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CLINICAL PRACTICE GUIDELINES

2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American Diabetes Association, the Obesity Association, a division of the American Diabetes Association, and the American Society of Nephrology

Writing Committee Members*

Chiadi E. Ndumele, MD, PhD, MHS, FAHA, Chair; Fatima Rodriguez, MD, MPH, FAHA, FACC, Vice Chair; Dave L. Dixon, PharmD, FAHA, FACC, BCACP, CLS, JC Liaison†; Sadiya S. Khan, MD, MSc, FAHA, FACC, JC Liaison†; Debabrata Mukherjee, MD, MS, FAHA, FACC, JC Liaison‡; Mandeep Bajaj, MBBS, FAHA§; Sripal Bangalore, MD, MHA, FAHA, FACC; Biykem Bozkurt, MD, PhD, FAHA, FACC; Khadijah Breathett, MD, MS, FAHA, FACC; Shoa L. Clarke, MD, PhD, FAHA; Ian H. de Boer, MD, MS, FAHA‖; David H. Ellison, MD, FASN, FAHA; Lorraine S. Evangelista, PhD, RN, FAHA; Sean P. Heffron, MD, MS, MSc, FAHA; Dhruv S. Kazi, MD, MSc, MS, FAHA, FACC; Ambar Kulshreshtha, MD, PhD, FAHA; Ildiko Lingvay, MD, MPH, MSCS, FAHA¶; Cecilia C. Low Wang, MD, FAHA; Claudia A. Mercado#; John Magaña Morton, MD, MPH, MHA; Ian J. Neeland, MD, FAHA; Neha Pagidipati, MD, MPH, FAHA, FACC; Tiffany M. Powell-Wiley, MD, MPH, FAHA; Janani Rangaswami, MD, FAHA; Goutham Rao, MD, FAHA; Nosheen Reza, MD, FAHA, FACC**; Anum Saeed, MD, FAHA; Wendy St. Peter, PharmD, FAHA; J. Bradley Starks#; Madeline Sterling, MD, MPH, FAHA; Amy W. Talbot, MPH††; Andrew H. Tran, MD, MPH, MS, FAHA; Katherine R. Tuttle, MD, FASN, FAHA; Lisa B. VanWagner, MD, MSc, FAHA; Amanda R. Vest, MBBS, MPH, FAHA, FACC; Salim S. Virani, MD, PhD, FAHA, FACC

AIM: The "2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome" retires, replaces, and expands upon the "2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults." The primary intended audience for this guideline is clinicians who care for patients across the spectrum of cardiovascular-kidney-metabolic syndrome, an interrelated condition characterized by the interconnections among metabolic risk factors (including obesity and type 2 diabetes), chronic kidney disease, and cardiovascular disease.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Joint Committee on Clinical Practice Guidelines liaison. ‡Former ACC/AHA Joint Committee on Clinical Practice Guidelines member; current member during the writing effort. §ADA representative. ‖ASN representative. ¶The Obesity Association representative. #Patient advocate representative. **JCPM representative. ††Former AHA/ACC joint staff; current staff member during the writing effort.

Peer Review Committee Members and AHA/ACC Joint Committee on Clinical Practice Guidelines Members, see page __.

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METHODS: A comprehensive literature search was conducted from October 29, 2024, to April 14, 2025, to identify clinical studies, systematic reviews and meta-analyses, and other evidence conducted on human subjects that were published since 2015 in English from MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline.

STRUCTURE: The focus of this clinical practice guideline is to create a living, working document that provides current knowledge in the field of cardiovascular-kidney-metabolic syndrome aimed at all practicing cardiologists, endocrinologists, nephrologists, and primary care and specialty clinicians who manage these patients.

Key Words: AHA Scientific Statements ■ atherosclerosis ■ atrial fibrillation ■ blood pressure/hypertension ■ cardiovascular disease ■ cardiovascular kidney metabolic ■ coronary disease ■ diabetes ■ diagnosis ■ heart failure ■ kidney disease(s), chronic ■ management, cardiovascular kidney metabolic ■ MASLD ■ metabolic syndrome ■ overweight/obesity ■ peripheral artery disease ■ renal insufficiency ■ risk factors ■ screenings ■ secondary prevention ■ venous thromboembolism ■ weight loss

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TOP TAKE-HOME MESSAGES

1. **Cardiovascular-Kidney-Metabolic Syndrome Staging:** Cardiovascular-kidney-metabolic (CKM) syndrome staging is recommended for youths and adults to prevent CKM stage progression, to tailor therapy to absolute risk, to reduce cardiovascular events and loss of kidney function across the life course, and to promote CKM stage regression through lifestyle changes and weight loss.
2. **Quantify Risk Using the PREVENT Equations:** Individuals at risk for cardiovascular disease (CVD) (CKM syndrome stage 0-3) should have their risk quantified with the PREVENT (Predicting Risk of Cardiovascular Disease EVENTS) equations to estimate 10- and 30-year risk for atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and total CVD. PREVENT estimates inform CKM syndrome staging, with ≥20% predicted 10-year CVD risk serving as 1 criterion for CKM syndrome Stage 3. A ≥7.5% predicted 10-year CVD risk further informs the prioritization of pharmacotherapies for the treatment of CKM syndrome.
3. **Routinely Assess for CKM Risk Factors:** Routine assessments for metabolic risk factors and kidney function are recommended among all adults, as well as selected assessments for pre-HF, metabolic dysfunction–associated steatotic liver disease (MASLD), and obstructive sleep apnea (OSA) in subsets of individuals.
4. **Evaluate and Address Social Determinants of Health:** Routine assessments for social determinants of health (SDOH) that are closely linked with the development of CKM syndrome and its complications are recommended. Addressing adverse SDOH when identified is a key component of holistic care for CKM syndrome.
5. **Emphasize Interdisciplinary Care With a CKM Coordination Point Person:** Use of interdisciplinary care models for those with overlap among the CKM conditions of type 2 diabetes (T2D), chronic kidney disease (CKD), and CVD is recommended to facilitate patient-centered care. The need for a point person is emphasized, to coordinate efforts of the CKM interdisciplinary team, to facilitate implementation of evidence-based care and guideline-directed medical therapy (GDMT), and to support patients and clinicians.
6. **Assess and Treat Overweight and Obesity:** Assessments for overweight/obesity and abdominal adiposity with both body mass index (BMI) and waist circumference are recommended to characterize risk related to excess adiposity. Overweight and obesity should be addressed to prevent CKM syndrome progression and to promote CKM syndrome regression. Support for lifestyle modification is emphasized, with adjunctive use of obesity pharmacotherapies and metabolic and bariatric surgery as needed to facilitate weight loss.
7. **Utilize Cardioprotective Antihyperglycemic Therapies in Diabetes**: Among patients with T2D with CVD or at increased risk for CVD, in addition to lifestyle modification, weight management, and risk factor control, utilization of cardioprotective antihyperglycemic GDMT is recommended, including sodium–glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 (GLP-1)–based therapy, or both, to improve cardiovascular and kidney outcomes. The choice of agent should be guided by clinical comorbidities such as CKD, ASCVD, HF, obesity, severe hyperglycemia, and MASLD.
8. **Assess for CKD and Utilize Kidney Protective Agents:** Use of both estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) is recommended to characterize CKD and guide the use of kidney-protective agents to confer both cardiovascular and kidney benefits. For patients with CKD and T2D or CKD and albuminuria, renin-angiotensin system inhibitors (RASi) and SGLT2i should be used as first-line therapy. If albuminuria persists among patients with CKD and T2D, nonsteroidal mineralocorticoid receptor antagonist (MRA) or a GLP-1–based therapy should be added for further kidney and cardiovascular protection.
9. **Address CKM Risk Factors in Patients With ASCVD:** Management of ASCVD should emphasize CKM syndrome comorbidities, including obesity treatment through lifestyle modification, pharmacotherapy, and, when appropriate, metabolic and bariatric surgery; the use of cardioprotective antihyperglycemic agents for T2D; and the use of kidney-protective agents for CKD to reduce the risk for adverse cardiovascular events and loss of kidney function.
10. **Address CKM Risk Factors in Patients With HF:** CKM factors should be incorporated into HF

management. For heart failure with reduced ejection fraction (HFrEF), emphasize the cardiovascular and kidney benefits of RASi (angiotensin receptor-neprilysin inhibitors [ARNI], angiotensin-converting enzyme inhibitors [ACEi], angiotensin II receptor blockers [ARB]) and SGLT2i as part of quadruple therapy with beta blockers and steroidal MRAs. For heart failure with mildly reduced ejection fraction (HFmrEF)/heart failure with preserved ejection fraction (HFpEF), use SGLT2i as first-line GDMT, add GLP-1–based therapies in patients with obesity or other CKM risk factors, and consider nonsteroidal MRAs in those with T2D and CKD to reduce adverse cardiovascular events and loss of kidney function.

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, based on systematic methods to evaluate and classify evidence, provide a foundation for delivering high-quality cardiovascular care. When applicable, the guidelines also provide economic value statements that apply cost-effectiveness analyses. The methodology for these economic value statements can be found in the AHA/ACC Statement on Cost Value Methodology.[1] The ACC/AHA Guideline Core Principles and Development Process publication describes best practices for cardiology clinicians and provides additional background on the methodology used in the creation of guidelines.[2] Details about the alignment between the US Food and Drug Administration (FDA) approval processes for drugs and devices and the AHA/ACC guideline methodology can be found in the Guidance for Incorporating FDA Processes publication.[3] Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances, and should not replace clinical judgment. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are the official policy of the ACC and AHA. For some guidelines, the ACC and AHA collaborate with other organizations.

Catherine M. Otto, MD, FAHA, FACC
Chair, ACC/AHA Joint Committee on
Clinical Practice Guidelines

1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this guideline are evidence-based whenever possible. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from October 2024 to April 2025. Select key studies published through November 2025 were added by the guideline writing committee as appropriate. The final evidence tables summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present guideline are not all-inclusive.

1.2. Organization of the Writing Committee

The writing committee included representation from general, preventive, and interventional cardiology, endocrinology, nephrology, bariatric surgery, family practice, internal medicine, pediatrics, gastroenterology, cardiovascular epidemiology, health economics, advanced practice nursing, and clinical pharmacology, in addition to patient advocates. The writing committee included representatives from the AHA, ACC, American Diabetes Association (ADA), including ADA Obesity Alliance representation, and the American Society of Nephrology.

1.3. Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found online. Appendix 1 of this guideline lists writing committee members' comprehensive and relevant RWI.

1.4. Peer Review Committee

The Joint Committee appointed a peer review committee to review the guideline. The peer review committee comprised individuals nominated by the ACC, AHA, and the collaborating organizations. Appendix 2 lists reviewers' comprehensive and relevant RWI.

1.5. Scope of the Guideline

This guideline is intended to be a resource for clinical and public health professionals. Clinicians should be advised that this guideline retires and replaces the previously published "2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults." This guideline does not provide recommendations regarding the general prevention and management of the following conditions: blood pressure (BP) management, chronic coronary disease (CCD), dyslipidemia/blood cholesterol, heart failure (HF), or peripheral artery disease (PAD). These topics are the focus of other AHA/ACC guidelines as listed in Table 1.

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Table 1. Associated AHA/ACC Publications

Title	Organization	Publication Year (Reference)
Guidelines		
Primary prevention of CVD	ACC/AHA	2019[2]
Prevention of stroke in patients with stroke and transient ischemic attack	AHA/ASA	2021[3]
Management of HF	AHA/ACC/HFSA	2022[4]
Management of patients with CCD	AHA/ACC/ACCP/ASPC/NLA/PCNA	2023[5]
Management of AF	ACC/AHA/ACCP/HRS	2023[6]
Management of lower extremity PAD	ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS	2024[7]
Prevention, detection, evaluation, and management of high BP in adults	AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM	2025[8]
Management of dyslipidemia	ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA	2026[9]
Other Relevant Documents		
Value of primordial and primary prevention for CVD	AHA	2011[10]
Social determinants of risk and outcomes for CVD	AHA	2015[11]
Promoting risk identification and reduction of CVD in women through collaboration with OB and GYN	AHA/ACOG	2018[12]
Use of risk assessment tools to guide decision-making in the primary prevention of ASCVD	AHA	2019[13]
T2D and HF	AHA/HFSA	2019[14]
Cardiovascular considerations in caring for pregnant patients	AHA	2020[15]
Obesity and CVD	AHA	2021[16]
OSA and CVD	AHA	2021[17]
Life's Essential 8	AHA	2022[18]
Nonalcoholic fatty liver disease and cardiovascular risk	AHA	2022[19]
Comprehensive management of cardiovascular risk factors for adults with T2D	AHA	2022[20]
CKM health	AHA	2023[1]
A synopsis of evidence for the science and clinical management of CKM health syndrome	AHA	2023[21]
Novel prediction equations for absolute risk assessment of total cardiovascular disease incorporating CKM health	AHA	2023[22]
Person-centered models for cardiovascular care	AHA	2023[23]
The role of primary care in achieving Life's Essential 8	AHA	2024[24]
Opportunities in the postpartum period to reduce CVD risk after APO	AHA	2024[25]
Implementation of obesity science into clinical practice	AHA	2024[26]
Management of obesity in adults with HF	ACC	2025[27]
Use of risk assessment to guide decision-making for BP management in the primary prevention of CVD	AHA	2025[28]
Risk-based primary prevention of HF	AHA	2025[29]
Medical weight management for optimization of cardiovascular health	ACC	2026[30]
Role of physical activity in obesity treatment and cardiometabolic health	AHA	2026[31]

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AANP, American Association of Nurse Practitioners; AAPA, American Academy of Physician Associates; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCP, American College of Clinical Pharmacy; ACOG, American College of Obstetricians and Gynecologists; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AF, atrial fibrillation; AGS, American Geriatrics Society; AHA, American Heart Association; AMA, American Medical Association; APhA, American Pharmacists Association; APMA, American Podiatric Medical Association; APO, adverse pregnancy outcome; ASA, American Stroke Association; ASPC, American Society for Preventive Cardiology; BP, blood pressure; CCD, chronic coronary disease; CKM, cardiovascular-kidney-metabolic; CVD; cardiovascular disease; GYN, gynecologists; HF, heart failure; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; NLA, National Lipid Association; NMA, National Medical Association; OB, obstetricians; OSA, obstructive sleep apnea; PAD, peripheral artery disease; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; SGIM, Society of General Internal Medicine; SIR, Society of Interventional Radiology; SVM, Society for Vascular Medicine; SVN, Society for Vascular Nursing; SVS, Society for Vascular Surgery; T2D, type 2 diabetes; and VESS, Vascular and Endovascular Surgery Society.

Table 2. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated December 2024)

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
Class 1 (STRONG) — **Benefit >>> Risk** **Suggested phrases for writing recommendations:** • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: - Treatment/strategy A is recommended/indicated in preference to treatment B - Treatment A should be chosen over treatment B	**Level A** • High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
Class 2a (MODERATE) — **Benefit >> Risk** **Suggested phrases for writing recommendations:** • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: - Treatment/strategy A is probably recommended/indicated in preference to treatment B - It is reasonable to choose treatment A over treatment B	**Level B-R (Randomized)** • Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
Class 2b (WEAK) — **Benefit ≥ Risk** **Suggested phrases for writing recommendations:** • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	**Level B-NR (Nonrandomized)** • Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
Class 3: No Benefit (MODERATE) — **Benefit = Risk** **(Generally, LOE A or B use only)** **Suggested phrases for writing recommendations:** • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	**Level C-LD (Limited Data)** • Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Class 3: HARM (STRONG) — **Risk > Benefit** **Suggested phrases for writing recommendations:** • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	**Level C-EO (Expert Opinion)** • Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

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The primary intended audience for this guideline is clinicians who care for patients across the spectrum of cardiovascular-kidney-metabolic (CKM) syndrome, a condition characterized by the interconnections among metabolic risk factors (including obesity and type 2 diabetes [T2D]), chronic kidney disease (CKD), and cardiovascular disease (CVD).[1] It aims to provide succinct guidance on the diagnosis, staging, treatment, and monitoring of patients with CKM syndrome. The clinical recommendations provided are intended for adults (≥18 years of age); recommendations for youths (<18 years of age) are anticipated to be the focus of future guideline documents. The guideline emphasizes the use of interdisciplinary care models to provide patient-centered, harmonized care, as well as the importance of addressing adverse social determinants of health (SDOH) to facilitate the holistic management of CKM syndrome. The guidelines further emphasize lifestyle modification and weight management to address the root cause of CKM syndrome, excess, and dysfunctional adiposity. For those individuals in later CKM stages, the document provides guidance on the use of cardiovascular and kidney-protective therapies with proven benefits and incorporates new updates in cardiovascular risk prediction to inform the targeting of preventive therapies. The guideline also provides statements about the cost value of several therapies indicated for the management of CKM syndrome, with a focus on providing these statements for brand-name medications. While these statements are located next to their related clinical recommendations, they are not intended to inform clinical decision-making for individual patients.

In developing this guideline, the writing committee reviewed previously published guidelines and other relevant clinical policy statements. Table 1 contains a list of AHA/ACC publications deemed pertinent to this writing effort and is intended for use as a resource, thus obviating the need to repeat existing guideline recommendations.

1.6. Class of Recommendations and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation and encompasses the estimated benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the type, quantity, and consistency of data from clinical trials and other sources (Table 2).

2. DEFINITIONS AND CLASSIFICATION

2.1. Definitions

CKM syndrome is a clinical syndrome with stages from 1 to 4, which are explained in Section 2.3, "CKM Syndrome and Stage Definitions." The writing committee recognizes that there are many frequently used terms to define the conditions that comprise CKM syndrome, conditions that are commonly observed in patients with CKM syndrome, and therapies that are used to treat CKM syndrome. Therefore, brief definitions are included in this section.

Guideline-directed medical therapy (GDMT): Encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

Additional Definitions for Conditions That Comprise CKM Syndrome

Clinical atherosclerotic cardiovascular disease (ASCVD): Includes a history of acute coronary syndromes, myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or PAD.

Clinical HF: HF with clinical symptomatology including heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF).

T2D: Defined as a complex metabolic disorder characterized by resistance to the action of insulin (insulin resistance) and progressive impairment in insulin secretion leading to hyperglycemia.

Obesity: Defined as excess body fat that presents a risk to health, diagnosed by a body mass index (BMI) of ≥30 kg/m^2. Abdominal obesity is diagnosed by a waist circumference ≥88 cm among women or ≥102 cm among men.

CKD: Defined as persistently reduced glomerular filtration (eGFR <60 mL/min/1.73 m^2) or evidence of albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g) on at least 2 measurements 3 months apart.

Hypertension: Defined as an elevated systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg based on an average of ≥2 careful readings obtained on ≥2 occasions.

Kidney Failure: Defined as an eGFR chronically <15 mL/min/1.73 m^2 (stage 5 CKD) or a chronic need for renal replacement therapy (dialysis). It is formerly known as "end-stage kidney disease."

Prediabetes: Elevated glucose levels conferring risk for T2D development, defined as a fasting plasma glucose of 100 to 125 mg/dL, impaired glucose tolerance (2-hour glucose, 140-199 mg/dL) on a 75-gram oral glucose tolerance test, or a glycated hemoglobin A1C (HbA1c) of 5.7% to 6.4%.

Pre-HF: Defined as the presence of subclinical myocardial disease in terms of structural or functional abnormalities, evidence of increased filling pressure, or elevated cardiac biomarkers, in the absence of clinical HF symptomatology.

Additional Definitions for Conditions That Are Common in Patients With CKM Syndrome

Metabolic dysfunction–associated steatotic liver disease (MASLD): Characterized by hepatic steatosis in the setting

of metabolic risk factors such as obesity or T2D and was recently defined to replace nonalcoholic fatty liver disease.

Risk Enhancers for CKM Syndrome Progression: Clinical (eg, chronic inflammatory conditions, a history of adverse pregnancy outcomes [APOs]), social, or demographic factors, or a family history of diabetes or kidney failure, which are associated with a higher risk of CKM syndrome progression and may inform preventive therapeutic decisions. While many of these overlap with risk enhancers defined in the ACC/AHA/Multisociety 2026 Dyslipidemia Guideline,[1] there are also different factors identified for the 2 related but distinct outcomes (eg, CKM syndrome progression versus ASCVD).

Lifestyle, Medical, and Surgical Therapies Used to Treat CKM Syndrome

Glucagon-like peptide-1 (GLP-1)–Based Therapy With Proven Benefit: Pharmacologic agents that mimic or enhance the activity of the incretin hormone GLP-1, either alone or as part of a dual agonist that also mimics the activity of the hormone glucose-dependent insulinotropic polypeptide, with evidence for risk reduction in cardiovascular outcome trials. These may also be referred to as "incretin-based" or "incretin-related" therapies.

RASi: A class of drugs that inhibit the renin-angiotensin system and include angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), to lower BP, reduce proteinuria, and prevent progression of CVD and kidney disease.

Renin-Angiotensin-Aldosterone System Inhibitors (RAASi): A class of drugs that represent the RASi (eg, ACEi, ARB) and additionally include drugs that inhibit the aldosterone system (eg, MRAs).

Metabolic and Bariatric Surgery (MBS): A group of surgical procedures (eg, gastric bypass, sleeve gastrectomy) performed to induce weight loss and improve metabolic health by altering gastrointestinal anatomy and physiology to alter energy balance.

Lifestyle Management: Encompasses assessment of each individual's baseline behavioral habits and provides counseling and support regarding healthy lifestyle modifications. It includes facilitating heart-healthy eating patterns, regular physical activity, avoidance of all nicotine-delivery products, healthy sleep habits, and maintaining a healthy weight. This includes the lifestyle elements of the American Heart Association's Life's Essential 8,[2–4] in addition to stress management.

2.2. Abbreviations

Abbreviations	Meaning
ACEi	angiotensin-converting enzyme inhibitors
APO	adverse pregnancy outcome
ARB	angiotensin II receptor blockers
ARNI	angiotensin receptor–neprilysin inhibitor
ASCVD	atherosclerotic cardiovascular disease
BNP	B-type natriuretic peptide
BP	blood pressure
CAC	coronary artery calcium
CCD	chronic coronary disease
CI	confidence interval
CKD	chronic kidney disease
CKM	cardiovascular-kidney-metabolic
CVD	cardiovascular disease
DOAC	direct oral anticoagulants
eGFR	estimated glomerular filtration rate
GDM	gestational diabetes mellitus
GDMT	guideline-directed medical therapy
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
Hs	high-sensitivity
ICER	incremental cost-effectiveness ratio
LDL-C	low-density lipoprotein cholesterol
LSG	laparoscopic sleeve gastrectomy
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
MASLD	metabolic dysfunction–associated steatotic liver disease
MBS	metabolic and bariatric surgery
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
nsMRA	nonsteroidal mineralocorticoid receptor antagonist
NT-proBNP	*N*-terminal prohormone of B-type natriuretic peptide
OR	odds ratio
OSA	obstructive sleep apnea
PAD	peripheral artery disease
PREVENT	Predicting Risk of Cardiovascular Disease Events
QALY	quality-adjusted life-year
RAASi	renin-angiotensin-aldosterone system inhibitors
RASi	renin-angiotensin system inhibitors
RCT	randomized controlled trial
RR	relative risk
RYGB	Roux-en-Y gastric bypass
SDOH	Social Determinants of Health
SGLT2i	Sodium–glucose cotransporter-2 inhibitors
T2D	type 2 diabetes
UACR	urine albumin-to-creatinine ratio
VKA	vitamin K antagonist
VTE	venous thromboembolism

(*Continued*)

Table 3. CKM Syndrome Definition

Definition	CKM syndrome is a systemic disorder characterized by pathophysiological interactions among metabolic risk factors, CKD, and the cardiovascular system, leading to multiorgan dysfunction and a high rate of adverse cardiovascular outcomes. CKM syndrome includes both individuals at risk for CVD due to the presence of metabolic risk factors, CKD, or both, and individuals with existing CKD or CVD that is potentially related to or complicates metabolic risk factors. The increased likelihood of CKM syndrome and its adverse outcomes is further influenced by unfavorable conditions for lifestyle and self-care resulting from policies, economics, and the environment.
Simplified Definition	CKM syndrome is a health disorder due to connections among heart disease, kidney disease, diabetes, and obesity, leading to poor health outcomes.

CKD indicates chronic kidney disease; CKM, cardiovascular-kidney-metabolic; and CVD, cardiovascular disease.

2.3. CKM Syndrome and Stage Definitions

Synopsis

The definition of CKM syndrome (Table 3) reflects the substantial interconnections among metabolic risk factors, CKD, and CVD, and their synergistic impacts on morbidity and mortality, as outlined in the CKM Health Presidential Advisory.[1] The CKM syndrome definition serves as a starting point to define and describe the stages of CKM syndrome, to develop tools to screen and risk-stratify individuals for adverse outcomes linked to CKM syndrome, and to identify best practices for addressing CKM syndrome in clinical practice through resultant prompt initiation of evidence-based preventive and treatment strategies.[2] The multisystem interplay highlighted in the CKM syndrome definition further supports the avoidance of siloed subspecialty care for the management of the component conditions within CKM syndrome, emphasizes the importance of screening for CKM syndrome in both primary care and relevant subspecialty clinics, and underscores the value of interdisciplinary collaboration. The definition also recognizes the integral roles of SDOH and lifestyle factors in CKM health promotion and preservation across the life course. Furthermore, a unifying definition facilitates communication between the scientific and lay communities to underscore the importance of identifying CKM syndrome and addressing its interconnected components, through lifestyle modification, weight management, and targeted pharmacotherapies, for advancing public health.

The timely detection of CKM syndrome conditions with adverse clinical consequences is an important preventive public health opportunity, especially given the availability of multiple therapies with proven efficacy. CKM syndrome stages (Figure 1) reflect the typical pathophysiologic progression of CKM syndrome, from excess/dysfunctional adiposity (stage 1); to the presence of metabolic risk factors, CKD, or both (stage 2); to subclinical CVD, or the risk equivalents of very high-risk CKD or high predicted CVD risk (stage 3); to clinical CVD with concomitant CKM risk factors (stage 4). A healthy lifestyle and weight management are major deterrents to advancing CKM syndrome stages. The staging framework prevents the progression to higher CKM syndrome stages, which include the adverse clinical outcomes of CVD and kidney failure, and highlights the higher absolute CVD risk in later stages, when intensified therapeutic approaches will have the greatest net clinical benefit. CVD is a primary focus because it is the clinical outcome with the highest incidence and mortality burden in CKM syndrome. However, CKD is also a key focus, with progressively higher risk of CKD per the KDIGO (Kidney Disease: Improving Global Outcomes) risk classification (Figure 2) corresponding to later CKM stages, owing to increasing cardiovascular and kidney risk. The diagnostic criteria for CKM syndrome staging among adults are presented in Table 4.

2.3.1. Definitions for CKM Stage Components Among Youth

Synopsis

Metabolic risk factors and CKD increasingly emerge in youth (<18 years) and often persist and progress through adulthood. CKM staging is therefore indicated across the life course. Definitions for abnormal values of CKM risk factors in youth have pediatric-specific thresholds. Due to age-related growth changes throughout childhood, BMI percentiles are used for youth to diagnose overweight and obesity rather than the set BMI values used in adults.[1] Specific criteria are in Table 5, with additional percentile-based thresholds for class 2 and 3 obesity. For BP, children aged <13 years are classified using BP percentiles, whereas children aged 13 to 17 years are classified using the same BP thresholds as adults. Due to insufficient data identifying a specific threshold of childhood BP associated with adult cardiovascular outcomes, hypertension is defined using the normative BP distribution in healthy children.[2] Because among adolescents, the corresponding BP percentile is sometimes higher than adult thresholds, adult thresholds were adopted for adolescents to facilitate implementation.[3] Abnormal lipid level thresholds in children can be seen in Table 5. While a fasting lipid panel is preferred for dyslipidemia diagnosis, a nonfasting sample can also be used.[4] Definitions for abnormal glucose levels in children align with adult criteria (Table 5).[5]

3. EVALUATION AND DIAGNOSIS

3.1. Diagnostic Approach to CKM Staging

Recommendations for Diagnostic Approach to CKM Staging Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
1	B-NR	1. Among both youth (<18 y) and adults (≥18 y), CKM syndrome staging should be performed by assessing metabolic risk factors, kidney function (calculating eGFR, with additional UACR assessments in CKM stage ≥2), and CVD status to support prevention of CKM syndrome stage progression, promote regression of CKM syndrome, and personalize treatment of individuals according to their absolute CVD risk and expected net benefit of therapies.[1–3]

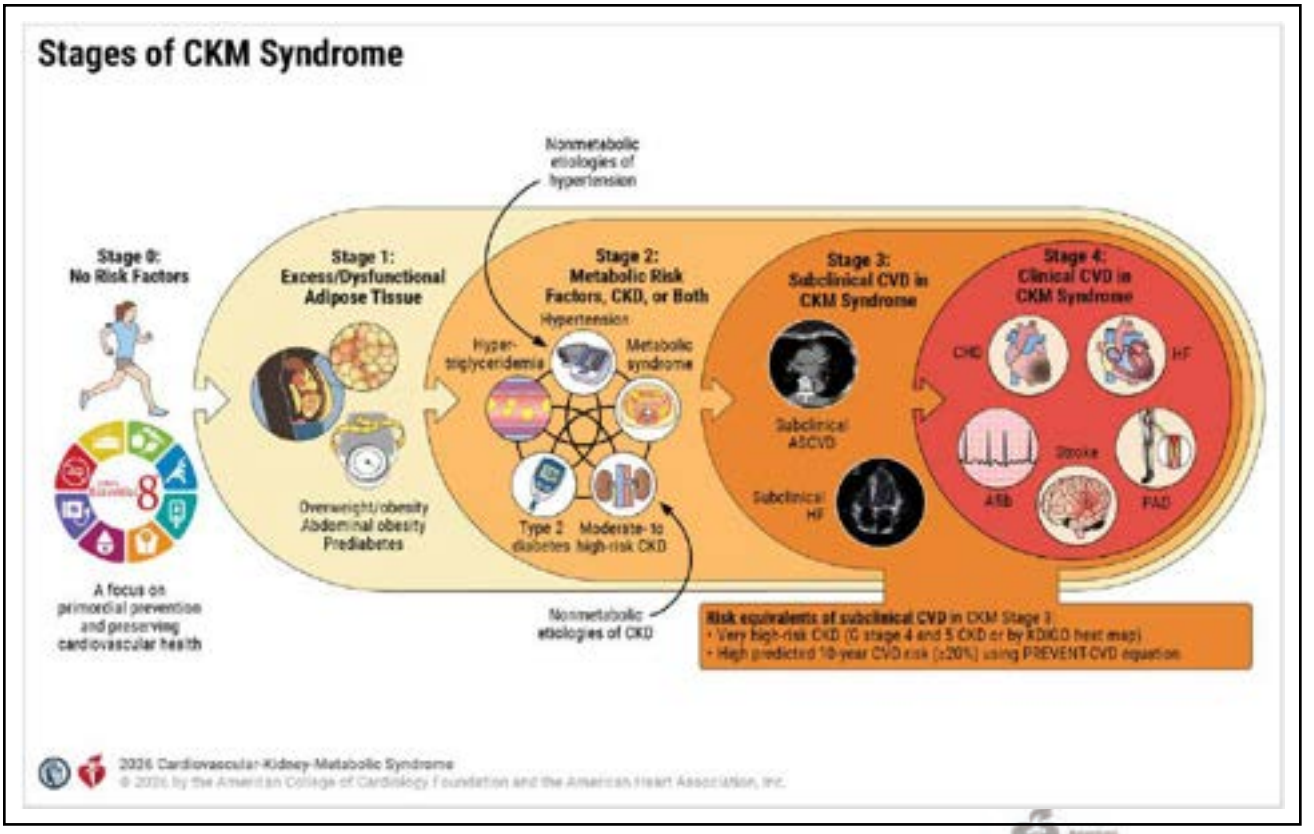

Figure 1. Stages of CKM Syndrome.
Adapted with permission from Ndumele et al.[1] Copyright 2023 American Heart Association, Inc. The CKM staging construct reflects the progressive pathophysiology and increasing absolute CVD risk along the spectrum of CKM syndrome. Stage 0 includes individuals without CKM syndrome with normal weight, normal glucose, normal blood pressure, normal lipids, normal kidney function, and no evidence of subclinical or clinical CVD; the focus in stage 0 CKM is primordial prevention and preserving cardiovascular health. CKM syndrome stage 1 includes individuals with excess adipose tissue, dysfunctional adipose tissue, or both. Excess adiposity is identified by either weight or abdominal obesity, and dysfunctional adipose tissue is reflected by prediabetes (elevated glucose or impaired glucose tolerance). CKM syndrome stage 2 includes individuals with metabolic risk factors (hypertriglyceridemia, hypertension, metabolic syndrome, or type 2 diabetes), moderate- to high-risk CKD, or both. Although hypertension and CKD are usually downstream of metabolic risk factors, the curved arrows represent individuals with nonmetabolic causes of these conditions; the risk implications and treatment approaches are similar. CKM syndrome stage 3 includes individuals with subclinical CVD with overlapping CKM risk factors (excess/dysfunctional adipose tissue, metabolic risk factors, or CKD) or those with the risk equivalents of very high-risk CKD or high 10-year predicted risk (≥20%) using the PREVENT risk equations. CKM syndrome stage 4 includes individuals with clinical CVD (coronary heart disease, HF, stroke, PAD, or atrial fibrillation) overlapping with CKM risk factors. Afib indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; PAD, peripheral artery disease; and PREVENT, Predicting Risk of Cardiovascular Disease Events.

Recommendations for Diagnostic Approach to CKM Staging (Continued)		
COR	**LOE**	**Recommendations**
2a	**B-NR**	2. Among adults at intermediate 10-y risk for ASCVD (PREVENT-ASCVD 5% to <10%) or select adults at borderline risk for ASCVD (PREVENT-ASCVD 3% to <5%) for whom decisions about preventive therapies remains uncertain, the presence of subclinical coronary atherosclerosis identified via coronary artery calcium (CAC) can be beneficial for informing optimal CVD prevention.[4–6]
2a	**B-NR**	3. Among adults with increased predicted 10-y risk of HF (PREVENT-HF ≥5%), evaluation for pre-HF using cardiac biomarkers (natriuretic peptides [B-type natriuretic peptide (BNP) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)], high-sensitivity cardiac troponin [hs-cTn]) can be beneficial to guide additional diagnostic testing (eg, cardiac imaging) and coordinated care for optimal HF prevention.[7–10]

Synopsis

The diagnosis of CKM syndrome stages requires assessment of metabolic health, kidney function, and cardiovascular risk factors, which enhances the identification of frequently unrecognized or asymptomatic CKM conditions. Identification of CKM syndrome stages can also guide efforts for prevention and treatment and promote the regression of CKM stage through marked lifestyle modification or substantial weight loss. It is important that CKM staging be performed when the patient is clinically stable, both for accuracy of staging at baseline and for repeatability and interpretability of changes in CKM stage during clinical follow-up. Anthropometric assessments ideally include measurement of waist circumference in addition to BMI, given the central role of

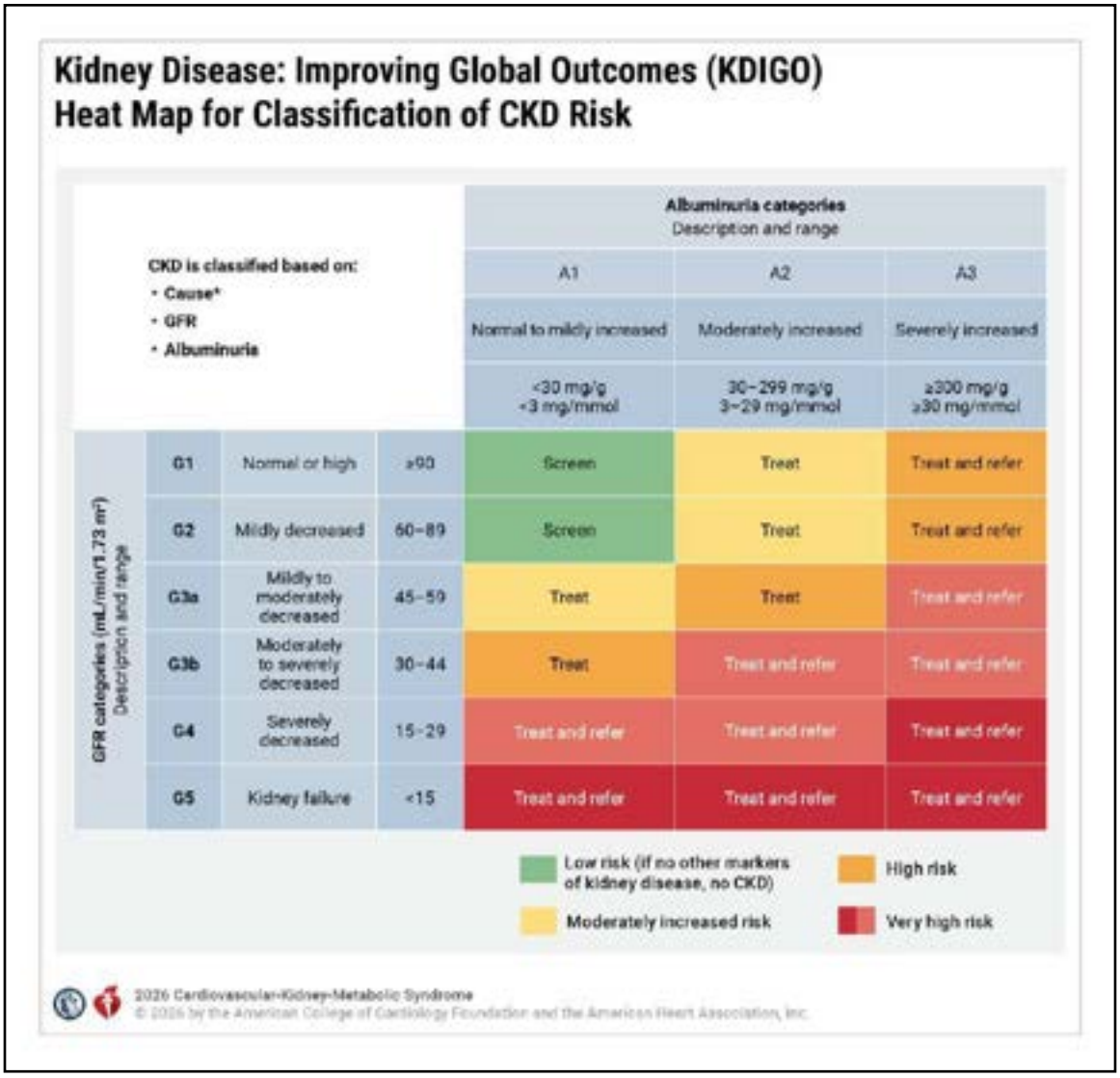

Figure 2. Kidney Disease: Improving Global Outcomes (KDIGO) Heat Map for Classification of CKD Risk.
Modified with permission from KDIGO via CC BY NC ND license.[3] Copyright 2022, KDIGO: Kidney Disease Improving Global Outcomes. Published by Elsevier Inc. on behalf of the International Society of Nephrology. "Treat" means that clinicians should initiate appropriate management for patients at risk for CKD progression or for cardiovascular disease as a consequence of CKD. "Refer" means consultation with the nephrology service should take place as needed depending on local arrangements regarding frequency of monitoring and timing of referral. *Cause reflects the etiology of CKD as diagnosed by the clinician. The majority of CKD cases in CKM syndrome are attributable to diabetes, hypertension, and other metabolic risk factors. However, kidney-protective therapies such as angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and sodium glucose cotransporter 2 inhibitors have demonstrated kidney and cardiovascular benefits for patients with CKD from metabolic etiologies as well as from some other causes. Therefore, the CKM staging construct is relevant for almost all patients with CKD. CKD indicates chronic kidney disease; CKM, cardiovascular-kidney-metabolic; GFR, estimated glomerular filtration rate; and KDIGO, Kidney Disease: Improving Global Outcomes. The colors depicted in this figure are not reflective of the American Heart Association/American College of Cardiology Class of Recommendation/Level of Evidence Table 2.

abdominal adiposity in CKM syndrome. Other direct/anthropometric measurements of body fat, when available, can provide further characterization of CKM risk. Measurement of UACR in addition to eGFR, to fully characterize CKD and related CVD risk, is advised in CKM stages 2 to 4 based on the higher observed prevalence of abnormal UACR in populations once metabolic risk factors or CKD are present. The identification of subclinical CVD (stage 3), either subclinical coronary atherosclerosis or pre-HF, can influence clinical management through CVD risk reclassification and enhanced prognostication to inform tailored intensified CVD prevention strategies for high-risk individuals.

Recommendation-Specific Supportive Text

1. Staging of CKM syndrome (Table 4) allows identification and treatment of individuals in different CKM syndrome stages according to their absolute CVD risk and the expected benefit of risk-reducing

Table 4. CKM Staging Definitions and Diagnostic Criteria for Adults

Stages of CKM Syndrome	Staging Criteria and Definition
Stage 0: No CKM risk factors	Individuals with normal BMI and waist circumference, normoglycemia, normotension, normal lipid profile, and no evidence of CKD or subclinical or clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD: BMI ≥25 kg/m² (or ≥23 kg/m² if Asian ancestry), waist circumference ≥88/102 cm in women/men (or if Asian ancestry ≥80/90 cm in women/men), or Fasting blood glucose ≥100 to 125 mg/dL or HbA1c between 5.7% and 6.4%*
Stage 2: Metabolic risk factors, CKD, or both	Individuals with metabolic risk factors, moderate-high–risk CKD, or both: hypertension (SBP ≥130 mm Hg, DBP ≥80 mm Hg or use of antihypertensive medications) hypertriglyceridemia (≥150 mg/dL) MetS (per AHA/NHLBI criteria)† T2D (fasting blood glucose ≥126 mg/dL or HbA1c ≥6.5%) and/or moderate-to-high risk CKD per the KDIGO risk categorization
Stage 3: Subclinical CVD in CKM	Subclinical CVD (subclinical coronary atherosclerosis or pre-HF) among individuals with excess/dysfunctional adiposity, or other metabolic risk factors, or CKD; or a risk equivalent of subclinical CVD: Subclinical coronary atherosclerosis principally diagnosed as CAC with Agatston score ≥100 (moderate to severe incidental CAC, subclinical coronary atherosclerosis by coronary catheterization/CT angiography, or low ankle-brachial index without claudication symptoms also meet criteria) Pre-HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-cTnT ≥14 ng/L for women and ≥22 ng/L for men, hs-cTnI ≥10 ng/L for women, and ≥12 ng/L for men) or by echocardiographic parameters,‡ with a combination of the 2 indicating highest HF risk. Risk equivalents of subclinical CVD: Very high-risk CKD (stages G4-G5 CKD or very high-risk per the KDIGO risk classification§) Predicted 10-y CVD risk ≥20% using PREVENT-CVD
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, HF, stroke, PAD, AF) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present (eGFR <15 mL/min/1.73m² or need for chronic kidney replacement therapy)

*Individuals with gestational diabetes should receive intensified screening for prediabetes after pregnancy.

†MetS is defined by the presence of 3 or more of the following: 1) waist circumference ≥88 cm for women and ≥102 cm for men (≥80 cm for women and ≥90 cm for men if Asian ancestry); 2) high-density lipoprotein cholesterol <40 mg/dL for men and <50 mg/dL for women; 3) triglycerides ≥150 mg/dL; 4) elevated blood pressure (SBP ≥130 mm Hg or DBP ≥80 mm Hg and/or use of antihypertensive medications); and 5) fasting blood glucose ≥100 mg/dL.

‡CAC >100 threshold based on high absolute CVD risk with an impact on therapeutic decision-making.

§KDIGO risk classification for moderate-high–risk CKD: stages G1-G2 with A2-A3, stage G3a with A1-A2, or stage G3b with A1; for very high-risk CKD: stages G3a with A3, stage G3b with A2-A3, or stages G4-G5 CKD. A1 albuminuria is UACR <30 mg/g; A2 albuminuria is UACR 30 to <300 mg/g; A3 albuminuria is UACR ≥300 mg/g.

