs, especially in persons with nausea and possible dehydration [218].

SGLT2 inhibitors reduce glycemia, weight, and BP. The class reduces HF hospitalizations and improves kidney function; some SGLT2 inhibitors have been shown to reduce the risk of other cardiovascular events [219–224]. Dapagliflozin and empagliflozin have been shown to improve HF and/or CKD outcomes in persons without diabetes [139,225]. The cardiorenal benefits of SGLT2 inhibitors are independent of glucose lowering, and the class may be used to an eGFR <20 mL/min/1.73 m^2. However, glucose reductions diminish as eGFR declines, and these agents are contraindicated in dialysis patients [218]. Adverse effects include increased risk of genital mycotic infections and LDL-C increases. Necrotizing fasciitis of the perineum is a rare complication. In persons with T1D or insulinopenic T2D, concomitant use of insulin and SGLT2 inhibitors may increase diabetic ketoacidosis risk [226].

The TZD pioglitazone may improve cardiovascular outcomes and MASLD/MASH [126,130,176,182]. TZDs have robust A1C-lowering effects and carry a low risk of hypoglycemia but increase the risk of weight gain, edema, HF exacerbation, and osteoporotic fractures [142,227]. Side effects can be mitigated by utilizing smaller doses (pioglitazone 15 or 30 mg/day). Concomitant use of SGLT2 inhibitors and/or diuretic therapy can mitigate fluid retention, whereas insulin may aggravate fluid retention.

DPP4 inhibitors prolong the half-life of endogenous incretin hormones but are less efficacious in A1C reduction than GLP-1 RAs. They also lack the weight loss and cardiovascular benefits of GLP-1 RAs. A possible increase in HF hospitalizations with saxagliptin has not been shown with other DPP4 inhibitors. Dosage adjustments in CKD are required for all DPP4 inhibitors except linagliptin [142].

Although insulin has the greatest glucose-lowering potential of all antihyperglycemic agents, in practice insulin is limited by the risk of hypoglycemia. Weight gain is also common, due to both the anabolic effects of the hormone and increased caloric consumption in fear of (or as a treatment for) hypoglycemia. In T2D, insulin (usually as basal insulin) should be started when glucose cannot be controlled with other agents, and the insulin regimen should be intensified as the disease progresses (see detailed reviews of insulin therapy in T2D) [142]. CGM (or structured SMBG for persons without access to CGM) is essential for patients on insulin therapy to ensure optimal dosing and safety. Glucagon should be prescribed for all patients on insulin.

Sulfonylureas elicit relatively potent glycemic reductions initially, but side effects may include hypoglycemia and weight gain. Glinides are short-acting insulin secretagogues that may not be as efficacious as sulfonylureas, but their shorter half-life and meal-time usage is associated with a lower risk of hypoglycemia [142].

Taken three times daily, AGIs modestly reduce A1C levels but might be associated with various gastrointestinal adverse effects. In prediabetes, these agents delayed progression to T2D [228]. Liver disease in persons with CKD treated with AGIs has been reported [142].

The bile acid sequestrant colesevelam has a modest glucose-lowering effect in addition to lowering LDL-C, but its use may be limited by gastrointestinal symptoms and triglyceride elevations in persons with pre-existing hypertriglyceridemia [142,229].

Bromocriptine-quick release (BCR-QR) reduces A1C without hypoglycemia or weight gain and may improve cardiovascular outcomes [230]. The major adverse effects include nausea and orthostatic hypotension, which can be mitigated by careful dose titration [142].

Pramlintide is an injectable amylin analog agent administered with insulin prior to meals to slow gastric emptying. It may contribute to hypoglycemia due to its co-administration with insulin. Insulin dosages need to be reduced when pramlintide is initiated and titrated [142].

2.4.1.3. Inflammation-reducing medications. An anti-inflammatory medication developed to treat gout flares, colchicine reduces hsCRP. In persons with established ASCVD, low dose colchicine reduced the risk of MACE events, including MI, stroke, and coronary revascularization risk [118]. Gastrointestinal symptoms are the most common adverse effects. Myotoxicity may occur, especially if used with a statin.