AF indicates atrial fibrillation; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; BMI, body mass index; CAC, coronary artery calcium; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CT, computed tomography; CVD, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HF, heart failure; hs-cTnI, high sensitivity-cardiac troponin I; hs-cTnT, high sensitivity-cardiac troponin T; KDIGO, Kidney Disease: Improving Global Outcomes; MetS, metabolic syndrome; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; PAD, peripheral artery disease; SBP, systolic blood pressure; T2D, type 2 diabetes; and UACR, urine albumin-to-creatinine ratio.

therapies. Interventional studies targeting various CKM risk factors suggest that earlier detection and intervention are often associated with greater clinical benefit. A 10-year longitudinal study conducted in the United Kingdom[11] evaluated the impact of a screening program whereby major risks for CVD, identified via screening, were measured and recorded. Individuals at high CVD risk were provided with health promotion advice using a standardized script. Screening was associated with improved risk factor levels (BP and cholesterol) and health behaviors. Prospective cohort studies have also contributed evidence that individuals can expect to benefit from preventive therapy based on risk-factor burden. A multicohort modeling study showed that measurement of clinical predictors of CVD (such as those utilized in CKM staging) was able to estimate individual-level prognosis and treatment-effects in terms of improved 10-year risk, lifetime risk, and life expectancy free of CVD.[1] Risk factor assessment, as required for CKM staging, enables quantification of the 10- and 30-year risk for ASCVD, HF, and total CVD using the PREVENT equations.[12]

2. CAC assessment improves prediction of ASCVD[4,5] and selection of patients for treatment with aggressive ASCVD risk factor modification (ie, statin therapy).[6] Data from MESA (Multi-Ethnic Study of Atherosclerosis)[4] showed that CAC is strongly associated with a 10-year risk of incident ASCVD, independent of standard risk factors, and similarly across

Table 5. Diagnostic Criteria for Obesity, Hypertension, Dyslipidemia, and Diabetes in Youth (<18 years)

Health Factor	Criteria
Overweight and Obesity[1]	Overweight: BMI ≥85th to <95th percentile Obesity: BMI ≥95th percentile Severe Obesity: BMI ≥120% of the 95th percentile **Class 2 Obesity:** BMI ≥120% to <140% of the 95th percentile or a BMI ≥35 kg/m² to <40 kg/m², whichever is lower based on age and sex **Class 3 Obesity:** ≥140% of the 95th percentile or BMI ≥40 kg/m², whichever is lower based on age and sex
Blood Pressure[2]	Age <13 y Normal: <90th percentile Elevated: ≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower) Stage 1 Hypertension: ≥95th percentile to <95th percentile + 12 mm Hg, or 130/80 to 139/89 mm Hg (whichever is lower) Stage 2 Hypertension: ≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower) Age ≥13 y Normal: <120/<80 mm Hg Elevated: 120/<80 to 129/<80 mm Hg Stage 1 Hypertension: 130/80 to 139/89 mm Hg Stage 2 Hypertension: ≥140/90 mm Hg
Dyslipidemia[4]	Fasting Lipid Panel Total cholesterol ≥200 mg/dL HDL-C <40 mg/dL LDL-C ≥130 mg/dL Triglycerides 0–9 y: ≥100 mg/dL 10–19 y: ≥130 mg/dL Non-HDL-C ≥145 mg/dL Nonfasting Lipid Panel Non–HDL-C ≥145 mg/dL HDL-C <40 mg/dL
Abnormal Glucose[5]	Prediabetes Fasting plasma glucose 100–125 mg/dL *OR* HbA1c 5.7%–6.4% *OR* 2-h plasma glucose during 75-g oral glucose tolerance test 140–199 mg/dL Diabetes Fasting plasma glucose ≥126 mg/dL *OR* HbA1c ≥6.5% *OR* 2-h plasma glucose during 75-g oral glucose tolerance ≥200 mg/dL *OR* Random plasma glucose ≥200 mg/dL in individual with classic symptoms of hyperglycemia or hyperglycemic crisis

BMI indicates body mass index; h, hour; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

demographic groups. CAC scores appear to demonstrate a logarithmic increase in risk, with no clear evidence of a risk plateau. For example, individuals with a CAC score ≥1000 have a greater risk of CVD and all-cause mortality than those with a CAC score of 400 to 999.[5] CorCal (Effectiveness of a Proactive Cardiovascular Primary Prevention Strategy, With or Without the Use of CAC Screening, in Preventing Future MACE)[6] randomized 601 primary prevention patients to CAC (n=302) or risk calculator guidance (n=299) for primary prevention; the CAC arm had a greater reclassification of risk compared with the group using a risk calculator. At 1 year, statin adherence was superior, low-density lipoprotein cholesterol (LDL-C) levels were lower, and estimated costs were similar or reduced in the CAC arm. Given the impact of CAC measures on risk reclassification, CAC assessments can be considered as per the 2026 ACC/AHA/Multisociety dyslipidemia guideline[13] among individuals with borderline-intermediate 10-year risk (PREVENT ASCVD 3% to 10%) when decisions regarding preventive therapies are uncertain.

3. Elevations of cardiac biomarkers (BNP, NT-proBNP,[7,8] or hs-cTn[9]) or structural or functional abnormalities on cardiac imaging (eg, echocardiography[10]) identify individuals with pre-HF who are at increased HF risk, with the co-occurrence of the 2 indicating greatest absolute HF risk.[14] The STOP-HF (St. Vincents Screening to Prevent HF) trial[7] among patients aged ≥40 years with at least 1 CVD risk factor demonstrated that BNP testing, with reflexive echocardiography and referral for coordinated care in those with BNP ≥50 pg/mL, was associated with an approximately 45% lower odds of developing left ventricular dysfunction or HF. Large, multiregional datasets demonstrate that cardiac biomarkers improve HF risk prediction. Left atrial enlargement, left ventricular hypertrophy, abnormal global longitudinal strain, and elevated E/e′ by echocardiography are all independent predictors of incident HF.[10] When a diagnosis of pre-HF is not known, a 10-year PREVENT-HF risk estimate ≥5% can be considered for selected cardiac biomarker testing, given a similar 3% to 5% 10-year incident HF risk associated with elevated cardiac biomarkers in community-based cohorts.[15–18] This can identify those at increased HF risk and inform coordinated preventive care, with the potential consideration for cardiac imaging to refine risk estimation.[15–18] Evidence also supports cardiac biomarker testing based on age and CKM risk factors (eg, age ≥40 years and at least 1 CKM risk factor as in STOP-HF[7]); however, such an approach has a lower yield than a strategy guided by an integrated measure of HF risk (PREVENT-HF).[19,20] The incremental prognostic value of cardiac biomarker testing

among individuals with advanced CKD or ASCVD is unclear, given the very high prevalence of elevated biomarkers in these subgroups.

3.1.1. Longitudinal Diagnostic Assessment for all CKM Stages

Recommendation for Longitudinal Diagnostic Assessment for all CKM Stages Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
1	B-NR	1. Among all adults with or at risk for CKM syndrome, it is recommended to measure BMI and waist circumference at least annually to identify the risk for CKM stage progression.[1,2]
1	B-NR	2. Among all adults without CKM syndrome (CKM stage 0), it is recommended to assess lipids, glycemia, and kidney function (to calculate eGFR) at least every 5 y and BP at least annually to ensure timely identification of CKM risk factors for optimal CVD prevention.[3,4]
1	B-NR	3. Among adults with CKM stage 1, it is recommended to assess lipids, glycemia, and kidney function (to calculate eGFR) at least every 2 to 3 y and BP at least annually to ensure timely identification of CKM risk factors and to facilitate timely risk factor modification for optimal CVD prevention.[5–9]
1	B-NR	4. Among adults in CKM stages 2 and above, it is recommended to assess lipids, glycemia, and BP at least annually to inform the optimal prevention and management of CVD.[10–13]
1	B-NR	5. Among adults in CKM stages 2 and above, assessments of both eGFR and UACR are recommended at least annually to characterize risk related to CKD and to guide the prevention and management of CVD and kidney disease.[14–16]

Synopsis

Longitudinal monitoring of CKM factors is important to inform clinicians and patients about the onset or progression of CKM syndrome. The earlier identification of CKM risk factors and the timely initiation of related therapies to mitigate risk associated with diabetes, hypertension, dyslipidemias, and CKD are associated with improved clinical outcomes. Excess and dysfunctional adipose tissue, particularly visceral adiposity, are at the root of CKM syndrome, and excess adiposity is a modifiable risk factor across all CKM syndrome stages.[1] Hence, BMI and waist circumference should be assessed annually for those with, and at risk for, CKM syndrome. As per existing guidelines, annual assessment of BP is also recommended for all adults.[17] The approach to longitudinal monitoring of other CKM factors depends on CKM stage (Figure 3). Regular assessments of lipids, glycemia, and kidney function (eg, eGFR) are recommended with increasing frequency for higher CKM stages, as the risk for progressive metabolic and kidney disease increases along the CKM spectrum.[13,18–21] For individuals with CKM stage 2 or higher, annual evaluation of CKM factors should include dual assessment of kidney health with both eGFR and UACR. Together, these 2 markers are necessary to adequately diagnose CKD, and they have complementary prognostic and therapeutic implications.[2,3]

Recommendation-Specific Supportive Text

1. Addressing overweight and obesity is central to CKM health, as excess and dysfunctional adiposity are the principal drivers for the development of metabolic risk factors and CKD, with subsequent increased CVD risk.[2,22,23] Visceral adiposity contributes to inflammation and insulin resistance, with resultant multisystem pathology that leads to progressive CKM syndrome. Regular anthropometric assessments over the life course are therefore important for the early detection of CKM risk.[24,25] The avoidance of weight gain with aging is associated with a lower likelihood of developing metabolic risk factors.[2] Annual screening for overweight (BMI ≥25 to <30 kg/m^2) and obesity (BMI ≥30 kg/m^2) is supported by multiple clinical guidelines.[18,26] In some population subgroups, such as Asian Americans, a BMI cut-off of ≥23 kg/m^2 is suggested for overweight due to increased metabolic risk at relatively low levels of weight.[27,28] BMI is limited, as it does not reflect body composition, particularly abdominal obesity that drives CKM risk. Using both BMI and waist circumference provides complementary prognostic information regarding risk for future metabolic derangements, incident CVD, and mortality. While waist-hip ratio provides improved characterization of metabolic and cardiovascular risk than waist circumference, challenges of complexity of measurement and lack of standardization make it less ideal for use in clinical settings.[18,29–32]
2. The emergence of hypertension and elevations in biomarkers such as triglycerides and glucose are critical indicators of cardiometabolic and kidney health.[4,33–35] Preventing the development of hypertension reduces risk more than treating existing hypertension.[36,37] As per current guidelines, BP should ideally be checked at every visit, with a goal of <130/80 mm Hg for most individuals.[17] High triglycerides and low high-density lipoprotein cholesterol (HDL-C) are markers of insulin resistance, with high triglycerides having a potential causal impact on atherosclerotic CVD.[38] Lipid testing, which includes these measures, is recommended every 5 years among healthy adults in current guidelines.[21] Assessments for prediabetes or diabetes with fasting blood glucose, HbA1c, or oral glucose tolerance tests are critical because of the strong association of hyperglycemia with cardiovascular and kidney disease.[39,40] Among individuals with normal weight, hyperglycemia more commonly develops among non-White individuals, so systematic assessments in all adults, regardless of BMI,

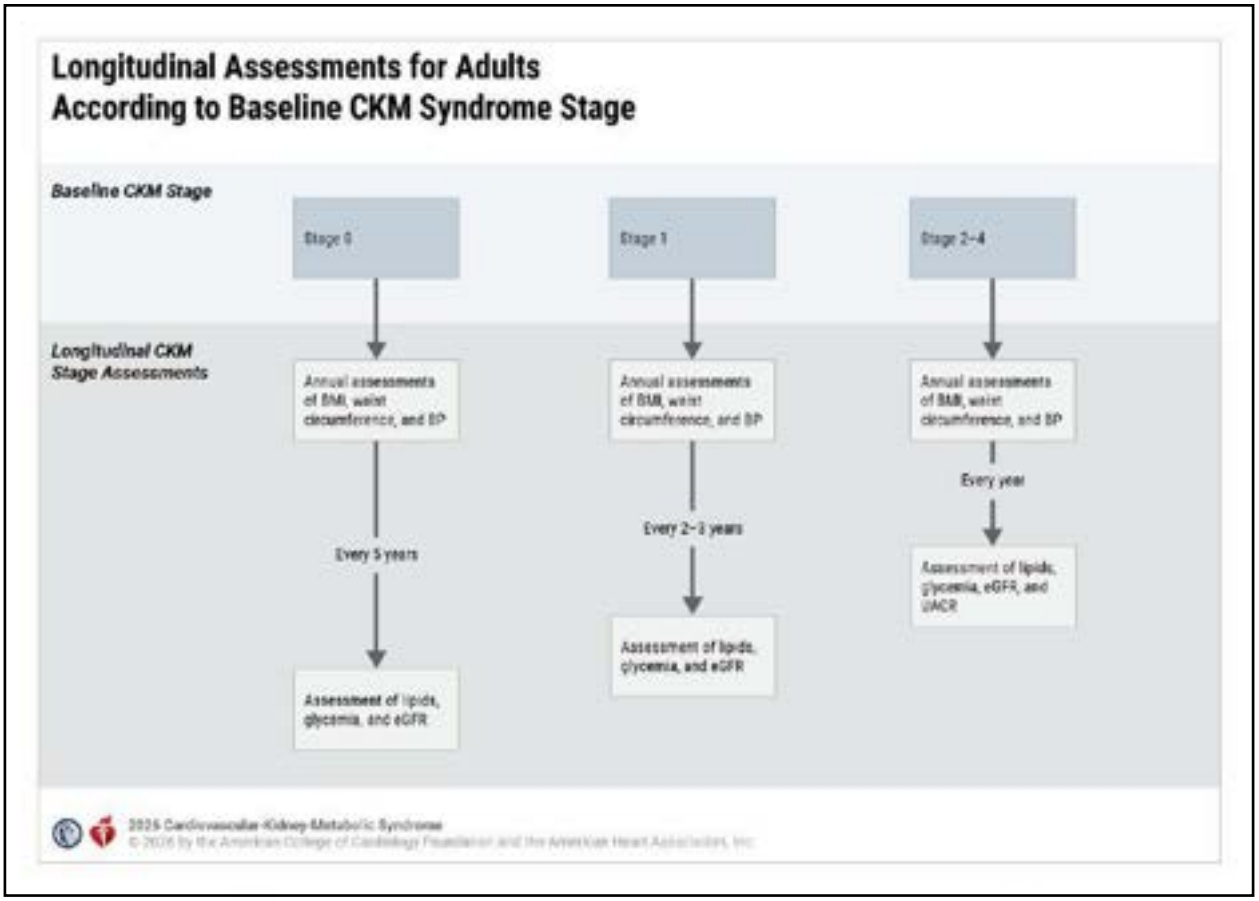

Figure 3. Longitudinal Assessments for Adults According to Baseline CKM Syndrome Stage.
Systematic assessments for CKM risk factors allow for the timely detection of risk factors and the quantification of cardiovascular risk using the PREVENT equations. The frequency and intensity of assessments for CKM syndrome risk factors increase with higher CKM stages. Annual assessments for anthropometrics and BP should be performed for all patients. Additional assessments for lipids, glycemia, and eGFR should occur at least every 5 years in CKM stage 0 and more frequently every 2 to 3 years in CKM stage 1. In CKM stage 2, with the presence of metabolic risk factors, CKD, or both, these assessments should occur yearly. Furthermore, the higher prevalence of albuminuria in CKM stage 2 supports yearly assessments for UACR to fully assess for CKD and related cardiovascular risk. BMI indicates body mass index; BP, blood pressure; CKM, cardiovascular-kidney-metabolic; eGFR, estimated glomerular filtration rate; and UACR, urine albumin-to-creatinine ratio.

may promote more equitable identification of hyperglycemia.[3] Early detection of decreased eGFR also confers clinical benefits. In CKM stage 0, assessments for glycemia and kidney function at least every 5 years will allow for comprehensive CKM risk assessments that coincide with the guideline-recommended timeline for lipid assessments in healthy adults, and for quantification of CVD risk with the PREVENT equations.

3. Individuals with CKM stage 1 due to overweight and obesity are at increased risk for developing metabolic risk factors and CKD compared with those who have a normal weight without risk factors (CKM stage 0).[5,6,41] Even in the absence of these metabolic risk factors, excess weight is associated with increased cardiovascular risk, particularly for HF.[6,42] Studies of "metabolically healthy obesity" have found that over 4 to 5 years of follow-up, approximately 30% to 45% develop metabolic syndrome or diabetes.[43,44] Because of the high short-term risk for diabetes development among those with overweight and obesity, major societies and the US Preventive Services Task Force recommend assessments for metabolic syndrome and diabetes every 3 years in those with excess weight.[35,42,45] Among adults with prediabetes, the risk for incident diabetes is very high,[7,8] indicating a need for even more intensive surveillance for T2D, with major societies recommending yearly assessments for T2D in those with prediabetes.[45] Intensified surveillance is also warranted in those with prior gestational diabetes (GDM), due to increased T2D risk.[46] Earlier onset of metabolic risk factors is associated with increased risk for CVD and mortality, motivating the timely identification and treatment of risk factors.[47–49] Thus, assessments for metabolic risk factors and eGFR in CKM stage 1 should occur at least every 2 to 3 years, to ensure the timely identification of CKM risk factors and resultant CKM restaging.

4. The presence of metabolic risk factors (excess weight, high waist circumference, high BP, high triglycerides, low HDL-C, and hyperglycemia) is associated with increased risk for CVD, with experimental, genetic, and interventional data supporting a causal association for all except for low HDL-C.[10–12,50] Additionally, the identification of metabolic syndrome indicates greater risk for diabetes and CVD, as well as a greater likelihood of additional pathophysiologic abnormalities contributing to CVD, including systemic inflammation, a higher number of LDL particles, prothrombosis, and endothelial dysfunction.[50,51] Among individuals with diabetes, glycemic assessments should be performed using HbA1c as a measure of glycemic control over the preceding 2 to 3 months, which indicates risk for microvascular and macrovascular complications.[52] Because of the interrelatedness of metabolic risk factors in CKM syndrome, their co-occurrence is common, supporting the need for collective evaluation for metabolic risk factors. Metabolic risk factors assessments at least yearly in CKM stage 2 can support the early intensification of lifestyle modification and pharmacotherapies as needed to address abnormal risk factor levels and reduce risk for cardiovascular events and CKD progression. More timely initiation of therapy is associated with improved cardiovascular clinical outcomes among individuals with hypertension, diabetes, and dyslipidemias.[18,53]
5. The diagnosis of CKD includes assessment of both eGFR and UACR, with CKD diagnosed by either chronic eGFR <60 mL/min/1.73 m^2 or UACR ≥30 mg/g.[54] Most individuals with CKD are unaware of their CKD diagnosis.[55] Most CKD is attributable to the metabolic risk factors of T2D and hypertension. The increased prevalence of albuminuria among those with these metabolic risk factors or lower eGFR warrants regular dual testing with eGFR and UACR for case finding.[16,55] Additionally, in patients with known CKD, the presence of albuminuria informs therapeutic approaches for reducing CKD-related risk (Section 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3"). As reflected in the KDIGO heat map (Figure 2), eGFR and UACR provide complementary and additive prognostic information regarding risks for progressive CKD, CVD, and mortality.[15] GFR is commonly estimated in clinical practice using creatinine-based formulas. Estimated GFR using both creatinine and cystatin C provides better accuracy than eGFR using either marker alone; however, the availability of cystatin C measurement is limited.[14] While at least annual assessment of eGFR and UACR is recommended for case finding in CKM stage 2, more frequent assessments (every 3 to 6 months) can be considered in those with advanced CKD to prognosticate or reclassify kidney and CVD risk as per the KDIGO guidelines.[54]

3.2. Social Determinants of Health Assessments

Recommendations for Social Determinants of Health Assessment Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
1	**B-NR**	1. In adults with or at risk for CKM syndrome (≥18 y), routine screening with a tool (Table 6) validated for assessing SDOH is recommended to inform the implementation of patient-centered care.[1–7]
1	**B-NR**	2. In youth with or at risk for CKM syndrome (<18 y of age), routine screening of their caregivers with a tool (Table 7) validated for assessing caregiver SDOH is recommended to inform the implementation of patient-centered care.[8–10]

Synopsis

SDOH, the nonmedical risk factors impacting disease risk and health outcomes, play a critical role in CKM health across the life course.[11–14] Adverse SDOH at multiple levels directly impact health behaviors. For youth populations, SDOH promote early life adversity during critical developmental periods, directly affecting cardiovascular health into adulthood.[12] Multilevel SDOH also modify biological pathways that promote cardiometabolic risk.[11,15] Through these mechanisms, adverse SDOH lead to CKM risk factor development.[16–20] Adverse SDOH also impair both self-care and engagement with the health care system. Ultimately, adverse SDOH have downstream consequences on cardiovascular and all-cause mortality[11,14] and contribute to disparities in CVD mortality.[21] Therefore, SDOH are critical to evaluating and mitigating risk for CKM syndrome and are central to the CKM syndrome care model.[5–7,20] The importance of SDOH in CKM syndrome is further reflected by the inclusion of the social deprivation index, a place-based measure of SDOH, in the PREVENT equation. Adverse SDOH that are identified in screening in the clinical setting should be addressed as part of the CKM interdisciplinary care model (Section 5.1, "Interdisciplinary Care").

From a patient perspective, while social needs screening is generally acceptable, it is essential to clearly communicate the link between SDOH and CKM-related outcomes to promote patient activation and engagement in the screening and referral process.[22,23] Medicare and Medicaid reimburse for SDOH assessments every 6 months in outpatient settings and annually during hospital stays; however, assessing social needs at every visit may better support CKM prevention and management.[24–26]

Recommendation-Specific Supportive Text

1. For adults with CKM syndrome, routine screening of SDOH and related social needs can be integrated

Table 6. SDOH Screening Tools for Adult Populations With or at Risk for CKM Syndrome

Social Determinants of Health Screening Tool	Essential or Core Domains Assessed by the Screening Tool
SDOH Screening Tools for Adults	
Health Leads[29]	Exposure to violence Financial strain Food insecurity Housing instability Sociodemographic information Transportation challenges Utility needs
Centers for Medicare & Medicaid Innovation: Accountable Health Communities (AHC) HRSN Screening Tool[30]	Food insecurity Housing instability Interpersonal safety Transportation problems Utility help needs
AAFP: The EveryONE Project[31]	Childcare Employment Education Finances Food Housing Interpersonal safety Transportation Utilities
PRAPARE Implementation and Action Toolkit[32]	Family and home Money and resources Social and emotional health Sociodemographics
OCHIN: Social Determinants of Health Electronic Health Record Tools in Community Health Centers[33]	Education Exposure to violence Financial resource strain Food insecurity Health behaviors (alcohol use, race, ethnicity, tobacco use and exposure, physical inactivity) Housing insecurity Mental health (depression, social isolation, stress)
HealthBegins Upstream Risks Screening Tool[34,35]*	Economic stability Education Food insecurity Housing insecurity Social and community context Neighborhood and physical environment Health behaviors (physical activity, dietary pattern)

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*Not yet validated or validity not specified.

AAFP indicates American Academy of Family Physicians; CKM, cardiovascular-kidney-metabolic; HRSN, Health-Related Social Needs; OCHIN, Oregon Community Health Information Network; PRAPARE, Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences; SDOH, social determinants of health.

Table 7. SDOH Screening Tools for Caregivers of Youth Populations With or at Risk for CKM Syndrome

Social Determinants of Health Screening Tool	Essential or Core Domains Assessed by the Screening Tool
Screening Tools for Caregivers of Youth	
HealthBegins Upstream Risks Screening Tool[34,35]*	Economic stability Education Food insecurity Housing insecurity Social and community context Neighborhood and physical environment Health behaviors (physical activity, dietary pattern)
Child ACE Tool[36]*	**Education:** parental education **Family context:** suspected child maltreatment, intimate partner violence in the household, mental illness in the household, substance abuse in the household, household member is incarcerated, parental marital status
SEEK PSQ[37]	**Economic stability:** food insufficiency **Family context:** parental intimate partner violence, parental depression, parental stress, parental substance or alcohol use disorder, tobacco use within home, gun in home, help with childcare when needed **Health and health care:** smoke alarm needed, contact information for poison control needed
IHELLP Screening Tool[38]	**Economic stability:** food insufficiency, housing instability **Education:** concerns about child's education needs **Family context:** violence in the household **Health and health care:** concerns about child's health insurance **Neighborhood environment:** concerns about physical conditions of housing
WE CARE Screening Tool[39]	**Economic stability:** food insufficiency, housing instability, difficulty paying bills, parental employment **Education:** parental education, lack of childcare **Family context:** intimate partner violence in household, parental depression symptoms, alcohol or substance use disorder in household

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*Not yet validated or validity not specified.

ACE indicates Adverse Childhood Experiences; CKM, cardiovascular-kidney-metabolic; IHELLP, Income, Housing, Education, Legal Status, Literacy, and Personal Safety; SDOH, social determinants of health; SEEK PSQ, Safe Environment for Every Kid Parent Screening Questionnaire; and WE CARE, Well Child Care, Evaluation, Community Resources, Advocacy, Referral, Education.

into health care delivery to identify nonmedical factors that can be addressed when implementing patient-centered care. Individual- and neighborhood-level or structural SDOH and related social needs can be assessed through validated screening tools.[1]

Screening tools developed for adult populations vary widely, but essential domains that are important for clinicians to evaluate include financial strain, food insecurity, housing instability, safety and exposure to violence, transportation challenges, and utility needs (Tables 6 and 7). Additional domains that can be screened in adult populations are family/social support, health behaviors, health literacy, and mental health.[3] Limited interventional studies have shown improvement in BP, lipids, tobacco cessation, and fruit and vegetable intake resulting from assessing and addressing adverse SDOH.[27] Screening tools can be embedded by clinicians into electronic health records to reduce barriers to utilization,[2,4] such as difficulty incorporating screening into patient workflow. Additional challenges to SDOH screening include limited standardization of screening methods and data elements, concerns for privacy, particularly in small, rural communities, and the need for optimizing referral systems and interventions to address social needs.[2,28]

2. While some SDOH screening tools have been validated for all ages, specific screening tools have been developed for caregivers of youth populations (Table 7). Screening caregivers of youth populations for SDOH identifies childhood exposures to social factors that can influence CKM health across the life course.[9] Essential SDOH domains to screen among caregivers of youth patients with CKM syndrome include economic stability, education, family context, health and health care access, and neighborhood environment.[9] Some of the SDOH screening tools for caregivers of youth populations have been validated and assessed for reliability.[9] Additional individual and neighborhood-level screening tools can be considered; these specifically address factors that may influence the development of CKM syndrome, such as residential segregation, social vulnerability, air quality index, neighborhood walking and biking environment, health literacy, discrimination, and spirituality, among others.[10] There are unique barriers to SDOH and social need screening for caregivers of youth with CKM syndrome; for instance, clinicians may be hesitant to screen because of concerns about maintaining caregiver privacy if social needs are addressed.[8]

4. RISK ASSESSMENT

4.1. Quantitative Assessment of CVD Risk

Recommendations for Quantitative Assessment of CVD Risk
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	B-NR	1. In adults 30 to 79 y of age without CVD (coronary heart disease, stroke, or HF), calculation of 10-y risk of CVD (and its components of ASCVD and HF) with the PREVENT equations is recommended to quantify risk related to CKM syndrome and to inform prevention strategies.[1–4]
2a	B-NR	2. In adults 30 to 59 y of age without CVD (coronary heart disease, stroke, or HF), calculation of 30-y risk of CVD (and its components of ASCVD and HF) with the PREVENT equations can be useful to quantify risk related to CKM syndrome and to inform prevention strategies.[1–4]

Synopsis

Quantitative CVD risk assessment is central to the evaluation and management of CKM syndrome, including defining CKM stage (Section 2.3, "CKM Syndrome and Stage Definitions"), guiding assessments for subclinical CVD (Section 3.1, "Diagnostic Approach to CKM Staging"), and informing treatment recommendations with the goal of matching the intensity of preventive efforts with an individual's CVD risk (Section 5.5.1, "Management of T2D in CKM Syndrome Stage 2 to 3"). Since the expected absolute risk reduction for any given therapy is directly proportional to an individual's baseline predicted risk, a risk-based strategy is more effective than a strategy based on risk factor levels alone in terms of CVD events avoided (ie, number-needed-to-treat to prevent 1 CVD event[5]), as discussed in a complementary AHA/ACC scientific statement.[6–8] The PREVENT equations (PREVENT Online Calculator) can accurately and precisely estimate 10- and 30-year risk for CVD and its components (ASCVD and HF), with PREVENT-CVD as the primary equation given increased risk for both ASCVD and HF in CKM syndrome. Quantitative risk estimates from PREVENT can inform therapeutic approaches to address CVD risk related to diabetes (Section 5.5.1, "Management of T2D in CKM Syndrome Stage 2 to 3") and other risk factors (ie, hypertension, dyslipidemia).[9,10] Quantitative risk assessment should guide clinician-patient discussions about risk-reducing strategies, including lifestyle modification and pharmacologic therapies, complementing additional strategies to assess risk based on individual comorbidities, the presence of CKM risk enhancers (Section 4.2, "Risk Enhancers for CKM Syndrome"), and the recognition of subclinical CVD (Sections 5.6.1, "Use of Markers of Subclinical Atherosclerosis" and 5.6.2, "Pre-Heart Failure").

Recommendation-Specific Supportive Text

1. For adults 30 to 79 years of age without CVD, quantitative CVD risk assessment is useful to prioritize the benefit and efficiency of therapy initiation for reducing CVD risk related to CKM syndrome. After screening for CVD risk factors (Section 3.1, "Diagnostic Approach to CKM Staging"), application of the PREVENT equations to estimate 10-year risk of CVD for asymptomatic adults aged 30 to 79 years is recommended.[1,11] The PREVENT equations inform CKM staging, subclinical CVD assessments, and intensification of preventive efforts for diabetes, as well as for dyslipidemia and hypertension,

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Table 8. Summary of Guideline-Based Recommendations for the Use of Outcome-Specific PREVENT Equations in the Primary Prevention of CVD-Based Risk Thresholds

PREVENT Equations	Outcome of Interest	Goal of Risk Assessment		Guideline Referenced
PREVENT-CVD	Total CVD: a composite of ASCVD and HF	CKM syndrome staging	To define CKM stage 3 syndrome when 10-y risk PREVENT-CVD ≥20% (risk equivalent with subclinical CVD)	2026 AHA/ACC/ADA/ASN CKM Guideline
		Treatment	To recommend initiation of GLP-1-based therapy or SGLT2i or both, with 10-y risk PREVENT-CVD ≥7.5% when indicated	2026 AHA/ACC/ADA/ASN CKM Guideline
			To recommend initiation of drug therapy for intensive BP-lowering in stage 1 hypertension, with 10-y risk of PREVENT-CVD ≥7.5%	2025 AHA/ACC High BP Guideline[9]
PREVENT-ASCVD	ASCVD: Fatal CHD, nonfatal MI, fatal and nonfatal stroke	CKM syndrome staging/detection of subclinical CVD	To recommend evaluation of subclinical atherosclerosis, with 10-y risk PREVENT-ASCVD 3% to <10% when there is uncertainty about the initiation or intensification of therapy	2026 ACC/AHA Dyslipidemia Guideline[10]
		Treatment	To recommend initiation of lipid-lowering treatment, with 10-y risk PREVENT-ASCVD ≥5% To consider initiation of lipid-lowering treatment, with 10-y risk PREVENT-ASCVD 3% to <5% after evaluation of risk enhancers, 30-y ASCVD risk, or CAC when there is uncertainty To consider initiation of lipid-lowering treatment, with 30-y risk PREVENT-ASCVD ≥10%	2026 ACC/AHA Dyslipidemia Guideline[10]
PREVENT-HF	HF, which includes HF with reduced, mildly reduced, and preserved ejection fraction	CKM syndrome staging/detection of subclinical CVD	To recommend evaluation of subclinical HF and care coordination, with 10-y risk PREVENT-HF ≥5%	2026 AHA/ACC/ADA/ASN CKM Guideline

See complementary AHA/ACC scientific statement on risk assessment in CKM syndrome.[8]

ACC indicates American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ASN, American Society of Nephrology; CAC, coronary artery calcium; CHD, coronary heart disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GLP-1, glucagon-like peptide; HF, heart failure; MI, myocardial infarction; PREVENT, Predicting Risk of Cardiovascular Disease Events; and SGLT2i, sodium–glucose cotransporter-2 inhibitors.

as described in prior guidelines (Table 8). The PREVENT base equations include traditional CVD risk factors, and newly include predictors relevant to CKM syndrome (BMI and eGFR), with add-on models incorporating UACR, HbA1c, and the social deprivation index.[1,11] The PREVENT equations have been externally validated in a diverse group of 3 330 085 US adults, with good to excellent discrimination (median [interquartile range] C-statistic for women: 0.79 [0.76–0.81] and men 0.76 [0.73–0.78]) and precision (calibration slopes for women: 1.03 [0.81–1.16] and men: 0.94 [0.81–1.13]) for CVD, and with similar performance for CVD subtypes (ie, ASCVD, HF). Nonetheless, the potential for inaccuracies remains, as with any risk model, particularly in groups that are underrepresented or at increased CVD risk due to CKM risk enhancers.[1,12]

2. For younger adults, 30-year risk of CVD can be calculated with the PREVENT equations in conjunction with the 10-year risk of CVD and can guide shared decision-making, particularly for lifestyle counseling. The utility of 10-year risk assessments may be limited for younger adults, as they are often unlikely to develop CVD in the next decade.[13] However, many younger adults are at an increased 30-year risk for CVD and its components, despite having a low 10-year risk.[14–16] Therefore, it could be beneficial to calculate 30-year CVD risk estimates with PREVENT. Both the absolute 30-year risk of CVD and the corresponding age/sex percentile may help to reclassify risk in younger adults, particularly if risk is ≥75th percentile, as utilized for CAC. Reference values to calculate 30-year risk percentiles are available at https://professional.heart.org/en/guidelines-and-statements/prevent-calculator.[17] Thirty-year risk estimation can specifically identify younger individuals with multiple risk factors who are at increased long-term risk of CVD, which may be helpful for facilitating risk communication between clinicians and patients.[1,11] Other tools that help communicate long-term risk include PREVENT-Risk Age, which provides an assessment of age based on predicted risk as a comparison to chronological age.[18] Thirty-year risk assessments may promote adherence to lifestyle recommendations, and in some cases, inform pharmacotherapy utilization, to prevent the progression of CKM syndrome.

4.2. Risk Enhancers for CKM Syndrome

Recommendation for Risk Enhancers for CKM Syndrome Referenced studies that support the recommendation are summarized in the evidence table.		
COR	**LOE**	**Recommendation**
2a	B-NR	1. In adults 30 to 79 y of age without CVD (coronary heart disease, stroke, or HF), it is reasonable to use risk enhancers for CKM syndrome progression to guide decisions about intensification of prevention strategies.[1–4]

Synopsis

Risk enhancers for CKM syndrome are factors that can identify an individual who has an increased likelihood of

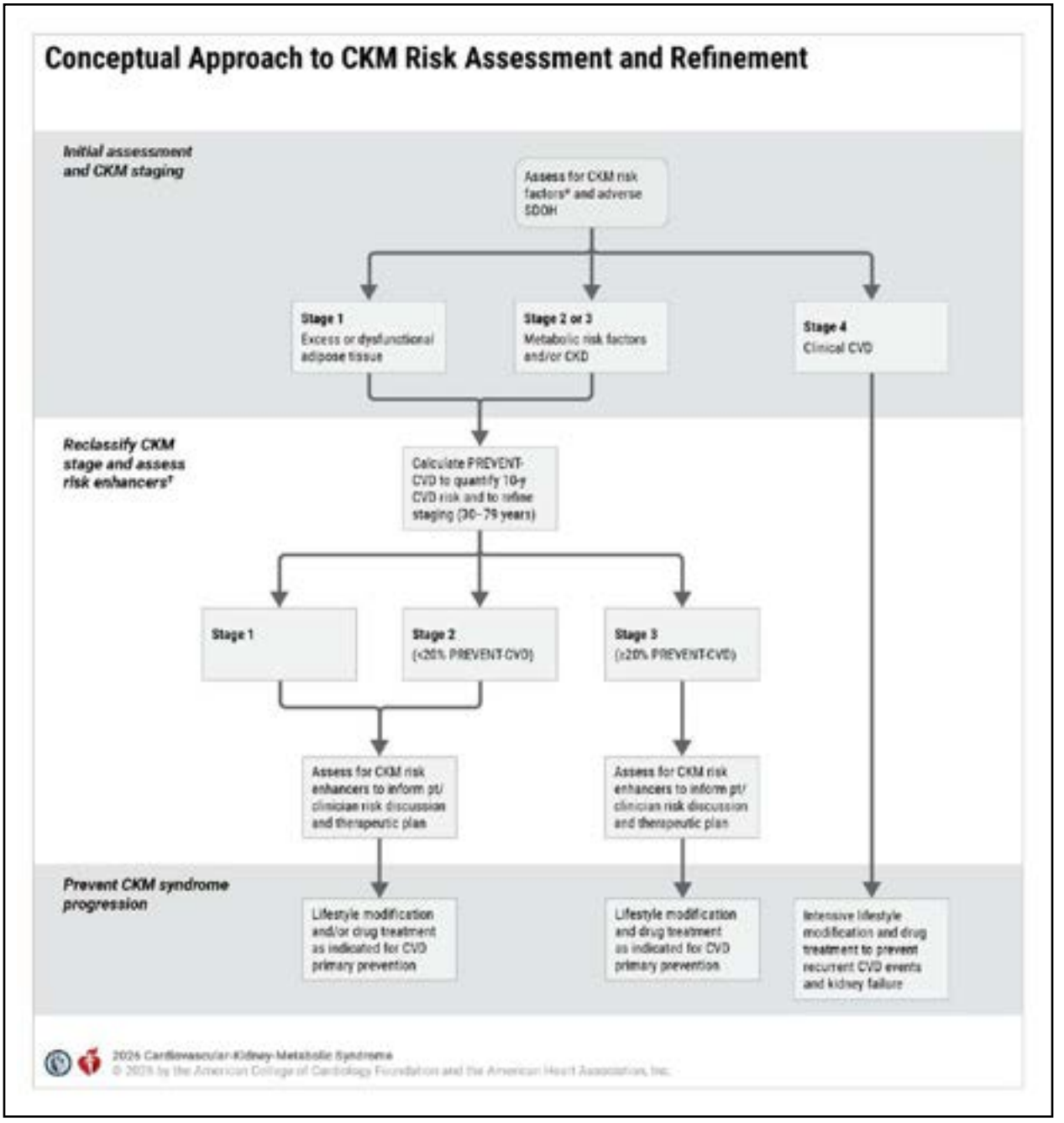

Figure 4. Conceptual Approach to CKM Risk Assessment and Refinement.
The systematic approach to evaluating risk in the patient with CKM syndrome starts with assessments for CKM risk factors and CKM syndrome staging. Subsequent PREVENT calculation helps to quantify CVD risk and can also help to differentiate between stage 2 (10-year score <20%) and stage 3 (10-year score ≥20%) for those with metabolic risk factors or CKD. The presence of subclinical CVD or very-high risk CKD also identifies those individuals with CKM stage 3. PREVENT is not indicated for those in CKM stage 4 with existing CVD. For patients in CKM stage 1 to 3, risk-enhancing factors that influence CKM stage progression can further inform patient-clinician risk discussions about the benefits versus risks of preventive therapies. *CKM risk factors include adiposity measures, blood pressure, lipids, glycemia, and kidney function. Conceptual overview of the approach to staging that integrates baseline CKM assessments, risk estimation with the PREVENT-CVD equations, and personalization with risk-enhancing factors. †Refers to Table 9 "Risk Enhancers for CKM Syndrome." CKM indicates cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; pt, patient; and SDOH, social determinants of health.

progression along CKM stages and is at greater risk of CVD or kidney failure (Figure 4).[1–5] Once an individual's risk of CVD is estimated with the PREVENT equations (Section 4.1, "Quantitative Assessment of CVD Risk") and their CKM stage is defined (Section 2, "Definitions and Classification"), CKM risk enhancers can further refine the estimation of an individual's risk of advancing to higher CKM stages and developing clinical CVD or worsening kidney function.[6,7] CKM risk enhancers comprise a broad range of factors (Table 9), which include personal history

Table 9. Risk Enhancers for CKM Syndrome

Risk Enhancers for CKM Syndrome	
Personal medical history	Chronic inflammatory or autoimmune conditions (eg, rheumatoid arthritis, SLE, HIV/AIDS)[4,11]
	Sleep disorders (eg, obstructive sleep apnea)[16]
	Poor psychological health (eg, depression, anxiety)[17]
	Sex-specific risk factors (eg, premature menopause age <40 y, adverse pregnancy outcomes, polycystic ovarian syndrome, erectile dysfunction)[2]
SDOH[1]	Lower socioeconomic status
	Higher burden of adverse individual- and place-based SDOH (Section 3.2)
Inflammation[13]	Elevated high-sensitivity C-reactive protein (≥2.0 mg/L if measured)
Family history[14]	Diabetes
	Kidney failure
Demographic[15]	Increased risk groups (eg, self-identified race or ethnicity of South Asian, American Indian, Pacific Islander)*

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*Mechanisms for increased risk may include social and/or genetic factors that disproportionately impact individuals from a certain ancestry.

CKM indicates cardiovascular-kidney-metabolic; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; SDOH, social determinants of health; and SLE, systemic lupus erythematosus.

of chronic inflammatory conditions, sex-specific risk factors, sleep disorders, and poor psychological health; family history of diabetes or kidney failure; greater exposure to adverse SDOH; and identification in a high-risk demographic subgroup.[5] While many CKM risk enhancers overlap with those identified for the prevention of ASCVD, there are differences based on the goal of recognizing individuals at increased risk of advancing along CKM stages (compared with risk only for ASCVD).[8,9] In addition, CKM risk enhancers, along with 30-year risk, may be considered if there is uncertainty about the benefits of a therapy for preventing CKM progression based on standard 10-year assessments of estimated risk, risk factor levels, or the patient's preferences.[6]

Recommendation-Specific Supportive Text

1. There is considerable heterogeneity in the risk of progression across CKM stages, which is associated with increased risk for CVD, kidney failure, and mortality.[1–4] Therefore, consideration of risk enhancers for CKM syndrome progression can facilitate clinician-patient shared decision-making about the initiation and intensification of CKM therapies to prevent progression of CKM syndrome and reduce risk of CVD.[10] Patients with specific clinical conditions associated with worsening CKM pathology,[4,11] or those who experience adverse SDOH,[1,12] have elevated biomarkers of inflammation (if measured),[3,13] family history of diabetes or kidney failure,[14] or belong to a high-risk demographic subgroup[15] that has been identified as at increased risk for CKM syndrome progression, may benefit from more intensive preventive approaches (Table 9). Therefore, risk enhancers for CKM syndrome progression represent readily available factors that can be useful to more comprehensively assess an individual's risk for CKM syndrome progression when integrated with baseline CKM syndrome staging (Section 3.1.1, "Longitudinal Diagnostic Assessment for all CKM Stages") and quantitative risk assessment (eg, with PREVENT, Section 4.1, "Quantitative Assessment of CVD Risk").[6,7]

5. GENERAL PRINCIPLES OF CARE IN CKM SYNDROME

Synopsis

The overarching principles for CKM syndrome management include implementing a nonjudgmental approach to obesity management, comprehensively addressing CKM syndrome risk factors, supporting an interdisciplinary care framework to minimize health care fragmentation, and integrating efforts to mitigate the impact of SDOH within CKM syndrome care.[1] The AHA's Life's Essential 8 framework represents a set of measures encompassing healthy lifestyle and risk factor optimization that are implementable at a population health level, with relevance across all CKM syndrome stages.[2–4] The interconnections among metabolic risk factors, CKD, and CVD have management implications, with considerations for the utilization of therapies with multiorgan benefits. Overlapping conditions are inherent to CKM syndrome and can be used as focal points in therapeutic decision-making to maximize clinical benefits (Table 10). Interdisciplinary CKM care models that utilize a CKM care coordination point person may facilitate the real-world implementation of CKM therapeutic strategies across varying clinical severity of CKM syndrome and heterogeneous clinical settings.[5–9] CKM syndrome care models may be adapted for flexibility in resource-challenged areas to accommodate differences in subspecialty density and economic considerations.[5] Patients identified as having more adverse SDOH via validated screening tools (Tables 6 and 7) should be linked with community resources to provide social support for optimal CKM syndrome care.[10]

5.1. Interdisciplinary Care

Recommendations for Interdisciplinary Care Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
1	B-R	1. For adults with stage 2 to 4 CKM syndrome with ≥2 CKM conditions of diabetes, CKD, and/or CVD, the use of interdisciplinary care teams with a CKM coordination point person is recommended to facilitate multisystem CKM syndrome care, including lifestyle interventions and optimization of GDMT.[1–5]

Table 10. Summary of Therapeutic Considerations Related to Overlapping CKM Conditions

	Major CKM Risk Factors		
	Obesity	**T2D**	**CKD**
Overlapping Condition	Core Management: Lifestyle modification; adjunctive obesity pharmacotherapy; or metabolic and bariatric surgery as needed (Section 5.4)	Core Management: Lifestyle modification; risk factor control; use of SGLT2i, GLP-1–based therapy, or both in those at increased risk for CVD events (Section 5.5.1)	Core Management: RASi and SGLT2i as first-line therapies in patients with albuminuric CKD to reduce CVD risk and prevent loss of kidney function (Section 5.5.4)
Obesity	N/A	With ≥ class II obesity, prioritize GLP-1–based therapy for managing T2D and reducing CVD risk	Intentional weight loss reduces albuminuria
T2D	With ≥ class II obesity, prioritize GLP-1–based therapy for managing T2D and reducing CVD risk	N/A	RASi and SGLT2i as first-line therapies to reduce CVD and kidney risk; addition of GLP-1 RA and/or finerenone for DKD with persistent albuminuria on first-line therapies
Albuminuric CKD	Intentional weight loss reduces albuminuria	RASi and SGLT2i as first-line therapies to reduce CVD and kidney risk; addition of GLP-1 RA and/or finerenone for DKD with persistent albuminuria on first-line therapies	N/A
MASLD (Section 7.2.)	Weight reduction advised; GLP-1 RA advised if fibrotic MASLD present	Weight reduction if appropriate; GLP-1 RA advised in MASLD given high risk of fibrosis	N/A
Subclinical Coronary Atherosclerosis (Section 6.2.)	Potential for greater absolute risk reduction with indicated preventive therapies	Potential for greater absolute risk reduction with indicated preventive therapies	Potential for greater absolute risk reduction with indicated preventive therapies
Pre-HF (Section 5.6.2.)	Marked weight loss may reduce risk for HF development	Prioritize SGLT2i as primary cardioprotective antihyperglycemic agent for HF prevention	Use SGLT2i for HF prevention; if DKD is present, pre-HF favors consideration of adding GLP-1 RA or finerenone
ASCVD (Section 6.2.)	Integrated weight management team to reduce weight and CKM risk; GLP-1–based therapy to decrease MACE/CV death	Lifestyle modification, risk factor control, and use of SGLT2i, GLP-1–based therapy, or both in those with ASCVD to reduce MACE/CV death	Use SGLT2i to reduce MACE, CV death, and loss of kidney function
HFpEF (Section 6.3.)	GLP-1–based therapy recommended to reduce HF events; consider exercise training and a caloric deficit diet	SGLT2i should be the first-line cardioprotective glucose-lowering therapy to reduce HF events; additionally consider GLP-1–based therapy if diabetes and obesity present	SGLT2i (as part of standard HF GDMT) reduces HF events and loss of kidney function; additionally consider finerenone if DKD is present
HFrEF (Section 6.3.)	Unclear risk/benefit of GLP-1–based therapy in HFrEF (particularly in the absence of ASCVD)	SGLT2i should be the first-line cardioprotective glucose-lowering therapy to reduce HF events and CV death	SGLT2i and ARNI/RASi (as part of standard HF GDMT) reduce HF events, CV death, and loss of kidney function

This table describes management considerations related to the overlap of the major CKM risk factors of obesity, diabetes, and CKD, with additional comorbid conditions in CKM syndrome. The top row describes core management for the CKM risk factors. Lower rows describe how the overlap of that CKM risk factor with another condition should impact clinical management. Recommendations regarding the management approach for obesity, T2D, and CKD, in those with and without CVD, are detailed in subsequent sections.

ARNI indicates angiotensin receptor/neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; GDMT, guideline-directed medical therapy; GLP-1, glucagon-like peptide-1; GLP-1 RA, GLP-1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction–associated steatotic liver disease; N/A, not applicable; RASi, renin-angiotensin system inhibitors; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

Recommendations for Interdisciplinary Care (Continued)		
COR	**LOE**	**Recommendations**
1	**C-EO**	2. In adults with CKM syndrome, mitigating the clinical impact of adverse SDOH should be prioritized to optimize holistic CKM syndrome care.

Synopsis

Patients with CKM syndrome often have multiple conditions requiring care from several clinicians, which can lead to fragmentation of care.[6] Incorporating clinical input from multiple disciplines within the CKM framework and coordinating care among team members are essential components of holistic CKM care. The AHA Presidential Advisory on CKM Health outlined 2 interdisciplinary care approaches: 1) value-based and 2) volume-based care models (Figure 5).[7] In value-based care, interdisciplinary teams consisting of a CKM care coordination point person, along with multispecialty representatives, develop protocols to manage patients with ≥2 of the CKM conditions of diabetes, CKD, and CVD, with cross-specialty communication facilitated by the CKM care coordination point person (Tables 11 and 12). In volume-based care, high-risk patients are referred to relevant subspecialists, and the care coordination point person helps patients to navigate care among multiple clinicians. The CKM care coordina-

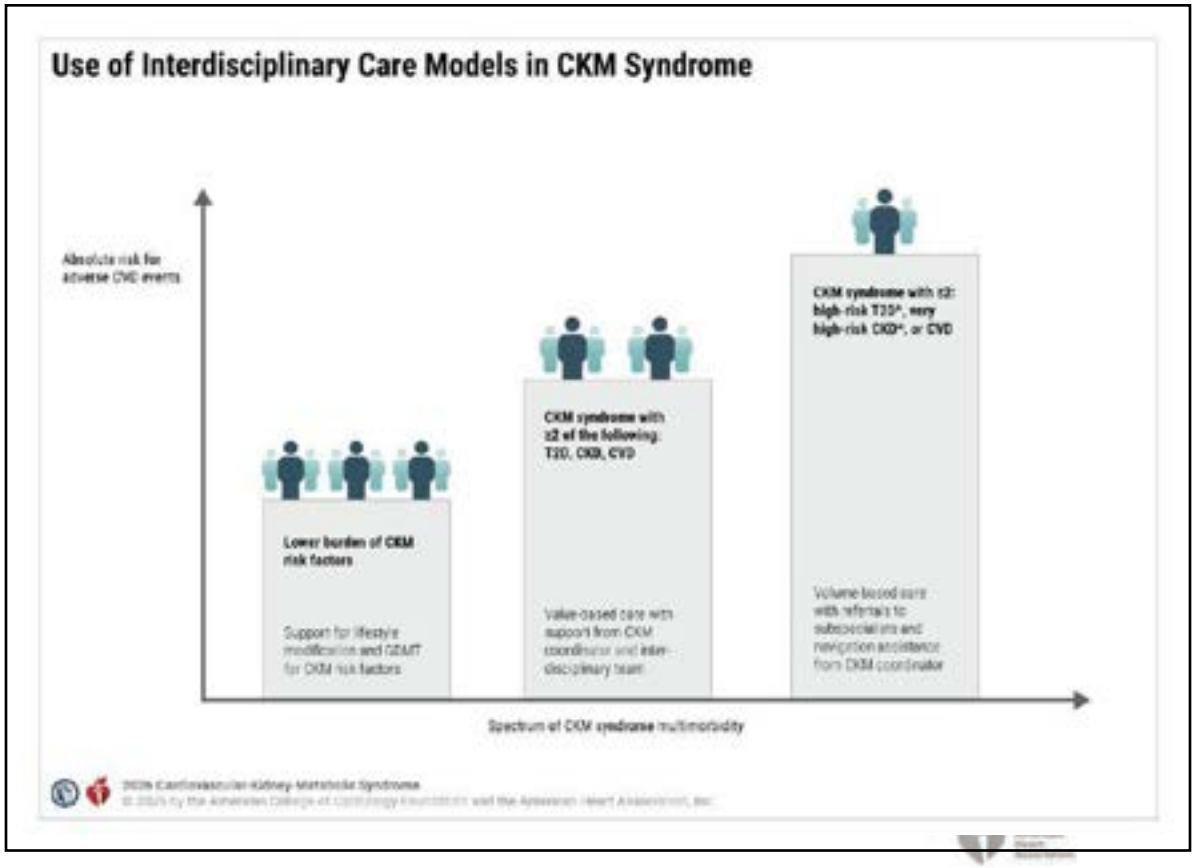

Figure 5. Use of Interdisciplinary Care Models in CKM Syndrome.
Conceptual framework for use of interdisciplinary care models in CKM syndrome, tailored to multimorbidity profiles and reflecting the corresponding absolute risk of CVD events. For most patients with CKM syndrome who have a lower burden of CKM risk factors, clinicians should facilitate and encourage lifestyle modification and initiation of guideline-directed therapies based on CKM risk profiles and estimated CVD risk. The smaller number of individuals with CKM syndrome and a confluence of ≥2 conditions of T2D, CKD, and CVD have higher absolute CVD risk, and a value-based care approach with support from a CKM coordinator and virtual interdisciplinary team is recommended. A yet smaller number of individuals with a confluence of ≥2 of high-risk T2D, very high-risk CKD, or clinical CVD are at the highest absolute CVD risk. For this group, a volume-based interdisciplinary strategy, with referrals for subspecialty care and navigation support from a CKM coordinator, is recommended. CKD indicates chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; and T2D, type 2 diabetes. *High-risk T2D is defined as a HbA1c ≥9% or microvascular complications of T2D, and very high-risk CKD is defined as per the KDIGO heat map (Figure 2).

tion point person can support several additional important elements of optimal CKM syndrome care, including comprehensive medication management, facilitation of lifestyle modification, and care coordination. In both value- and volume-based approaches, care may be delivered virtually or in-person. Adverse SDOH identified through systematic SDOH assessments (Section 3.2, "Social Determinants of Health Assessments") should be mitigated through incorporating community health workers, social workers, case managers, or patient navigators on the interdisciplinary team and leveraging local community resources.[6,7]

Recommendation-Specific Supportive Text

1. Interdisciplinary teams are critical to address the interdependent pathologies and multilevel adverse SDOH that contribute to CKM syndrome.[6] Several randomized controlled trials (RCTs) have demonstrated improved implementation of CKM therapies, lifestyle modification, or both with the use of interdisciplinary teams across overlapping CKM conditions.[1–4,8–10] Long-term follow-up of the STENO-2 (Intensified Multifactorial Intervention in Patients With T2D and Microalbuminuria) trial showed that a multifactorial intervention delivered by a multidisciplinary team (doctor, nurse, dietician), focused on risk factor control through lifestyle modification and targeted pharmacotherapy, improved all-cause mortality among individuals with T2D, overweight/obesity, and albuminuria.[4] In COORDINATE-Diabetes (Coordinating Cardiology Clinics Randomized Trial of Interventions to Improve Outcomes-Diabetes), a multifaceted intervention that emphasized collaboration between cardiologists and diabetes care clinicians improved the prescription of evidence-based therapies for patients with T2D and ASCVD.[1] A meta-analysis of 19 RCTs showed that teams with professionals from at least

Table 11. CKM Interdisciplinary Team

Care Category	Team Members
General Medical Care	Primary care clinician*
	CKM coordination point person†
	Clinical pharmacist
	Nurse
	Dietician
Subspeciality Care	Cardiology clinician*
	Endocrinology clinician*
	Nephrology clinician*
	Hepatology clinician*
	Diabetes educator
Social Support	Social worker
	Community health worker

*Could include MD, DO, or advanced practice professional.
†Individuals in subspecialty roles such as diabetes educators or heart failure care coordinators can also play the role of the CKM coordination point person.
CKM indicates cardiovascular-kidney-metabolic.

3 health disciplines significantly reduced cardiovascular risk factors among patients with diabetes in primary care settings.[2] Several observational clinical studies support the use of an interdisciplinary approach in managing patients with CKM syndrome.[11–13] Randomized data support the utilization of pharmacists,[3,8,14–16] nurses,[15] nonlicensed navigators,[3] and community health workers[5,15] to facilitate interdisciplinary team-based care and initiation and follow-up of evidence-based therapies. Several studies suggest long-term cost-effectiveness of interdisciplinary care.[17–19]

Table 12. Coordinated Services for Optimal CKM Management

Task	Details
*Comprehensive medication management	Patient education on CKM conditions and related medications to encourage patient empowerment
	Medication reconciliation
	Initiation, titration, monitoring of evidence-based CKM therapies
	Address side effects or inappropriate medication discontinuation
	Use of shared decision-making when deprescribing medications that are not indicated
	Assessment of and coaching to increase adherence
	Facilitate access to therapies, including patient assistance programs
Facilitation of lifestyle management	Education and coaching for dietary and exercise modification and tobacco cessation
Care coordination	Facilitate communication between patient's clinicians
	Ensure that the patient's entire team is aware of challenges of initiating or adherence to evidence-based therapies
	Ensure patient's understanding of complex care plans
Patient navigation	Ensure patient understands the role of care team members and their entire care plan
	Facilitate communication between patient and clinicians
	Ensure patient is aware of follow-up testing and appointments
	Facilitate access to social assistance programs

*Comprehensive medication management is a standard of practice that assures that patients' medications (ie, prescription, nonprescription, medication alternatives, vitamins, or nutritional supplements) are individually assessed to make sure each medication is indicated (appropriate), effective for their medical conditions, safe given comorbidities and other medications being taken, and able to be taken by the patient as intended as per an individualized care plan.
CKM indicates cardiovascular-kidney-metabolic.

2. Adverse SDOH contribute to increased risk for CVD and all-cause mortality in people with CKM syndrome.[20] Addressing adverse SDOH is likely to improve the quality of holistic care that individuals with CKM syndrome receive, due to the multilevel impact of adverse SDOH on CKM syndrome complications. Addressing adverse SDOH in CKM syndrome may improve clinical outcomes; however, robust data to support this hypothesis are lacking. One small, randomized crossover trial among 44 adults with diabetes and food insecurity found that a medically tailored meal delivery program improved dietary quality and food insecurity and reduced hypoglycemia.[21] Another nonrandomized prospective study found that screening for and attempting to address adverse SDOH was associated with modest improvements in BP and lipid parameters, but not in HbA1c.[22] A community health worker intervention delivered to inpatients with low socioeconomic status led to increased access to primary care postdischarge and reduced 30-day readmissions.[23] Another small RCT showed that a social work–led care coordination intervention reduced 30-day readmission rates by 22% among older inpatients with high risk of readmission.[24] Support to address adverse SDOH is likely beneficial to patients and of minimal risk, but more research is urgently needed to demonstrate clinical benefit and cost-effectiveness, and to define optimal interventions.

5.2. CKM Syndrome Stage 0

Synopsis

Stage 0 represents individuals without CKM syndrome due to the absence of CKM risk factors, with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD.[1] Because CKM risk factor development is more common with aging, stage 0 is most commonly, although not exclusively, found among youth and young adults. Men and Black adults are less likely to have no CKM risk factors compared with women and White adults, respectively.[2] Unfortunately, 90% to 95% of US adults are in CKM stage 1 to 4, indicating an imperative to better facilitate the maintenance of ideal cardiovascular health starting early in life.[2–4] Longitudinal data demonstrates that most middle-aged individuals

with stage 0 progress to a higher CKM stage over a 10-year period, which is associated with greater risk for CVD and mortality.[5] Therefore, the focus of stage 0 is primordial prevention, with a goal of preventing the development of CKM risk factors. There is a particular focus on preventing the development of excess and dysfunctional adipose tissue because the emergence of metabolic risk factors from youth and young adulthood into middle age is primarily related to weight gain with aging.[6] Recommendations for facilitating primordial prevention are discussed in the 2019 ACC/AHA primary prevention guideline.[7]

5.3. Prevention of CVD in CKM Syndrome

Synopsis

Among individuals in CKM syndrome stage 1 to 3, a principal focus is preventing progression to later CKM syndrome stages and to clinical CVD, with additional positive impacts on CKD, MASLD, and other multiorgan manifestations of CKM syndrome.[1] This involves applying the general principles of CKM syndrome management (Section 5 "General Principles of Care in CKM Syndrome") and addressing the key CKM risk factors of obesity, T2D, and CKD to reduce

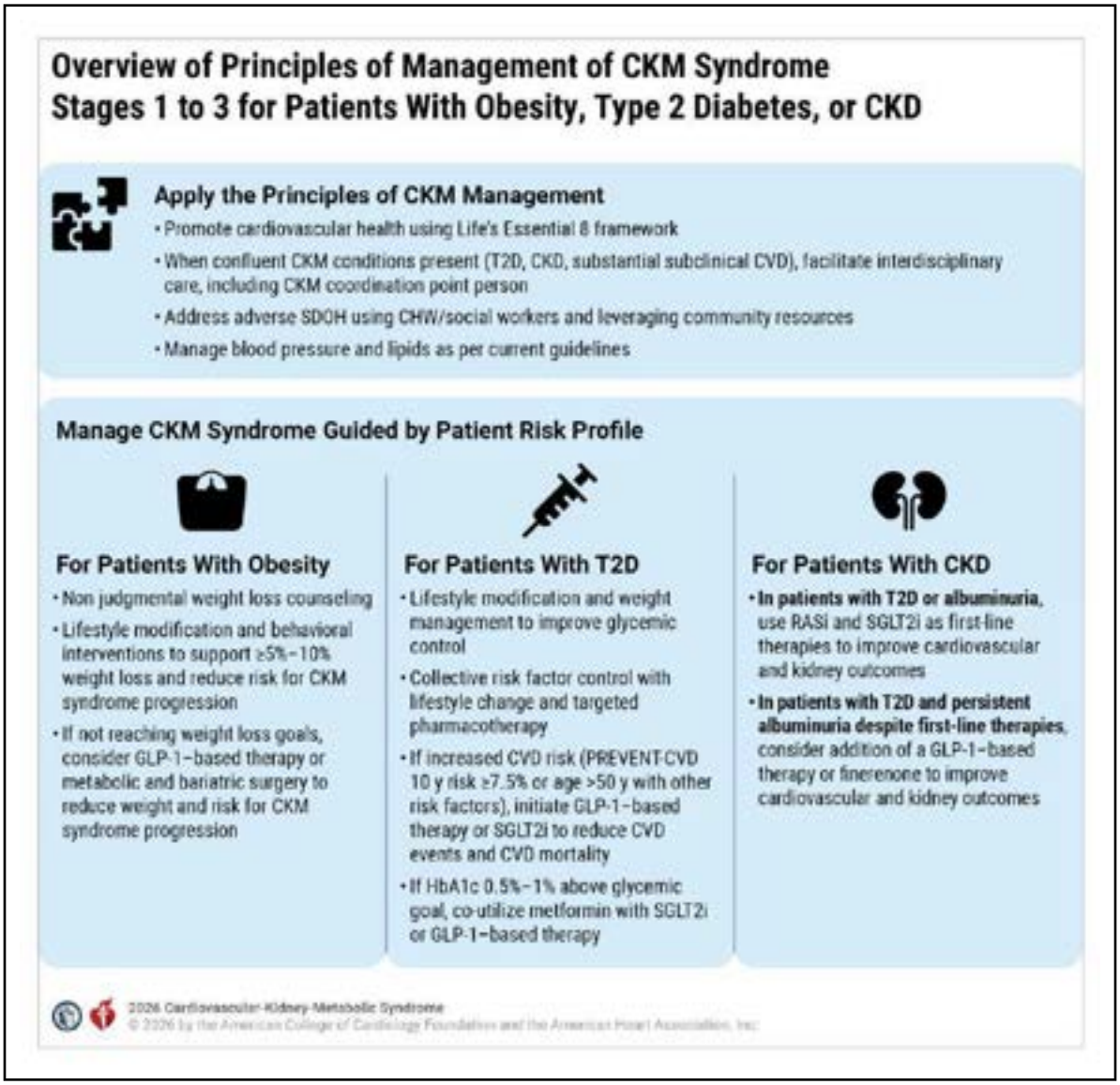

Figure 6. Overview of Management Principles for CKM Syndrome Stages 1 to 3 for Patients With Obesity, Type 2 Diabetes, or CKD.

The approach to CKM syndrome management in patients with obesity, diabetes, and/or CKD in CKM syndrome stage 1 to 3 should involve applying general principles of CKM syndrome management, as well as additional therapeutic approaches for the individual CKM risk factors, as depicted. If HbA1c is sufficiently above glycemic goal (≥0.5% to 1% above), metformin can be co-initiated with an SGLT2i (most necessary, given the limited glycemic effects of these agents) or a GLP-1–based agent; alternatively, metformin can be added later depending on patient preferences. CHW indicates community health worker; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes; GLP-1, glucagon-like peptide-1; RASi; renin-angiotensin system inhibitors; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

the likelihood of CVD events and kidney failure (Figure 6). In addition, BP and lipids should be monitored and managed as per current clinical guidelines.[2–6] The following Sections 5.4, "CKM Syndrome Stage 1," 5.5, "CKM Syndrome Stage 2," and 5.6, "CKM Syndrome Stage 3," detail therapeutic recommendations for patients in CKM syndrome stage 1 to 3.

5.4. CKM Syndrome Stage 1

Synopsis

CKM syndrome stage 1 is defined as overweight/obesity, abdominal obesity, or dysfunctional adipose tissue without other metabolic risk factors, CKD, or subclinical/clinical CVD.[1] Measuring BMI and waist circumference in concert enhances characterization of body composition and metabolic risk, with elevations in both parameters (Table 4), indicating a priority group for weight loss efforts. While other measures, such as waist-to-hip ratio, bioimpedance, and DEXA, can also help characterize body composition better than BMI alone, waist circumference is emphasized due to accessibility and ease. The definition of dysfunctional adipose tissue includes individuals with prediabetes, reflecting metabolic derangements contributing to insulin resistance that occur even in the absence of excess adiposity. The goal of management in CKM syndrome stage 1 is to prevent additional metabolic risk factor development with lifestyle changes and weight loss. Weight management should involve a multimodality approach with counseling on lifestyle modification and the addition of pharmacotherapy and/or metabolic and bariatric surgery as needed, with at least 5% to 10% weight loss targeted to reduce CKM-related risk, with increased benefits seen with greater weight loss. Individuals with prediabetes, regardless of BMI, should be prioritized for lifestyle modification, with weight loss where indicated. For individuals with persistent and progressive hyperglycemia despite lifestyle modification and weight loss efforts, pharmacotherapy (eg, metformin) can be considered to prevent progression to diabetes.[2]

5.4.1. Overarching Approach to Obesity Management

Recommendations for Overarching Approach to Obesity Management Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. Among adults with overweight or obesity, lifestyle modification is recommended as the first-line strategy to facilitate weight loss of at least 5% to 10% of baseline weight.[1–3]
1	B-NR	2. Among adults with overweight or obesity receiving weight loss counseling, a nonjudgmental approach to initiating weight loss discussions is recommended in order to increase the effectiveness of weight loss.[4]
2a	B-NR	3. Among adults with obesity, integrated interdisciplinary weight management teams can be effective to enhance patient-centered approaches to weight loss.[2]

Synopsis

Weight management is fundamental to CKM syndrome care, with maintenance of a healthy weight associated with less risk of CKM syndrome progression and marked weight loss supporting CVD risk reduction and CKM syndrome regression. Obesity is a complex chronic condition, with a multifactorial etiology resulting from an interplay of social, behavioral, and biological factors.[5] Once obesity is established, multiple compensatory mechanisms impacting metabolism, hunger, and satiety are triggered in the setting of intentional weight loss, which commonly result in weight regain.[6] Therefore, long-term engagement with patients is needed for optimal weight management. In CKM syndrome stage 1 to 3, there are a growing number of effective options supporting weight loss, with lifestyle modification through behavior change being first-line, and the increasingly effective adjunctive therapies of obesity pharmacotherapies and MBS as additional considerations (Figure 7). No single approach to weight loss is optimal for all patients at any CKM stage. Therefore, the approach to weight loss should be individualized for each patient, taking into consideration the degree of obesity, CKM stage, resource availability, and patient preferences. Strategies that support patients in navigating the range of therapeutic options for weight management, such as integrated multidisciplinary teams, are important for patient-centered weight management.

Recommendation-Specific Supportive Text

1. Overweight and obesity are leading public health challenges, impacting more than 70% of adults in the United States.[7] Lifestyle modification, supported by behavior change to facilitate long-term dietary and physical activity changes, remains the first-line therapy for weight management. Lifestyle modification is not only effective for supporting moderate weight loss (5% to 10% of weight), but it also has favorable effects on multiple metabolic risk factors, even independent of weight loss.[8–11] Additionally, lifestyle change addresses several pathophysiologic processes associated with excess adiposity and insulin resistance that contribute to CVD risk, including systemic inflammation, endothelial dysfunction, atherogenic dyslipidemia, and hypercoagulability, which may be inadequately addressed by pharmacologic management of obesity-related comorbidities alone. However, owing to the chronicity of obesity and multiple compensatory changes in metabolism, hunger, and satiety promoting weight recidivism,[6] frequent and long-term engagement and behavioral support for lifestyle modification are needed for optimal effectiveness.
2. Weight loss counseling is an important first step in supporting patients in weight management efforts. However, because of highly pervasive weight

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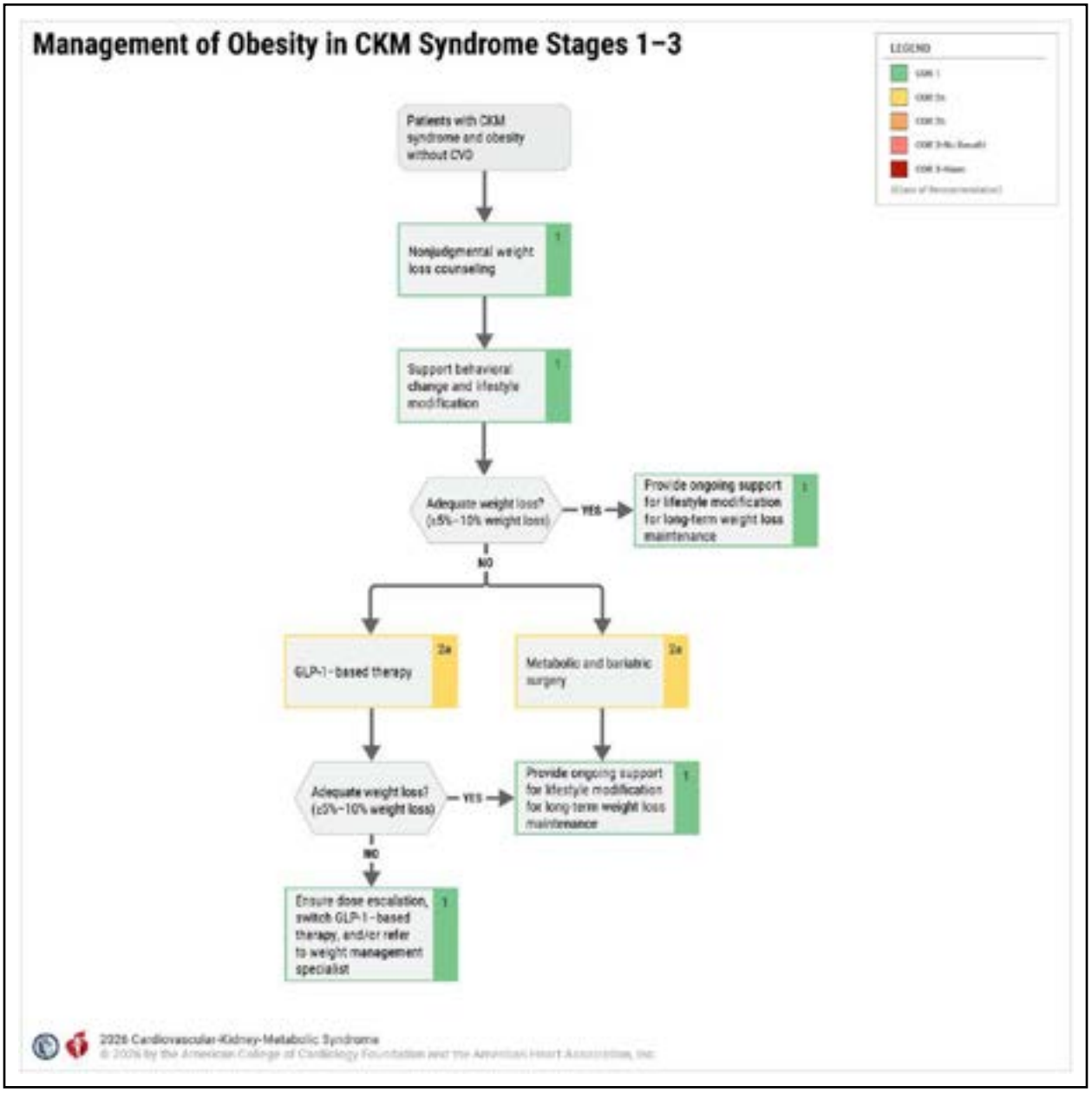

Figure 7. Management of Obesity in CKM Syndrome Stage 1 to 3.
CKM indicates cardiovascular-kidney-metabolic; and GLP-1, glucagon-like peptide-1.

stigma and bias in clinical settings, weight management discussions are often judgmental, reflecting an outsized focus on personal responsibility relative to the complex social and biological factors that contribute to the development of obesity and to weight regain after weight loss.[12] Experiencing weight stigma may be independently associated with worse clinical outcomes.[13] Studies demonstrate that individuals with obesity have a greater likelihood of successfully achieving >10% weight loss after a nonjudgmental weight loss discussion compared to one that is perceived as judgmental.[14] Additionally, individuals who experience weight bias are less likely to engage with obesity-related care. The STOP Obesity Alliance has provided a toolkit that outlines the approach to an effective and nonjudgmental weight loss discussion, based on a focus on obesity as a chronic clinical condition with multifactorial etiology that has a substantial influence on health and quality of life.[15] The Weight Can't Wait - Guide for the Management of Obesity in the Primary Care Setting toolkit also includes strategies to connect the discussion to action to support patient weight loss efforts.[15]

3. The landscape of obesity management has advanced considerably in recent years, with several effective strategies for supporting weight loss.[16] Support from an interdisciplinary team that may

include nutritionists, kinesiologists, pharmacists, and mental health specialists, in addition to obesity medicine specialists, can be particularly effective for facilitating lifestyle modification and weight loss.[17,18] While pharmacotherapies, particularly GLP-1–based therapies, are effective adjunctive therapies for weight management, interdisciplinary approaches may help ensure adequate access and appropriate use.[19] MBS, the most potent weight loss therapy, has become safer, with less invasive surgical options over time.[20,21] Integration of MBS clinicians within interdisciplinary weight management teams can enhance patient access to surgical therapies. Multidisciplinary team involvement is further recommended by surgical guidelines to optimize preoperative and postoperative care.[22] Patients have varied responses to different weight loss therapies, with choice of therapy further influenced by weight, prior weight loss experiences, CKM risk profiles, access to therapies, and patient preferences. There is some evidence that integrated weight management teams, including obesity medicine and bariatric surgery, in addition to other team members supporting weight management and providing social support, can enhance patient-centered obesity care by helping individuals navigate the expanding options for weight management.[23,24]

5.4.2. Intensive Lifestyle Modification for Weight Loss

Recommendations for Intensive Lifestyle Modification for Weight Loss Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. Among adults with overweight or obesity, clinicians should provide counseling at least annually regarding the benefits of achieving at least 5% to 10% weight loss for CKM syndrome risk reduction.[1,2]
1	A	2. Among adults with overweight or obesity, clinician referral to in-person or virtual multicomponent behavioral interventions is beneficial for promoting weight loss for CKM syndrome risk reduction.[1,3,4]
2a	B-R	3. For adults with overweight or obesity who have significant barriers to participating in multicomponent behavioral weight loss interventions, self-directed digital health solutions can be beneficial to promote weight loss for CKM syndrome risk reduction.[5–7]
1	A	4. Among adults with overweight or obesity, lifestyle modification that incorporates moderate caloric restriction and regular physical activity should be recommended to promote weight loss and reduce cardiovascular risk.[8]
1	B-NR	5. Among adults who have successfully lost weight, long-term weight management programs that, in part, emphasize increased physical activity should be recommended to maintain lost weight.[4]

Synopsis

The AHA/ACC and several societies recommend intensive, multicomponent behavioral weight loss interventions led by clinicians having the ability to successfully initiate weight loss counseling.[9–11] Components should include dietary changes to promote a calorie deficit of 500 to 750 kcal/day, ≥150 minutes per week of moderately vigorous aerobic activity, and ≥14 months of behavioral therapy, including self-monitoring of dietary intake, physical activity, and weight, and guided problem solving.[9,10] Such interventions lead to weight loss averaging 8%,[10] a degree of weight loss shown to improve metabolic risk.[12] However, this may overestimate real-world weight loss outcomes due to several factors. Studies typically enroll participants who are more motivated than the majority of patients. Furthermore, weight loss maintenance is often challenging.[13] The availability of intensive programs is limited, especially in rural and disadvantaged urban areas. Cost and coverage for such programs are often barriers to participation.[14] Effective programs are often delivered by multidisciplinary teams, rather than only by physicians.[15] In addition to their effect on weight, the success of weight management programs should be based on: 1) accessibility; 2) low enough cost to be delivered efficiently; and 3) allowance for long-term participation, since obesity is a chronic condition. Technology-based solutions have the potential to meet these criteria.[16]

Recommendation-Specific Supportive Text

1. Counseling by physicians is recommended to engage patients in weight loss efforts. The provision of structured weight loss counseling can increase motivation to lose weight and engagement in weight loss efforts.[17] A systematic review of motivational interviewing in primary care reported that some interventions have led to modest (5%) weight loss.[2] Weight loss discussions should emphasize the benefits of weight loss for CKM risk reduction. Individuals with both elevated BMI and waist circumference should be a priority group for weight loss efforts. Modest weight loss of 5% to 10% among patients with overweight or obesity and diabetes is associated with improvement in glycemic measures, BP, HDL-C, and triglycerides, among others. This can result in risk reduction for incident CKM risk factors such as diabetes and hypertension.[18] Intentional weight loss also results in enhanced risk factor control for those with existing CKM risk factors, with improvements in BP, glycemia, dyslipidemia, albuminuria, and systemic inflammation.[19] Greater amounts of intentional weight loss are associated with more substantial improvement in CKM risk factors,[20] with some possible reductions in CVD risk with ≥10% weight loss.[21]
2. Multicomponent interventions combine different approaches such as group sessions, clinician

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guidance, specific dietary modification, and physical activity facilitation.[1] These interventions are most effectively supported through behavior modification to facilitate long-term adherence to lifestyle modification.[1] Randomized trials of multicomponent interventions have demonstrated a significant impact on weight loss, with associated improvement in metabolic risk factors and kidney function. Importantly, multicomponent interventions have demonstrated similar weight loss efficacy when delivered in-person or virtually.[22] A systematic review published in 2024 reported that behavioral lifestyle interventions with varying durations, regardless of their specific mix of behavioral, dietary, and physical activity components, are associated with a weight loss of roughly 5% among patients with overweight or obesity and T2D over a duration of approximately 12 months.[23] Successful interventions included frequent feedback and support, which have been shown to positively impact program adherence.[24] Additionally, comorbid conditions such as CVD and obstructive sleep apnea (OSA) do not interfere with the success of weight loss in several studies.[9] While the evidence that multicomponent lifestyle interventions lead to significant weight loss and improvement of metabolic- and kidney-related risks is convincing, expanding availability to areas with fewer resources, and participants with lower health literacy and other barriers to participation, remains a challenge.

3. Self-directed digital health interventions include a large variety of applications designed to promote calorie restriction, physical activity, self-monitoring, and education, as well as to provide motivation. Such interventions are predominantly delivered by smartphone applications, with some programs utilizing wearable technology. Most interventions are available from private companies, but many are inexpensive or even available free in limited forms. Relatively few have been rigorously studied or compared to alternatives. There are, however, many published qualitative systematic reviews and meta-analyses on this topic.[25–29] A 2024 Cochrane review demonstrated that some smartphone applications were associated with modest short-term weight loss (−2.6 kg at 6 to 8 months) but showed little relative benefit at 12 months. The significant heterogeneity of smartphone applications in terms of content and approach makes it difficult to draw conclusions. High attrition rates among digital health solutions are also a significant problem.[30] Nevertheless, for many patients with overweight or obesity and CKM syndrome, inexpensive digital health solutions may be the only alternative. This is an evolving field with new artificial intelligence–powered digital health coaches and similar applications recently becoming available. Although there are some promising outcomes data,[31] the effectiveness of artificial intelligence–based approaches has yet to be systematically studied.
4. Moderate caloric restriction causes a sustainable energy deficit, with various dietary approaches available for support of weight loss. Several eating plans, including low-fat and low-carbohydrate approaches, have a modest impact on weight loss (roughly 4 kg) and BP according to a systematic review and network meta-analysis among 121 clinical trials.[8] Unfortunately, at 12 months, weight loss and risk factor benefits disappear in most studies, likely due to diminishing adherence. A Scientific Statement describes the extent to which popular diets align with AHA dietary guidance, with the Dietary Approaches to Stop Hypertension (DASH), Mediterranean, pescatarian, and vegetarian dietary patterns providing particularly notable cardiometabolic benefits by reducing the risks of hypertension, T2D, and CVD.[32] In contrast, ketogenic diets, with very low-carbohydrate and high saturated fat composition, induce weight loss but cause severe hypercholesterolemia with the potential for increased cardiovascular risk. Clinician awareness of optimal dietary patterns for enhancing cardiometabolic health can inform the provision of accurate and effective dietary counseling for patients. Time-restricted eating, the most popular form of which is intermittent fasting, has demonstrated some weight loss efficacy,[33,34] but studies indicate it is no more effective than a calorie-limited approach in promoting weight loss or improving cardiovascular risk.[35,36] While physical activity alone is unlikely to result in clinically significant weight loss, combining dietary modification with exercise results in greater long-term weight loss than dietary modification alone.[37,38]
5. Weight loss maintenance is a major challenge among patients who have successfully lost weight. Weight regain is a complex phenomenon that includes behavioral, physiological, and environmental factors.[39] Weight loss registries provide meaningful insights into successful weight loss maintenance. A systematic review of registry data reported several strategies for successful weight loss maintenance, including regular breakfast intake and having healthy food at home.[40] The most consistent reported behavior associated with weight loss maintenance is increasing physical activity, with several studies indicating that higher levels of physical activity are associated with a greater likelihood of sustaining weight reductions.[38,41] In an RCT report of an 8-week low-calorie intervention that resulted in weight loss, exercise was more effective in promoting weight loss at 12 months (−4.1 kg [95% CI, −7.8 to −0.4]) than no weight loss maintenance intervention, but was less effective than liraglutide (−7.8 kg [95%

CI, −10.1 to −3.1]) or a combination of exercise and liraglutide (−9.5 kg [95% CI, −13.1 to −5.9]) among patients with obesity.[42]

5.4.3. Obesity Pharmacotherapy for Weight Management in CKM Syndrome Stage 1

Recommendations for Obesity Pharmacotherapy for Weight Management in CKM Stage 1 Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
2a	**A**	1. In adults with CKM stage 1 (ie, overweight/obesity [BMI ≥27 kg/m^2] without other metabolic risk factors, CKD, or subclinical/clinical CVD), the addition of GLP-1–based therapy with proven benefit to structured lifestyle intervention can be beneficial in promoting weight loss and improving glycemia and CKM risk profiles.[1–3]
Economic Value:* Not Cost-Effective (High Level of Certainty)		2. In adults with CKM stage 1, the addition of GLP-1–based therapy with proven benefit to a structured lifestyle intervention is projected to not be cost effective at 2025 US prices.
2b	**A**	3. In adults with CKM stage 1, non-GLP-1–based obesity pharmacotherapy may be reasonable to use for promotion of weight loss.[1]

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

Synopsis

This section addresses obesity pharmacotherapies for those with overweight/obesity without other CKM conditions. Subsequent sections will provide recommendations for GLP-1–based pharmacotherapy for individuals with additional CKM conditions including T2D (Section 5.5.1, "Management of T2D in CKM Syndrome Stage 2 to 3"), CKD (Section 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3"), ASCVD (Section 6.2, "Management of ASCVD"), HF (Section 6.3, "Management of HF") and MASLD (Section 7.2, "Metabolic Dysfunction–Associated Steatotic Liver Disease"). GLP-1–based therapy is meant to be inclusive of the broader class of agents involving GLP-1 receptor agonism (ie, the GLP-1/glucose-dependent insulinotropic polypeptide [GIP] receptor agonist [RA] tirzepatide).

The landscape of effective medical therapies for weight management has advanced significantly with the emergence of GLP-1–based therapies. Three agents are currently available as options (liraglutide, semaglutide, and tirzepatide), with many more in development. In addition to semaglutide and tirzepatide promoting up to 15% to 21% weight loss, these agents also improve CKM risk factor profiles. Despite their benefits, these medications often cause gastrointestinal side effects, and their benefits reverse after discontinuation.[1,4] The cost of these therapies also remains a barrier for many.

Additionally, several non-GLP-1–based obesity pharmacotherapies are approved by the FDA to treat obesity in the United States, including orlistat, phentermine, phentermine-topiramate, and naltrexone-bupropion. These agents induce weight loss and some CKM risk factor improvement, though the effects are modest relative to GLP-1–based therapies, and side effects can impact utilization. Table 13 summarizes the clinical effects and contraindications for approved obesity pharmacotherapies.

Recommendation-Specific Supportive Text

1. Multiple randomized, placebo (plus lifestyle intervention) controlled trials of liraglutide, semaglutide, and tirzepatide demonstrate the effectiveness of these medications in promoting weight loss among individuals without diabetes.[5] In these studies, the achievement of >5% body weight loss was very common, as were substantial decreases in waist circumference. BP reductions parallel declines in body weight and lipids and hs-C-reactive protein also improve. Glycemia consistently improves with use of these agents, with some evidence for preventing progression to diabetes in those with insulin resistance.[6] More recently developed agents (semaglutide and tirzepatide) exhibit greater weight loss efficacy, and possibly better tolerability, than the older agent liraglutide.[1–3,7] The SURMOUNT-5 (A Study of Tirzepatide in Participants With Obesity or Overweight With Weight Related Comorbidities) trial demonstrated that tirzepatide is superior to semaglutide for overall weight loss and weight loss maintenance.[8] At present, only 1 oral GLP-1–based therapy, semaglutide, is available. The oral formulation appears slightly less efficacious than the subcutaneous version for facilitating weight loss.[9] As discussed in the monitoring and follow-up section (Section 8, "Monitoring and Follow-Up After Initiation of Therapies"), for those with inadequate weight loss or weight regain on GLP-1–based therapy, referral to weight management is indicated for consideration of alternative pharmacotherapy or metabolic and bariatric surgery.
2. A modeling-based study examined the cost-effectiveness of semaglutide and tirzepatide compared with lifestyle modification alone from a US health care perspective and a lifetime analytic horizon.[10] In a subgroup analysis of individuals with obesity but without comorbidities such as diabetes, hypertension, or established CVD, the incremental cost-effectiveness ratio (ICER) of semaglutide (at US net price of $8412) was $1 012 000 per quality-adjusted life-year (QALY) gained, and tirzepatide (at US net price of $6236) was $449 000 per QALY gained. Another modeling-based analysis, which modeled a higher-risk cohort of individuals without diabetes but with other comorbidities such as hypertension, found that semaglutide, at an annual cost of $13 618 (US list price), would not be cost-effective

Table 13. Average Changes in Weight and Metabolic Risk Profiles, as Well as Common Side Effects of Approved Obesity Pharmacotherapies

Agent	Average Maximal Placebo-Corrected Weight Loss*	Maximal Weight Loss*	Duration of Trial (weeks)	Placebo-Corrected Impact on Metabolic Risk Factor Reduction at RCT Completion	Most Common Side Effects	Cautions
Tirzepatide[1,3,19–21] 15 mg†	15%	21%	72	SBP: 6.5 mm Hg; DBP: 3 mm Hg; A1c: 0.4%; TG: 19%	Nausea, diarrhea, constipation	Avoid in type II multiple endocrine neoplasia, history of pancreatitis
Semaglutide[2,5,22–24] 2.4 mg	12%	15%	68	SBP: 4.5 mm Hg; DBP: 2 mm Hg; A1c: 0.3%; TG: 16%	Nausea, diarrhea, vomiting, constipation	Avoid in type II multiple endocrine neoplasia, history of pancreatitis
Liraglutide[1,19,25] 3 mg	5%	8%	56	SBP: 3 mm Hg; A1c: 0.3%; TG: 8 mg/dL	Increased heart rate, nausea, diarrhea, constipation	Avoid in type II multiple endocrine neoplasia, history of pancreatitis
Phentermine/topiramate[1,13,17,19] 15 mg/92 mg	8%	13%	56	SBP: 3 mm Hg; DBP: 1 mm Hg; TG: 20 mg/dL	Increased heart rate, dizziness, dry mouth, constipation	Limit dose with GFR <50, avoid in CAD, abrupt withdrawal is seizure risk
Naltrexone/bupropion[1,14,19] 32 mg/360 mg	4%	8%	56	TG: 9 mg/dL; A1c: 1% in T2D	SBP +2 mm Hg, headache, nausea, constipation	Limit dose with GFR <50, monitor BP, avoid in HTN and CAD, contraindicated in individuals at risk for seizures
Orlistat[1,18,19] 120 mg	3%	10%	52‡	SBP: 2.5 mm Hg; may help prevent progression to DM	Fecal spotting, steatorrhea, fecal urgency	Fat-soluble vitamin supplementation is recommended
Phentermine[26–28] 15–37.5 mg	3%–5%	10%	28	SBP: 1.3 mm Hg; heart rate: 5 bpm; 10% in TG	Dry mouth, insomnia, headache, anxiety, agitation, hypertension (rare)	Avoid in uncontrolled HTN and CVD, history of substance abuse disorder, glaucoma

*Assuming maximum approved or tolerated dose during RCT.

†Includes outcomes in patients without diabetes.

‡Peak weight loss occurred at the end of year 1, during which participants adhered to a "weight loss diet." The trial continued for an additional year with a "weight maintenance diet" during which weight was regained.

A1c indicates hemoglobin A1c; BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; GFR, glomerular filtration rate; HTN, hypertension; RCT, randomized controlled trial; SBP, systolic blood pressure; T2D, type 2 diabetes; and TG, triglycerides.

compared with standard lifestyle modification alone, with an ICER of $237 000 per QALY gained.[11] The ICER was even higher when semaglutide was compared with other obesity pharmacotherapies (eg, $469 000 per QALY gained relative to phentermine/topiramate) or when liraglutide was compared with lifestyle modification alone ($483 000 per QALY gained). The cost of semaglutide has declined in the past year due to negotiations, rebates, and direct-to-customer sales, and a preliminary update of the prior analysis suggests improved cost-effectiveness in this higher-risk subpopulation using the therapy for weight management.[12]

3. Several non-GLP-1–based obesity medications are available in the United States, with generally less substantial impacts on weight loss and CKM risk profiles than GLP-1–based therapy. Of these, phentermine/topiramate[13] is associated with the greatest amount of weight loss, followed by bupropion/naltrexone,[14–16] and lastly, orlistat.[17,18] Bupropion/naltrexone, phentermine/topiramate, and orlistat have all shown efficacy in improving glycemia, and the latter 2, in reducing BP. Despite the relative efficacy of phentermine/topiramate, the presence of a stimulant in the combination therapy has raised concerns about its use among those who might be particularly susceptible to complications or side effects. Phentermine alone can also be used for obesity management, but it is often used short-term (12 weeks) due to concerns for cardiovascular side effects and potential for abuse. Additionally, bupropion/naltrexone use is associated with slight increases in BP.[1,4] Therefore, as discussed in later sections (Section 6.3.1, "CKM Syndrome Stage 4 With Obesity and HF), these agents should generally be avoided in those with CVD due to their potential for increasing cardiovascular risk. As with GLP-1–based therapies, gastrointestinal side effects are common with bupropion/naltrexone and, in particular, with orlistat.