2.4.1.4. LDL-C–reducing medications. Comprehensive reviews of LDL-C and triglyceride-lowering agents are available elsewhere [31,87]. Statins, the mainstay of lipid-lowering therapy, reduce both LDL-C and triglycerides and have demonstrated consistent reductions in ASCVD in numerous CVOTs [31,87]. Myopathy and in rare cases rhabdomyolysis are the primary adverse effects of concern. Worsening glucose tolerance and hastened development of T2D may also occur, but these effects are outweighed by the ASCVD benefits [231,232].

Ezetimibe, a cholesterol absorption inhibitor, is often used adjunctively with statins or other non-statin agents to further lower LDL-C [31,87]. In Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the cardiovascular benefit was additive to baseline statin therapy, especially among persons with T2D [82]. Ezetimibe is generally well tolerated but can cause some GI discomfort.

PCSK9 inhibitors, which include formulations based on monoclonal antibodies (mAb) and small interfering RNA (siRNA) have been studied mainly in combination with statins and yield robust LDL-C reductions. The mAb compounds, which are injected bimonthly or monthly, have demonstrated substantial reductions in ASCVD risk [31,87]. A CVOT is underway for the siRNA formulation, which, as maintenance therapy, is administered via subcutaneous injection in a clinician's office every 6 months.

Bempedoic acid is an oral agent that lowers LDL-C by inhibiting ATP citrate lyase, a precursor of cholesterol synthesis that is available alone and in a single-pill combination with ezetimibe. In a statin intolerant population, bempedoic acid reduced ASCVD events [83]. It is associated with increases in uric acid and gout, and tendon rupture is a rare complication [87].

An ANGPTL3 inhibitor, evinacumab is administered by once monthly infusion to treat homozygous familial hypercholesterolemia. At this time, this therapy is generally prescribed by a lipid specialist.

Bile acid sequestrants were used more frequently before statins became available. These agents may cause significant gastrointestinal distress and can interfere with the absorption of other medications. In addition, they may modestly increase triglyceride levels. CVOTs involving small numbers of patients have shown a neutral to mild benefit [87].

2.4.1.5. Triglyceride-reducing medications. IPE is a purified formulation of EPA that reduces triglycerides and also confers cardiovascular benefits that may be mediated by anti-inflammatory, antiplatelet, antioxidant, and possibly other mechanisms beyond triglyceride reductions. IPE is associated with gastrointestinal adverse effects, increased bleeding, and atrial fibrillation [87].

Combination EPA/DHA formulations reduce triglycerides levels but do not appear to reduce cardiovascular risk. Adverse effects include gastrointestinal intolerance. Prescription strength formulations of EPA/DHA are preferred because over-the-counter formulations may have impurities; may be contaminated with saturated, polyunsaturated, and trans fats; or may not contain consistent quantities of EPA/DHA [87].

Fibrates may be the most potent triglyceride-lowering class, but these agents are associated with LDL-C increases, and fenofibrate may also increase creatinine. The risk of myopathy is increased when some fibrates are combined with certain statins; gemfibrozil is contraindicated with simvastatin [87].

Niacin reduces triglycerides and may also modestly reduce LDL-C. Adverse effects include flushing, pruritus, nausea, and glucose increases, as well as possibly increased myopathy when combined with

statins. Hepatotoxicity may occur, especially in persons taking over-the-counter niacin supplements [87]. One needs to weigh the benefits of niacin for improving dyslipidemia in light of recent reports of a potential negative impact on ASCVD [106].

2.4.1.6. Blood pressure–reducing medications. All BP-reducing classes have a well-established efficacy and safety profile. The ACE inhibitors, ARBs, CCBs, and diuretics have been shown to reduce the risk of ASCVD events, and ACE inhibitors, ARBs, beta blockers, and steroidal MRAs to reduce improve outcomes in HF [108,109].