5.4.4. Surgical Interventions for Weight Loss in CKM Syndrome Stage 1 to 3

Recommendations for Surgical Interventions for Weight Loss in CKM Syndrome Stage 1 to 3 Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
2a	A	1. Among patients with CKM stage 1 to 3 and obesity without an adequate weight loss response to lifestyle modification, with or without the use of adjunctive obesity pharmacotherapies, MBS can be beneficial to facilitate weight loss and to mitigate CKM syndrome progression.[1–8]

Recommendations for Surgical Interventions for Weight Loss in CKM Syndrome Stage 1 to 3 (Continued)		
COR	LOE	Recommendations
Economic Value:* Cost-Effective (High Level of Certainty)		2. Among patients with severe obesity, bariatric surgery is cost-effective compared with medical treatment regardless of baseline diabetes status.
2a	B-NR	3. Among patients who have undergone MBS and have regained a significant amount of weight (≥25% or more of total lost weight), GLP-1–based therapies can be useful in promoting weight loss and management of comorbidities.[9–13]

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

Synopsis

MBS is the term now used to encompass surgical weight loss procedures, which have demonstrated clinical value beyond weight loss, including reductions in comorbidities and long-term mortality. MBS has long been an effective option for those unable to lose weight through other means. Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) comprise 90% of all procedures.[9] Though GLP-1–based therapy has promising effects on weight loss and CKM-related risk, long-term data are still lacking, and medication discontinuation with resultant weight regain is common. MBS has, to date, been shown to be superior overall in promoting long-term weight loss and reducing cardiovascular risks, morbidity, and mortality, though this may change as evidence for the benefits of GLP-1 accumulates.[14–16] While MBS is generally safe,[17] the surgical and pharmacologic approaches are not mutually exclusive. GLP-1–based therapy can be used to promote weight loss prior to surgery or to treat weight regain after surgery, and for those who fail to lose sufficient weight with pharmacotherapy, MBS can be offered as an alternative. Shared decision-making, ideally with support from an interdisciplinary team, is appropriate for navigating the different surgical and medical options for weight loss to reduce CKM progression.

Recommendation-Specific Supportive Text

1. MBS has efficacy among individuals with a BMI ≥35 kg/m^2 regardless of the presence of comorbidities and can be beneficial in patients with T2D with a threshold BMI of 30 kg/m^2.[6] Furthermore, there is evidence that among Asian patients, those with a BMI of <30 kg/m^2 can benefit.[3] Average excess weight loss is greater with RYGB (56%) than LSG (46%),[2,18] with persistent differences at 10 years.[4] MBS has favorable effects on all CKM risk factors, as well as OSA and MASLD. In the GATEWAY (Gastric Bypass to Treat Obese Patients With Steady Hypertension) RCT, MBS resulted in greater hypertension remission (2.4% versus 46.9%) and reductions in antihypertensive medications versus medical therapy.[7,19] The STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) and ARMMS-T2D (Alliance of Randomized Trials of Medicine versus Metabolic Surgery in T2D) trials demonstrated that MBS was associated with greater rates of diabetes remission than medical/lifestyle therapy, with 40% of participants using GLP-1–based therapy in ARMMS-T2D.[6,8] CKM risk factor remission is superior with RYGB bypass compared with LSG.[20,21] Matched observational studies also demonstrate a reduction in fatal and nonfatal CVD events (42%) and all-cause mortality (49%) comparing MBS to routine care.[1,5] Large registries demonstrate rates of major surgical complications <5% and mortality <0.1%. The American College of Surgeons offers an online tool for patients to assist with shared decision-making about MBS (https://riskcalculator.facs.org/bariatric/).
2. Modeling studies have examined the cost-effectiveness of bariatric procedures (LSG, RYGB) compared with medical therapy alone in people with severe obesity, with or without diabetes at baseline.[22,23] Synthesizing data from various clinical trials, they have found that although the ICER for bariatric surgery compared with medical care varies depending on the population and intervention studied, it is consistently less than the ACC/AHA threshold of $120 000 per QALY gained. For instance, 1 study found that over 5 years of follow-up, RYGB compared with medical therapy produced 0.44 additional QALYs at an incremental cost of $20 633, resulting in an ICER of $46 877 per QALY gained (in 2020 US dollars).[23] The ICER varied inversely with baseline BMI and diabetes severity; that is, bariatric surgery was more economically attractive in individuals with higher BMI and more severe diabetes. The ICER also declined with duration of follow-up in that bariatric surgery became more economically attractive if benefits were sustained over the long-term. An important caveat is that these studies compared surgery with prior obesity pharmacotherapies. A recently published modeling study suggested that GLP-1-based therapies, at an annual cost of $19 881, would not be cost-effective compared with RYGB surgery.[24] However, the study does not provide sufficient details to test calibration and assumes a base-case drug price that is substantially higher than the 2023 cost of the agents. Therefore, the comparative effectiveness of bariatric surgery compared with high-intensity GLP-1–based therapies is uncertain.
3. Patients who undergo MBS generally have excellent weight loss; however, 10% of patients who had RYGB and 30% of patients who had LSG have inadequate weight loss defined as <20% total body weight loss.[25] Some weight regain from the

nadir at 12 to 18 months postsurgery is common.[26] In a prospective cohort study of 1406 adults who underwent MBS and were followed up for 6.6 years, patients with >20% of weight gain after MBS had a 42% clinically important decline in quality of life, and 35.3% had worsening of diabetes.[27] Additionally, the PCORnet Bariatric Study reported modest weight regain for RYGB (mean weight regained, 7.2 kg) and LSG (mean weight regained, 8.2 kg).[25] Until recently, options to address insufficient weight loss and weight regain have been limited with surgical revision as 1 option.[28] Fortunately, GLP-1–based therapy has been shown to mitigate postsurgical weight regain in several observational studies.[10–12,29] Effective agents include liraglutide, semaglutide, and tirzepatide (a GIP/GLP-1 agonist). The use of these medications to mitigate weight regain is consistent with the notion that obesity is a chronic condition, and re-engagement with treatment is often necessary over the course of a patient's lifetime.[30]

5.4.5. Management After Gestational Diabetes

Recommendations for Management After Gestational Diabetes
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	B-R	1. In women diagnosed with GDM, an oral glucose tolerance test 4 to 12 wk postpartum is recommended for prediabetes and diabetes screening and to identify increased risk for development of T2D and for CKM stage progression.[1–4]
1	C-LD	2. In women diagnosed with GDM, counseling by a health care clinician is recommended to provide education regarding the increased risk for developing T2D and for CKM stage progression.[5]
1	B-R	3. Among postpartum women with a history of GDM and prediabetes, optimizing glucose and metabolic risk factors through lifestyle interventions or metformin use is recommended to reduce the risk for incident T2D and CKM stage progression.[6–9]

Synopsis

Gestational diabetes mellitus (GDM) refers to glucose or carbohydrate intolerance identified or shown during pregnancy. Because of increased risk for T2D among individuals with prior GDM, their approach to longitudinal assessments for CKM risk factors of glycemia, lipids, and kidney function (at least every 2 to 3 years) should be the same as that for individuals with stage 1 CKM syndrome (Section 3.1.1. "Longitudinal Diagnostic Assessment for all CKM Stages"). Untreated GDM impacts 2% to 10% of births in the United States, presenting a 35% to 60% likelihood of progressing to T2D within 10 to 20 years.[10] Obesity, excessive weight gain during pregnancy, and postpartum weight retention are risk factors for GDM, with subsequent 10-fold T2D risk and 2-fold CVD risk. This highlights the importance of early postpartum diagnosis and management, including T2D screening, timely initiation of postpartum care to improve risk awareness and prevention, counseling on lactation and healthy lifestyle practices, and pharmacologic and nonpharmacologic strategies to reduce further risk. Individuals at risk should implement lifestyle modifications and achieve weight loss to mitigate the likelihood of T2D development and CKM progression.[11] This required enhanced monitoring, diagnosis, and early intervention. However, current prognostic models for T2D following GDM have methodological deficiencies, and pharmacological intervention approaches to facilitate lifestyle modifications in women with GDM warrant further investigation.

Recommendation-Specific Supportive Text

1. Evidence supports the recommendation of a 75-g oral glucose tolerance test to screen for diabetes and prediabetes at 4 to 12 weeks postpartum in women with GDM.[1] Alternative strategies include early testing (ie, before hospital discharge) to mitigate the possibility of missed screening at 4 to 12 weeks postpartum,[2,3] fasting plasma glucose test at 6 to 12 weeks, or an HbA1c test after 13 weeks.[12] A higher prevalence of glucose intolerance is reported in the early postpartum period using fasting plasma glucose and HbA1c (≥7.5%) compared with the oral glucose tolerance test criteria.[1] Few studies have compared fasting plasma glucose and/or HbA1c tests to the oral glucose tolerance test in detecting postpartum glucose intolerance in women with GDM. HbA1c alone, whether assessed early or late postpartum, showed insufficient sensitivity for detecting abnormal glucose tolerance.[4] While continuous glucose monitoring is not a routine component of care for all women with GDM,[13] there is a growing interest in its use both during and after pregnancy.[14] After normal oral glucose tolerance test results in the early postpartum period, long-term postpartum testing at 1- to 3-year intervals may be considered to minimize maternal diabetes risk.[15] Likewise, annual HbA1c testing is supported.[12]
2. Traditionally, counseling for women with GDM begins and ends with a single postpartum visit 4 to 6 weeks after delivery. However, recent evidence suggests that counseling related to risk reduction for CKM syndrome in high-risk women should start in the prenatal period and continue until the completion of postpartum follow-up visits for the mother and baby.[16–18] The integration of counseling before, during, and after pregnancy significantly improved glucose screening and mitigated risks and complications of CKM syndrome in this population.[5] Counseling should address the needs and concerns of mothers, increase their awareness of the risks associated with CKM progression, and enable them to engage in proactive strategies for managing these risks (eg, postpartum weight retention).

Counseling on dietary or combined dietary and exercise modifications effectively facilitates weight loss in postpartum women with GDM.[6,19–21] Insulin resistance, blood glucose, serotonin, and beta cell proliferation decrease during lactation. Lactation also reduces pancreatic oxidative stress and risks for T2D in women with GDM and should be discussed with them before, during, and after pregnancy.[22–24] Finally, women with GDM should receive a biopsychosocial assessment for postpartum depression, which is linked to CKM risks, to support early detection, referral, and risk management.[25]

3. To reduce the risk of incident T2D and CKM stage progression, postpartum women with GDM and prediabetes should optimize glucose and metabolic risk factors with lifestyle interventions or metformin administration.[6–9] A post hoc analysis of the DPP (Diabetes Prevention Program) trial data showed that women with GDM who participated in a 12-month lifestyle intervention or received metformin had improved glycemic control and reduced risk for T2D by 50% to 60% compared with controls.[19] Intensive lifestyle interventions showed long-term advantages after 10 years. It confirmed that goal planning, self-monitoring, fat and calorie reductions, and weekly 150 minutes of moderate-intensity exercise reduced CKM risk.[6] Implementing lifestyle interventions to reduce postpartum CKM risk has been expanded in later trials, yielding comparable results.[20,26,27] A postpartum lifestyle intervention (education, weight management program, pedometer, telephone, and text support) in overweight women with GDM resulted in greater weight loss at 6 months (−3.9 kg [SD, 7.0] versus −0.7 [SD, 3.8]) than control.[8] Observational studies indicate that women with GDM who follow a DASH or Mediterranean diet postpartum have a lower incidence of hypertension and T2D.[9,28,29] Pioglitazone reduces the risk of T2D in Hispanic women with GDM, but it also increases the risk of weight gain, edema, and fractures.[30,31]

5.5. CKM Syndrome Stage 2

Synopsis

CKM syndrome stage 2 is defined as the presence of metabolic risk factors, moderate- to high-risk CKD, or both in the absence of subclinical or clinical CVD. CVD prevention in stage 2 builds on the management principles outlined for CKM stages 0 and 1 and shifts to a more specific focus on addressing metabolic risk factors and CKD in a timely fashion to prevent progression to clinical CVD and kidney failure. While lifestyle modification remains the foundation of preventive efforts, pharmacologic management of metabolic risk factors, CKD, or both is also central to the care model in stage 2, to reduce risk for CKM syndrome progression. As described in subsequent sections, in addition to utilizing therapies for hypertension[1] and hypertriglyceridemia[2] as per current guidelines, there is an emphasis on using cardioprotective antihyperglycemic agents in T2D and kidney-protective agents in CKD, which confer risk reduction for adverse cardiovascular and kidney events. A 10-year CVD risk of ≥7.5% using the PREVENT-CVD equation can further guide the targeting of pharmacotherapy and should be included in patient-clinical risk discussions. Weight loss, through lifestyle modification, obesity pharmacotherapy, or bariatric surgery, is key for preventing CKM syndrome progression and promoting CKM stage regression.

5.5.1. Management of T2D in CKM Syndrome Stage 2 to 3

Recommendations for T2D in CKM Syndrome Stage 2 to 3
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. In adults with CKM syndrome stage 2 to 3 with T2D, lifestyle modification that includes behavior modification, healthy diet, and recommended physical activity levels, with adjunctive pharmacological and/or surgical approaches as needed, is recommended to achieve and maintain a healthy weight and to improve glycemia control.[1–5]
1	B-R	2. In adults with CKM syndrome stage 2 to 3 with T2D, intensified multifactorial interventions including both lifestyle change and targeted pharmacotherapy to address hyperglycemia, hypertension, dyslipidemia, and albuminuria is recommended to reduce the risk of CVD, mortality, and kidney complications.[6–8]
1	A	3. In adults with CKM syndrome stage 2 to 3 with T2D and increased risk for CVD (10-y PREVENT-CVD ≥7.5%), the treatment plan should include an sodium–glucose cotransporter-2 inhibitors (SGLT2i) or a GLP-1–based therapy with demonstrated benefit to reduce cardiovascular events and mortality.[9–12]
Economic Value Statement:* Cost-Effective (Moderate Level of Certainty)		4. In adults with CKM syndrome stage 2 to 3 with T2D and increased risk for CVD treatment with SGLT2i at 2025 US prices is projected to be cost effective compared with usual care.
Economic Value:* Not Cost-Effective (Moderate Level of Certainty)		5. In adults with CKM syndrome stage 2 to 3 with T2D at increased risk for CVD, treatment with a GLP-1–based therapy at 2025 US prices is projected to be not cost-effective compared with usual care.
2a	A	6. In adults with CKM syndrome stage 2 to 3 with T2D and increased risk of CVD with A1C levels 0.5% to 1% above their individualized glycemic goal, metformin therapy can be effective when combined with cardioprotective antihyperglycemic therapies (GLP-1–based therapy or SGLT2i) to achieve glycemic targets.[13–15]
2b	B-NR	7. In adults with CKM syndrome stage 2 to 3 with T2D and increased risk for CVD or multiple CKM risk factors, or both, combination therapy with a GLP-1–based therapy with proven benefit and an SGLT2i may be considered for reducing the risk of cardiovascular events beyond that conferred by a single cardioprotective antihyperglycemic agent.[16–21]

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

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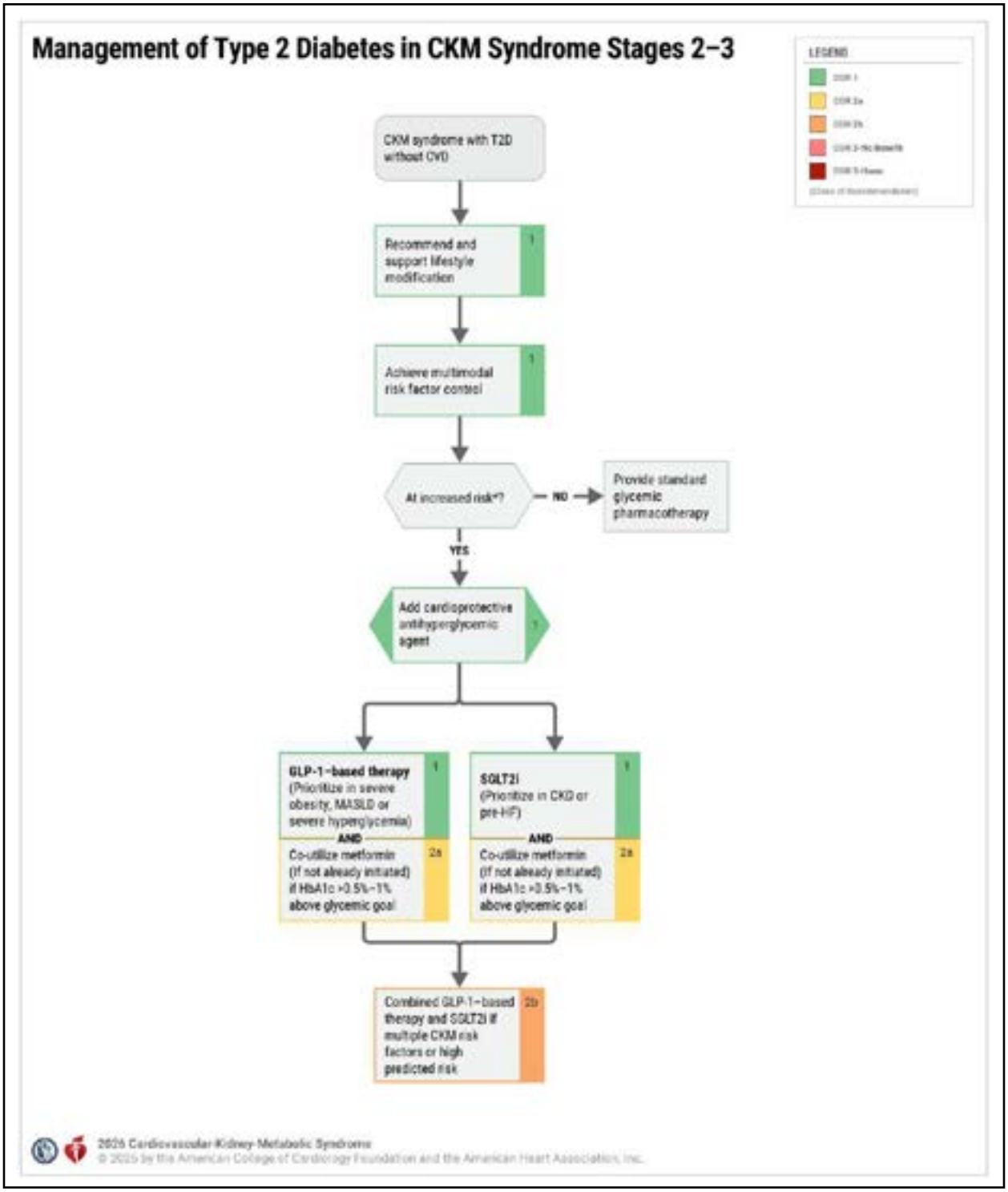

Figure 8. Management of Type 2 Diabetes in CKM Syndrome Stage 2 to 3.
*Increased risk is defined as a 10-year PREVENT-CVD of ≥7.5% or age ≥50 years with T2D and additional CKM risk factors. CKM indicates cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1C; HF, heart failure; MASLD, metabolic dysfunction–associated steatotic liver disease; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

Synopsis

T2D is a frequent complication of overweight and obesity, and is a major CVD risk factor.[22] Most individuals with T2D have additional metabolic risk factors for CVD, including excess adiposity, hypertension, and dyslipidemia. Lifestyle modification is critical for supporting glycemic control, weight reduction, and improvement in metabolic risk factors and associated pathophysiologic abnormalities. Optimizing management of glycemia and comorbid

conditions is key for reducing microvascular and macrovascular complications of T2D, by achieving targets for comprehensive risk factor control and utilizing antiplatelet medications if indicated.[6,7,23,24] Targets for HbA1c and BP include an HbA1c <7.0% for nonpregnant adults without significant hypoglycemia and BP <130/80 mm Hg.[23,25,26] Less stringent A1C goals (eg, <8.0%) may be appropriate for patients with limited life expectancy or where the harms of more aggressive glycemic control may exceed the benefits.[26] Since most individuals with diabetes aged ≥40 years have at least intermediate ASCVD risk, moderate- to high-intensity statin therapy is advised with consideration for adding ezetimibe for those with higher ASCVD risk, to lower LDL-C by ≥50%.[23,27,28] Use of an SGLT2i or GLP-1–based therapy is advised for CVD risk reduction in those with increased predicted CVD risk, with the choice of agent guided by comorbidities such as CKD, pre-HF, obesity, severe hyperglycemia, and MASLD (Figure 8).[9–12,23,26]

Recommendation-Specific Supportive Text

1. Weight management has myriad benefits in T2D, including reductions of A1C and hepatic steatosis, and improvement in cardiovascular risk factors.[26,29] Cohort studies and interventional trials have provided evidence for the weight, glycemic, and metabolic benefits of lifestyle modification, including regular physical activity and a balanced diet, in those with T2D.[30–32] Obesity pharmacotherapies, particularly GLP-1–based therapies, are advantageous as adjuncts to lifestyle modification to support weight loss for selected patients with T2D and BMI ≥27 kg/m^2. Of the currently available agents, tirzepatide (dual GIP and GLP-1 RA) and semaglutide (GLP-1 RA) have the highest efficacy in terms of weight loss and metabolic benefits.[4,5] Evidence also supports the use of MBS for the treatment of comorbid obesity in individuals with T2D.[3] In addition to improvements in weight, glycemia, and CKM risk factors in clinical trials, reductions in CVD, CVD mortality, and all-cause mortality among individuals with T2D have been observed in observational and matched cohort studies.[33–35] MBS should therefore be considered for people with T2D and a BMI ≥30 kg/m^2 (or ≥27.5 kg/m^2 for Asian American individuals), and is recommended in this population by the American Society for Metabolic and Bariatric Surgery and the ADA.[29,36]
2. Most individuals with T2D have multiple additional metabolic risk factors for CVD, including excess abdominal adiposity, hypertension and dyslipidemia, with the majority meeting criteria for metabolic syndrome.[37] Beyond the diagnostic components of metabolic syndrome, additional pathophysiologic features, including inflammation, endothelial dysfunction, an increased concentration of atherogenic lipoproteins, and a prothrombotic state, contribute to CVD risk and should be addressed through lifestyle modification and weight loss. Among patients with T2D and concomitant risk factors of overweight/obesity and albuminuria, use of an intensive multifactorial intervention regimen of behavior modification (diet, exercise, and smoking cessation) and polypharmacologic therapy (antihyperglycemic therapy, ACEi or ARB, lipid-lowering therapy, and aspirin) that targeted risk factor optimization was associated with reduced CVD events and all-cause and cardiovascular mortality compared with conventional therapy in the STENO-2 (Intensified Multifactorial Intervention in Patients With T2D and Microalbuminuria) trial.[6,7] The benefits of the intervention strategy expanded throughout the 8 years of the study, suggesting the continual reinforcement of risk factor reduction was effective. Furthermore, at 21 years of follow-up, patients who received intensive therapy for the initial 7.8 years survived longer than the conventional-therapy group, with the increase in lifespan related to time free from incident CVD.[38]
3. For people with T2D and high CVD risk, an SGLT2i and/or GLP-1–based therapy with demonstrated cardiovascular benefit is recommended independent of HbA1c or metformin use.[9,12] Both classes of agents reduce major adverse cardiovascular events (MACE) and CVD mortality across multiple clinical trials,[39,40] with SGLT2i having a particular impact on HF hospitalizations and GLP-1–based therapy having a more substantial impact than SGLT2i on incident ASCVD events. Clinical trials of these agents in T2D included individuals with either CVD or additional risk factors beyond T2D, reflecting a population at increased CVD risk. Based on the distribution of risk within clinical trials, as well as the absolute risk reduction and number needed to treat associated with risk thresholds in other clinical guidelines, a 10-year PREVENT-CVD score of ≥7.5% is recommended to identify individuals who should be prioritized for SGLT2i or GLP-1–based therapy.[41] A complementary approach is to prioritize therapy for those aged ≥50 years with T2D and additional risk factors. Nonetheless, observational data suggests that individuals with T2D and moderate CVD risk may also derive cardiovascular benefit from preferential use of GLP-1–based therapy and SGLT2i.[11] For young and middle-aged adults without increased 10-year risk, a higher 30-year risk (≥75% for age and sex) is an additional metric to consider during clinician-patient risk discussions about pharmacotherapy. Based on the differing physiologic and clinical effects of these classes of therapies, treatment with SGLT2i can be prioritized in those with CKD and/or pre-HF, while GLP-1–based therapy is preferred in those with class II or higher obesity, severe hyperglycemia (HbA1c ≥9%), and/or MASLD. Side effects

and related mitigation strategies for these agents are discussed in Tables 14 and 15.

4. Prior studies examining the cost-effectiveness of adding SGLT2i relative to the prior standard of care therapy among patients with diabetes from a US health care sector perspective suggested that the use of an SGLT2i in this population is projected to be cost-effective compared with standard of care therapy and cost-saving or cost-effective when compared with dipeptidyl peptidase 4 inhibitors. With the caveat that the prices in these studies were somewhat lower than the current wholesale acquisition cost of SGLT2i ($3500 to $5700 per year compared with the 2025 wholesale acquisition cost of approximately $6500 per year), the studies suggest that the use of SGLT2i in this population is likely to be cost-effective at a threshold of $120 000 per QALY gained.[42,43] The economic value of therapies may be further improved by a reduction in prices due to Medicare negotiations or the entry of generic formulations of SGLT2i.
5. Several studies have assessed the cost-effectiveness of adding GLP-1–based therapies, as a drug class and including older members of the class, compared with standard of care among patients with diabetes from a US health care sector perspective.[44–48] In general, these studies found that GLP-1–based therapies would not be cost-effective compared with usual care, especially when used as first-line therapy. However, the ICER varied widely based on the cost of therapy and the comparator chosen.[49] Future research should focus on conducting a comprehensive economic evaluation of newer GLP-1–based therapies to clarify the economic value of these high-cost therapies, including in combination with SGLT2i.
6. While reducing cardiovascular risk with GLP-1–based therapy or SGLT2i is a priority in T2D management, glycemic control is an additional focus for reducing microvascular T2D complications. To this end, SGLT2i only have modest glycemic effects (0.5% to 1% HbA1c reduction). GLP-1–based therapy has a more substantial impact on glycemia, but inadequate dose titration or discontinuation due to side effects or cost are common and can also limit glycemic impact. Therefore, for individuals with HbA1c >0.5% to 1% above their glycemic control, co-utilization of additional glucose-lowering

Table 14. Adverse Effects of SGLT2i in T2D

Adverse Effect	Preventive and Therapeutic Considerations
DKA risk in individuals with insulin deficiency	Much less common in those with T2D. Discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors (ketogenic diet) and clinical presentations (including euglycemic DKA); mitigate risk with sick-day planning; discontinue before scheduled surgery (eg, 3–4 d), during critical illness, or during prolonged fasting
Genital mycotic infections	Mitigate risk with genital hygiene and avoid use in high-risk individuals. Use with caution or avoid in the setting of severe hyperglycemia to reduce infectious risk.
Necrotizing fasciitis of the perineum (Fournier gangrene)	Rare; prompt treatment if suspected.
Intravascular volume depletion	Attention to volume status and blood pressure, particularly when ill or fasting; consider dose reduction of other volume contracting agents as applicable; monitor kidney function after initiation.

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DKA indicates diabetic ketoacidosis; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

Table 15. Adverse Effects of GLP-1–Based Therapy in T2D

Adverse Effect	Preventive and Therapeutic Considerations
Gastrointestinal adverse effects	Counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects; consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.
Thyroid C-cell tumors	Thyroid C-cell tumors identified in rodents; human relevance not determined. Contraindicated in patients with personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2
Pancreatitis	Acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected.
Acute gallbladder disease	Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals
Ileus	Reported; risk level is not well-established.
Potential to impact concomitantly administered oral medications due to delayed gastric emptying	Orally administered drug absorption may be impaired during dose titration including oral contraceptives. Advise patients using oral contraceptives to switch to a nonoral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation.
Diabetic retinopathy complications in patients with a history of diabetic retinopathy	Close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 y]).
Nonarteritic anterior ischemic optic neuropathy (NAION)	Rare; monitor for NAION during eye examinations
Acute kidney injury	Monitor kidney function in patients with CKD reporting severe adverse GI reactions
Risk of pulmonary aspiration	Provide guidance on discontinuation prior to surgical procedures to mitigate potential for pulmonary aspiration with general anesthesia or deep sedation.

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GI indicates gastrointestinal; GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes.

therapy alongside SGLT2i or GLP-1–based therapy can be considered to ensure attainment of glycemic control. Metformin is emphasized here due to beneficial effects on HbA1c and weight, very low associated risk for hypoglycemia in the absence of insulin therapy, widespread accessibility, and the ability to safely combine it with cardioprotective glucose-lowering therapies to achieve glycemic targets.[13–15,26] Both SGLT2i and GLP-1–based therapy confer cardiovascular benefits independent of metformin and should be first-line therapeutic considerations.[14,15] Pioglitazone may be combined with cardioprotective glucose therapy to achieve glycemic targets and may lower ASCVD risk, but it is associated with increased risk of HF.[50] The approach to glycemic management should be guided by ADA recommendations.[26]

7. There is a lack of interventional data assessing the impact of combined SGLT2i and GLP-1–based therapy on cardiovascular and kidney outcomes, relative to the use of each of these agents alone. However, while both classes of agents reduce MACE and CVD mortality in T2D,[39,40] the mechanisms and cardiovascular benefits associated with these agents are somewhat distinct.[16] Clinical trials have indicated a lack of heterogeneity in the effects of each class of these cardioprotective glucose-lowering therapies between those who were and were not taking the other agent.[17–19,21] Observational data and modeling studies suggest an additive cardiovascular benefit of combined SGLT2i and GLP-1–based therapy versus each agent alone.[19,20] Such an approach may be considered for selected high-risk patients with T2D. Additional considerations for dual SGLT2i and GLP-1–based therapy use may relate to their impact on CKM risk profiles, for example, addressing obesity, severe hyperglycemia, or MASLD with GLP-1–based therapy or addressing CKD or high HF risk with SGLT2i. However, the clinical benefit of combination SGLT2i and GLP-1–based therapy has not been quantified in clinical trials. The potential benefits of combination therapy need to be balanced against polypharmacy, costs of therapy, and patient preferences.

5.5.2. Hypertriglyceridemia

Synopsis

Hypertriglyceridemia is defined as a fasting triglyceride level of ≥150 mg/dL or a nonfasting triglyceride level of ≥175 mg/dL.[1,2] Some Mendelian randomization studies suggest a causal link between elevated triglycerides and ASCVD development.[3] Additionally, as per clinical guidelines, persistently elevated triglycerides are considered a risk enhancer for ASCVD.[2,4–6] Elevated triglycerides are also associated with a higher incidence of CKD and faster decline in eGFR, possibly mediated by albuminuria.[7,8] When hypertriglyceridemia is identified, reversible secondary causes, such as poor lifestyle, hypothyroidism, uncontrolled hyperglycemia, severe albuminuria, and medications, should be identified and addressed.[1,6–8] As per clinical guidelines, initial therapeutic considerations should be lifestyle modification and statin therapy in those with borderline-intermediate or higher predicted risk. For those with persistent hypertriglyceridemia on maximally tolerated statins, or with additional cardiovascular risk factors, icosapent ethyl can be considered to lower ASCVD risk.[9] Severe hypertriglyceridemia (≥500 mg/dL) is associated with even greater ASCVD risk and increased risk for pancreatitis. Among patients with severe hypertriglyceridemia, in addition to LDL-C–lowering therapy, measures may include implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, referral to a dietitian, and addition of a fibrate or prescription omega-3 fatty acids to lower triglycerides and prevent acute pancreatitis.[1]

5.5.3. Hypertension

Synopsis

Hypertension is an important component of CKM syndrome, contributing to progressive end-organ damage, including worsening kidney function and CVD.[1,2] Among adults with CKM syndrome stage 2, hypertension contributes to CKD development, and CKD, in turn, increases the risk for and severity of hypertension. Effective BP management in adults with CKM syndrome is therefore essential for reducing morbidity and mortality. Lifestyle modification, including sodium reduction, weight loss, increased physical activity, and adherence to heart-healthy dietary patterns such as the DASH or Mediterranean diet, have shown benefit for reducing BP.[3,4] Current guidelines support lifestyle modification plus antihypertensive pharmacotherapy for adults with average BP ≥140/90 mm Hg, or with average BP ≥130/80 mm Hg and clinical CVD, prior stroke, diabetes, CKD, or a 10-year PREVENT-CVD score ≥7.5%.[5] The overarching therapeutic goal for BP treatment is <130/80 mm Hg. First-line pharmacologic therapies for hypertension management include RASi, thiazide-type diuretics, and long-acting dihydropyridine calcium channel blockers, with initiation of single-pill combination therapy that includes first-line agents preferred for faster BP control and better adherence. RASi provide BP control and kidney and cardiovascular protection[6] and are therefore preferred in patients with CKD and albuminuria. For specific BP management recommendations, please refer to the AHA/ACC 2025 blood pressure guideline.[5]

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5.5.4. Management of CKD in CKM Syndrome Stage 2 to 3

Recommendations for Management of CKD in CKM Syndrome Stage 2 to 3 Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
1	**B-R**	1. In adults with CKM syndrome stage 2 to 3 who have CKD and T2D, or CKD without T2D but with UACR ≥30 mg/g, and with eGFR ≥30 mL/min/1.73 m^2, use of a RASi (eg, ACEi or ARB) at the maximum tolerated dose is recommended to reduce the loss of kidney function and to lower the risk of CVD.[1–4]
1	**A**	2. In adults with CKM syndrome stage 2 to 3 who have CKD and T2D, or CKD without T2D but with UACR ≥200 mg/g, and with eGFR ≥20 mL/min/1.73 m^2, use of an SGLT2i is recommended to reduce the loss of kidney function and to lower the risks of HF hospitalization and CVD mortality.[5–10]
2a	**B-R**	3. In adults with CKM syndrome stage 2 to 3 who have CKD without T2D but with UACR ≥30 to 199 mg/g, SGLT2i can be considered to reduce the loss of kidney function and to lower the risks of HF hospitalization and CVD mortality.[6,10]
Economic Value:* Cost-Effective (High Level of Certainty)		4. In adults with CKM syndrome stage 2 to 3 who have CKD with or without T2D, treatment with SGLT2i at 2025 US prices is projected to be cost-effective compared with not using an SGLT2i.
1	**A**	5. In adults with CKM syndrome stage 2 to 3 who have CKD, T2D, and UACR ≥30 mg/g despite ACEi/ARB and SGLT2i as tolerated, with eGFR ≥25 mL/min/1.73 m^2, the addition of a nonsteroidal mineralocorticoid receptor antagonist (nsMRA) with proven kidney and cardiovascular benefit is recommended to reduce the risks of losing kidney function and kidney failure, and to lower the risk of CVD.[11–15]
Economic Value:* Not Cost-Effective (Moderate Level of Certainty)		6. In adults with CKM syndrome stage 2 to 3 who have CKD, T2D, and UACR ≥30 mg/g, treatment with finerenone at US 2025 prices is projected to not be cost-effective compared with usual care.
1	**B-R**	7. In adults with CKM syndrome stage 2 to 3 who have CKD, T2D, and UACR ≥100 mg/g despite ACEi/ARB and SGLT2i as tolerated, treatment with GLP-1–based therapy with proven kidney and cardiovascular benefit is recommended to reduce the risks of losing kidney function and kidney failure, and to lower the risk of CVD.[16–18]
Economic Value:* Indeterminate (Insufficient Evidence)		8. In adults with CKM syndrome stage 2 to 3, CKD, T2D, and UACR ≥100 mg/g despite ACEi/ARB and SGLT2i as tolerated, the cost effectiveness of adding GLP-1–based therapy is indeterminate.

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

Synopsis

The overarching goal for patients in CKM syndrome stage 2 to 3 with CKD is to lower the risks of loss of kidney function and MACE. Aggressive management of comorbid risk factors, including hypertension and dyslipidemia, using lifestyle measures and pharmacotherapy, reduces kidney and cardiovascular risk. RCTs suggest that atorvastatin may reduce progression of CKD.[19,20] A central component of CKD management is the use of agents that prevent loss of kidney function while additionally conferring cardiovascular benefit (Figure 9). In patients with CKD and T2D or with CKD and albuminuria (UACR ≥30 mg/g), use of RASi (ACEi or ARB) and SGLT2i (with strongest data in those with UACR ≥200 mg/g in the absence of T2D) are recommended as first-line therapies given an extended track record of efficacy and safety and high levels of accessibility, while finerenone and/or a GLP-1–based therapy with proven benefit should be considered as additional therapies for high-risk patients with T2D, CKD, and persistent albuminuria on first-line therapy. The cardiovascular benefits of these agents in clinical trials of CKD are largely related to reduced HF hospitalizations, MACE, and cardiovascular death. The recommended approach is aligned with the overarching premise of targeting individuals at the highest absolute risk for the most intensive treatments. As such, individuals with CKD and T2D or CKD and albuminuria represent key benefit groups at high baseline absolute risk, with population-based analyses demonstrating that the overwhelming majority of individuals with CKD and T2D or albuminuria have a 10-year PREVENT-CVD score ≥7.5%.[21] Albuminuria is a key marker for guiding CKD management (Figures 10 and 11), with cut points of UACR ≥30 mg/g for utilization of RASi, SGLT2i, and finerenone (the latter in those with T2D) and of UACR ≥100 mg/g for GLP-1–based therapy in T2D. Although clinical trial data in patients with CKD and T2D demonstrate the additive benefits of combined therapy with SGLT2i and finerenone on albuminuria relative to either agent alone (with almost all trial participants on background RASi),[22] there are scarce clinical trial data evaluating the cardiovascular benefit of combination therapy with more than 2 of the above 4 classes of kidney-protective agents. However, no significant heterogeneity in risk reduction has been observed between those who are and are not taking other kidney-protective agents. Modeling exercises suggest meaningful gains in major cardiovascular and kidney event-free and overall survival when multiple kidney-protective agents are combined, compared with RASi alone.[23]

Recommendation-Specific Supportive Text

1. In patients with CKD, multiple randomized trials and meta-analyses of RCTs have shown a benefit of RASi at reducing the risk of losing kidney function and kidney failure in patients with CKD and T2D or CKD and albuminuria.[1–4] In the RENAAL (Reduction of Endpoints in NIDDM With the Angiotensin II Agonist Losartan) trial, losartan significantly reduced the primary outcome (composite of a doubling of the baseline serum creatinine concentration, end-stage renal disease, or death), reduced the incidence of a doubling of the serum creatinine concentration and end-stage renal disease and lowered first hospitalization for HF, but had no effect on the rate of death in patients with T2D and albuminuria.[24] Similarly, meta-analysis of RCTs among individuals with diabetes

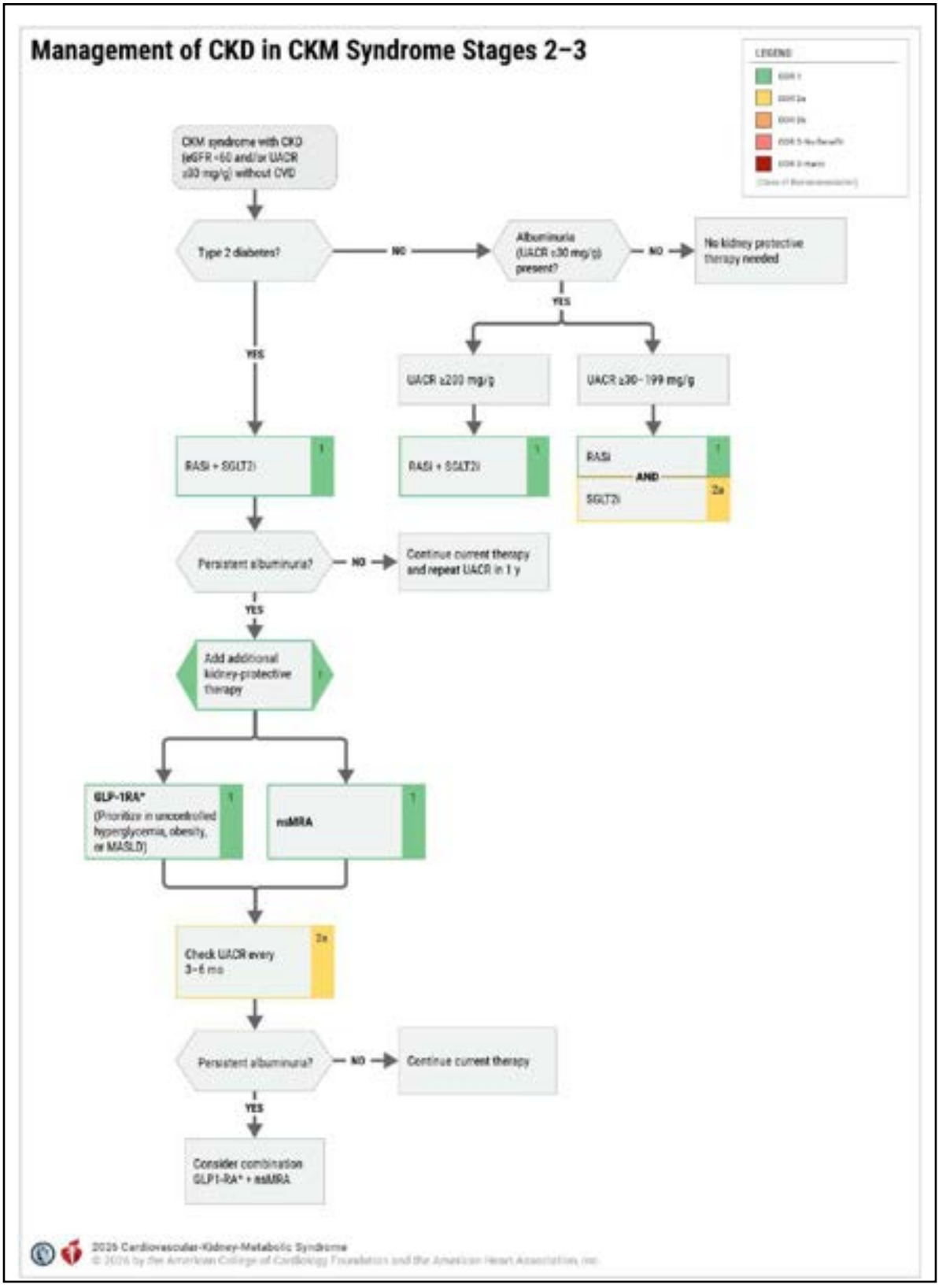

Figure 9. Management of CKD in CKM Syndrome Stage 2 to 3.
*Semaglutide is currently the only GLP-1 RA demonstrated to improve kidney and CVD outcomes among patients with T2D and CKD with albuminuria. CKD indicates chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; GLP-RA, GLP receptor agonist; MASLD, metabolic dysfunction–associated steatotic liver disease; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitors; SGLT2i; sodium–glucose cotransporter-2 inhibitors; and UACR, urine albumin-to-creatinine ratio.

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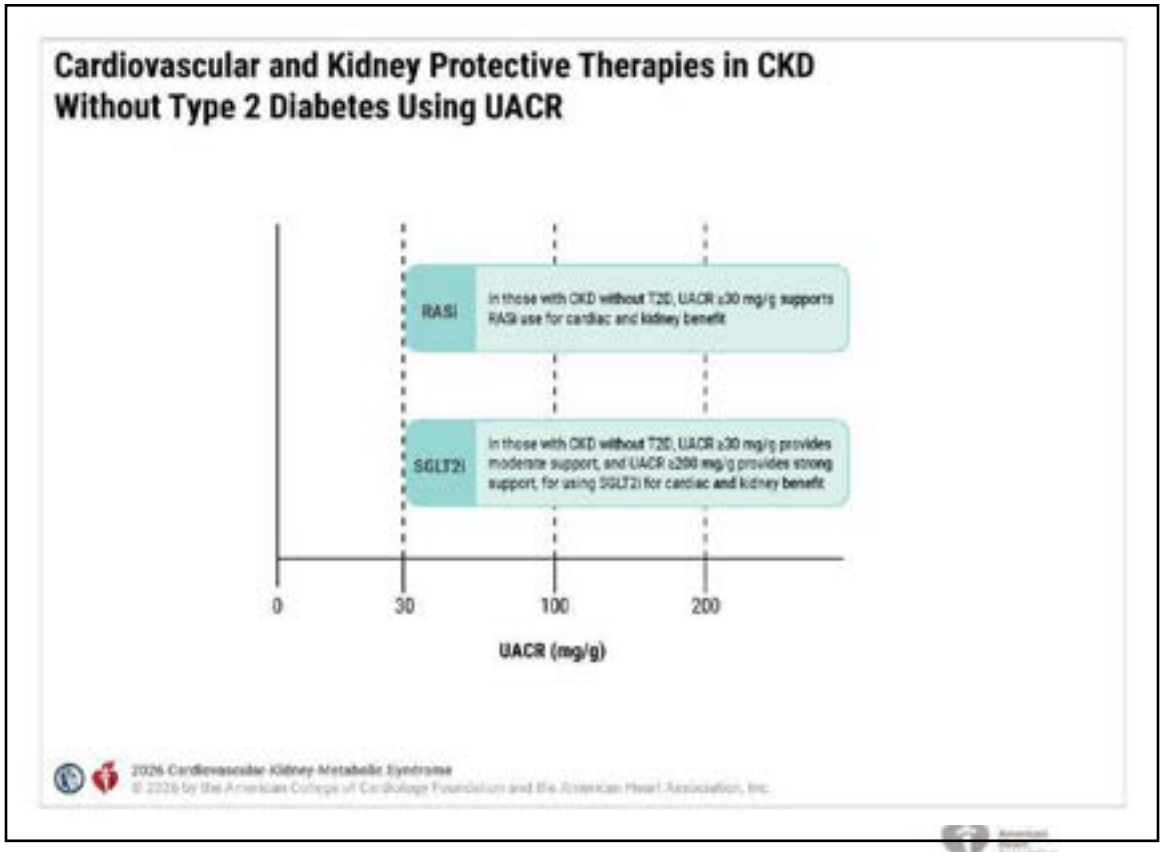

Figure 10. Cardiovascular and Kidney Protective Therapies in CKD Without Type 2 Diabetes Using UACR.
In patients without T2D, a UACR ≥30 mg/g is an indication for kidney-protective therapy. RASi is recommended for all patients with UACR ≥30 mg/g. SGLT2i have strong evidence for cardiac and kidney benefit for those with UACR ≥200 mg/g and more moderate evidence for benefit in those with UACR 30 to 199 mg/g. CKD indicates chronic kidney disease; CVD, cardiovascular disease; RASi; renin-angiotensin system inhibitors; SGLT2i, sodium–glucose cotransporter-2 inhibitors; T2D, type 2 diabetes; and UACR, urine albumin-creatinine ratio.

have shown a reduction in cardiovascular events with RASi when compared with placebo.[25] Of note, these meta-analyses show an attenuated benefit of RASi when compared with active controls of other antihypertensive agents, both for reducing the risk of CKD progression and for prevention of CVD.[4,25]

2. Clinical trials and meta-analyses of SGLT2i in patients with CKD and T2D or CKD and UACR ≥200 mg/g without T2D have shown a significant reduction in risks of losing kidney function, kidney failure, cardiovascular death, and HF hospitalization when compared with placebo.[5–7] The beneficial effect on kidney and cardiovascular events with SGLT-2i was observed in patients regardless of background RASi[26] or GLP-1 RA[10] use, suggesting an independent and incremental benefit of SGLT-2i. Trials of SGLT2i generally included individuals with eGFR ≥20 mL/min/1.73 m^2, supporting therapy initiation in this population, but therapy was continued until kidney failure with evidence for ongoing kidney and cardiac benefits. Overall, the cardiovascular benefits observed were driven primarily by a reduction in cardiovascular death, particularly HF death and sudden cardiac death, without a significant effect on MI or stroke.[27]
3. In the SMART-C collaborative meta-analysis, SGLT2i lowered MACE (hazard ratio [HR], 0.90; 95% CI, 0.84–0.96) and cardiovascular death (HR, 0.80; 95% CI, 0.72–0.88) in patients with albuminuria (defined as UACR ≥30 mg/g).[10] However, the proportion of patients without diabetes was low and only contributed by the EMPA-Kidney (The Study of Heart and Kidney Protection With Empagliflozin) trial, where patients with UACR 30–199 were also required to have an eGFR 20 to 45 mL/min/1.73 m^2. In EMPA-Kidney, the risk reduction for the primary outcome (a composite of progression of kidney disease or death from cardiovascular causes) with empagliflozin compared with placebo was larger among patients with higher UACR (UACR ≥30–300: HR, 0.91; 95% CI, 0.65–1.26 versus UACR ≥300: HR, 0.67; 95% CI, 0.58–0.78).[6] However, the rate of eGFR decline after the initial decrease was slower in the empagliflozin group than in the placebo group in all key subgroups, including in the subgroup of patients with a UACR <30 mg/g.[6] Therefore, SGLT2i can be considered among individuals with CKD without T2D but with UACR 30 to 199 mg/g; however, data regarding

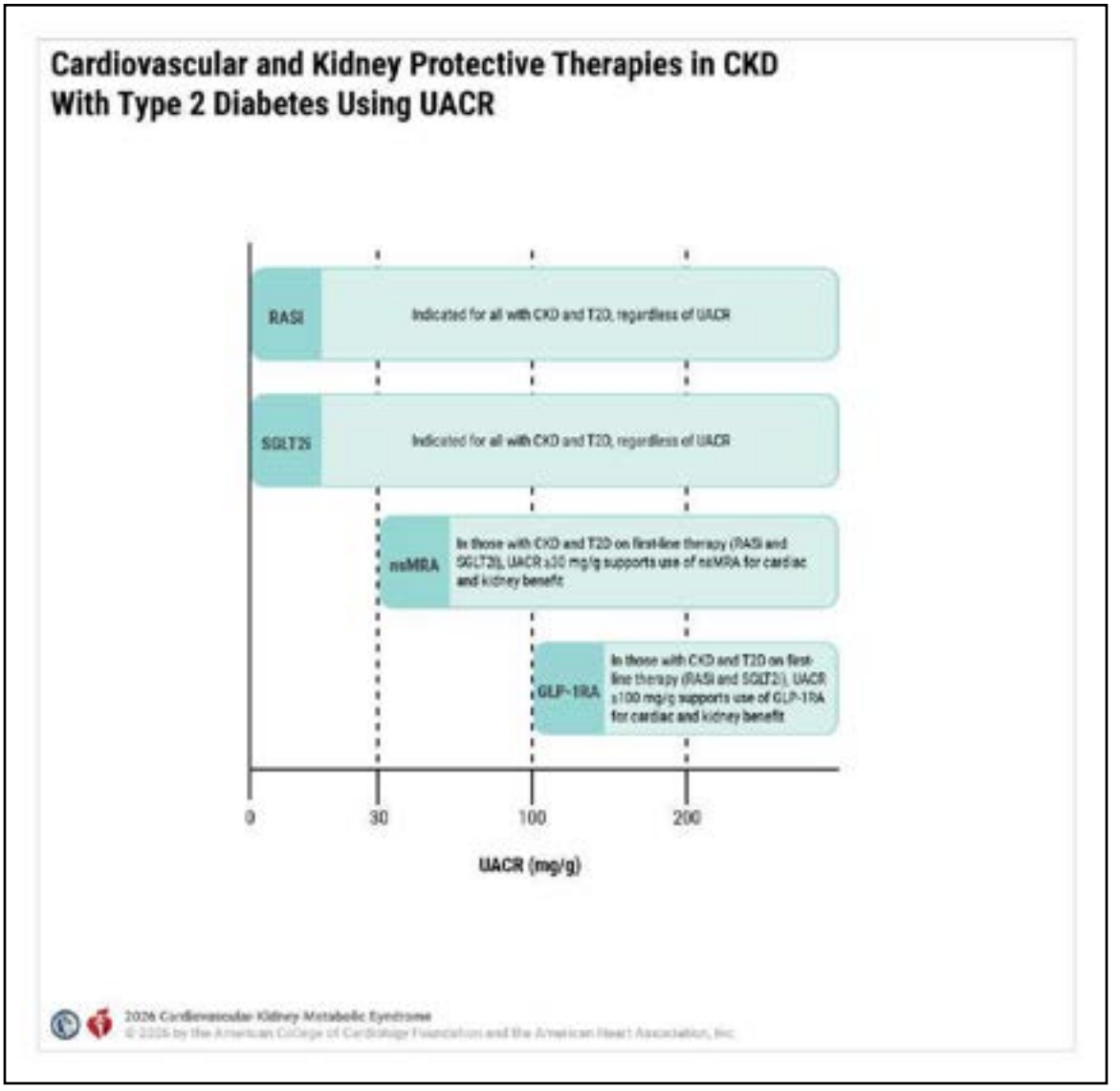

Figure 11. Cardiovascular and Kidney Protective Therapies in CKD With Type 2 Diabetes Using UACR.
In patients with T2D, RASI and SGLT2i are recommended as first-line therapy for all patients with CKD. For those with persistent albuminuria on first-line therapy, UACR ≥30 mg/g is an indication for adding nsMRA and UACR ≥100 mg/g is an indication for adding GLP-1 RA therapy. CKD indicates chronic kidney disease; GLP-1, glucagon-like peptide 1; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; RASi; renin-angiotensin system inhibitors; SGLT2i, sodium–glucose cotransporter-2 inhibitors; T2D, type 2 diabetes; and UACR, urine albumin-creatinine ratio.

the combined kidney and cardiovascular benefits are less robust than for those with UACR ≥200 mg/g.

4. Studies examining the cost-effectiveness of adding SGLT2i to prior standard care in patients with diabetes found that, from a US health care sector perspective, this approach is projected to be cost-effective compared with standard therapy. A modeling study among those with diabetic kidney disease (DKD) found that adding empagliflozin to the standard of care is projected to be cost-effective relative to the standard of care alone from a US health care sector perspective.[28] The study assumed an annual cost of $3200 (approximately 50% rebate from the wholesale acquisition cost), which is substantially lower than that assumed by other studies but higher than the Medicare negotiated price that will be implemented in 2026. A high-quality modeling study examining the cost-effectiveness of dapagliflozin in nondiabetic CKD found that dapagliflozin improved life expectancy by 2 years, increased discounted QALY (from 6.75 to 8.06), and reduced incident kidney failure requiring kidney replacement therapy over the lifetime of the cohort. At an annual cost of $4416, adding dapagliflozin to standard care was projected to be cost-effective over the lifetime, with an incremental cost-effectiveness ratio of $60 000 per QALY gained.[29] Collectively, this evidence

points to high certainty that SGLT2i use is cost-effective in patients with CKD.

5. Clinical trials of the nsMRA finerenone in patients with CKD, T2D, and albuminuria despite RASi, as well as eGFR ≥25 mL/min/1.73 m^2, have shown significant kidney and cardiovascular benefits of finerenone.[11,12,30–32] In the FIDELIO DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) clinical trials among patients with CKD, T2D, and albuminuria, finerenone significantly reduced albuminuria, loss of kidney function, kidney failure, kidney disease death, HF, and cardiovascular mortality compared with placebo.[11–13,30–32] There was no heterogeneity of treatment effect related to the utilization of SGLT-2i or GLP-1 RA, though the trials were not adequately powered for these subgroups. Only those with potassium ≤4.8 mmol/L at baseline were included in trials, and the incidence of hyperkalemia-related discontinuation was higher with finerenone than placebo.[13] Clinical trials of finerenone in CKD did not require prior use of both RASi and SGLT2i; however, as described above, owing to the extended efficacy and safety record of RASi and SGLT2i, these agents are recommended as first-line, with the addition of finerenone advised for the high-risk subgroup with T2D and persistent albuminuria despite first-line agents.
6. An analysis that examined the cost-effectiveness of adding finerenone to standard of care for patients with diabetes and CKD assumed an annual cost of $7300 and computed an ICER for finerenone relative to standard of care treatment of $135 000 per QALY gained.[33] As a result, the use of finerenone for this indication is projected to be not cost-effective at a threshold of $120 000 per QALY gained. In probabilistic sensitivity analyses, approximately 35% of the simulations had an ICER <$120 000 per QALY gained. The cost of a 1-year supply of finerenone in the Federal Supply Schedule was $7600 in August 2025.[34]
7. Meta-analyses of clinical trials of GLP-1 RA among the subgroup of patients with T2D and CKD have shown lower risks of declining kidney function, kidney failure, MACE, HF hospitalization, cardiovascular death, and all-cause mortality compared with placebo, regardless of SGLT2 inhibitor use.[16] In the FLOW (A Research Study to see how Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial, semaglutide 1.0 mg weekly subcutaneously lowered the risks of major adverse kidney outcomes (dialysis, transplantation, incident eGFR of <15 mL/min/1.73 m^2, a ≥50% reduction in eGFR, or death from kidney causes), MACE, HF hospitalization, cardiovascular death, and all-cause death in patients with T2D and CKD with albuminuria when compared with placebo.[17] As for finerenone, semaglutide is recommended as additional therapy for those high-risk individuals with T2D and CKD with persistent albuminuria (≥100 mg/g, based on trial criteria) despite first-line therapy with RASi and SGLT2i. Given the additional physiologic and clinical benefits of GLP-1 RA described in other sections of this guideline, for patients with T2D, CKD, and persistent albuminuria on first-line therapy, semaglutide can be prioritized over finerenone in the setting of uncontrolled hyperglycemia, obesity, or MASLD.
8. We identified no economic evaluations examining the cost-effectiveness of semaglutide based on the results of the FLOW trial, in patients with diabetes and CKD, with or without concurrent ASCVD. The large health benefits observed in the FLOW trial suggest the potential for substantial population health benefit if there is widespread uptake of the drug for this indication. However, the high cost of semaglutide,[34] and the large number of individuals eligible for therapy underscore the urgent need for a rigorous economic evaluation of semaglutide therapy for this indication.

5.6. CKM Syndrome Stage 3

CKM syndrome stage 3 represents a high-risk primary prevention population with subclinical CVD (ASCVD or HF), or risk equivalents of very-high-risk CKD per the KDIGO risk classification, or high predicted CVD risk (10-year PREVENT-CVD score >20%).[1–3] The 10-year threshold of 20% for "high" predicted risk by PREVENT CVD reflects a CVD event rate (2% per year) equivalent to that typically encountered among patients with existing CVD. The management principles for CKM stage 2 carry over into CKM stage 3.[1,2,4] However, the substantially greater absolute risk of the CKM stage 3 population justifies intensified lifestyle and pharmacologic therapies to avert risk for short-term clinical events with an expectation for greater absolute risk reduction than in CKM stage 2. While studies have not specifically recruited CKM stage 3 patients, trials of SGLT2i,[5,6] GLP-1 RAs,[7–9] and finerenone[10–13] that have included populations aligned with CKM stage 3 with regards to absolute risk demonstrate low numbers needed to treat to prevent adverse cardiovascular and kidney events. In the high-risk CKM stage 3 population, combination pharmacotherapies may be more strongly considered, as benefits may outweigh harm related to polypharmacy, cost, and side effects. Simulation studies suggest that combinations of CKM therapies may have additive benefits for heart and kidney protection.[6]

5.6.1. Use of Markers of Subclinical Atherosclerosis

Recommendation for Use of Markers of Subclinical Atherosclerosis Referenced studies that support the recommendation are summarized in the evidence table.		
COR	**LOE**	**Recommendation**
2a	**B-NR**	1. In adults with CKM syndrome stage 3 due to the presence of clinically significant CAC (CAC score >100 or moderate to severe CAC on qualitative assessment), initiation or intensification of preventive therapies indicated for CKM syndrome can be beneficial to reduce cardiovascular events.[1–4]

Synopsis

The presence of subclinical atherosclerosis (eg, elevated CAC) is associated with an increased cardiovascular risk among those with CKM risk factors (eg, diabetes, CKD).[5–7] CAC represents total atherosclerotic plaque burden, which enables reclassification of risk when added to multivariable risk equations.[8] The presence and severity of CAC can inform the initiation or intensification of lipid-lowering therapies (Section 7.1, "LDL-C Management in CKM Syndrome") as well as other preventive therapies for CKM syndrome. Although other measures of atherosclerosis (eg, ankle brachial index, carotid intima media thickness) have shown utility in risk assessment,[9–11] studies have been limited in demonstrating their utility for guiding clinical care. Although zero CAC is associated with a low risk of short- to intermediate-term events in the general population, its utility may be limited in CKM syndrome patients. This may be especially true in younger adults with CKM syndrome with accelerated CAC development due to multiple interrelated risk factors with high long-term CVD risk, indicating the need to start risk factor management early in the course of CKM syndrome.[12–16] Lastly, CAC is associated with increased cardiovascular risk in patients with CKD and requires aggressive modification of this risk,[17] and interpretation needs to be individualized in patients with CKD treated with dialysis or transplantation.

Recommendation-Specific Supportive Text

1. Studies using relative-risk reduction estimates from RCTs and absolute event rates from epidemiologic studies of CAC demonstrate that moderate-to-severe CAC identifies patients at high absolute CVD risk who are most likely to benefit from several preventive therapies indicated for CKM syndrome (statins, GLP-1–based therapy, aggressive BP lowering, and icosapent ethyl in those with hypertriglyceridemia).[1–4] Although not yet evaluated with CAC, the same principles likely apply to other CKM syndrome therapies such as SGLT2i, RASi, and nsMRA. A CAC score >100 identifies patients most likely to benefit from preventive therapies due to high absolute risk and, therefore, low numbers needed to treat, with higher CAC scores associated with an even lower number needed to treat. Alternatively, a ≥75th CAC percentile for age and sex may indicate an increased risk among women and in younger populations despite lower absolute CAC levels.[18,19] Notably, these studies represent simulations of RCT results applied to epidemiologic studies with drop-in of preventive therapies affecting event rates[20] and do not indicate the order for adding therapies. Incidentally identified moderate-to-severe coronary calcifications on a nongated chest computed tomography scan typically correlates with CAC ≥100, carries similar prognostic value, and can also identify patients with CKM syndrome most likely to benefit from preventive therapies.[21–24]

5.6.2. Pre–Heart Failure

Recommendations for Pre–Heart Failure Referenced studies that support the recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
1	**B-R**	1. In adults with CKM stage 3 due to pre-HF, intensive lifestyle interventions and intensive risk factor control are recommended to improve CKM health and prevent progression to clinical HF.[1,2]
1	**B-NR**	2. In adults with CKM stage 3 due to pre-HF with T2D or CKD, the use of SGLT2i is recommended as first-line therapy for the prevention of HF.[3–6]
2a	**B-NR**	3. In adults with CKM stage 3 due to pre-HF with diabetes, CKD, and UACR ≥100 mg/g, the addition of GLP-1–based therapy with proven benefit to SGLT2i therapy is reasonable for the prevention of HF.[7–10]
2a	**B-NR**	4. In adults with CKM stage 3 due to pre-HF with diabetes, CKD, and UACR ≥30 mg/g, the addition of nsMRA to SGLT2i therapy is reasonable for the prevention of HF.[7–10]

Synopsis

Pre-HF (or subclinical HF), defined as cardiac biomarker elevation or imaging evidence of cardiac dysfunction in the absence of HF symptoms (Table 16), is included in stage 3 CKM syndrome. Pre-HF is highly prevalent by midlife, particularly among adults with CKM risk factors, with the highest risk of incident HF among those with abnormalities in both biomarkers and echocardiography.[11,12] However, trials specifically recruiting patients with diagnosed pre-HF and targeting HF prevention have been limited, and most evidence is based on post-hoc analyses.[13] The overarching goal for the management of pre-HF is to reduce progression to clinical HF (Figure 12). As described in Section 3.1, "Diagnostic Approach to CKM Staging," assessments for cardiac biomarkers can be performed in those with PREVENT-HF risk of ≥5%. In pre-HF, cardiac imaging can refine assessments of absolute HF risk and further prompt referral for coordinated care to prevent progression to HF. Preventive strategies should include lifestyle modification, intensification of risk factor control, and use of evidence-based CKM ther-

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Table 16. Definition of Pre-HF

Pre-HF* Echocardiographic and Biomarker-Based Thresholds	
Structural Heart Disease	LAVI ≥29 mL/m²
	LVMI >116 g/m² in men; >95 g/m² in women
	RWT >0.42
	LV wall thickness ≥12 mm
	LVEF <50%
	GLS <16%
	Septal e′ <7 cm/s
	TR velocity >2.8 m/s
	TR velocity >2.8 m/s
Noninvasive Imaging to Estimate Filling Pressures	Estimated PA systolic pressure >35 mm Hg
	Average E/e′ ≥15
Cardiac Biomarkers†	BNP ≥35 pg/mL‡
	NT-proBNP ≥125 pg/mL†

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*Pre-HF, also referred to as stage B HF in the 2022 HF Guidelines, is defined as no symptoms or signs of HF, and evidence of 1 of the following: [1] structural heart disease, [2] noninvasive evidence for increased filling pressure, or [3] risk factors with elevated levels of cardiac biomarkers (in the absence of a competing diagnosis resulting in such biomarker elevations such as acute coronary syndrome, CKD,† pulmonary embolus, or myopericarditis).

†BNP/NT-proBNP only cited in the 2022 ACC/AHA HF guidelines; in contrast, the universal definition of HF includes persistently elevated troponin (>99th percentile in a normal reference population).

‡Cutoffs provided for natriuretic peptide levels may have lower specificity, especially in older patients or in patients with AF or CKD.

BNP indicates B-type natriuretic peptide; GLS, global longitudinal strain; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; and RWT, relative wall thickness.

apies where indicated. Beyond treatment of risk factors, beta blockers, and ACEi/ARB are also recommended in those with left ventricular systolic dysfunction.[14,15] Guidelines for specific conditions that can precipitate pre-HF (ie, inherited risk of cardiomyopathy,[16] cardiotoxic exposures,[17] and congenital heart disease,[18] as well as various forms of CVD [coronary artery disease,[19] valvular heart disease,[20] and atrial fibrillation (AF)[21]]) are discussed elsewhere.

Recommendation-Specific Supportive Text

1. In adults across the CKM stages, intensive lifestyle interventions and intensive risk factor control with coordinated care and pharmacotherapies have robust evidence of improving CKM health.[22–24] Few large, randomized studies of health behavior interventions have examined their impact on patients with pre-HF. One small single-center study of 46 patients with pre-HF (left ventricular septum >11 mm and either NT-proBNP >40 pg/mL or hs-cTnT >0.6 pg/mL) demonstrated that high-intensity exercise training for 1 year compared with the control arm improved myocardial mechanics at follow-up.[1] A post-hoc analysis of the Look AHEAD (Action for Health in Diabetes) trial that enrolled adults aged 45 to 76 years with overweight or obesity and diabetes demonstrated a significant reduction in hs-cTn at 1-year and 4-year follow-up that was attributed to meaningful weight loss (≥5%) compared with minimal weight loss (<5%).[2] In the same population, an intensive lifestyle intervention was associated with lower HFpEF risk in those with high baseline NT-proBNP or with stable/decreasing NT-proBNP over 1 year.[2,25] Moreover, epidemiologic data from observational cohorts suggest that higher levels of physical activity are associated with a lower risk of progression to HF among adults with elevated cardiac biomarkers.[26]
2. In adults with diabetes, SGLT2i have demonstrated robust evidence for the primary prevention of HF. A meta-analysis of 3 SGLT2i trials (EMPA-REG, CANVAS [Canagliflozin Cardiovascular Assessment Study], DECLARE-TIMI 58 [Dapagliflozin Effect on Cardiovascular Events]) that included 30 431 patients with T2D but without HF demonstrated a 21% reduction in incident HF hospitalization (HR, 0.79 [95% CI, 0.71–0.88]).[6] While these trials did not recruit patients with pre-HF or analyze this subgroup, post-hoc biomarker substudies of these trials suggested a high median NT-proBNP and hs-cTn, with >50% of the trial population demonstrating biomarker levels consistent with pre-HF.[27–30] In a small study of 44 patients with diabetes and impaired global longitudinal strain, randomization to empagliflozin was associated with a significant improvement in strain (+2% increase at 6 months),[31] with similar findings in other small mechanistic trials of SGLT2i.[32–34]
3. In adults with diabetes, a meta-analysis of 5 trials (4 trials with older lower-potency GLP-1 RAs and 1 trial with semaglutide) demonstrated no significant reduction in HF hospitalization.[35] However, a more recent meta-analysis that included 10 GLP-1 RA trials estimated a 13% reduction in HF hospitalization (HR, 0.87 [95% CI, 0.80–0.94]).[36] In post-hoc analyses of the SURPASS 4 (A Study of Tirzepatide Once a Week Versus Insulin Glargine Once a day in Participants With T2D and Increased Cardiovascular Risk) trial, which enrolled patients with T2D with or at high risk for CVD, individuals with pre-HF defined by elevated NT-proBNP and without a history of HF hospitalization had a significant reduction in NT-proBNP from baseline to 52 weeks.[37] In the only dedicated GLP-1 RA trial of patients with diabetes and albuminuric CKD (FLOW), semaglutide demonstrated a significant reduction in HF events in the overall sample (HR, 0.74 [95% CI, 0.58–0.94]) with similar reduction in incident HF among those without baseline HF (HR, 0.68

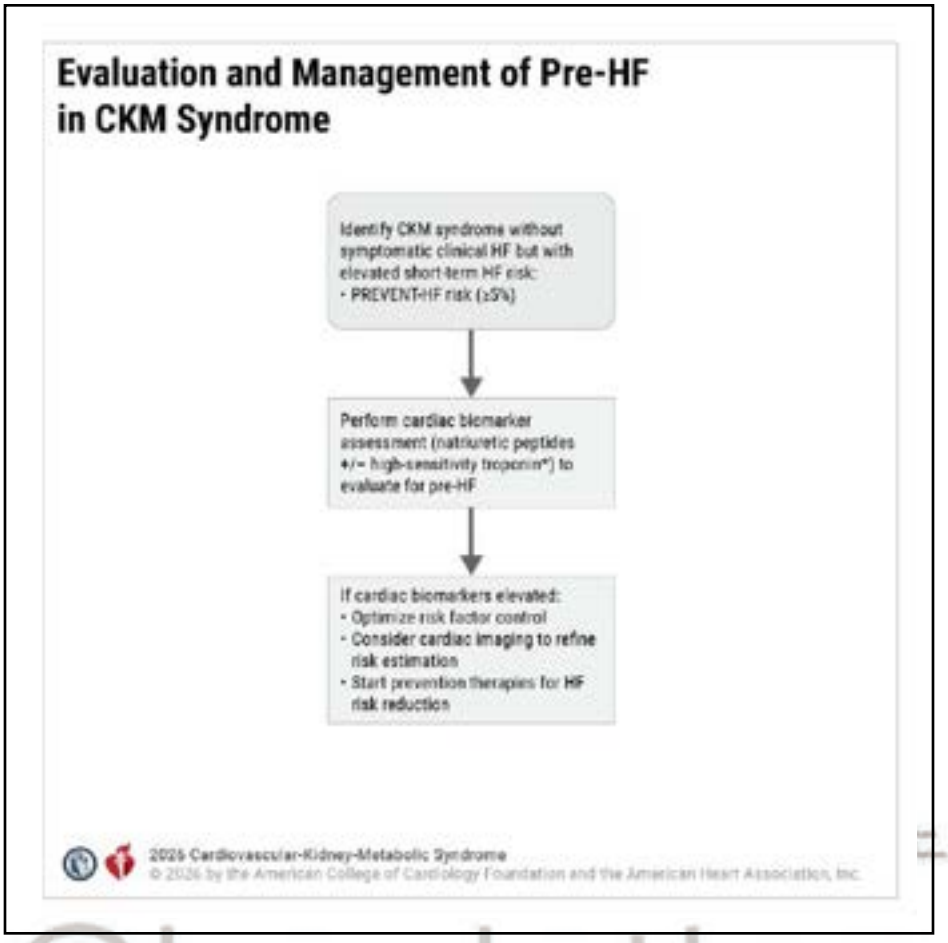

Figure 12. Evaluation and Management of Pre-HF in CKM Syndrome.
*High-sensitivity troponin can be considered for those with obesity, where natriuretic peptides may be low even in the setting of cardiac dysfunction and increased risk for developing HF. Assessments for pre-HF in patients with CKM syndrome are indicated for those with increased predicted HF risk (PREVENT-HF risk ≥5%). CKM indicates cardiovascular-kidney-metabolic; HF, heart failure; and PREVENT, Predicting Risk of Cardiovascular Disease Events.

[95% CI, 0.50–0.91]).[8,9] This translated into a number needed to treat of 49 over 3 years to prevent 1 HF event.[9] Among those with diabetes and CKD, modeling exercises suggest an additive benefit when GLP-1 RA are added to SGLT2i, with an estimated 43% reduction in HF hospitalization (HR, 0.57 [95% CI, 0.47–0.70]) when assuming lifetime use of therapies.[38]

4. Among patients with diabetes and albuminuric CKD in the FIDELITY pooled analyses, finerenone demonstrated a 21% reduction in HF (HR, 0.79 [95% CI, 0.66–0.92]),[7] with similar benefits observed in those without a history of HF[10] and in those with baseline LVH.[39] This benefit was consistent with or without background SGLT2i[40] or GLP-1 RA use.[41] These data suggest that second-line therapy with either a GLP-1 RA with proven cardiovascular benefit or nsMRA is reasonable for the prevention of HF in patients with diabetes and albuminuric CKD after initiation of SGLT2i, or if an SGLT2i is contraindicated.[42] However, in trials of GLP-1 RA and nsMRA in patients with diabetes and CKD, a large proportion had baseline ASCVD (FIDELITY: 46%; FLOW: 23%). While a modeling exercise suggested stepwise additive benefit in patients with diabetes and CKD when nsMRA are added to SGLT2i, with an estimated 50% reduction in HF hospitalization (HR, 0.50 [95% CI, 0.39–0.64]), this was based on the assumption of lifetime use of therapies and likely driven by kidney protection benefits.[38]

6. MANAGEMENT OF CVD IN CKM SYNDROME

6.1. CKM Syndrome Stage 4

Synopsis

CKM syndrome stage 4 is defined by the presence of clinical CVD (ASCVD, HF, or AF) among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD. This stage is further refined by the ab-

sence (stage 4a) or presence (stage 4b) of kidney failure, which can impact clinical management. Resulting from complex multidirectional relationships, CKM risk factors potentiate poorer outcomes in individuals with established CVD. For individuals with CKM syndrome stage 4, management focuses on optimizing secondary prevention strategies for CVD in the setting of CKM risk factors. In all individuals, intensive and comprehensive lifestyle and risk factor modification with achievement and maintenance of a healthy weight and optimal control of clinical risk factors are emphasized. The following sections provide recommendations for the management of CKM syndrome stage 4, with a focus on the intersections of CVD with obesity, T2D, and CKD. The heightened risks of cardiovascular-kidney events and mortality in individuals with CKM syndrome stage 4 emphasize the need for coordinated interdisciplinary care in this population. Importantly, several additional guidelines provide further recommendations relevant to this population, such as hypertension[1] and cholesterol[2] management for secondary prevention of ASCVD[3]; GDMT for CCD,[3] PAD,[4] stroke,[5] and HF[6]; and rate/rhythm control strategies for AF.[7]

6.2. Management of ASCVD

Synopsis

The goal for the management of ASCVD, which represents 1 phenotype of CKM stage 4, is to improve function and quality of life and to optimize secondary prevention and avert recurrent ASCVD events (Figure 13).[1] The recommendations for optimal management of CCD,[2] PAD,[3] and cerebrovascular disease[4] are documented in their respective AHA/ACC guidelines. These emphasize the utilization of antiplatelet agents and high-intensity or maximally tolerated statin therapy as a first-line pharmacotherapies, with consideration of additional lipid-lowering therapies as indicated for more intensive LDL-C lowering or management of triglycerides.[5] For management of PAD, there is additional consideration for use of rivaroxaban combined with low-dose aspirin to avert MACE and limb events, in those without increased bleeding risk.[3] For adults with comorbid hypertension, intensive BP management is indicated with a target BP <130/80 mm Hg and with antihypertensive choice tailored by comorbid conditions (eg, prioritization of ACEi/ARB if diabetes or CKD are present).[6] Furthermore, individuals with ASCVD often have comorbid obesity (Section 6.2.1, "CKM Syndrome Stage 4 With Obesity and ASCVD"), diabetes (Section 6.2.2, "CKM Syndrome Stage 4 With T2D and ASCVD"), and/or CKD (Section 6.2.3, "CKM Syndrome Stage 4 With CKD and ASCVD") for which there are unique management considerations as detailed in the subsequent sections.

6.2.1. CKM Syndrome Stage 4 With Obesity and ASCVD

Recommendations for CKM Syndrome Stage 4 With Obesity and ASCVD
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. In adults with CKM syndrome stage 4 with overweight or obesity and ASCVD, treatment with an intensive, multicomponent, behavioral lifestyle intervention is recommended to promote weight loss and improvement in CKM risk factors.[1–5]
1	B-R	2. In adults with CKM syndrome stage 4 with overweight or obesity (BMI ≥27 kg/m^2) and ASCVD, treatment with a GLP-1–based therapy with proven cardiovascular benefit in addition to counseling to promote healthy dietary intake and regular physical activity is recommended to reduce the risk of cardiovascular events.[6,7]
Economic Value:* Cost-Effective (Moderate Level of Certainty)		3. In adults with CKM syndrome stage 4 with overweight or obesity (BMI ≥27 kg/m^2) and ASCVD, treatment with a GLP-1–based therapy with proven cardiovascular benefit at 2025 US prices is projected to be cost-effective compared with usual care.
2a	B-NR	4. In adults with CKM syndrome stage 4 with obesity (BMI ≥30 kg/m^2) and ASCVD who have not reached weight loss goals with lifestyle interventions, with or without maximally tolerated pharmacotherapy, MBS can be beneficial to facilitate a minimum weight loss of 5% to 10% to improve CKM health and to reduce the risk of cardiovascular events.[8,9]
3: Harm	B-R	5. In adults with CKM syndrome stage 4 with overweight or obesity (BMI ≥27 kg/m^2) and ASCVD, treatment with naltrexone/bupropion or phentermine-containing agents is potentially harmful as they can increase BP and heart rate.[10,11]

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

Synopsis

For patients with overweight or obesity and established ASCVD (CKM stage 4), treatment to address excess weight can include intensive lifestyle interventions, pharmacotherapy, and bariatric surgery (Figure 14), with therapeutic approach guided by the patient's CKM risk profile, personal preferences, and access to therapy. Approximately 5% weight loss through intensive lifestyle interventions significantly improves multiple metabolic risk factors in patients with obesity.[12,13] Lifestyle interventions for weight loss can be implemented during or immediately following cardiac rehabilitation for patients with ASCVD and overweight or obesity, although the efficacy of this approach needs further evidence.[14] Weight loss with lifestyle interventions can be limited, however, necessitating considerations for adding obesity pharmacotherapy to reduce weight and CVD risk among those with ASCVD and excess weight. In the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial, subcutaneous semaglutide among patients with BMI ≥27 kg/m^2 and ASCVD without T2D resulted in significant reduc-

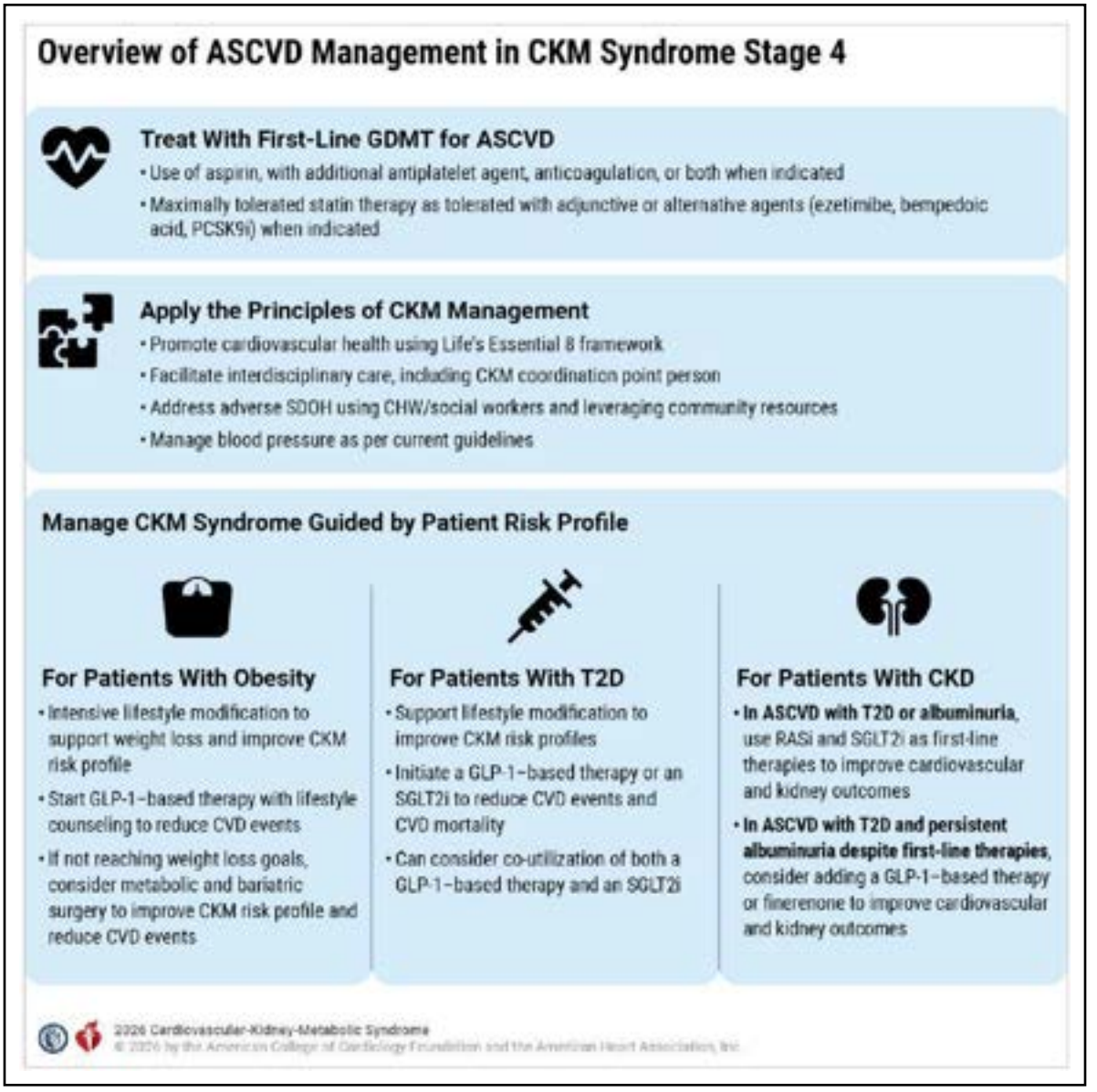

Figure 13. Overview of ASCVD Management in CKM Syndrome Stage 4.
The approach to CKM syndrome management in patients with ASCVD in CKM syndrome stage 4 should involve the use of first-line GDMT for ASCVD, applying general principles of CKM syndrome management and additional therapeutic approaches for the individual CKM risk factors, as depicted. CHW indicates community health worker; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; GLP-1, glucagon-like peptide-1; RASi; renin-angiotensin system inhibitors; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

tions in reduced both weight and MACE,[6] with evidence for some weight-independent cardiovascular benefits.[8,9,15] For patients with BMI ≥30 kg/m^2 and ASCVD, referral for bariatric surgery for obesity treatment can be beneficial if intensive lifestyle intervention and obesity pharmacotherapy do not result in clinically significant weight loss, given substantial improvements in CKM risk profiles and CVD outcomes in matched observational studies.[8,9,15]

Recommendation-Specific Supportive Text

1. A systematic review of lifestyle-based interventions, the majority of which were RCTs, showed a higher likelihood of achieving clinically significant (5%) weight loss with behavioral interventions versus controls.[2] The Look AHEAD trial of an intensive lifestyle intervention in patients with overweight/obesity and T2D, with and without CVD, did not demonstrate an impact of the intensive lifestyle intervention on cardiovascular events, possibly due to modest weight loss from the intervention and high statin use among controls.[16] Despite the lack of CVD event reduction, lifestyle modification with behavior change, healthy dietary modification, and physical activity, resulting in weight loss of 5% to 10%, causes improvements in CKM risk factors including remission of T2D,[17,18]

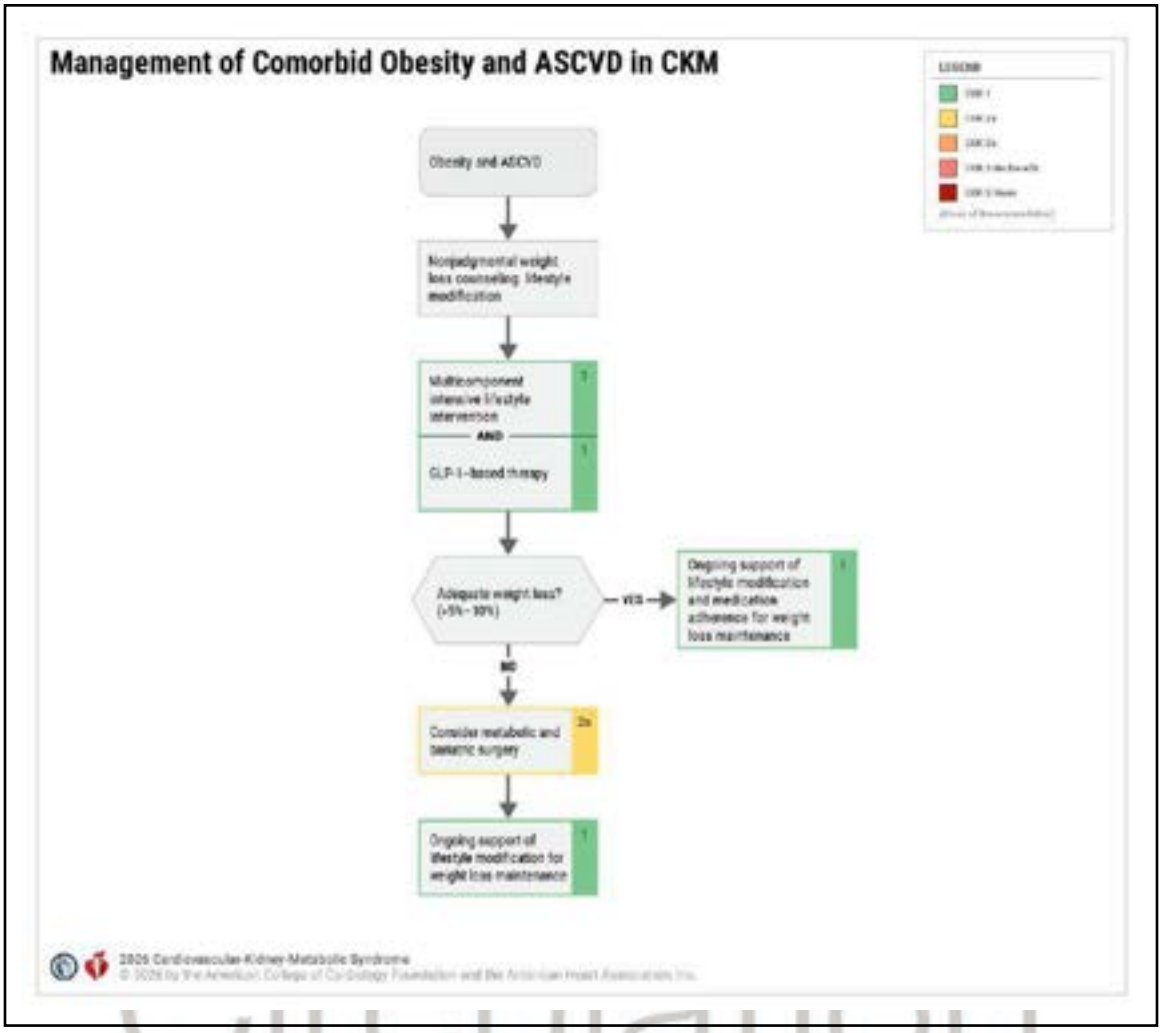

Figure 14. Management of Comorbid Obesity and ASCVD in CKM.
Note that the cardiovascular benefits associated with semaglutide in the setting of obesity and ASCVD appear to be largely independent of the extent of weight loss achieved, which may support ongoing treatment with GLP-1–based therapy, even in the absence of adequate weight loss. ASCVD indicates atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; COR, Class of Recommendation; and GLP-1, glucagon-like peptide 1.

with the CKM benefits of lifestyle modification observed across a range of populations and geographic settings.[19] A meta-analysis of primary and secondary CVD prevention trials demonstrated that a Mediterranean diet was associated with a 38% lower risk of CVD events.[4] Unfortunately, lifestyle interventions do not address the compensatory neurometabolic pathways activated with weight loss (eg, decreased adipose tissue leptin, increased gastric ghrelin) that commonly promote weight regain due to increased hunger and changes in metabolism, often necessitating consideration for adjunctive therapies for more substantial and sustained weight loss.[3]

2. In the SELECT trial,[6] 17 604 participants with BMI ≥27 kg/m^2 and established ASCVD (prior MI, stroke, or symptomatic PAD), and without T2D, end-stage kidney disease, or dialysis, were enrolled. The trial demonstrated a 20% reduction in risk of the composite primary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke for those treated with semaglutide (2.4 mg) as compared with placebo. Semaglutide was also associated with an average 9% reduction in weight over 4 years of follow-up, with significant improvements in cardiometabolic endpoints, systemic inflammation, and reductions in cardiovascular events regardless of baseline HbA1c.[3,20] Importantly, CVD risk reduction was observed with semaglutide prior to clinically significant weight loss, and similar CVD event reductions were observed regardless of the magnitude of weight achieved,[21] indicating some cardiovascular benefits that are weight-independent. Although semaglutide was discontinued more often than placebo, primarily due to gastrointestinal side effects, the overall rate of serious adverse events was lower with semaglutide as compared with placebo.