The RAS-inhibiting classes (ACE inhibitors and ARBs) reduce albuminuria and slow progression of CKD in addition to reducing BP. Both ACE inhibitors and ARBs may increase potassium levels. In addition, ACE inhibitors are associated with dry cough in roughly 5–10 % of persons taking them; these individuals should be given an ARB instead. Do not combine an ACE inhibitor with an ARB, which may potentially cause harm [108,109].

Beta blockers have benefits in persons with ischemic heart disease and HFrEF and may also be beneficial in persons with atrial fibrillation or hypertrophic cardiomyopathy or in pregnant women with hypertension. If discontinued, beta blockers should be tapered rather than stopped abruptly [108,109].

CCBs include dihydropyridine and non-dihydropyridine CCBs. Dihydropyridine CCBs are associated with dose-related pedal edema, particularly in women. Beta blockers and non-dihydropyridine CCBs should not be used in combination because of increased risk of bradycardia and heart block [108,109].

Individuals taking a thiazide-type or thiazide-like diuretic should be monitored for hyponatremia and hypokalemia as well as uric acid and calcium. These agents should be used with caution in persons with a history of acute gout unless they are on uric acid–lowering therapy. They have also been associated with increases in insulin resistance and a higher risk of progression to T2D [108,109].

The steroidal MRAs spironolactone and eplerenone are typically used in resistant hypertension. These agents increase the risk of hyperkalemia. Spironolactone may also be associated with sexual dysfunction [108,109].

2.4.1.7. Other medications for heart and kidney disease. Finerenone is a nonsteroidal MRA that blocks sodium reabsorption through the mineralocorticoid receptor and also reduces overactivation of this receptor in the kidney, heart, and blood vessels [233,234]. In clinical trials, it reduced CKD progression, end-stage kidney disease, HF hospitalization, and other cardiovascular outcomes in persons with CKD and T2D [204]. It is associated with an increased risk of hyperkalemia. Finerenone should not be initiated if eGFR is <25 mL/min/1.73 m^2, and it is contraindicated in persons with adrenal insufficiency.

The ARNI sacubitril/valsartan is a single-pill combination of a neprilysin inhibitor (sacubitril) and an ARB (valsartan). In persons with HFrEF, sacubitril/valsartan reduced BP and the risk of death and HF hospitalizations; it may also help preserve kidney function [191,235,236]. Modest decreases in triglycerides and increases in HDL-C and LDL-C have been reported [237]. Sacubitril/valsartan may increase the risk of hypotension, hyperkalemia, and acute renal failure, and it should not be used with other RAS inhibitors, including ARBs, ACE inhibitors, or aliskiren.

2.4.1.8. Antiplatelet and anticoagulation medications. All agents that hinder platelet formation and/or coagulation carry a risk of gastrointestinal bleeding, which can be serious. Low-dose aspirin (75–100 mg), with a long-established efficacy and safety profile, is frequently combined with other antiplatelet agents (DAPT) or with NOACs, depending on the specific condition being treated and/or bleeding risk [238,239].

P2Y12 inhibitors, including clopidogrel, prasugrel, and ticagrelor, directly reduce platelet activation and the amplification of arterial thrombus formation by blocking the platelet P2Y12 receptor. Clopidogrel is a thienopyridine prodrug that irreversibly blocks P2Y12 via active metabolites, whereas ticagrelor reversibly binds P2Y12 and does not require metabolic activation [238,239].

The NOAC rivaroxaban is a direct oral anticoagulant that inhibits factor Xa, which plays a key role in the blood coagulation pathway leading to thrombin generation and clot formation [238,239].

2.5. Future outlook and conclusions

With the original DCRM publication [8], we sought to bridge the gap between separate, individual specialties and make integrated recommendations that could be directly applied to complex individuals within primary care or specialty practices. With this updated, expanded, and revised edition of the DCRM, we hope to further help clinicians develop treatment plans that lead to improved health for persons with DCRM.

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Declaration of competing interest

None of the Task Force members received monetary renumeration for their contributions to the creation or writing of this consensus document. See the Supplementary Appendix for full declarations of competing interests for each author.

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Appendix A. Supplementary data

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