3. A modeling-based study examined the cost-effectiveness of semaglutide for the secondary prevention of ASCVD in a nationally representative cohort of treatment-eligible US adults.[22] It found that compared with usual care alone, adding semaglutide for the estimated 4 million US adults without diabetes who are eligible for secondary prevention of CVD is projected to avert approximately 360 000 instances of MACE. At the 2023 US net price of $8604, the ICER for semaglutide compared with usual care for this indication was $148 100 per QALY gained (95% uncertainty interval, $127 100 to $173 400). In sensitivity analyses, semaglutide would be cost-effective at a threshold of $120 000 per QALY gained if the annual cost were lowered an additional 18% to $7055 (Figure 15). The average annual cost of semaglutide has declined in the past year, and the direct-to-consumer cash price ($5988) is already lower than the threshold price at which the drug would be considered cost-effective.
4. Patients with ASCVD and obesity (BMI ≥30 kg/m^2) who have not met weight loss goals with lifestyle and pharmacologic intervention can benefit from MBS, including RYGB or LSG. MBS causes substantial weight loss (up to 30% to 35% body weight) and improvements in multiple CKM risk factors.[23–25] An analysis of individuals with prior MI in the SWEDEHEART (Intensive Early and Sustained Lowering of Non–High-Density Lipoprotein Cholesterol After MI and Prognosis) registry demonstrated that patients who underwent MBS were less likely than matched controls to experience cardiovascular death and recurrent MI, but not stroke (HR, 0.45 [95% CI, 0.29–0.70] for death; HR, 0.24 [95% CI, 0.14–0.41] for MI; HR, 0.91 [95% CI, 0.38–2.20] for stroke).[8] In the general population, MBS has low complication rates, with outcomes equivalent to a

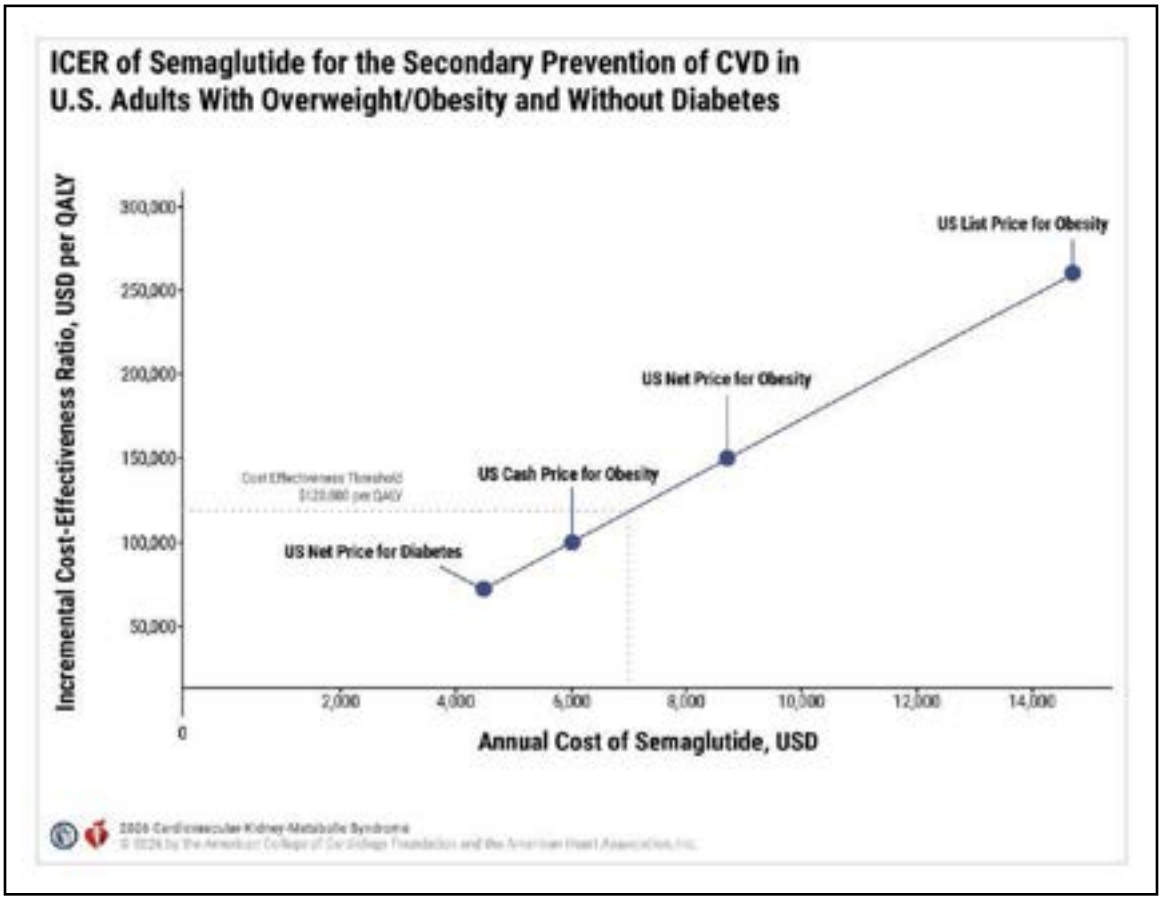

Figure 15. ICER of Semaglutide for the Secondary Prevention of CVD in US Adults With Overweight/Obesity and Without Diabetes. Adapted with permission from Hennessy et al.[22] Copyright 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies. The ICER for injectable semaglutide therapy increases with the annual cost of the drug; at the 2023 US price net of rebates and discounts ($8604), the ICER relative to usual care is $148 100 per QALY gained. The vertical lines indicate the cost at which semaglutide would become cost-effective in the United States at cost-effectiveness thresholds of $50 000 per QALY gained ($3295), $100 000 per QALY gained ($5940), $120 000 per QALY gained ($7055), and $150 000 per QALY gained ($8710). Note that if the current US cash price (ie, the price for patients who pay for the therapy themselves instead of through insurance, $5988 per year) were available to all patients, semaglutide therapy would be cost-effective for the secondary prevention of cardiovascular disease, with an ICER of $99 610 per QALY gained. CVD indicates cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; and USD, US dollars.

laparoscopic cholecystectomy.[26] However, the absolute risk of cardiovascular and noncardiovascular perioperative complications after MBS is significantly higher in patients with versus without ASCVD.[27,28] With the lack of randomized data on MBS in this population, the absolute benefit/risk ratio is not fully defined, though MBS is likely safe and effective for stable ASCVD patients with low surgical risk. Long-term data regarding the impact of MBS on malabsorption, kidney stones, and other complications are needed in patients with ASCVD.[29]

5. A systematic review and meta-analysis of placebo-controlled randomized trials of obesity pharmacotherapy in patients with overweight or obesity (N=154 trials) demonstrated that naltrexone was associated with significantly higher systolic and diastolic BP when given alone (systolic BP weighted mean difference, 2.70 mm Hg [95% CI, 2.00–3.70]; diastolic BP weighted mean difference, 4.00 mm Hg [95% CI, 3.49–4.51]) and in combination with bupropion (systolic BP weighted mean difference, 2.01 mm Hg [95% CI, 1.26–2.76]; diastolic BP weighted mean difference, 1.25 mm Hg [95% CI, 0.52–1.97]). Phentermine was associated with significantly higher heart rate when used alone (heart rate weighted mean difference, 4.20 mm Hg [95% CI, 0.46–7.94]).[11] Given these adverse cardiovascular effects, the use of naltrexone/bupropion and phentermine-containing agents is not advised in patients with CVD.[10]

6.2.2. CKM Syndrome Stage 4 With T2D and ASCVD

Recommendations for CKM Syndrome Stage 4 With T2D and ASCVD
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. For adults with CKM syndrome stage 4 with T2D and ASCVD, a tailored lifestyle modification plan focusing on a heart-healthy dietary pattern and physical activity is recommended to improve glycemic control, achieve and maintain a healthy weight, and improve other ASCVD risk factors.[1,2]
1	A	2. For adults with CKM syndrome stage 4 with T2D and ASCVD, the use of either an SGLT2i or a GLP-1–based therapy with proven cardiovascular benefit is recommended to reduce the risk of cardiovascular events and cardiovascular mortality.[3]
Economic Value:* Cost-Effective (Moderate Level of Certainty)		3. In adults with CKM syndrome stage 4 with T2D and ASCVD, treatment with SGLT2i at 2025 US prices is projected to be cost-effective compared with usual care.
Economic Value:* Indeterminate (Insufficient Evidence)		4. In adults with CKM syndrome stage 4 with T2D and ASCVD, treatment with GLP-1–based therapy at 2025 US prices is indeterminate.
2a	C-LD	5. For adults with CKM syndrome stage 4 with T2D and ASCVD, the use of a combination of SGLT2i and a GLP-1–based therapy can be beneficial to improve cardiovascular outcomes.[4]

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

Synopsis

A heart-healthy diet and regular physical activity remain the cornerstones of therapy in patients with T2D and ASCVD, with demonstrated benefits for CKM risk profiles.[5–12] Control of risk factors, including smoking, BP, and cholesterol, also remain important.[13,14] Lifestyle modification, and targeted pharmacotherapy to improve collective risk factor control, reduced cardiovascular events and mortality among patients with T2D, overweight/obesity, and microalbuminuria.[15] Among patients with T2D and ASCVD, the use of cardioprotective glucose-lowering therapies, including SGLT2i or GLP-1–based therapy, is central to management (Figure 16). Both agents reduce MACE and CVD mortality, with SGLT2i having a principal impact on HF events and GLP-1–based therapy on atherosclerotic events.[3,16,17] In patients with symptomatic PAD, semaglutide increases walking distance.[18] GLP-1–based therapy often causes significant weight loss and improvements in CKM risk profiles and MASLD, while SGLT2i has a marked impact on CKD.[19–30] These 2 classes of medications should be considered first-line therapy in patients with concomitant T2D and ASCVD.[31] The choice of the first agent utilized should be individualized based on CKM risk profile, the presence of MASLD (Section 7.2, "Metabolic Dysfunction–Associated Steatotic Liver Disease"), the type of CVD risk reduction prioritized, patient preference, and cost. Lastly, in patients with significant hyperglycemia, SGLT2i or GLP-1–based therapies may not be sufficient to achieve glycemic control, and therefore, other glucose-lowering agents can be an option with metformin having an excellent efficacy and safety profile with low risk for hypoglycemia.

Recommendation-Specific Supportive Text

1. A heart-healthy dietary pattern is a key intervention in the treatment of T2D. The Mediterranean, DASH, and vegetarian/vegan diets have all been shown to help in the achievement of weight loss and improvement of glycemic control in T2D.[1,2] Prospective cohorts have demonstrated a significantly lower likelihood of CVD events and CVD death in adults with T2D who follow a healthy dietary pattern.[32] However, an RCT targeting aggressive lifestyle interventions in T2D, in which 14% of the patients had CVD, was unable to show a reduction in ASCVD events despite early success in achieving weight loss.[33] Weight loss is an essential treatment component for T2D, and dietary recommendations should be adjusted to achieve meaningful weight loss, if needed. Establishing an appropriate nutrition plan requires time and effort and is best accomplished with assistance from a registered dietitian-nutritionist or a diabetes education program. In addition, habitual physical activity, including activities that reduce sedentary time, aerobic physical activity, and

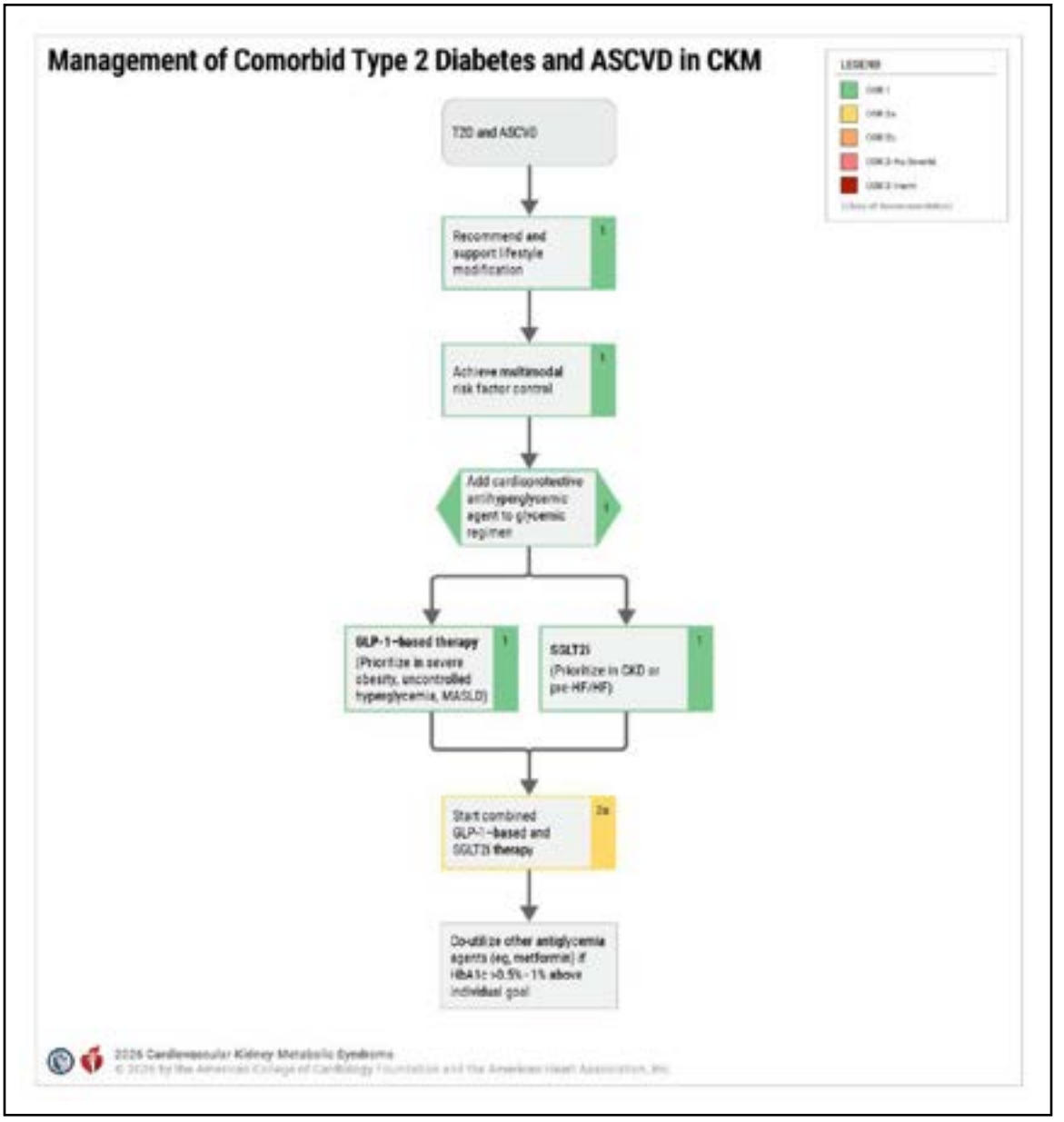

Figure 16. Management of Comorbid Type 2 Diabetes and ASCVD in CKM.
ASCVD indicates atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; COR, Class of Recommendation; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1C; HF, heart failure; MASLD, metabolic dysfunction–associated steatotic liver disease; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

resistance training, are associated with improvements in several CKM risk factors (HbA1c, waist circumference, fat percentage, BP) and mortality.[5–12] Therefore, every effort should be made to institute a tailored heart-healthy lifestyle in adults with CKM stage 4 and T2D and ASCVD.

2. In patients with T2D and ASCVD, SGLT2i and GLP-1–based therapy significantly reduces the risk of MACE and cardiovascular mortality, promotes weight loss,[34] and reduces progression of kidney disease (Section 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3").[17,35,36] SGLT2i appear to primarily reduce incident and worsening HF.[17,37–44] In contrast, GLP-1 RAs appear to primarily reduce the risk of atherosclerotic events, such as MI and stroke.[45–48] Both SGLT2i and GLP-1–based therapy improve kidney outcomes,[49–51] with GLP-1–based therapy additionally promoting significant weight reduction and glycemic control (especially semaglutide and tirzepatide)[19–25] and reducing liver fibrosis in MASH (Section 7.2, "Metabolic Dysfunction–Associated Steatotic Liver Disease").[52–58] Whether to prioritize SGLT2i or a GLP-1–based therapy first should be individualized based on the extent of desired glycemic control or weight loss, presence of CKD and current

eGFR (SGLT2i should not be initiated if eGFR is <20 mL/min/1.73 m^2), presence of additional CKM risk factors and MASLD or MASH, cost, and patient preferences. Given their distinct mechanisms, cardiovascular risk reduction may be greater with concomitant use of both medication classes.

3. Several studies have examined the cost-effectiveness of adding SGLT2i relative to the prior standard of care therapy among patients with diabetes from a US health care sector perspective.[59,60] Although differences in the modeling approach and key input parameters preclude direct comparisons of the findings, these studies suggested that the use of an SGLT2i in this population is projected to be cost-effective compared with standard of care alone. The population modeled in these analyses was not restricted to patients with established ASCVD, but the results of the analyses appear to be robust to a range of assumptions regarding the underlying risk of MACE. The findings are therefore likely to be generalizable to patients with ASCVD. The economic value of therapies may be further improved by a reduction in prices due to Medicare negotiations,[61] or the entry of generic formulations of SGLT2i.
4. A recent modeling study showed that at current US prices, the use of GLP-1–based therapies, compared with usual care, is not cost-effective in US adults with diabetes and overweight/obesity.[62] We did not identify high-quality studies examining the subgroup of individuals with diabetes and ASCVD. This subpopulation is at higher risk of ASCVD events than the overall population with diabetes and may derive additional health benefits. However, given the absence of available evidence, we deemed the cost-effectiveness of GLP-1–based therapies in individuals with diabetes and ASCVD to be indeterminate due to insufficient evidence.
5. Studies of concomitant SGLT2i and GLP-1–based therapy show benefits for A1C, BP, and weight. Prespecified and post-hoc subgroup analyses of trials suggest that the combination may further reduce cardiovascular risk.[63–69] A meta-analysis of RCTs of SGLT2i showed cardiovascular and kidney benefits regardless of background GLP-1–based therapy use.[66] Similarly, a meta-analysis of RCTs of GLP-1–based therapy showed reduced MACE irrespective of background SGLT2i use.[68] A meta-analysis combining RCTs and nonrandomized trial data showed improved cardiovascular outcomes with a combination of SGLT2i and GLP-1–based therapy along with a higher incidence of hypoglycemia,[64] as did a population-based cohort study.[70] However, a meta-analysis combining data of RCTs of SGLT2i or GLP-1–based therapy could not assess the impact of combination therapy on cardiovascular outcomes and mortality due to insufficient data, despite showing improved CKM risk profiles.[65] Finally, prespecified analyses from a study of oral semaglutide[4] showed that the observed benefits were independent of concomitant SGT2i use (26.9% use at baseline, 48.9% use at any point during the trial). Therefore, the use of a combination SGLT2i and GLP-1–based therapy can be considered to improve glycemic control (especially adding GLP-1 based therapy to an SGLT2i), CKM risk factor control, and cardiovascular and renal outcomes.

6.2.3. CKM Syndrome Stage 4 With CKD and ASCVD

Synopsis

Guidelines for ASCVD management recognize those with CKD as having a high risk for recurrent ASCVD.[1–3] Having a bidirectional risk relationship, ASCVD events also increase risk for subsequent kidney failure.[4] As for those with CKD in stage 2 to 3 CKM syndrome, statin therapy is recommended for persons with ASCVD and CKD to reduce cardiovascular risk.[5–8] CKD increases risk for acute kidney injury and bleeding with coronary angiography or interventions, indicating a need for careful consideration regarding the performance of these procedures. In patients with stable coronary artery disease and CKD who may require revascularization, please refer to the 2021 ACC/AHA/SCAI guideline for coronary artery revascularization, Section 9.3.[9]

The use of kidney-protective therapies for CKD improves both kidney and cardiovascular outcomes, with similar benefits in persons with or without ASCVD. As such, management of CKD in ASCVD is analogous to management of CKD in CKM stages 2 to 3 (Section 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3"). The use of RASi and SGLT2i is first-line therapy given broad eligibility and extensive evidence for efficacy and safety. The addition of GLP-1–based therapy or finerenone should be considered in patients with CKD, ASCVD, and T2D who have residual albuminuria despite first-line therapies, with the choice of agent based on CKM risk profile and other comorbidities.

6.3. Management of HF

Synopsis

In patients with CKM stage 4 and HF, standard GDMT is indicated, in addition to management of CKM risk factors including obesity, diabetes, and CKD. Quadruple therapy is first-line GDMT for patients with HFrEF. This includes RASi (angiotensin receptor-neprilysin inhibitor [ARNI]/ACEi/ARB), beta blockers, mineralocorticoid receptor antagonist (MRA), and SGLT2i.[1,2] Clinical trials demonstrate that these therapies reduce cardiovascular mortality and HF hospitalizations within 30 days after starting treatment, underscoring the importance of early intervention.[3–5]After quadruple therapy, hydralazine/isosorbide dinitrate are recommended to reduce

cardiovascular mortality and HF hospitalizations among self-identified Black patients.[1,6] For patients with fluid retention, diuretics alleviate signs and symptoms of congestion.[1] Device-based interventions such as implantable cardioverter-defibrillators and cardiac resynchronization therapy play an essential role in HFrEF management when indicated.[1] For patients with HFmrEF or HFpEF, first-line treatment includes SGLT2i[2] and diuretics for those with congestion.[1] Evidence supporting ARNI, ARB, and steroidal MRA in HFpEF remains limited to post-hoc and secondary analyses, leading to Class 2b recommendations in US guidelines.[1] However, data are emerging regarding the effectiveness of the nsMRA finerenone in HFmrEF/HFpEF.[7] Beta blockers are not recommended for HFpEF due to no benefit in the absence of secondary beta blocker indications (eg, AF, symptomatic CHD).[1] Several CKM conditions impact HF morbidity and mortality.[8] Recommendations for addressing obesity, diabetes, and CKD among patients with HF are outlined in subsequent sections (Figure 17). For specific recommendations on HF management, please refer to the AHA/ACC HF guideline.[1]

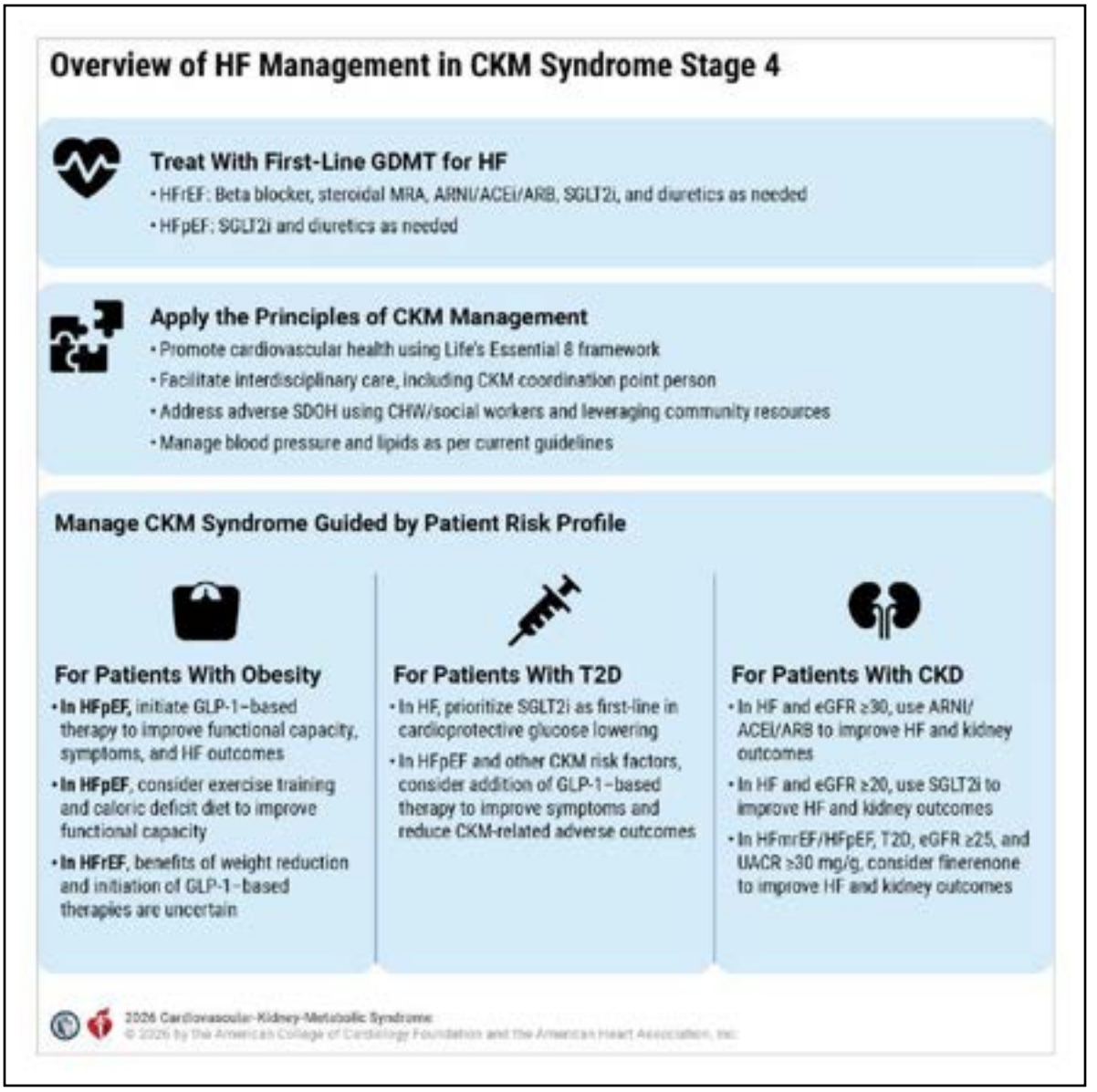

Figure 17. Overview of HF Management in CKM Syndrome Stage 4.
The approach to CKM syndrome management in patients with HF in CKM syndrome stage 4 should involve use of first-line GDMT for HF, applying general principles of CKM syndrome management and additional therapeutic approaches for the individual CKM risk factors, as depicted. ACEi indicates angiotensin-converting enzyme inhibitors; ARNI, angiotensin receptor/neprilysin inhibitors; CHW, community health worker; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; GLP-1, glucagon-like peptide-1; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

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6.3.1. CKM Syndrome Stage 4 With Obesity and HF

Recommendations for CKM Syndrome Stage 4 With Obesity and HF Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. Among adults with CKM syndrome stage 4, obesity, and symptomatic HFpEF, a GLP-1–based therapy with proven cardiovascular benefit is indicated to improve CKM risk profile, functional capacity, and HF symptoms, and prevent worsening HF events.[1–3]
Economic Value:* Indeterminate (Insufficient Evidence)		2. Among adults with CKM syndrome stage 4, obesity, and symptomatic HFpEF, the cost-effectiveness of adding a GLP-1–based therapy with proven cardiovascular benefit to GDMT is indeterminate.
2a	B-R	3. Among adults with CKM syndrome stage 4, obesity, and HFpEF, a combination of exercise training and a caloric deficit diet can be beneficial for improving functional capacity.[4–6]
2b	B-NR	4. In select adults with CKM syndrome stage 4, obesity, and symptomatic HFrEF, treatment of obesity may be considered to improve functional capacity and facilitate heart transplantation in otherwise eligible patients.[7–11]

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

Synopsis

Evidence-based HF GDMT should be prioritized for all patients with HF without contraindications, regardless of obesity status, to improve HF clinical outcomes.[12] For patients with HFrEF, 4 medication classes are recommended as core therapy: RASi (ARNI, ACEi, or ARB), beta blockers, MRA, and SGLT2i. For patients with HFmrEF or HFpEF, SGLT2i are the recommended therapy (Figure 18).[12] Beyond standard GDMT, treatment of obesity is emerging as a potential opportunity to improve functional capacity and HF symptomatology. This is particularly evident in HFpEF, which is more strongly epidemiologically linked to obesity than HFrEF, and in which there are now completed clinical trials of obesity treatment.[13,14] Lifestyle interventions, such as a caloric-deficit diet and aerobic exercise training, have shown modest but clinically important improvements in weight and functional capacity among older adults with HFpEF.[4] Limited retrospective studies of bariatric surgery in patients with baseline HF suggest medium-term outcome benefits with reductions in HF hospitalization and all-cause mortality at 4 to 5 years' follow-up.[15,16] Treatment of obesity-related HFpEF with the GLP-1–based therapies semaglutide and tirzepatide

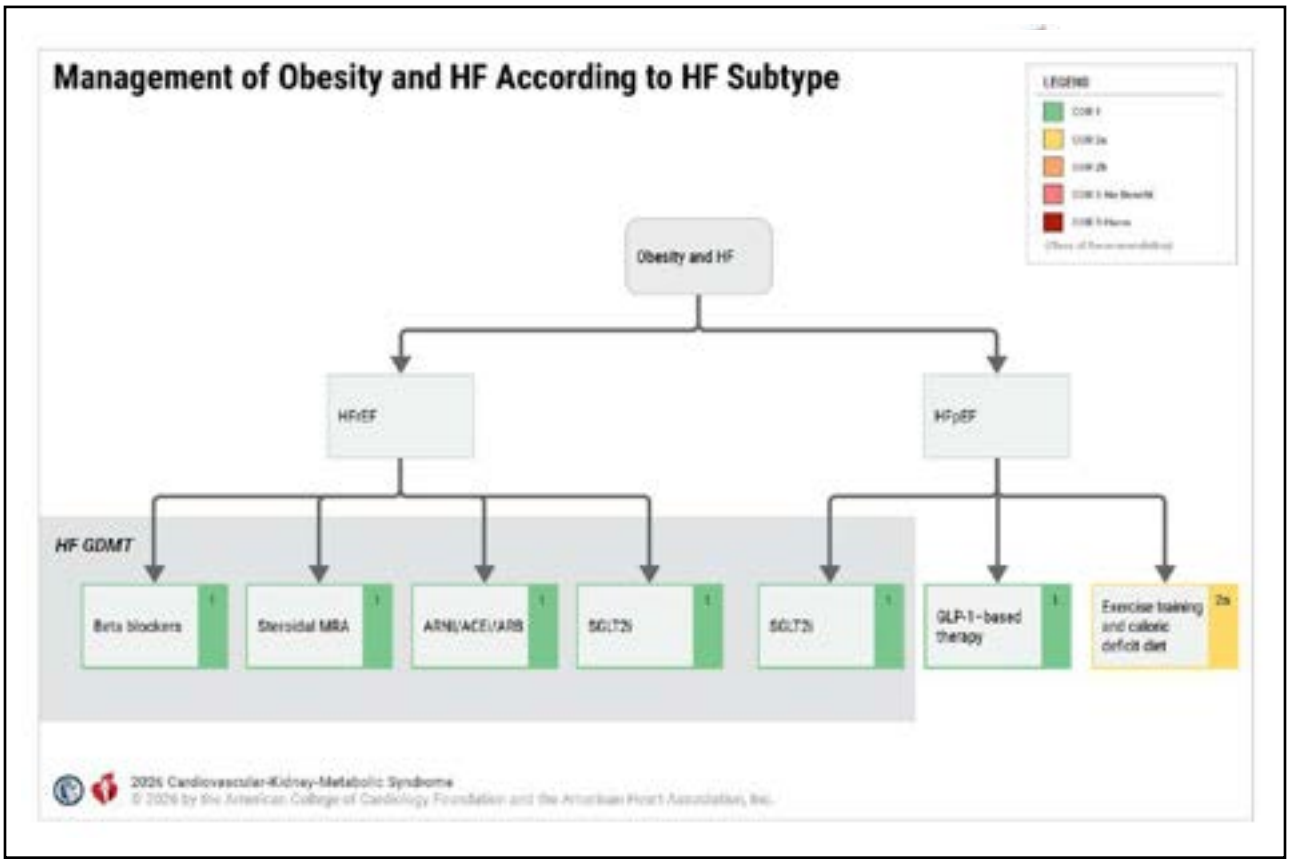

Figure 18. Management of Obesity and HF According to HF Subtype.
Adapted with permission from Heidenreich et al.[12] Copyright 2022 American Heart Association, Inc. and American College of Cardiology Foundation. With the exception of the SGLT2i COR for HFpEF, which is anticipated to be updated in the next 2022 HF guideline iteration, GDMT is concordant with the 2022 HF guideline per HF subtype, which is highlighted in gray. COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; GLP-1, glucagon-like peptide-1; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and SGLT2i, sodium–glucose cotransporter-2 inhibitors.

achieves improvements in HF patient-reported health status and quality of life, functional capacity as measured by the 6-minute walk distance (6MWD), and freedom from worsening HF events, including HF hospitalizations.[1,3,17,18]

Recommendation-Specific Supportive Text

1. In the STEP-HFpEF (Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction) study of adults with HFpEF (left ventricular ejection fraction [LVEF] ≥45%), obesity without T2D, and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) <90, semaglutide significantly reduced weight and improved patient-reported HF health status per KCCQ-CSS (change from baseline, 16.6 versus 8.7 points; $P<0.001$).[1,19] There were also improvements in 6MWD, NT-proBNP, and C-reactive protein. STEP-HFpEF-DM (Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus) recruited patients with obesity-related HFpEF plus T2D and yielded similar results.[2] STEP-HFpEF and STEP-HFpEF DM participants who were already prescribed loop diuretics experienced the greatest improvement in KCCQ-CSS with semaglutide, and semaglutide was associated with lesser diuretic dose requirements.[20] These observations were expanded upon in the SUMMIT (Study of Tirzepatide in Participants with Heart Failure With Preserved Ejection Fraction and Obesity) trial, where tirzepatide was associated with substantial weight loss, an improved KCCQ-CSS score (19.5 versus 12.7 points, $P<0.001$) and a 38% reduction in the primary composite endpoint (death from CV causes, worsening HF event resulting in hospitalization, or HF medication intensification).[3]
2. Although several analyses have examined the cost-effectiveness of GLP-1 RA or GLP-1/GIP-RA therapy for management of weight loss, no studies have specifically examined the cost-effectiveness of this strategy in patients with HFpEF based on the results of the STEP-HFpEF and SUMMIT trials. Therefore, the cost-effectiveness of GLP-1 RA or GLP-1/GIP RA therapy for this indication is indeterminate due to insufficient evidence.
3. SECRET (Study of the Effect of Caloric Restriction and Exercise Training in Patients With Heart Failure and a Normal Ejection Fraction) evaluated the impact of 20 weeks of a calorie-restricted diet, a supervised exercise program, or both on metabolic and functional outcomes among 100 older adults (mean age 67 years) with HFpEF and obesity.[4] Peak oxygen consumption (VO_2, mL/kg/min) increased, and body weight decreased most in those receiving both interventions, with slight reductions in lean mass in the diet arm. In the SECRET-II (Exercise Intolerance in Elderly Patients With HFpEF) trial, 88 older patients with obesity-related HFpEF were randomized into a 20-week trial of caloric restriction and aerobic exercise training, with or without resistance exercise training.[5] Both groups experienced significant weight loss and improved peak VO_2. Resistance training did not attenuate the decrease in lean mass with weight loss, but did increase leg muscle strength and skeletal muscle quality.[5] A single-arm 15-week pragmatic weight management program (weekly consultations with exercise specialists, dietitians, and behavioral specialists), achieved a mean weight loss of 8.1 kg (−6.7%) for patients with obesity-related HFpEF.[6] Several trials corroborate the safety and efficacy of exercise training for HFpEF, but these did not exclusively recruit patients with obesity.[21–23]
4. The risk-benefit and appropriate strategies for treating obesity in patients with HFrEF remain undefined.[24] Exercise alone is minimally impactful for weight management in HFrEF.[25] Small lifestyle intervention trials suggest weight loss efficacy and safety in HFrEF,[8–10] and a pilot trial of orlistat (n=21) indicated improved functional capacity.[7] However, the LIVE (Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients) and FIGHT (Functional Impact of GLP-1 for HF Treatment) trials demonstrated numerically higher rates of CVD events with liraglutide, with the greatest risk in those with NYHA class III-IV functional status.[26] The SELECT trial, among adults with BMI ≥27 kg/m^2 and ASCVD without T2D, demonstrated lower CVD risk with semaglutide in the subgroup with HFrEF, but 90% of these patients had NYHA class I-II status. The risk-benefit profile of GLP-1 RA in advanced HFrEF therefore, remains uncertain, and close monitoring of patients receiving GLP-1RA up-titration is advisable.[27] The safety of MBS in HFrEF is also undefined.[28] These knowledge gaps are particularly relevant when severe obesity contraindicates heart transplantation for advanced HFrEF. Evolving observational data suggest that surgical weight loss can help bridge patients with obesity receiving durable left ventricular assist device support to transplantation.[11,29]

6.3.2. CKM Syndrome Stage 4 With T2D and HF

Recommendations for CKM Syndrome Stage 4 With T2D and HF
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. In patients with CKM syndrome stage 4 with T2D and HF, SGLT2i should be prioritized as the first-line cardioprotective glucose-lowering medications to reduce cardiovascular death and HF hospitalizations.[1–3]

Recommendations for CKM Syndrome Stage 4 With T2D and HF (Continued)		
COR	LOE	Recommendations
Economic Value:* Cost-Effective (High Level of Certainty)		2. In patients with CKM syndrome stage 4 with T2D and symptomatic HF with LVEF ≤40%, addition of an SGLT2i to prior GDMT at 2025 US prices is projected to be cost-effective compared with prior GDMT (incremental cost-effectiveness ratio <$120 000 per QALY gained).
Economic Value:* Indeterminate (Conflicting Evidence)		3. In patients with CKM syndrome stage 4 with T2D and symptomatic HFpEF, cost-effectiveness of adding an SGLT2i at 2025 US prices is indeterminate.
2a	**B-R**	4. In patients with CKM syndrome stage 4 with T2D, HFpEF, and other CKM risk factors, the addition of GLP-1–based therapy with proven cardiovascular benefit to foundational SGLT2i therapy can be beneficial to improve HF symptomology and reduce CKM-related adverse outcomes.[4–6]
2a	**B-NR**	5. In patients with CKM syndrome stage 4 with T2D, stable HF, eGFR ≥30 mL/min/1.73 m^2, and A1c levels above their individualized glycemic goal, the addition of metformin therapy to SGLT2i can be beneficial to help achieve glycemic targets.[7–10]

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

Synopsis

T2D substantially increases the risk of developing HF. If current epidemiologic trends persist, HF is poised to become the leading cardiovascular complication of T2D.[11] Resultantly, T2D and HF frequently co-occur in patients with CKM syndrome, with particularly notable overlap between T2D and HFpEF. These recommendations (Figure 19) emphasize the use of therapies to improve CKM-related outcomes in stage 4 CKM syndrome with T2D and HF. Standard HF GDMT is foundational therapy for all patients. Subgroup analyses from major trials and several RCTs in T2D and HFpEF demonstrate the efficacy of SGLT2i for reducing HF events and cardiovascular mortality, with benefits in both HFrEF and HFpEF.[12,13] Therefore, SGLT2i should be prioritized as the first-line cardioprotective glucose-lowering medications in all patients with T2D and HF.

Although not separately addressed within this section, the foundational role of RASi in managing patients with T2D and HF should not be overlooked, as these agents provide vascular benefits in T2D in addition to HF benefits. The addition of GLP-1–based therapy in the setting of T2D with obesity and HFpEF improves symptoms and functional capacity.[4,5] The addition of GLP-1–based therapy to SGLT2i can also address additional CKM risk factors in patients with T2D and HFpEF.

Recommendation-Specific Supportive Text

1. SGLT2i have demonstrated broad efficacy in reducing HF hospitalizations and cardiovascular death among patients with CKM stage 4 with T2D and HF with any ejection fraction. A meta-analysis of EMPEROR-Reduced (50% T2D) and DAPA-HF (45% T2D) found an HR of 0.74 (95% CI, 0.65–0.84) for the composite outcome of cardiovascular death and first HF hospitalization in subjects with T2D and HFrEF.[1] A post-hoc analysis of DECLARE-TIMI 58, in subjects with T2D and HFrEF (n=671, 3.9% of trial population), found that dapagliflozin also reduced cardiovascular death and HF hospitalization (HR, 0.62; 95% CI, 0.45–0.86).[2] More recently, a meta-analysis of DELIVER and EMPEROR-Preserved found that dapagliflozin and empagliflozin likewise reduced the incidence of the composite of cardiovascular death and HF hospitalization by >20% in individuals with T2D (approximately 45% and 49% of the trial populations) and HF with LVEF >40%.[3] Based on the broad benefits of SGLT2i in HFrEF, HFmrEF, and HFpEF, they should be the first-line cardioprotective glucose-lowering agents utilized among individuals with diabetes and HF in the absence of contraindications.
2. Two high-quality simulation model–based cost-effectiveness analyses evaluated the economic value of adding SGLT2i therapy to prior GDMT in adults with symptomatic HFrEF, from a US health care sector perspective and a lifetime analytic horizon.[14,15] Subgroup analyses in both studies specifically examined individuals with diabetes at baseline. The studies assumed an annual drug cost of $4192 to $5684, which is consistent with the Federal Supply Schedule cost in April 2025 ($5200 to $5600).[16] One study found that the addition of SGLT2i therapy resulted in incremental quality-adjusted survival of 0.70 (95% uncertainty interval [UI], 0.23–1.20) QALYs, at an incremental cost of $46 500 (95% UI, $32 700–$49 700), producing an incremental cost-effectiveness ratio of $66 800 (95% UI, $53 800–$116 600) per QALY gained and making it a cost-effective strategy in 95% of 10 000 probabilistic simulations. The study also reported incremental cost-effectiveness ratios of $57 300 (95% UI, $44 800–$123 800) per life year gained and $53 400 (95% UI, $42 800–$97 200) per equal value of life-years gained. A second analysis found an incremental cost-effectiveness ratio of $79 700 per QALY gained for patients with diabetes (with a similar cost-effectiveness estimate in individuals without diabetes).
3. Two high-quality simulation model–based cost-effectiveness analyses evaluated the economic value of adding SGLT2i therapy to prior GDMT in adults with symptomatic HFpEF, but neither study reported subgroup analyses by diabetes status.[17,18] Given that randomized trials of SGLT2i in HFpEF did not note an effect-modification by diabetes status, it is plausible that the cost-effectiveness of this

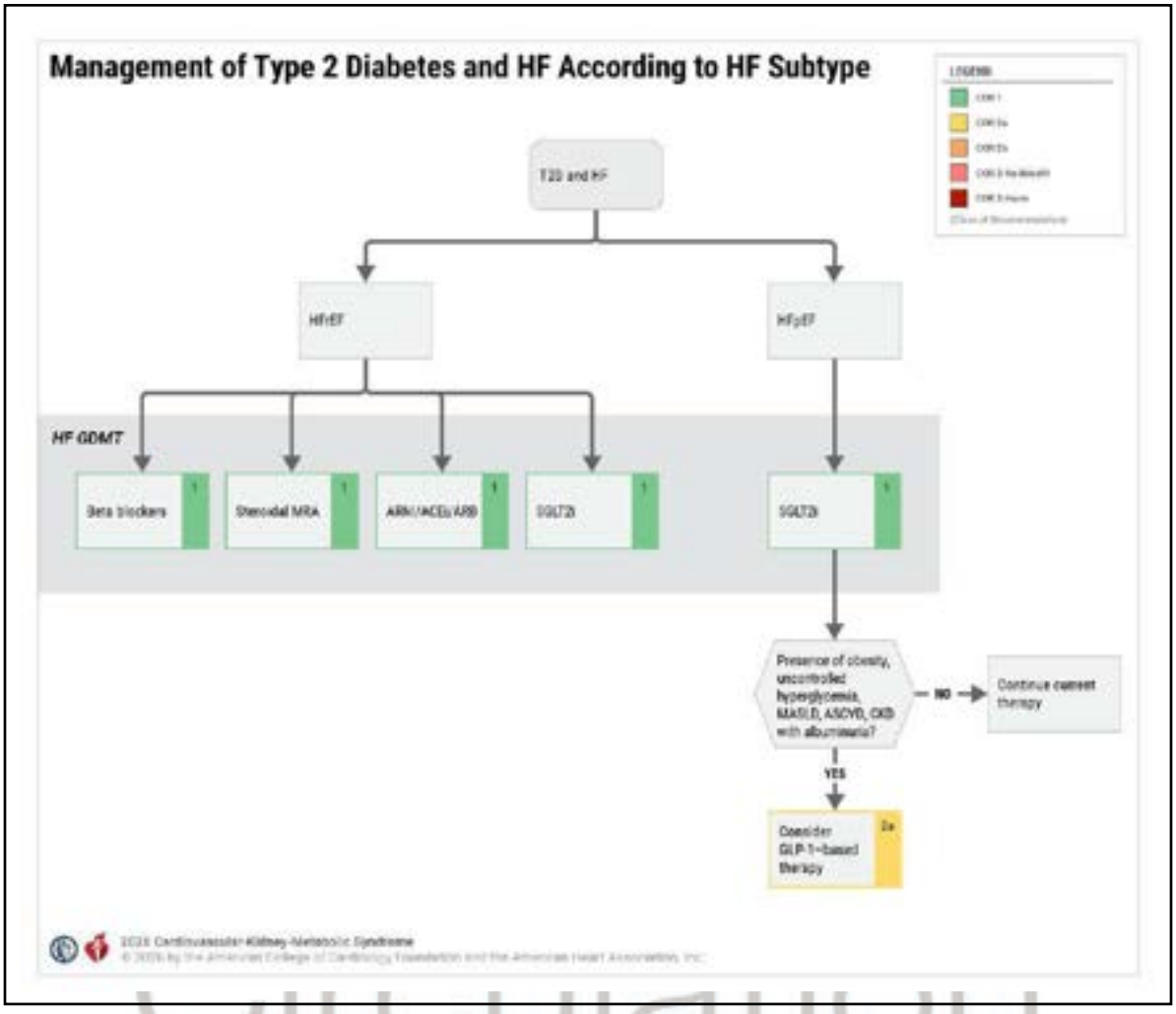

Figure 19. Management of Type 2 Diabetes and HF According to HF Subtype.
Adapted with permission from Heidenreich et al.[34] Copyright 2022 American Heart Association, Inc. and American College of Cardiology Foundation. Management of patients with comorbid T2D and HF according to HF subtype, with HF GDMT as recommended by the 2022 HF guidelines highlighted in gray. ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitors; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; COR, Class of Recommendation; GDMT, guideline directed medical therapy; GLP-1, glucagon-like peptide-1; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MASLD, metabolic dysfunction–associated steatotic liver disease; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

therapy in HFpEF is also unaffected by diabetes status (as was true in the case of SGLT2i therapy for HFrEF, as noted above). Prior studies performed using a US health care sector perspective and a lifetime analytic horizon noted that SGLT2i therapy was unlikely to be cost-effective for HFpEF, but that the incremental cost-effectiveness ratio was sensitive to the effect on mortality. One analysis was based on the results of the EMPEROR-PRESERVED trial, in which the effect of SLGT2i on cardiovascular mortality in HFpEF was not statistically significant (HR, 0.91; 95% CI, 0.76–1.09). In the main analysis, assuming no cardiovascular mortality benefit, the ICER was $437 400 per QALY gained (the study pooled patients with and without diabetes), at an annual cost of $3920.[18] In a sensitivity analysis assuming a 9% cardiovascular mortality benefit, the ICER was $174 053 per QALY gained. A second study pooled data from both EMPORER-PRESERVED and DELIVER and probabilistically accounted for reduction in cardiovascular mortality with SGLT2i therapy from a published meta-analysis (HR, 0.88; 95% CI, 0.77–1.00). It found that at an annual cost of $4506,[17] SGLT2i therapy would have an incremental cost-effectiveness ratio of $141 200 per QALY gained compared with prior GDMT. These analyses suggest that SGLT2i therapy is not cost-effective at current drug prices (incremental cost-effectiveness ratio ≥$120 000 per QALY gained), but these analyses pooled individuals with and without diabetes, and there may be additional cardiovascular and

kidney benefits in individuals with diabetes. In light of this conflicting evidence, the cost-effectiveness of SGLT2i in patients with diabetes and HFpEF was deemed to be indeterminate.

4. As discussed in Section 6.2.1, "CKM Syndrome Stage 4 With Obesity and ASCVD," STEP-HFpEF DM tested the effects of GLP-1s in patients with HFpEF and obesity who also had T2D. Subcutaneous semaglutide significantly reduced body weight and improved KCCQ-CSS and 6MWD compared with placebo.[4] In SUMMIT, in which half of the participants had T2D, tirzepatide reduced weight, improved KCCQ-CSS and 6MWD, and also decreased worsening HF events by 38%, with no heterogeneity by T2D status.[5] While there is growing evidence for GLP-1 benefit in HFpEF, there is less clarity regarding efficacy and safety in HFrEF, based on somewhat increased risk for adverse outcomes among patients taking GLP-1 RA in small HFrEF trials.[19–21] Despite limited interventional data examining the efficacy of combined SGLT2i and GLP-1–based therapy, data have generally suggested no heterogeneity in GLP-1 efficacy according to the absence or presence of SGLT2i use.[22] Additionally, improvements in CKM risk factors have been consistently demonstrated among those receiving GLP-1 therapy in clinical trials. Thus, it is reasonable to use GLP-1–based therapy as "add-on" therapy to SGLT2i in individuals with T2D, HFpEF, and additional CKM risk factors or related conditions, such as obesity (Section 6.3.1, "CKM Syndrome Stage 4 With Obesity and HF"), CKD with albuminuria (Section 6.3.3, "CKM Syndrome Stage 4 With CKD and HF"), MASLD (Section 7.2, "Metabolic Dysfunction–Associated Steatotic Liver Disease"), and ASCVD (Section 6.2.2, "CKM Syndrome Stage 4 With T2D and ASCVD").
5. Data on metformin use in patients with HF predate current GDMT and are wholly observational. With that background, numerous observational studies support a positive, linear association of glycemia with HF incidence and events.[23–25] However, a U-shaped curve is observed for mortality among patients with T2D and *existing* HF,[26–28] highlighting the potential harm associated with very aggressively targeting glycemia in this population. Maintenance of HbA1c between 7% and 8% is felt to be appropriate among patients with T2D and HF.[29] Nonrandomized reports across a spectrum of HF (ambulatory patients with chronic HF, a new HF diagnosis, and individuals with a recent hospitalization) and a variety of ages do not support harm with metformin therapy, though metformin is contraindicated in decompensated HF.[9,30] Thus, when needed for additional glycemic control, it is reasonable to add metformin therapy to SGLT2i (particularly given the modest impact of SGLT2i on glycemia) in patients with CKM syndrome with T2D and stable HF, cognizant of the need for dose reductions depending on kidney function (eGFR ≥60 mL/min/1.73 m^2, normal dose; eGFR 45 to 59 mL/min/1.73 m^2, 1000 to 1500 mg per day; eGFR 30 to 44 mL/min/1.73 m^2, ≤1000 mg per day; eGFR <30 mL/min/1.73 m^2, contraindicated).[31] We encourage referral to the ADA guidelines for more guidance on glycemic management.[32,33]

6.3.3. CKM Syndrome Stage 4 With CKD and HF

Recommendations for CKM Syndrome Stage 4 With CKD and HF
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	A	1. In adults with CKM syndrome stage 4 with CKD, eGFR ≥30 mL/min/1.73 m^2, and HFrEF, the initiation of an ARNI, or other RASi if an ARNI cannot be initiated, is recommended to reduce the risk of cardiovascular death or HF hospitalization and loss of kidney function.[1–8]
Economic Value:* Cost-Effective (Moderate Level of Certainty)		2. In adults with CKM syndrome stage 4 with CKD, eGFR ≥30 mL/min/1.73 m^2, and HFrEF, treatment with an ARNI is projected to be cost-effective compared with RASi therapy.
1	A	3. In adults with CKM syndrome stage 4 with CKD and HF with any ejection fraction, who have eGFR ≥20 mL/min/1.73 m^2, initiation of a SGLT2i is recommended to reduce cardiovascular mortality, HF hospitalization, and possibly, loss of kidney function.[9–12]
Economic Value:* Cost-Effective (Moderate Level of Certainty)		4. In adults with CKM syndrome stage 4 syndrome with CKD and symptomatic HF with LVEF ≤40%, addition of an SGLT2i prior to GDMT at 2025 US prices is projected to be cost-effective compared with prior GDMT.
Economic Value:* Indeterminate (Conflicting Evidence)		5. In adults with CKM syndrome stage 4 syndrome with CKD and symptomatic HFpEF, the cost-effectiveness of adding a SGLT2i prior to GDMT at 2025 US prices is indeterminate.
2a	B-R	6. In adults with CKM syndrome stage 4 with CKD, T2D, UACR ≥30 mg/g and HF with LVEF >40% (HFmrEF and HFpEF), who have eGFR ≥25 mL/min/1.73 m^2, initiation of a nonsteroidal MRA is reasonable to reduce risk of HF hospitalization and loss of kidney function.[13]
Economic Value:* Indeterminate (Insufficient Evidence)		7. In adults with CKM syndrome stage 4 with CKD and eGFR ≥25 mL/min/1.73 m^2, T2D, and HF with LVEF >40% (HFmrEF and HFpEF), the cost effectiveness of adding nsMRA to other GDMT is indeterminate.
2b	B-R	8. In adults with CKM syndrome stage 4 with CKD and HFrEF, who have eGFR >30 mL/min/1.73 m^2, use of novel oral potassium-binding agents may be reasonable to reduce risk of hyperkalemia and allow use of RAAS inhibition.[14–17]
Economic Value:* Indeterminate (Insufficient Evidence)		9. In adults with CKM syndrome stage 4 with CKD, and HFrEF who have eGFR >30 mL/min/1.73 m^2, the cost-effectiveness of adding newer oral potassium-binding agents to GDMT is uncertain.

*Economic value statements inform population- and health system–level decisions and are not meant to directly influence clinical decision-making for individual patients.

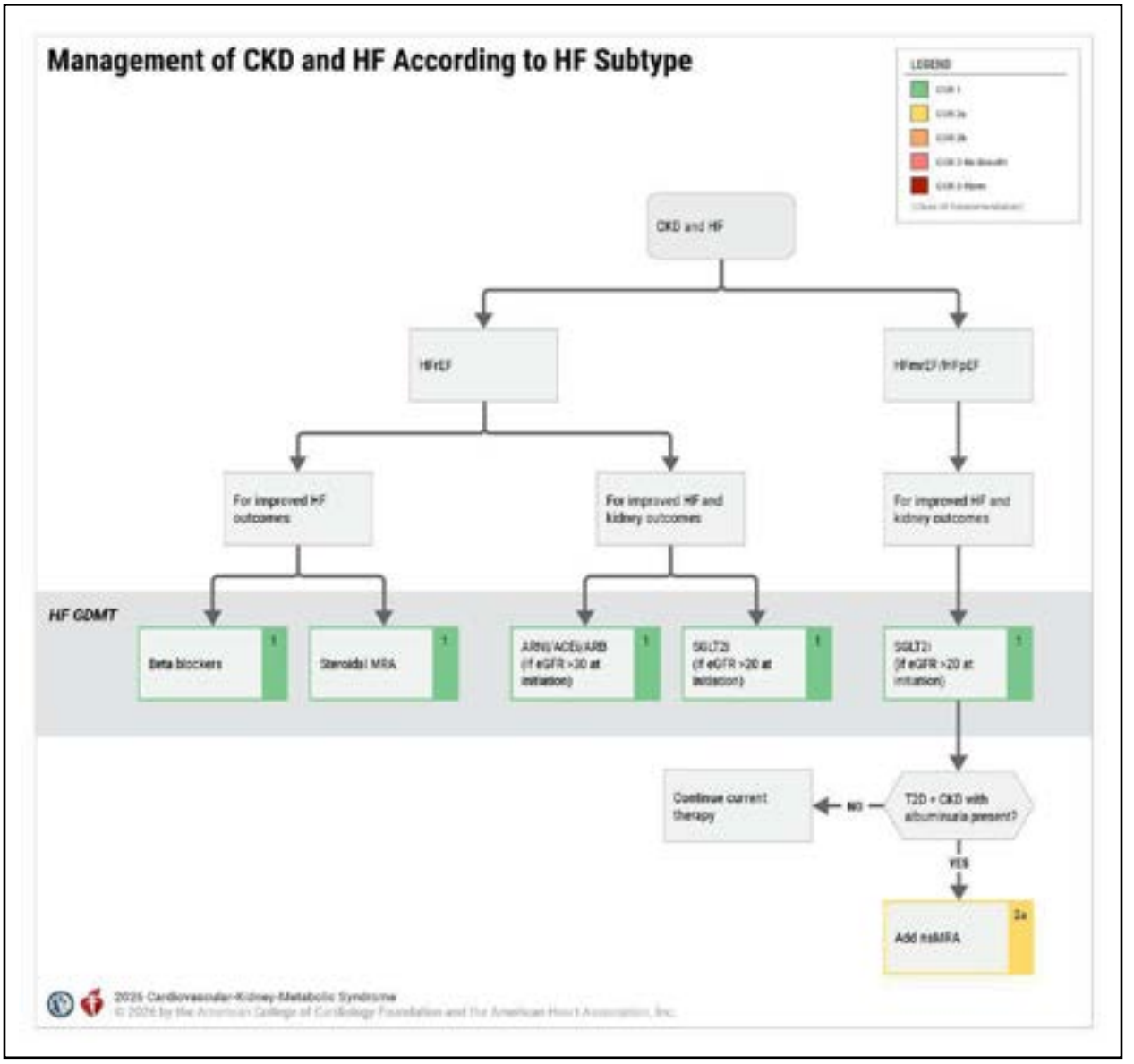

Figure 20. Management of CKD and HF According to HF Subtype.
Adapted with permission from Heidenreich et al.[18] Copyright 2022 American Heart Association, Inc. and American College of Cardiology Foundation. Management of patients with comorbid CKD and HF according to HF subtype with HF GDMT as recommended by the 2022 Heart Failure Guidelines highlighted in gray. CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

Synopsis

HF often presents or develops in tandem with CKD. There are 4 established pillars of pharmacologic treatment that improve survival and reduce the risk of HF hospitalization in HFrEF (Figure 20).[18–20] Among these 4 medication classes (6 classes if the patient also self-identifies as Black race), 2 are kidney-protective; namely, 1) RASi, with ARNI having superior HF benefits over ACEi/ARB; and 2) SGLT2i.[13,21–25] Dual therapy with more than 1 RASi (ACEi/ARB/ARNI) should be avoided since it can worsen kidney function and lead to angioedema, hyperkalemia, and hypotension.[26]

Among patients with CKD and HFpEF or HFmrEF, SGLT2i have the most substantial data for being kidney-protective as well as reducing the composite outcomes of mortality and HF hospitalization.[27] Finerenone is also a consideration for the subpopulation with T2D, CKD, and HFmrEF/HFpEF, based on clinical benefits demonstrated across different trials, for individuals without hyperkalemia. This set of recommendations complements existing Class 1 and 2 recommendations in the ACC/AHA guidelines for HF[18] and offers additional recommendations for addressing risk related to CKD and HF. Guidance for medication initiation reflects the eGFR inclusion criteria from clinical trials.

Recommendations for medication continuation after falling below the eGFR threshold for initiating therapies are addressed separately in Section 6.5, "Treating CKM Syndrome in Patients With Advanced CKD."

Recommendation-Specific Supportive Text

1. Among patients with HFrEF, RASi improves both HF outcomes and risk for worsening kidney disease in several clinical trials.[1–8,28] Among RASi, ARNI is associated with greater reduction in the composite of cardiovascular death and HF hospitalization relative to other RASi and is therefore the preferred agent in HFrEF, when available.[2] ARNI has demonstrated benefit for patients with eGFR >30 mL/min/1.73 m^2. Most trials have excluded patients with stage G4 to G5 CKD from study; data for these populations are limited to post-hoc analyses with small populations.[1,5,22] The UK HARP 3 (UK Heart and Renal Protection III) trial in patients with CKD demonstrated no significant difference between the kidney effects of ARNI and ARB, although only a small proportion of participants had HF.[29] Limited data support possible similar ARNI benefits among patients with HFpEF with stage G2 to G3b CKD.[30] Changes in kidney function were not routinely evaluated in the initial studies of ACEi and ARB for HF, and patients with creatinine >2.5 mg/dL were usually excluded.[28] RASi may be associated with modest acute decline in kidney function (usually due to hemodynamic changes), but this is not indicative of harm and may be associated with better long-term outcomes.[23,31,32] Efforts to examine other contributing etiologies should be considered before discontinuing therapy.
2. At least 2 high-quality cost-effectiveness analyses have examined the cost-effectiveness of treatment with ARNI compared with a RASi in patients with HFrEF (NYHA class II-IV) from a US health care sector perspective and a lifetime analytic horizon.[33,34] These studies found incremental cost-effectiveness ratios of approximately $50 000 per QALY (in 2015 US dollars). Even after adjusting for interval inflation (approximately 35% between 2015 and 2025), the incremental cost-effectiveness ratio increases to approximately $68 000 per QALY, which is well below the $120 000 per QALY cost-effectiveness threshold, and suggests that treatment with an ARNI is cost-effective compared with RASi in patients with symptomatic HFrEF. However, 2 sources of uncertainty remain. First, neither cost-effectiveness analysis examined the subgroup with CKD. Individuals with CKD are likely to have a higher risk for HF events during follow-up compared with individuals without CKD. Since there was no effect modification (on the relative scale) by eGFR in the PARADIGM-HF trial, the absolute benefit in this population may be larger in the population with CKD, provided this is not offset by an increase in adverse events. This is true for early to moderate CKD but may not be true for advanced CKD, where hospitalizations due to volume overload may not be modifiable by an ARNI. Another source of uncertainty is the drug cost. The cost effectiveness of ARNI is sensitive to its price, which has increased substantially since the cost-effectiveness analyses were performed, but is expected to decline for Medicare Part D beneficiaries in 2026 (for a 1-year supply). Taken together, these results suggest that the use of ARNI in a population with stage 4 CKM syndrome with CKD and HF is likely to be cost-effective, particularly at 2026 US prices.
3. Initiation of SGLT2i is efficacious in reducing risk of the outcomes of cardiovascular mortality, HF hospitalization, and decline in eGFR for patients with stage 4 CKM with CKD (GFR >20 mL/min/1.73 m^2) and HFrEF, particularly for those with albuminuria.[9–12] SGLT2i initiation have demonstrated efficacy among patients with eGFR >20 mL/min/1.73 m^2 and HFmrEF/HFpEF in reducing composite cardiovascular mortality and HF hospitalizations, but data are more sparse in patients with severely decreased kidney disease (stage G4 CKD), and the presence/absence of albuminuria is understudied in HF trials.[9–12] In an analysis of the EMPEROR-Preserved (HFpEF/HFmrEF) and EMPEROR-Reduced (HFrEF) study populations, the SGLT2i empagliflozin improved HF outcomes and reduced the rate of eGFR slope decline similarly across all KDIGO risk categories. However, further evidence is needed for SGLT2i initiation in patients with eGFR <20 mL/min/1.73 m^2.[12]
4. Two high-quality simulation model–based cost-effectiveness analyses projected that adding SGLT2i therapy to prior GDMT in adults with symptomatic HFrEF was cost-effective from a US health care sector perspective and a lifetime analytic horizon,[35,36] with an incremental cost-effectiveness ratio between $68 000 and $84 000 per QALY gained (assuming an annual drug cost of $4192 to $5684, which is consistent with the Federal Supply Schedule cost in April 2025 [$5200 to $5600]).[37] In probabilistic sensitivity analyses, the incremental cost-effectiveness ratio was <$120 000 per QALY gained in >95% of the simulations in 1 analysis,[35] and approximately 70% of the simulations in the other.[36] However, neither study specifically examined the subgroup of individuals with CKD. Patients with CKD have a higher risk of atherosclerotic CVD and HF events and derive additional benefit from SGLT2 inhibitor therapy in the form of slowing of the decline in kidney function. Since pivotal randomized trials showed no effect modification in the relative reduction in major adverse cardiovascular events by the presence of CKD, it is

likely that the absolute benefit of SGLT2i is greater among individuals with HFrEF with CKD, compared with individuals with HFrEF without CKD. The caveat is that this is likely to be true in early- and moderate-stage CKD, but less certain in advanced CKD. Thus, it is reasonable to extrapolate the cost-effectiveness of the therapy in HFrEF overall to this higher-risk subpopulation, where the absolute health gains are likely larger. The cost-effectiveness of SGLT2i is expected to improve as drug costs decline in the coming years (due to increasing availability of generic formulations and Medicare price negotiation).[38]

5. In 2 high-quality simulation model–based cost-effectiveness analyses that evaluated the economic value of adding SGLT2i therapy to prior GDMT in adults with symptomatic HFpEF using a US health care sector perspective and a lifetime analytic horizon, addition of SGLT2i therapy to GDMT was projected to be not cost-effective, but the incremental cost-effectiveness ratio was sensitive to the effect on mortality.[39,40] One analysis based on the results of the EMPEROR-PRESERVED trial found that empagliflozin therapy, at an annual cost of $3920, would have an incremental cost-effectiveness ratio $437 400 per QALY gained.[40] A second study probabilistically accounted for the reduction in cardiovascular mortality with SGLT2i therapy from a published meta-analysis of EMPEROR-Preserved and DELIVER trials. It found that at an annual cost of $4506, SGLT2i therapy would have an incremental cost-effectiveness ratio of $141 200 per QALY gained compared with prior GDMT.[39] However, these analyses pooled individuals without, and with, CKD and did not directly incorporate the benefit of SGLT2i therapy on kidney outcomes. Taken together, these analyses suggest that SGLT2i therapy is not cost-effective at current drug prices (incremental cost-effectiveness ratio ≥$120 000 per QALY gained).
6. Trials of finerenone in diabetic kidney disease demonstrated a significant positive impact on both reducing loss of kidney function and incident HF, with most of the HF benefit likely conferred via kidney protection.[41,42] The FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure) trial demonstrated that finerenone reduced the composite outcome of all-cause death and HF hospitalization among patients with HFmrEF/HFrEF.[43] Although a pooled meta-analysis of these finerenone trials demonstrated less[28] decline in eGFR with finerenone,[13] in FINEARTS-HF alone, finerenone did not result in a reduction in the primary kidney endpoint.[44] This is likely because of the absence of more substantial CKD in FINEARTS-HF, with a mean baseline eGFR of 62 mL/min/1.73 m^2 and a mean UACR <20 mg/g. Based on the results across these trials, it is likely that finerenone confers both cardiovascular and kidney benefits in those with albuminuric DKD and HFmrEF/HFpEF, though a more dedicated study of this population is needed. Recommendations for finerenone initiation do not currently extend to those with eGFR <25 mL/min/1.73 m^2 or potassium >5 mmol L−1 since this population has been excluded from clinical trials.[13]
7. We could not identify any rigorous cost-effectiveness analyses examining the economic value of adding a nsMRA to GDMT from a US health care sector perspective. Given the cost of finerenone (Federal Supply Schedule cost in April 2025 of $7612 for a 1-year supply)[37] and the potentially large number of patients eligible for therapy, examining the cost-effectiveness and budget impact of this therapy should be a research priority.
8. Novel oral potassium binding agents such as patiromer may allow for improved use of RAAS inhibition across eGFR by lowering risk of hyperkalemia, although few patients with eGFR <30 mL/min/1.73 m^2 have been included in prior trials with co-existing HF.[14,15,45] However, sodium zirconium cyclosilicate may increase risk of HF events.[16] Current data do not determine whether HF event risk is greater with sodium zirconium cyclosilicate versus patiromer.[46]
9. We did not identify rigorous cost-effectiveness analyses of patiromer or sodium zirconium cyclosilicate in patients with stage 4 CKM with CKD and HF performed from a US health care sector perspective. The avoidance of hyperkalemic events and the ability to tolerate higher doses of RAAS inhibition are likely to produce substantial health gains, but these are high-cost therapies in the United States, with the cost of patiromer 24% to 28% higher than the cost of sodium zirconium silicate. Examining the cost-effectiveness and budget impact of these therapies is an urgent research priority.

6.4. Atrial Fibrillation

Synopsis

The progressive consequences of excess and dysfunctional adiposity increase risk for incident AF, and AF is also associated with increased risk for multiple components of CKM syndrome stage 4, including stroke, MI, HF, CKD, and PAD. Several components of CKM syndrome stage 1 to 3, including overweight/obesity, hypertension, T2D, and CKD, increase risk for AF. In CKM stages 1 to 3, prevention of AF includes healthy lifestyle modification, weight management, glycemic and BP control, smoking cessation, alcohol moderation or avoidance, and treatment of sleep-disordered breathing.[1] Limited data support the efficacy of ACEi, ARB, statins, SGLT2i, and GLP-1–based therapies for preventing AF onset.[1] MRAs have been associated with decreased new-onset and

recurrent AF.[2] In individuals with prevalent AF, 1 component of CKM syndrome stage 4, lifestyle modification and management of overweight or obesity (Sections 5.4.1, "Overarching Approach to Obesity Management," 5.4.2, "Intensive Lifestyle Modification for Weight Loss," 5.4.3, "Obesity Pharmacotherapy for Weight Management in CKM Syndrome Stage 1," and 5.4.4, "Surgical Interventions for Weight Loss in CKM Syndrome Stage 1 to 3"), hypertension (Section 5.5.3, "Hypertension"), T2D (Section 5.5.1, "Management of T2D in CKM Syndrome Stage 2 to 3"), and CKD (Section 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3") are advised to reduce AF burden, recurrence, and progression. In individuals with AF and BMI ≥40 kg/m^2 without prior bariatric surgery, direct oral anticoagulants (DOACs), namely apixaban and rivaroxaban, are potential options for thromboprophylaxis. AF prevention and management are discussed comprehensively in the "2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation."[1]

6.5. Treating CKM Syndrome in Patients With Advanced CKD

Recommendation for Treating CKM Syndrome in Patients With Advanced CKD
Referenced studies that support the recommendation are summarized in the evidence table.

COR	LOE	Recommendation
2a	B-R	1. Among adults with CKD who are being treated with kidney-protective therapies for both kidney and cardiovascular benefit and whose eGFR falls below drug-specific initiation thresholds, it is reasonable to continue those treatments as safely tolerated.[1–8]

Synopsis

As emphasized by the KDIGO heat map (Figure 2), CKD G4 and G5 confer very high risk for adverse kidney and cardiovascular outcomes. Unfortunately, evidence regarding CKM therapeutic agents targeting this group is limited, with most data coming from underpowered subgroup analyses within randomized trials. These have generally indicated that the agents are safe in CKD G4 and G5, with some suggesting retention of their salutary effects. Several RCTs of kidney-protective agents, however, demonstrate that continuation of these therapies after the eGFR declines below the initiation threshold can be associated with ongoing cardiovascular benefit.

Among patients with kidney failure (end-stage kidney disease) receiving dialysis, CVD rates are high and the leading cause of death, with unique CVD phenotypes.[9] In chronic dialysis patients, HF and extracellular fluid overload are especially prominent, with a potential mitigating impact of more frequent dialysis.[10] Medial arterial calcification contributes to vascular disease, which may partially explain the negative results of statin trials in dialysis populations.[11] Unfortunately, preventing and treating CVD in dialysis patients presents unique challenges, owing to distinct pathophysiology, unique risk and safety concerns, and scarce clinical trials testing therapeutic approaches. The use of CKM therapies in kidney transplant patients is being investigated and is not addressed here.

Recommendation-Specific Supportive Text

1. As described in prior sections (Section 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3," 6.2.3, "CKM Syndrome Stage 4 With CKD and ASCVD," and 6.3.3, "CKM Syndrome Stage 4 With CKD and HF"), the use of agents to preserve kidney function, including RASi, SGLT2i, finerenone, and GLP-1–based therapy, is associated with improved kidney and cardiovascular outcomes. The drug-specific eGFR initiation thresholds for these therapies are: RASi ≥30 mL/min/1.73 m^2, SGLT2i ≥20 mL/min/1.73 m^2, and finerenone ≥25 mL/min/1.73 m^2. Several major clinical trials allowed study drugs to be continued after eGFR dropped below eGFR initiation thresholds, and even after starting dialysis, with ongoing benefit and without apparent increased adverse effects.[3,8] A directionally similar reduction in risk of the cardiovascular outcome (cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for HF) was observed in a subgroup with CKD G4 in the FIDELITY meta-analysis of finerenone in diabetic patients, but this was nonsignificant and requires further investigation.[6] Hyperkalemia was more frequent in those with CKD G4 treated with finerenone.[6] A recent meta-analysis suggested that RAASi use in patients with advanced CKD reduces the rate of kidney failure with replacement therapy but not of death.[7] While risk factor control (blood pressure, lipids, glycemia) is central to optimal CKM management overall, targets in CKD with eGFR <15 mL/min/1.73 m^2 (CKD stage G5) are uncertain and rely on clinical judgement and shared decision-making with patients.

7. IMPORTANT CONSIDERATIONS

7.1. LDL-C Management in CKM Syndrome

Synopsis

CKM syndrome contributes to accelerated atherogenesis and increased risk for ASCVD events.[1,2] Among individuals with CKM syndrome, lowering LDL-C with lifestyle and pharmacological interventions is central to primary and secondary ASCVD prevention. Among CKM syndrome patients with hypertriglyceridemia, non–HDL-C or apolipoprotein B should also be considered as more reliable measures of atherogenic particle burden than LDL-C in this subpopulation.[3,4]

In stage 1 to 2 CKM syndrome, the presence of T2D or CKD in adults ≥40 years or of intermediate predicted

ASCVD risk (PREVENT ASCVD, 5% to 9.9%) support the use of statins and other LDL-C lowering therapies for ASCVD event risk reduction. In those with borderline predicted ASCVD risk (PREVENT ASCVD, 3% to 4.9%), lipid-lowering therapy can be considered as part of a risk discussion that incorporates ASCVD risk enhancers. Among individuals with CKM stage 3, the presence and extent of subclinical coronary atherosclerosis can inform LDL-C lowering goals. Per the ACC/AHA 2026 Guideline for the Management of Dyslipidemia, for those with CAC scores of 100 to 999 Agatston units (AU) or moderate to severe incidental CAC, an LDL-C goal of <70 mg/dL is recommended. In those with very severe CAC with a CAC score of ≥1000 AU, an even more aggressive LDL-C goal of <55 mg/dL is recommended. The VESALIUS-CV (Effect of Evolocumab in Patients at High Cardiovascular Risk without Prior Myocardial Infarction or Stroke) trial demonstrated cardiovascular benefits of similarly aggressive LDL-C lowering in patients with high-risk diabetes, coronary atherosclerosis, or both, but without prior MI or stroke.[5]

Among CKM syndrome patients with existing ASCVD (CKM Stage 4), the presence of CKM syndrome components such as diabetes and CKD are associated with increased risk for recurrent ASCVD events, and these patients frequently fall into the subgroup with very high-risk ASCVD. These patients should receive intensive LDL-C lowering to <55 mg/dL using high-intensity statins, ezetimibe, and, if needed, adjunctive therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies, inclisiran, or bempedoic acid. For specific LDL-C management recommendations, please refer to the ACC/AHA 2026 guideline on the management of dyslipidemia.[4]

7.2. Metabolic Dysfunction–Associated Steatotic Liver Disease

Recommendations for Metabolic Dysfunction–Associated Steatotic Liver Disease
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	B-NR	1. Among adults with CKM syndrome and diabetes or ≥2 cardiometabolic risk factors, calculation of the Fibrosis-4 (FIB-4) index is recommended every 1 to 2 y to assess risk for liver fibrosis related to MASLD.[1–3]
2a	C-LD	2. Among adults with CKM stage 1 due to prediabetes, it is reasonable to calculate the FIB-4 index every 2 to 3 y to assess risk for liver fibrosis related to MASLD.[4]
1	B-R	3. For adults with CKM syndrome and MASLD, lifestyle modification through physical activity and dietary approaches for weight loss, with adjunctive use of obesity pharmacotherapy and/or MBS as needed, is recommended to reduce MASLD severity, reduce risk of MASLD progression, and improve CKM risk profiles.[5–7]
1	B-R	4. In adults with CKM syndrome and MASLD with T2D or MASH with evidence of clinically significant liver fibrosis, treatment with a GLP-1–based therapy with proven benefit is indicated to facilitate histologic improvements in MASLD.[8–11]

Synopsis

MASLD, formally nonalcoholic fatty liver disease, is a highly prevalent, chronic, progressive, and life-threatening disease.[12–14] Metabolic dysfunction–associated steatohepatitis (MASH, previously NASH) is the severe form of MASLD and a leading cause of cirrhosis, liver cancer, and indication for liver transplantation.[14,15] MASLD is the pathophysiologic result of ectopic fat deposition, inflammation, and insulin resistance, which are central to CKM syndrome.[16,17] These patients also have high CVD rates, and there is a need for CKM risk factor screening and prevention in this population. Fibrosis stage best predicts adverse outcomes in MASLD.[1,18] Assessment of fibrosis risk starts with the FIB-4 index, with further sequential assessments as needed to rule out (or rule in) clinically significant fibrosis (≥ stage 2).[19–21] In MASLD, lifestyle modification leading to weight loss is critical, with ≥10% weight loss leading to improvement and remission of MASLD.[22,23] Metabolic and bariatric surgery causes remission of MASLD, even in advanced stages.[6,24,25] Additionally, in persons with MASH and stage 2 or 3 fibrosis, the GLP-1RA semaglutide is associated with reductions in steatohepatitis and liver fibrosis.[11,26] Resmetirom, a thyroid hormone receptor beta agonist, is also now approved for improving liver histology in patients with MASH and stage 2 to 3 fibrosis. Statins are safe and effective in patients with MASLD and should be used according to guidelines.[12,19,20,27] Referral to gastroenterology or hepatology in the presence of clinically significant fibrosis (≥stage 2) is appropriate for consideration of medical and surgical weight loss, liver-directed pharmacotherapy, and subsequent monitoring.[12,19,20]

Recommendation-Specific Supportive Text

1. Data from meta-analyses and pooled studies demonstrate that individuals at highest risk for MASLD and its progression include those with T2D and/or those with more than 2 cardiometabolic risk factors such as obesity, hyperlipidemia, or hypertension.[14,28–30] Using data from the National Health and Nutrition Examination Survey (NHANES) III, MASLD prevalence and severity increased with a higher number of metabolic comorbidities, particularly in persons with T2D, and those with MASLD and T2D had the highest risk of mortality.[29,30] In the general population, FIB-4 index, a score derived

Table 17. Increased Risk of MASLD*

Age (Years)	FIB-4[20]	Follow-Up[55]
<35	Not applicable	
35-64	<1.3	Routine monitoring
	1.3–2.67	Refer for VCTE or ELF
	>2.67	Refer to hepatology
65+	<2.0	Routine monitoring
	2.0–2.67	Refer for VCTE or ELF
	>2.67	Refer to hepatology

*FIB-4 indicates liver fibrosis calculation (age×AST)/(platelet count×√ALT); FIB-4 should not be used in acutely ill patients; see Table 18.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; ELF indicates enhanced liver fibrosis score; and VCTE, vibration-controlled transient elastography.

from available clinical (age) and laboratory data (aspartate aminotransferase, alanine aminotransferase, platelet count), is cost-effective, predicts clinical outcomes, and can effectively exclude clinically significant fibrosis (Table 17).[31,32] In addition, a change in FIB-4 status category from low risk to intermediate or high risk may be used to assess MASLD progression.[33] For those individuals with cardiometabolic risk factors, recommended screening for high-risk MASLD is every 1 to 2 years in those with T2D or ≥2 cardiometabolic risk factors, and every 2 to 3 years if <2 cardiometabolic risk factors and no T2D.[12,19,20,34]

2. MASLD is a leading cause of liver failure in the United States and is frequently comorbid across the spectrum of CKM.[15,35] Moreover, it is an independent risk factor for CVD morbidity and mortality.[36] Among individuals with MASLD, those with advanced liver fibrosis are at the highest risk.[37,38] MASLD has often studied in the context of diabetes.[39,40] However, data suggest that adults with prediabetes are also at risk,[4] and clinical endocrinology guidelines recognize prediabetes as a high-risk condition for MASLD.[34] Notably, the population of individuals with prediabetes is large and heterogenous and there is a paucity of evidence specific to those with prediabetes in the absence of other risk factors. Given the current evidence, it is reasonable to screen adults with CKM stage 1 due to prediabetes for advanced liver fibrosis. Guidelines from the American Association for the Study of Liver Diseases recommend the FIB-4 as the preferred noninvasive screening test due to its high negative predictive value.[20] FIB-4 interpretation and next steps depend on age and test results (Table 17). Secondary assessment may include vibration-controlled transient elastography or enhanced liver fibrosis testing with referral to gastroenterology/hepatology in those with abnormal results (Table 18).[20]
3. A meta-analysis demonstrated that various weight loss interventions are associated with clinically significant improvements in biomarkers of liver disease in persons with MASLD, though studies with long-term health outcomes are lacking.[5] In persons with overweight/obesity, remission of MASLD and improvements in inflammation, fibrosis, and cardiometabolic risk factors can be achieved with ≥10% total body weight loss.[5,22] Even modest weight loss (3% to 5%) can reduce liver fat in MASLD, including in individuals with normal weight.[5,41] GLP-1–based therapy can be an effective adjunctive treatment to achieve weight loss goals in MASLD, with additional favorable effects on liver histology as discussed below.[8,9,42] MBS is associated with a lower risk of incident major adverse liver outcomes and MACE in large cohort studies.[6,24,25] In a meta-analysis, exercise, even without dietary intervention or weight loss, reduced hepatic steatosis, biomarkers of liver health, and cardiorespiratory fitness in persons with MASLD.[43] Exercise interventions improve quality of life and several cardiometabolic parameters, even in those with advanced liver disease.[44,45] Moreover, observational studies link regular physical activity to lower risks of liver fibrosis,

Table 18. Secondary Risk Assessment Tools for Clinically Significant Fibrosis Among Patients at Risk for MASLD

Test	Score	Risk Level	Action
Vibration-controlled transient elastography (VCTE)*	<8	Low	Standard risk surveillance for MASLD every 1 to 3 y† with FIB-4 calculation.
	8–12	Intermediate	Referral to GI/hepatology
	>12	High	
Enhanced Liver Fibrosis‡ (ELF) Score[55]	<7.7	Low	Standard risk surveillance for MASLD every 1 to 3 y† with FIB-4 calculation.
	7.7–9.8	Intermediate	Referral to GI/hepatology
	>9.8	High	

*Point-of-care ultrasound-based test performed in clinic. The individual must fast for ≥3 hours. Body habitus affects accuracy and is not recommended if BMI ≥40 kg/m^2.

†FIB-4 indicates liver fibrosis calculation (age × AST)/(platelet count × √ALT); FIB-4 is recommended every 1 to 2 years if T2D or ≥2 CKM risk factors; FIB-4 is reasonable every 2 to 3 years if at CKM stage 1 due to prediabetes.

‡Blood-based biomarker score sent to reference laboratory.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CKM, cardiovascular-kidney-metabolic; GI, gastroenterology; and MASLD, metabolic dysfunction–associated steatotic liver disease.

cirrhosis, liver cancer, and all-cause mortality.[46–48] Finally, sedentary behavior is an independent predictor of MASLD and is associated with a high risk for MASLD progression.[49,50]

4. GLP-1–based therapies improve weight, insulin resistance, and noninvasive liver parameters, and have beneficial effects on cardiovascular and kidney outcomes.[51] A Phase IIb dose-finding study of semaglutide demonstrated a significantly higher rate of MASH resolution in patients with stage 1 to 3 fibrosis receiving the 0.4-mg dose compared to those who received placebo.[8] The ESSENCE (Research Study on Whether Semaglutide Works in People With Non-Alcoholic Steatohepatitis) trial, testing semaglutide in persons with MASH and stage 2 or 3 fibrosis, demonstrated improvement in steatohepatitis and liver fibrosis in the intervention versus placebo arm.[11,52] In a substudy of the randomized, open-label, parallel-group, Phase III SURPASS-3 trial, tirzepatide, a GLP-1/GIP receptor agonist approved for treatment of T2D, compared to insulin degludec, significantly reduced liver fat content among persons with T2D.[9] Finally, case-control studies have indicated that in individuals with cirrhosis and T2D, exposure to GLP-1 receptor agonists is associated with improved liver-related outcomes.[53,54] In terms of other pharmacotherapeutic options, resmetirom has been the first FDA-approved MASLD treatment whose mechanism for improving liver histology is independent of weight loss.[26] When clinically significant liver fibrosis is identified, involvement of a hepatologist is encouraged for guiding liver-directed pharmacotherapy and subsequent monitoring.

7.3. VENOUS THROMBOEMBOLISM

Synopsis

CKM syndrome is linked to a prothrombotic state that may lead to venous thromboembolism (VTE).[1] In acute VTE, the risk of recurrence increases stepwise with the number of CKM syndrome components.[2–4] Abdominal adiposity is one of the strongest VTE risk factors.[3,5–7] While evidence linking diabetes and VTE is inconsistent,[8–15] a lower eGFR, higher UACR, and higher CKD stages are associated with VTE development and worse outcomes.[16–20] VTE treatment and prevention involve anticoagulation with parenteral agents (eg, unfractionated or low-molecular-weight heparin) or oral therapy (DOAC or vitamin K antagonist [VKA]). DOACs offer advantages over VKAs: rapid onset, predictable effect, wider therapeutic window, no routine monitoring, and fewer food/drug interactions.[21] Emerging data suggest DOACs may also prevent cardiovascular events in patients with VTE.[22–24] Anticoagulation is more complex in CKD, obesity, or post–metabolic and bariatric surgery due to altered pharmacokinetics.[21] This section focuses on the management of acute VTE in persons with obesity or CKD without metabolic and bariatric surgery.[25] Pulmonary embolism-specific management, including management among individuals with obesity or CKD, is covered in the 2026 AHA/ACC acute PE guideline.[26]

In obesity, no prospective RCTs compare individual DOACs to low-molecular-weight heparin/VKA for VTE. Studies generally compare DOAC versus VKA: 1) within weight categories[24,27]; or 2) across weight categories.[28,29] Most studies pooled results from multiple DOAC agents rather than evaluating individual drugs separately. In patients with BMI ≥30 kg/m^2, pooled DOAC use was linked to a 20% reduction in stroke/systemic embolism/MI/all-cause mortality and a 44% reduction in major bleeding versus VKA, with similar VTE prevention.[24] In class 3 obesity, meta-analyses found DOACs more effective and safer than VKAs, mainly in studies of rivaroxaban or apixaban.[30–33] Data are limited in more severe obesity (BMI ≥50 kg/m^2 or weight >150 kg).[27,34]

In CKD, patients face high risks of both VTE formation and anticoagulant-related bleeding. DOAC kidney clearance varies (dabigatran 80%, edoxaban 50%, rivaroxaban 35%, apixaban 27%).[21] Phase 3 VTE trials excluded those with eGFR <30 mL/min/1.73 m^2 or on kidney replacement therapy. In stage G3 CKD (eGFR, 30-59 mL/min/1.73 m^2), subgroup analyses suggest DOACs are noninferior to VKA for recurrent VTE or major bleeding.[35–38] Meta-analyses in G2 to G3 CKD (eGFR, 30-89 mL/min/1.73 m^2) show most DOACs reduce major bleeding relative to VKA with similar efficacy for VTE prevention.[39–42]

In end-stage kidney disease on dialysis, 2 high-quality observational studies using data from the US Renal Data System found that apixaban was associated with lower major bleeding and similar mortality compared to warfarin.[43,44] A meta-analysis of observational studies in patients with G4 to G5 CKD show apixaban has lower VTE recurrence and bleeding risk versus warfarin, with similar all-cause mortality.[45] There are minimal data on rivaroxaban, edoxaban, or dabigatran in advanced CKD.[35,46]

7.4. Obstructive Sleep Apnea

Recommendations for Obstructive Sleep Apnea Referenced studies that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
2a	**C-LD**	1. For adults with CKM syndrome and obesity, annual assessments for symptoms of sleep apnea, including utilization of validated screening tools, are reasonable to facilitate the detection of OSA.[1,2]

Recommendations for Obstructive Sleep Apnea (Continued)		
COR	LOE	Recommendations
1	B-R	2. For adults with CKM syndrome and OSA, the treatment strategy should include weight management interventions where indicated, in addition to continuous positive airway pressure (CPAP) and other therapies, to improve OSA-related symptoms and to reduce the risk for CKM stage progression.[3–6]

Synopsis

The estimated prevalence of OSA among adults (aged 30 to 70 years) in the United States, based on a cohort study from 2007 to 2010 and defined as an apnea–hypopnea index (AHI) ≥5 events/hour, is 33.9% among men and 17.4% among women.[7] Conservative modeling predicts a significant rise in OSA prevalence in the US population by 2050, to 55% among men and 35% among women in the 30 to 69-year-old age group.[8] CVD and OSA share many CKM risk factors. As such, 1) OSA prevalence is higher among those with CKM syndrome and obesity compared to the general population; and 2) CKM syndrome prevalence is higher amongst those with OSA. OSA causes sleep fragmentation and sleep deprivation, leading to multiple consequences either due to direct impairment of function and quality of life, or indirectly through activating pathophysiologic pathways, contributing to CKM syndrome progression (CVD, cerebrovascular events, T2D, hypertension).[9,10] OSA treatment improves symptomatology, quality of life, and blood pressure.[11] However, randomized trials of CPAP versus usual care failed to demonstrate reductions in mortality, cardiovascular events, or kidney events.[11–14] Severe OSA is associated with increased all-cause mortality[9,10] and cardiovascular mortality has been rising over the past 2 decades among those with OSA in the United States.[8]

Recommendation-Specific Supportive Text

1. The American Academy of Sleep Medicine recommends annual OSA screening for adult patients in certain high-risk groups, including: obesity, HF, AF, treatment-resistant hypertension, impaired glucose tolerance or T2D, nocturnal dysrhythmias, stroke, pulmonary hypertension, preoperative for bariatric surgery, and CAD.[1] People with CKM syndrome have many of these OSA risk factors and have a high OSA prevalence. Therefore, despite limited data to support this recommendation, screening for OSA in people with CKM syndrome and obesity is reasonable. Screening for OSA can be performed using several approaches, including targeted OSA symptom checks, use of validated screening questionnaires, or use of sleep apnea screening devices. Commonly used screening questionnaires include the Berlin Questionnaire, STOP-BANG, and STOP.[15,16] It is important to recognize the limitations of these questionnaires and maintain a high level of clinical suspicion, as these questionnaires can underperform in certain populations, especially women and those with CVD.[2,15] If there is clinical suspicion for OSA, polysomnography or home sleep apnea testing with a technically adequate device should be performed for diagnostic confirmation.[15,17] Polysomnography is preferred for individuals with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular conditions, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia.[15,17]
2. Among individuals with excess weight, weight loss of >15% significantly improves OSA, with a substantial reduction in the AHI score. Additionally, this degree of weight loss improves CKM risk factors and has a potential effect on CVD events. In the SURMOUNT-OSA (A Study of Tirzepatide in Participants With OSA) study,[5] tirzepatide (titrated to 15 mg subcutaneously) versus placebo improved mean AHI −20.0 (95% CI, −25.8 to −14.2) events/hour among those not treated with CPAP and −23.8 (95% CI, −29.6 to −17.9) events/hour among those also treated with CPAP. Those treated with tirzepatide experienced reductions in hs-C-reactive protein, BP, and sleep-apnea–specific hypoxia burden. MBS, which induces body weight loss of >20%, also improves OSA, and is associated with reductions in CV and renal events, and in cardiovascular and all-cause mortality among people with OSA.[3,18] In the Sleep AHEAD (Sleep Apnea in Look Ahead-Action for Health in Diabetes) study,[4] people with T2D, obesity, and OSA who lost ≥10 kg via behavioral intervention had significant improvement in the AHI score. Given the demonstrated benefits of significant weight loss on OSA and CKM syndrome outcomes, weight management should be the cornerstone of OSA treatment in CKM syndrome.[19] Referral to sleep medicine for consideration for CPAP and other treatment modalities is advised to improve OSA-related symptoms. CPAP improves blood pressure control but has not been shown to reduce CVD events.[15]

7.5. Pregnancy and CKM Health

Recommendations for Pregnancy and CKM Health Referenced studies that support recommendations are summarized in the evidence table.		
COR	LOE	Recommendations for Prepartum CKM Management
1	B-NR	1. Among persons with CKM syndrome planning pregnancy, optimizing weight, kidney function, glycemia, and BP control, through lifestyle modification and appropriate medication, is recommended to reduce the risk of APOs and optimize postpartum CKM health.[1–4]

Recommendations for Pregnancy and CKM Health (Continued)		
COR	**LOE**	**Recommendations for Prepartum CKM Management**
1	B-R	2. Among persons with diabetes planning pregnancy, optimizing glucose control (with a target HbA1c <6.5%) through lifestyle modification and medication as needed is recommended to reduce the risk of APOs and optimize postpartum CKM health.[5–7]
1	C-LD	3. Persons planning pregnancy who have CKM syndrome stage 2 to 4 should receive care from an interdisciplinary care team to reduce the risk of APOs and optimize postpartum CKM health.[8–11]
Recommendations for Postpartum CKM Management		
1	B-NR	4. Among persons who have experienced an APO, screening for CKM risk factors (BP, lipids, glycemia, CKD, BMI, and waist circumference), at least once within the first postpartum year, and lifestyle counseling are recommended to guide optimization of CKM health.[12–15]
1	B-NR	5. Persons who have experienced an APO are recommended to transition from postpartum to longitudinal primary care to facilitate monitoring for CKM risk factors and optimization of CKM health.[16,17]

Synopsis

Pregnancy results in many physiologic vascular and metabolic changes to support fetal growth. However, dysregulation of these changes leading to excess insulin resistance, adipose deposition, hypercoagulability, cardiac remodeling, and decreased vascular resistance,[12,18] may result in APOs. APOs, which include GDM, hypertensive disorders of pregnancy, small-for-gestational age, low birth weight, placental abruption, and a preterm birth, share overlapping risk factors with CKM syndrome.[19] To minimize risk of APOs, women planning pregnancy with CKM syndrome should undergo preconception counseling[20–22] and optimize CKM risk factors before pregnancy, with lifestyle modification and medication when appropriate. Women planning pregnancy with CKM stages 2 to 4 should work with a multidisciplinary, interprofessional care team. APOs are also associated with higher subsequent risk for developing CKM risk factors (hypertension, diabetes, dyslipidemia) and CVD (including HF, coronary heart disease, PAD, and vascular dementia).[12,23–27] To reduce the risk of adverse subsequent cardiovascular events after an APO, screening and management for CVD risk factors within 1 year of delivery is appropriate. A multidisciplinary approach with engagement from primary care is advised. For specific recommendations on BP and dyslipidemia management, please refer to the 2025 AHA/ACC high BP guideline and 2026 ACC/AHA dyslipidemia guideline.[28]

Recommendation-Specific Supportive Text

1. Adverse CKM risk factor levels (overweight/obesity, hypertension, hypertriglyceridemia, diabetes, CKD) during the prepregnancy period are associated with increased risk of APOs.[18,29] Data from observational cohort studies support optimizing these risk factors through lifestyle modification, medication, and/or surgery prepregnancy.[29–31] In a cohort study of 226 958 pregnancies, a 10% prepregnancy weight loss was associated with an approximately 10% lower risk of APOs.[1] Systematic reviews and meta-analyses have found that women who underwent bariatric surgery prepregnancy had lower risk of APOs compared to those without surgery.[2,32] Optimal prepregnancy diet and physical activity are also associated with lower APO risk.[3] In observational studies, a healthier dietary pattern, which may include a Mediterranean-style diet, was associated with lower odds of hypertensive disorders of pregnancy (odds ratio [OR], 0.6; 95% CI, 0.4–0.9).[33,34] A meta-analysis found that greater prepregnancy physical activity is associated with lower risk of GDM (OR, 0.45; 95% CI, 0.28–0.75).[35] The CHAP (Chronic Hypertension and Pregnancy) trial demonstrated that optimizing BP control during pregnancy to target <140/90 mm Hg was associated with lower risk of adverse maternal and fetal outcomes.[36] While medications can optimize CKM risk factors during the prepregnancy period, medications contraindicated during pregnancy should be avoided when safely possible.
2. Women planning pregnancy with diabetes are at greater risk of experiencing APOs compared to women without diabetes or those who develop GDM.[18] The risk is directly related to hyperglycemia pre-and during pregnancy.[5] Observational studies, alongside the American Diabetes Association, support optimizing glycemic levels prepregnancy to a HbA1c of <6.5%.[5,12] While insulin is standard for glucose management during pregnancy and for type 1 diabetes, women with type 2 diabetes taking noninsulin antihyperglycemic agents may be started on insulin prepregnancy.[37] Few RCTs have examined the effect of prepregnancy lifestyle interventions on APOs among women with diabetes.[6,7] In an RCT of 199 overweight/obese adults with a history of GDM, those randomized to 16 weeks of prepregnancy lifestyle intervention until conception had significantly greater weight loss compared to controls (4.8 kg; 95% CI, 3.4–6.0 vs 0.7 kg; 95% CI, −0.9 to 2.3) and a greater proportion lost ≥5% of body weight (50.0% [17/34] versus 13.6% [3/22])[7]; however, there was no significant difference in the incidence of GDM recurrence between intervention (57.9%) and control group (44.0%). During the prepregnancy period, testing should include HbA1c, creatinine, and UACR. Among those intending pregnancy, BP levels according to the 2025 Multisociety Guideline should be targeted. Clinicians should review and replace teratogenic medications for those planning pregnancy with hypertension, CKD, and diabetes (eg, ACEi, ARB).[5,28]

3. An interprofessional care team, which may include an obstetrician, maternal-fetal medicine specialist, endocrinologist, nephrologist, cardiologist, and registered dietician, should evaluate and monitor women planning pregnancy who have CKM syndrome stage ≥2. Team specialists may vary based on individuals' risk profiles.[38] While few RCTs exist, observational data, especially for women with diabetes and CKD, support this approach. A prospective cohort found that prepregnancy care in women with diabetes was associated with improved glycemic control, and lower risk of APOs (OR, 0.2; 95% CI, 0.05–0.89) versus those who did not attend.[8] Meta-analyses and cohort studies have found that women with CKD are at increased risk of APOs.[9–11,39] Thus, women with CKD require careful antenatal monitoring and management with an interprofessional team, including nephrologists and maternal-fetal medicine specialists, to optimize risk factors before pregnancy.[11] Specific issues including optimizing BP control before and during pregnancy, using medications with favorable safety profiles for pregnancy and avoiding therapies that may worsen kidney function as addressed in the 2025 AHA/ACC HBP and associated ACOG guidelines.[11,28] In settings where such teams are unavailable, clinicians should consider referral to relevant subspecialists as appropriate.
4. The AHA and ACOG recommend frequent CVD risk factor screening and lifestyle counseling among postpartum women who experience APOs.[40,41] Screening and counseling for CKM risk factors is recommended within 1 year postpartum.[12] Screening includes: BP, weight/BMI/waist circumference, HbA1c, lipids, serum creatinine, and UACR. Observational evidence suggests that certain CKM risk factors, such as BMI/wait circumference, be screened 6 to 12 months postpartum,[42] whereas others warrant more frequent monitoring (ie, sooner BP assessments to monitor and manage hypertension).[13,43–45] For women without a history of CVD, ACC/AHA's primary prevention guideline recommendations should be followed.[46] For those with established CVD, ACC/AHA's secondary prevention guidelines should be followed.[47,48] There is limited evidence to guide optimal BP treatment thresholds postpartum. For recommendations related to HTN or HDP, please see Section 5.5. of the AHA/ACC 2025 HBP guideline.[28] For recommendations related to HF, please see Section 11.3 of the AHA/ACC 2022 HF guideline.[49] Once medically cleared, all postpartum women are encouraged to participate in ≥150 minutes/week of moderate-intensity activity, consistent with physical activity guidelines for nonpregnant adults.[15,46] Lactation is associated with more favorable cardio-metabolic profiles, including lower fasting glucose, insulin resistance and triglycerides, and BP.[12]
5. The early postpartum period representing the 12 weeks following delivery, sometimes referred to as the fourth trimester, is a critical window to optimize women's CKM health, particularly for women with APOs.[40] The AHA and the ACOG call for optimizing hand-offs from obstetric to primary care,[16,50] and potentially cardiology and other subspecialists (ie, nephrology, endocrinology), is needed for early detection and management of hypertension, weight, glycemic control, stress and mood, and long-term cardiovascular risk reduction. Transitional clinics for postpartum care after APOs (hypertensive disorders of pregnancy, GDM), including integration of maternal care at pediatric visits, patient navigation, BP monitoring, and use of electronic nudges for timely transition to primary care have been studied in local, small trials.[17] Rigorous and large RCTs that examine their effect on CVD outcomes, however, have not been conducted.[51] Additionally, since studies have found that primary care visit utilization is low (in 1 study, 60% of women with APOs attended a primary care visit within 12 months of delivery),[52] and disparities exist with even lower attendance for women with adverse SDOH, strategies to improve implementation and adoption of transitional care programs to primary care are needed and integrate interdisciplinary care models that assess and address SDOH are also needed.[40]

8. MONITORING AND FOLLOW-UP AFTER INITIATION OF THERAPIES

Recommendations for Monitoring and Follow-Up After Initiation of Therapies
Referenced studies that support recommendations are summarized in the evidence table.

COR	LOE	Recommendations
1	B-NR	1. For patients with CKM syndrome who start treatment with GLP-1–based therapy for weight loss, hyporesponsiveness for weight loss should be reassessed periodically (within 3 to 6 mo), and insufficient weight loss (<5%) should be addressed with dose escalations, switching to another agent with similar CKM syndrome benefits, and/or referral to a weight management specialist to consider additional therapeutic approaches to optimize weight loss.[1–4]
1	A	2. In patients with stage 2 to 4 CKM syndrome and T2D who have initiated a cardioprotective glucose-lowering agent (SGLT2i or GLP-1–based therapy), glycemic status should be assessed by A1C, blood glucose monitoring, and/or continuous glucose monitoring metrics every 3 to 6 mo and more frequently in individuals not meeting glycemic goals to guide further glycemic management.[5–7]

Recommendations for Monitoring and Follow-Up After Initiation of Therapies (Continued)		
COR	**LOE**	**Recommendations**
2a	**B-R**	3. For patients with CKM stage 2 to 4 and albuminuria (UACR ≥30 mg/g) who initiate kidney-protective therapies, it is reasonable to remeasure albuminuria after 3 to 6 mo to assess residual CKM risk and indications for additional kidney-protective therapies to prevent CVD events and loss of kidney function.[8–11]
2a	**B-R**	4. For patients with CKM stage 2 to 4 who initiate a drug that acts on the RAAS system (RASi or MRA), it is reasonable to recalculate eGFR and measure potassium after 2 to 4 wk to assess tolerance and safety of the medication regimen.[12–15]

Synopsis

Sustained tolerability, adherence, and access to therapy are required for effective pharmacologic treatment of CKM syndrome. Drugs that treat CKM syndrome have potential adverse effects that can be ascertained by history, physical examination, and/or laboratory testing, and mitigated through adjustments to the treatment regimen. For example, RASi and nsMRA can cause hypotension, changes in kidney function, and hyperkalemia that can be mitigated with dosing changes, concomitant lifestyle or pharmacologic interventions, or discontinuation of therapy. Regular assessment of adverse effects and other treatment barriers is important to facilitate safe, sustained intervention and promote adherence to complementary lifestyle and pharmacologic therapies. In addition, regular measurement of response to therapy allows dose titration, selection of alternative treatments, identification of residual CKM risk, and timely addition of other interventions to optimize CKM treatment (ie, combination therapies), as needed. Monitoring for both adverse effects and response to therapy is therefore critical to achieve optimal individualized CKM treatment regimens. For monitoring medical therapy for hypertension and blood cholesterol, please refer to the AHA/ACC guidelines on high BP[16] and dyslipidemia.[17]

Recommendation-Specific Supportive Text

1. An effective response to obesity pharmacotherapy has historically been described as at least 5% of body weight loss after 3 months of treatment.[18] Newer GLP-1–based therapies demonstrate continued weight loss through 52 weeks, and often up to 68 to 72 weeks, of treatment.[3,19] Therefore, the therapeutic window to assess benefit from these medications may be extended beyond 3 months and up to 6 months. Optimal weight loss with these agents requires consistent therapy and appropriate dose escalation, and discontinuation results in weight regain and worsening of CKM risk profiles.[2] Providers should expectantly counsel patients regarding the plateau phase of obesity pharmacotherapy and the need for continued lifestyle efforts. Patients should understand that GLP-1–based therapies are long-term weight management strategies requiring ongoing adherence. Approximately 10% to 15% of patients in clinical trials demonstrate inadequate weight reduction with GLP-1–based therapy. When expected weight loss is not seen despite dose escalation, switching to an alternative GLP-1–based agent that provides similar protection for other CKM conditions is recommended, as this has been shown to improve weight reduction and glycemic control.[1,20] If the desired weight reduction is still not achieved, metabolic and bariatric surgery can be considered. Providers should counsel patients on potential side effects of GLP-1–based therapies (Table 15) and employ strategies to mitigate common gastrointestinal side effects (Table 19).

Table 19. Management of Gastrointestinal Adverse Effects of GLP-1–Based Therapies

Lifestyle changes	Eating habits: Eat smaller meals more frequently, eat slowly, and stop when full; avoid high-fat and spicy foods, and limit or avoid alcohol. Hydration: Drink plenty of water and sugar-free beverages throughout the day. Activity: Avoid vigorous activity after meals, and opt for light activities such as walking. Sleep: Wait ≥2 to 3 h after eating a meal before lying down. Relaxation: Techniques such as guided imagery can help to control nausea.
Medication supplementation	Consider temporary use of antiemetic and/or prokinetic medications, or probiotic and/or antidiarrheal supplements.
Dose escalation	Slowing dose escalation and waiting longer to escalate can help reduce gastrointestinal adverse effects* (usually occurring with dose changes). Extend current phase for 2 to 4 more wk before moving forward to next dose. Go back to prior dose for a few days and then increase dose gradually.
Switching to alternative therapies	Consider switching to a different GLP-1–based therapy. For example, dulaglutide may be better tolerated than semaglutide or tirzepatide, though the efficacy for weight loss may be less.

*Many gastrointestinal adverse effects will improve over time with consistent dosing, but patient tolerance is highly variable.
GLP-1 indicates glucagon-like peptide-1; GLP-1 RA, GLP-1 receptor agonist.

2. Glycemic status is best assessed by HbA1c measurement, finger-stick blood glucose measurement, or continuous glucose monitoring every 3 to 6 months or more frequently (eg, monthly) with treatment changes, among individuals not meeting glycemic targets or for those with frequent or severe hypoglycemia or hyperglycemia (Table 20).[5–7,21–23] The largest HbA1c reductions are achieved by treatment plans that include GLP-1–based treatments, particularly semaglutide and tirzepatide, in addition to insulin.[24,25] In adults with T2D with symptoms of hyperglycemia, or when A1C or blood glucose levels are very high (ie, A1C >10% or blood glucose ≥300 mg/dL), referral to an endocrinologist is recommended for further glycemic management as per ADA guidelines.[26] For individuals with T2D and CVD/high risk for CVD with mild to moderate residual hyperglycemia (eg, A1C <8.5%-9.0%), metformin can be added to cardioprotective therapies (SGLT2i or GLP-1–based therapy).[27,28] For patients with T2D with CVD/high risk for CVD with significant residual hyperglycemia (A1C ≥8.5%-9.0%), it is recommended to add semaglutide or tirzepatide to achieve glycemic goals if patients are already on SGLT2i therapy.[26,29,30] Insulin dosing should be reassessed upon addition or dose escalation of GLP-1–based therapy given the risk of hypoglycemia with insulin therapy. Concurrent use of dipeptidyl peptidase 4 inhibitors with GLP-1–based therapy is not recommended due to lack of additional glucose-lowering benefit.[26,31]
3. Albuminuria (persistent UACR ≥30 mg/g) is a defining feature of CKD and a strong modifiable risk factor for CVD and CKD progression.[32] Multiple RCTs of CKM therapies included albuminuria as an eligibility criterion, with absolute risk reductions for cardiovascular and kidney outcomes commonly greater for those with more baseline albuminuria.[12,15,33–38] Therefore, albuminuria is an indication for drugs that target CKD and CKM syndrome, including RASi, SGLT2i, GLP-1 RA, and nsMRA (Sections 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3," 6.2.3, "CKM Syndrome Stage 4 With CKD and ASCVD," and 6.3.3, "CKM Syndrome Stage 4 With CKD and HF"), each of which reduces urine albumin excretion.[8] Residual albuminuria on CKM therapy remains a strong risk factor for ASCVD, HF, and CKD progression.[9–11] Therefore, reassessing albuminuria after initiation of drugs that target CKD and CKM syndrome allows assessment of response to therapy, identification of residual CKM risk, and timely addition of other pharmacologic interventions to optimize CKM treatment.[39] For example, for people with T2D, residual albuminuria despite treatment with an RASi and SGLT2i is an indication to add a GLP-1 RA or nsMRA (Section 5.5.4, "Management of CKD in CKM Syndrome Stage 2 to 3"). The effects of RASi, SGLT2i, and nsMRA on albuminuria are evident within weeks of initiation,[40–42] so albuminuria reassessment 3 to 6 months after initiation or maximum planned dose of these agents is appropriate. For GLP-1 RA,[38] the full effects on albuminuria may not be evident until closer to 6 months, perhaps partially because additional time is needed for dose titration.
4. Drugs that affect the renin-angiotensin-aldosterone system, including RASi, MRA, and SGLT2i, change intrarenal hemodynamics and alter renal electrolyte handling, potentially causing changes in serum creatinine and electrolyte concentrations.[43] RASi and MRA-related increases in serum creatinine and serum potassium occur quickly and can be assessed 2 to 4 weeks after drug initiation. Decreases in eGFR up to 30% after initiation of a RASi or MRA are expected and acceptable.[44] When eGFR decreases >30% after initiation of a RASi or MRA, other causes of these abnormalities should be evaluated (eg, volume depletion, NSAID use, interaction with other drugs that affect circulating volume or intrarenal hemodynamics), and medication adjustments should be considered (eg, dose reduction or discontinuation of the drug or changes to concomitant medications or volume management), with subsequent additional monitoring. Similarly, mild increases in serum potassium (≤5.5 mEq/L) may be tolerated, while larger increases in serum potassium (>5.5 mEq/L) may require medications to mitigate hyperkalemia (eg, thiazide-type or loop diuretics, dietary potassium binders), dietary changes, or dose reduction or discontinuation of agents promoting

Table 20. Recommendations for Achieving Glycemic Goals in Patients With T2D With CVD or High Risk for CVD After Initiation of Cardioprotective Therapy

HbA1c 7% to 8.5% (mild-moderate hyperglycemia)	Metformin can be added to SGLT2i or GLP-1–based therapy to achieve glycemic goals.
HbA1c >8.5% (severe hyperglycemia)	Add semaglutide or tirzepatide if patients are already on SGLT2i therapy. If symptoms of hyperglycemia are present or when HbA1c or blood glucose levels are very high (ie, HbA1c >10.0% or blood glucose ≥300 mg/dL), referral to an endocrinologist is recommended for further management of hyperglycemia as per ADA guidelines.

CVD indicates cardiovascular disease; GLP, glucagon-like peptide-1; HbA1c, hemoglobin A1c; SGLT2i, sodium–glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes.

hyperkalemia. Low eGFR and use of concomitant medications that affect glomerular pressure (eg, diuretics, SGLT2i, NSAIDs) are risk factors for RASi- and MRA-induced increases in serum creatinine and potassium. SGLT2i-induced decreases in eGFR up to 30% are not associated with adverse outcomes.[13,14] Larger declines in eGFR are more common in those with low eGFR, HF, prior AKI, and diuretic use,[13,14,45] for whom eGFR assessment after SGLT2i initiation may be considered. SGLT2i reduce the incidence of hyperkalemia during RASi treatment.[46]

9. EVIDENCE GAPS AND FUTURE DIRECTIONS

The body of evidence related to risk assessments and clinical management for individuals with CKM syndrome is rapidly evolving. However, as detailed below and in Table 21, there are several key evidence gaps in CKM syndrome care that should be the focus of future investigation.

The PREVENT calculator represents a significant advance in quantitative risk assessment, incorporating CKM syndrome components, adding the outcomes of HF and total CVD, and quantifying risk over 10- and 30-year time horizons, with improved accuracy relative to prior risk calculators. However, further refinement of risk prediction is needed, and the impact of systematically considering measures of subclinical CVD, genetic predisposition, and novel risk markers; incorporating multilevel SDOH; and utilizing artificial intelligence–based methodology to enhance risk estimation, should be quantified.

While 30-year risk estimates may provide a more useful time horizon for describing risk among young adults, the optimal use of these estimates for informing preventive care is presently unclear. Additionally, strategies for optimizing risk communication with personalized decision aids and tools require further development. There

Table 21. Future Directions in CKM Syndrome: Research Summary Table

Domain	Evidence Gaps	Key Research Questions	Clinical/Policy Relevance
Risk Prediction and Stratification	Refinement needed in PREVENT calculator; unclear use of 30-y risk estimates; limited risk communication tools.	How do biomarkers, genetics, and artificial intelligence improve CKM risk prediction? What is the role of 30-y risk estimates?	Improves prediction accuracy, supports tailored prevention, informs patient engagement strategies.
Early Identification of CKD and MASLD	Delayed recognition of CKD/MASLD; unclear role of systematic assessments; underutilization of fibrosis screening.	Can systematic CKD/MASLD screening improve detection and outcomes?	Promotes earlier treatment, reduces progression, informs testing policy and population health planning.
HF Prevention	Rising HF prevalence; undefined multidisciplinary care; unclear prognostic echocardiographic markers; limited preventive therapy data.	Which imaging abnormalities best predict HF risk in those with elevated biomarkers? What are essential components of HF-preventive care?	Enables early HF intervention, reduces morbidity/mortality, defines preventive care frameworks.
Interdisciplinary and Coordinated Care	Fragmented subspecialty care; undefined team roles; untested CKM coordinator impact; impact of addressing SDOH unclear.	What outcomes result from interdisciplinary CKM teams? How can CKM coordinators improve patient navigation/education and CKM syndrome care?	Enhances care coordination, reduces fragmentation, supports reimbursement for team-based care.
Weight Management Strategies	Unclear design of integrated programs; reimbursement barriers; high GLP-1 discontinuation and weight regain.	What are the most effective integrated weight programs? What supports long-term GLP-1 weight loss maintenance?	Improves long-term outcomes, informs reimbursement policy, addresses sustainability of weight loss.
Therapeutic Combinations in T2D and CKD	Limited interventional data on additive benefits; underexplored polypharmacy effects; lacking cost-effectiveness studies.	What are outcomes of CKM-targeted therapy combinations? How does polypharmacy affect adherence/outcomes?	Optimizes therapy strategies, improves adherence, informs cost-effectiveness and coverage policy.
CKM Syndrome and HF Subtypes	HFpEF/HFmrEF obesity treatment benefits established; HFrEF obesity management unclear; some uncertainty with MRAs.	How should obesity be managed in HFrEF? Can steroidal MRAs replicate finerenone benefits? Does finerenone improve CKD outcomes in HF?	Guides safe obesity management in HFrEF, informs optimal MRA use, improves HF+CKD outcomes.
Advanced CKD and Dialysis	Exclusion from major trials; lack of evidence for therapies in advanced CKD/dialysis.	Which therapies are safe/effective in advanced CKD and dialysis? Does continuation of therapies at low eGFRs sustain benefit?	Addresses high-risk population needs, informs trial design and therapy use in dialysis patients.
Education, Training, and Infrastructure	Training models remain siloed; insufficient structural supports (automation, telemedicine, reimbursement).	How should curricula evolve for CKM syndrome? Which infrastructure models best support integrated care?	Prepares workforce for integrated CKM care, supports investment in infrastructure and policy reform.
Cross-Cutting Themes	Equity gaps; limited implementation science; underemphasis on patient-centered outcomes; global relevance underdeveloped.	How can equity, implementation science, patient-centered outcomes, and global health be embedded across CKM care?	Reduces disparities, scales interventions globally, improves patient-centered outcomes, informs health equity policy.

CKD indicates chronic kidney disease; CKM, cardiovascular-kidney-metabolic; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MASLD, metabolic dysfunction–associated steatotic liver disease; MRA, mineralocorticoid receptor antagonist; PREVENT, Predicting Risk of Cardiovascular Disease Events; SDOH, social determinants of health; and T2D, type 2 diabetes.

is also a need to clarify strategies for incorporating CKM risk enhancers, which are associated with a greater risk of CKM progression and of adverse cardiac or kidney events, into clinical decision-making. Among the CKM risk enhancers, understanding how critical life periods such as pregnancy and menopause impact trajectories of CKM health is an investigative subject of clinical and public health importance.

A common challenge for individuals with CKM syndrome is the delayed recognition of risk factors and conditions that confer substantial risk for adverse outcomes. This is a particular challenge for CKD, where many individuals are unaware of their diagnosis, and MASLD, which is now the leading cause of cryptogenic cirrhosis and liver transplantation in the United States. Earlier identification of these conditions and timely initiation of proven therapies are associated with improved outcomes. Whether systematic assessments for CKD with both eGFR and UACR, and testing for evidence of liver fibrosis using the FIB-4 index, can improve population-wide recognition and early therapy for CKD and MASLD, and whether the adoption of such approaches can improve outcomes related to these conditions, is a key clinical and public health question.

With the rising prevalence of HF and worsening trends in HF mortality, the detection of those with early cardiac dysfunction prior to clinical HF is desirable for targeting preventive efforts. In clinical trials, cardiac biomarker assessments, followed by coordinated care, are associated with lower HF risk. However, the essential elements of multidisciplinary preventive care for targeting pre-HF and reducing HF risk are not well defined. Echocardiographic imaging refines assessments of absolute HF risk in those with elevated cardiac biomarkers, but the echocardiographic abnormalities that are most important for risk prognostication remain unknown. Generally, there is a need for more dedicated evaluations of therapies for HF prevention, targeting CKM risk factors and pathologies that are known to drive a large proportion of HF risk.

Because individuals with CKM syndrome often receive care from multiple subspecialists due to multisystem pathology, strategies to reduce care fragmentation are of critical importance. The facilitation of interdisciplinary care is desired, but the optimal roles and responsibilities of members of the interdisciplinary team should be further clarified. There is a particular need for evidence regarding the impact and optimal utilization of CKM coordination point persons for supporting patient education and navigation and enhancing cross-disciplinary collaborative care. It is also important to characterize the impact of addressing adverse SDOH, when identified, on CKM care and clinical outcomes. Effective strategies for implementing interdisciplinary care models across settings with differing clinical resources and needs should be further defined.

Weight management is a fundamental goal within CKM syndrome care to reduce the likelihood of CKM syndrome progression and promote CKM regression. Integrated weight management teams are recommended for higher-risk patients to provide a patient-centered approach to navigating the expanding selection of tools for weight management. The ideal design and clinical impact of such programs should be further elucidated. Limited reimbursement for chronic behavioral support is a key impediment to supporting lifestyle modification, and the cost/value of investing in lifestyle modification programs is a major policy question. For those individuals using GLP-1–based therapy, medication discontinuation is common and associated with weight recidivism and the reversal of multiple beneficial changes in CKM risk profiles. It is important to better define effective strategies for long-term weight loss maintenance for individuals taking GLP-1–based therapy.

T2D and CKD are major risk factors for adverse cardiovascular and kidney events in CKM syndrome. Fortunately, there is a growing array of therapies proven to improve outcomes for individuals with these conditions. However, there are presently limited interventional data regarding the additive benefits and optimal approaches to using these therapies in combination. Related questions remain regarding patient preferences and the impact of polypharmacy on adherence and satisfaction among patients with CKM syndrome. Additionally, given the typical need for chronic therapy for T2D and CKD, the performance of cost-effectiveness assessments of such combination therapy would also be helpful for informing policy.

Some unanswered questions remain for CKM syndrome patients with HF. The benefits of addressing obesity in patients with HFmrEF/HFpEF are now clear, with randomized trials of GLP-1–based therapy demonstrating improved functional capacity and quality of life, and reduced risk for worsening HF events. In contrast, the approach to addressing obesity in HFrEF is unclear, with some studies suggesting harm associated with GLP-1–based therapy. Further clarity is needed regarding the management of excess weight in HFrEF, which is often an impediment to the receipt of advanced HF therapies. Additionally, while finerenone has demonstrated benefit in diabetic kidney disease from the FIDELIO and FIGARO trials, as well as in HFmrEF/HFpEF from the FINEARTS HF trial, we have limited data regarding its efficacy in those with both HF and CKD. Further interventional data will help inform its utility in this common and clinically important subpopulation. It is also presently unclear whether similar CKM benefits to those seen with nonsteroidal MRAs (eg, finerenone) can be obtained with the use of steroidal MRAs (eg, eplerenone, spironolactone).

There is a particular lack of interventional data for patients with advanced CKD and dialysis. Randomized trials have largely excluded such individuals, so we lack robust data to inform the management of this clinical subgroup. Clinical trials of kidney-protective therapies have typically continued to include individuals with CKD after

their eGFR falls below the treatment initiation threshold for these agents, with evidence of ongoing cardiovascular and kidney benefit and acceptable safety. It is therefore time to perform dedicated trials among patients with advanced CKD, to clarify treatment strategies for this high-risk population, for whom CVD is the leading cause of death.

Finally, the CKM syndrome care model reflects a paradigm shift to less-siloed, more integrated clinical care for those with multiple interconnected clinical conditions. It will be important to reconsider how education and training need to adapt to reflect this shift in clinical approach. The structural factors needed to support such integrated care, including automated technology, personnel, billing and reimbursement policies, telemedicine, shared physical and virtual clinical space, and platforms to optimize communication, should be elucidated and supported to implement optimal CKM syndrome care across a variety of clinical and geographic settings.

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*Former Task Force member; current member during the writing effort.

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Appendix 1. Writing Committee Relationships With Industry and Other Entities 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Chiadi E. Ndumele	Johns Hopkins University School of Medicine–Associate Professor of Medicine and Epidemiology, Director of Obesity and Cardiometabolic Research	None	None	None	NOT RELEVANT • AHA • NIH	None	None
Fatima Rodriguez, Chair	Stanford University School of Medicine–Associate Professor, Cardiovascular Medicine, Section Chief, Preventive Cardiology	NOT RELEVANT • Amgen • Arrowhead Pharmaceuticals* • Cleerly • Edwards Lifesciences • Esperion • Health Pals* • Heartflow* • Inclusive Health • Kento Health RELEVANT • Movano Health • Novartis*	None	NOT RELEVANT • Health Pals	NOT RELEVANT • Novo Nordisk (End Point Review Committee)*	None	None
Mandeep Bajaj	Baylor College of Medicine–Professor of Medicine and Molecular and Cellular Biology	None	None	None	None	NOT RELEVANT • ADA	None
Sripal Bangalore	NYU Langone Medical Center–Professor of Medicine	NOT RELEVANT • Abbott Vascular* • Biotronik • Boston Scientific RELEVANT • Inari • Truvic	None	None	NOT RELEVANT • NHLBI*	None	None
Biykem Bozkurt	Baylor College–Professor of Medicine, Senior Dean of Faculty	NOT RELEVANT • Abbott • Amgen • Cytokinetics • Hanger Clinic • Idorsia • Regeneron* • Respicardia/Zoll • Roche • Sanofi* RELEVANT • Abiomed/Johnson & Johnson • AstraZeneca • Bayer* • Boehringer Ingelheim* • Daiichi Sankyo* • Eli Lilly • Janssen/Johnson & Johnson* • Medtronic • Merck* • scPharmaceuticals • Vifor Pharma/ CSL Vifor	None	None	NOT RELEVANT • Abbott (End Point Review Committee)* • Cardurion (DSMB) • Cytokinetics (Steering Committee) • LivaNova (DSMB) • Novo Nordisk (DSMB) • Regeneron (DSMB) • Salubris Pharmaceuticals (DSMB)	NOT RELEVANT • *JACC: Heart Failure* (Editor-in-Chief)*	None

(*Continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Khadijah Breathett	Indiana University–Associate Professor of Medicine	None	None	None	NOT RELEVANT • CTSI* • HRSA* • NHLBI*	NOT RELEVANT • *American Heart Journal*† • Black Health Matters† • *Circulation Cardiovascular Quality and Outcomes**	None
Shoa L. Clarke	Stanford University School of Medicine–Assistant Professor	None	None	NOT RELEVANT • Apple	NOT RELEVANT • Glycomine (DSMB)	NOT RELEVANT • NIH*	None
Ian H. de Boer	University of Washington–Professor of Medicine	NOT RELEVANT • Mitre Corporation RELEVANT • Boehringer Ingelheim • Eli Lilly • Lexicon* • Novo Nordisk	None	None	NOT RELEVANT • Breakthrough T1D (formerly JDRF)* • Novo Nordisk*	NOT RELEVANT • Dexcom*	None
Dave L. Dixon	Virginia Commonwealth University–Professor and Chair	NOT RELEVANT • APA* • Innovation Horizons	None	None	None	NOT RELEVANT • Pharmacy Times CE	None
David H. Ellison	Oregon Health & Science University–Professor	None	None	None	NOT RELEVANT • NIDDK*	NOT RELEVANT • Elsevier Publishing* • Fondation Leducq*	None
Lorraine S. Evangelista	University of Nevada, Las Vegas–Associate Dean for Research	None	None	None	None	None	None
Sean P. Heffron	NYU Langone Medical Center–Assistant Professor	None	None	None	None	NOT RELEVANT • NIH* • Pfizer	None
Dhruv S. Kazi	Beth Israel Deaconess Medical Center–Associate Director of the Smith Center for Outcomes Research, Director, Cardiac Critical Care	NOT RELEVANT • PCORI	None	None	NOT RELEVANT • AHRQ* • Institute for Clinical and Economic Review* • NIH*	NOT RELEVANT • Boston Scientific*	None
Sadiya S. Khan	Northwestern University Feinberg School of Medicine–Associate Professor of Medicine	None	None	None	NOT RELEVANT • NIH*	NOT RELEVANT • AHA*	None
Ambar Kulshreshtha	Emory University–Associate Professor	NOT RELEVANT • Lucent Diagnostics	None	None	NOT RELEVANT • NIH*	NOT RELEVANT • Cleer*	NOT RELEVANT • Defendant, Prostate Cancer, 2023

(*Continued*)

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ildiko Lingvay	University of Texas Southwestern Medical Center–Professor of Medicine, Internal Medicine/Endocrinology, Medical Director, Office of Clinical Trials, Executive Director, Diabetes and Obesity Research Program	NOT RELEVANT • AbbVie* • Altimmune • Alveus • Amgen • Arrowhead Pharmaceuticals • Betagenon • BIOIO • Biomea Fusion* • Boehringer Ingelheim* • Carmot/Roche* • Juvena • Keros Therapeutics • Mediflix • Metsera* • Neurocrine* • Regeneron* • Sanofi • Shionogi • Source Bio • Structure Therapeutics*/Terns Pharmaceuticals • Zealand Pharma RELEVANT • Antag Therapeutics • AstraZeneca* • Bayer • Boehringer Ingelheim* • Eli Lilly* • Gan & Lee • Johnson & Johnson • Merck • Novo Nordisk* • Pfizer*	None	None	RELEVANT • Boehringer Ingelheim* • Dexcom Inc. • Novo Nordisk*	NOT RELEVANT • *Diabetes Care* • *Diabetes and Vascular Disease Research* • NIH* • Sanofi • The Comm Group • *Journal of Diabetes and its Complications* • Translational Medical Academy • WebMD Health • Zealand Pharma RELEVANT • Boehringer Ingelheim* • Eli Lilly* • Johnson & Johnson • Novo Nordisk*	None
Cecilia C. Low Wang	University of Colorado Denver Anschutz Medical Campus–Professor of Medicine	None	None	None	RELEVANT • Dexcom*	NOT RELEVANT • AACE • ACD (Board of Directors) • ACDES • ADA* • CDEI (Board of Directors) • Continuing Education Company* • FDA • IMNE* • Massachusetts General Hospital (DSMB) • Medical Education Resources • Sanofi	None
Claudia A. Mercado	Retired	None	None	None	None	None	None
John Magaña Morton	Yale School of Medicine–Professor and Vice Chair, Quality Division Chief, Bariatric and Minimally Invasive Surgery	RELEVANT • Eli Lilly* • Novo Nordisk* • Olympus* • Regeneron • Standard Bariatrics/Teleflex*	None	None	None	None	None

(*Continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Debabrata Mukherjee	Texas Tech University–Chairman, Department of Internal Medicine	None	None	None	None	None	None
Ian J. Neeland	Case Western Reserve University School of Medicine–Director, UH Center for Cardiovascular Prevention; University Hospitals Cleveland–Staff Physician	NOT RELEVANT • Nestle Healthcare Nutrition RELEVANT • Bayer* • Boehringer Ingelheim* • Eli Lilly* • Novo Nordisk*	REL-EVANT • Lilly USA*	None	RELEVANT • Dexcom • Novartis*	NOT RELEVANT • Amgen* • NIH*	None
Neha Pagidipati	Duke Clinical Research Institute–Associate Professor	NOT RELEVANT • Amgen* • Corcept Therapeutics* • Corsera* • CRISPR Therapeutics • Eggland's Best • Esperion* • Metsera • NewAmsterdam RELEVANT • AstraZeneca* • Bayer* • Boehringer Ingelheim* • Eli Lilly* • Merck • Novartis* • Novo Nordisk*	None	NOT REL-EVANT • Miga Health	NOT RELEVANT • Alnylam* • Amgen* • Janssen Pharmaceuticals (DSMB)† • Medtronic‡ • Metsara* • NHLBI* • Novartis (DSMB)* RELEVANT • Bayer* • Boehringer Ingelheim* • Eli Lilly* • Merck* • Novartis*	NOT RELEVANT • Amgen*	None
Tiffany M. Powell-Wiley	National Heart Lung and Blood Institute–Stadtman Investigator	None	None	None	NOT RELEVANT • NIH*	NOT RELEVANT • *Journal of the American Heart Association**	None
Janani Rangaswami	George Washington University School of Medicine and Health Sciences–Professor of Medicine	NOT RELEVANT • Edwards Lifesciences • Procyrion† RELEVANT • Bayer • Boehringer Ingelheim* • Lilly USA*	None	None	NOT RELEVANT • Bioporto (End Point Review Committee)†	None	None
Goutham Rao	Case Western Reserve University School of Medicine–Professor and Chair, Department of Family Medicine and Community Health	None	None	None	None	None	None

(*Continued*)

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nosheen Reza	Perelman School of Medicine at the University of Pennsylvania–Assistant Professor of Medicine	NOT RELEVANT • American Regent • Cytokinetics† • Idorsia* • Roche RELEVANT • AstraZeneca • Bristol Myers Squibb* • Novo Nordisk	NOT RELEVANT • Zoll	None	NOT RELEVANT • Alleviant Medical (CEC) • NIH* RELEVANT • AstraZeneca (Executive Committee)† • Bristol Myers Squibb (Co-PI)*	NOT RELEVANT • Bristol Myers Squibb • *Current Cardiovascular Risk Reports* • Cytokinetics* • *Journal of Cardiac Failure* • Med Learning Group* • Medscape • MJH Life Sciences • Pfizer • Scripps Research Institute • DSMB, Otsuka	None
Anum Saeed	University of Pittsburgh Medical Center–Assistant Professor	None	None	None	NOT RELEVANT • AHA* • NIH* RELEVANT • Novartis	None	None
Wendy St. Peter	University of Minnesota–Professor, Department of Pharmaceutical Care & Health Systems	RELEVANT • Fresenius*	None	None	None	NOT RELEVANT • Kidney Health through Optimal Medication Management (Director)	None
J. Bradley Starks	Retired	None	None	None	None	NOT RELEVANT • AHA	None
Madeleine Sterling	Weill Cornell Medical College–Assistant Professor of Medicine	None	None	None	NOT RELEVANT • AHA* • Doris Duke Charitable Foundation* • NIH*	None	None
Amy W. Talbot§	AHA/ACC Science and Health Advisor, Guidelines	None	None	None	None	None	None
Andrew H. Tran	Nationwide Children's Hospital–Physician and Assistant Professor, The Heart Center	None	None	None	NOT RELEVANT • Inozyme Pharmaceuticals* • PEDSnet Scholars Program	None	None
Katherine R. Tuttle	Providence Inland Northwest Health–Executive Director for Research; University of Washington–Professor of Medicine	NOT RELEVANT • ProKidney RELEVANT • Bayer • Boehringer Ingelheim* • Eli Lilly • Novo Nordisk* • Pfizer*	None	None	NOT RELEVANT • AstraZeneca (DSMB) • Eli Lilly*	NOT RELEVANT • ACCP Research Institute* • Benaroya Research Institute • CDC* • Doris Duke Charitable Foundation* • Breakthrough T1D (formerly JDRF)* • NCAT* • NHLBI* • NIAID* • NIDDK* • NIH* • Travere Therapeutics*	None

(*Continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Lisa B. VanWagner	University of Texas Southwestern Medical Center–Associate Professor and Director of Clinical Research, Division of Digestive and Liver Diseases	NOT RELEVANT • Alpha Sights • Gerson Lehrman Group • Slingshot Insights RELEVANT • Madrigal Pharmaceuticals • Novo Nordisk	None	None	NOT RELEVANT • NHLBI* • NIAAA* • NIDDK*	NOT RELEVANT • AASLD† • AHA† • AST • Expert Institute† • International Liver Transplant Society† • *Liver Transplantation* • Madrigal Pharmaceuticals‡ • NIDDK* • WL Gore & Associates	NOT RELEVANT • Defendant, drug-induced liver injury, 2024 • Plaintiff, cerebral edema from hepatic encephalopathy and AKI from Toradol, 2024 • Plaintiff, liver decompensation after cholecystectomy in cirrhosis, 2024 • Plaintiff, alcoholic hepatitis, 2024
Amanda R. Vest	Cleveland Clinic–Section Head, Heart Failure and Transplant Cardiology; Tufts Medical Center–Physician	None	None	None	NOT RELEVANT • NIH*	NOT RELEVANT • ACC† • AHA† • BrioHealth† • *Circulation: Heart Failure*† • Cleveland Clinic Heart Failure CME program • HFSA† • *JACC: Heart Failure*†	None
Salim S. Virani	Baylor College of Medicine–Professor of Medicine; Texas Heart Institute–Professional Staff; US Department of Veterans Affairs–Staff Cardiologist; Aga Khan University (Pakistan)–Vice Provost, Research, Professor of Medicine; Aga Khan University (Kenya) – Professor of Population Health	None	None	None	NOT RELEVANT • NIH* • NIHR* • Tahir and Jooma Family* • US Department of Veterans Affairs*	NOT RELEVANT • *Current Atherosclerosis Reports* • *Current Cardiology Reports* • *Journal of Clinical Lipidology*	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

‡Clinical trial enroller.

§Amy Talbot is an AHA/ACC joint staff member and acted as Science and Health Advisor for the "2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome." No relevant relationships to report. Nonvoting author on recommendations and not included/counted in the RWI balance for this writing committee.

AACE indicates American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; ACC, American College of Cardiology; ACCP, American College of Clinical Pharmacy; ACD, American College of Diabetology; ADA, American Diabetes Association; AHA, American Heart Association; AHRQ, Agency for Healthcare Quality and Research; AKI, acute kidney injury; ASN, American Society of Nephrology; AST, American Society of Transplantation; CDC, Centers for Disease Control and Prevention; CDEI, Clinical Diabetes and Endocrine Institute; CEC, clinical endpoint committee; CME, continuing medical education; CTSI, Clinical and Translational Sciences Institute; DSMB, data and safety monitoring board; FDA, US Food and Drug Administration; HFSA, Heart Failure Society of America; HRSA, Health Resources and Services Administration; IMNE, Institute of Medical and Nursing Education; *JACC*, *Journal of the American College of Cardiology*; NCAT, National Center for Advancing Translational Sciences; NHLBI, National Heart, Lung, and Blood Institute; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIAID, National Institute of Allergy and Infectious Diseases; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; NIHR, National Institute for Health and Care Research; NYU, New York University; PCORI, Patient-Centered Outcomes Research Institute; PI, principal investigator; and UH, University Hospitals.

Appendix 2. Reviewer Relationships With Industry and Other Entities 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation and Management of Cardiovascular-Kidney-Metabolic Syndrome

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nicole Bhave	Medical School, University of Michigan–Clinical Professor of Medicine	• American College of Cardiology Foundation • Rednvia	None	• Doximity	None	None	None
Amit Khera	UT Southwestern Medical Center–Professor of Medicine	None	None	None	None	• *American Journal of Preventive Cardiology*† • NIH*	None
Kevin M. Alexander	Stanford University School of Medicine–Assistant Professor	• Alexion Pharmaceuticals, Inc. • Alnylam Pharmaceuticals • Arbor Biotechnologies* • Bayer • Novo Nordisk* • Pfizer*	None	None	NIH*	• AHA* • BridgeBio* • Janssen Pharmaceuticals†	None
Alison L. Bailey	Centennial Heart at Parkridge–Cardiologist	• Bristol-Myers Squibb*	None	None	None	• American Society of Preventative Cardiology†	None
Marc P. Bonaca	University of Colorado–Professor of Medicine	• Regeneron Pharmaceuticals*	None	None	None	• Abbott Vascular* • AHA† • Amgen* • AstraZeneca* • Bayer* • Cleerly* • CPC Clinical Research and Community Health • Faraday* • Janssen Pharmaceuticals* • Merck* • Novartis* • Novo Nordisk* • Silence Pharmaceuticals* • Teladoc	None
Tara I. Chang	Stanford University School of Medicine–Division Chief, Professor	• Bayer • George Clinical Institute* • Nucleus Global • ProKidney	None	None	None	• National Kidney Foundation* • NIH • Novo Nordisk AS*	None
Maria Rosa Constanzo	Midwest Cardiovascular Institute–Medical Director Heart Failure Program	• Abbott Laboratories • Boehringer Ingelheim	None	None	None	• Abbott Laboratories • Nuwellis	None
Cyrille K. Cornelio	University of South Florida–Assistant Professor and Clinical Pharmacy Specialist	None	None	None	None	• Florida Pharmacy Association	None
Colette DeJong	Stanford University School of Medicine–Clinical Instructor (Affiliated); VA Palo Alto Health Care System–Cardiologist	None	None	• iRhythm Technologies, Inc.*	None	• Center for AIDS Prevention Studies, UCSF* • iRhythm Technologies, Inc. • Merck • UCSF	None
Adam DeVore	Duke Clinical Research Institute–Associate Professor	• Abiomed • Natera • Novo Nordisk* • Zoll*	None	None	None	• American Regent* • Biofourmis* • Bodyport* • NHLBI* • StoryHealth* • Ventricle Health*	None
Patrick O. Gee Sr.	University of South Florida–Associate Professor, Department of Medicine	• Bayer • P.Gee Consulting, LLC • Walgreens	None	None	None	• iAdvocate, Inc.	None

(*Continued*)

Appendix 2. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Beverly B. Green	Kaiser Foundation Research Institute–Senior Investigator and Family Physician; Kaiser Permanente Bernard J. Tyson School of Medicine–Professor	None	None	None	None	• NCI* • NHLBI* • NYU Langone Medical Center • Patient Centered Outcomes Research Institute*	None
Jennifer B. Green	Duke University–Professor of Medicine; Durham VA Medical Center–Endocrinologist	• Anji Pharmaceuticals • AstraZeneca • Bayer Healthcare • Boehringer Ingelheim* • Corcept Therapeutics • Eli Lilly and Company* • Merck* • Mineralys • Novo Nordisk* • Valo Health • Vertex Pharmaceuticals	None	None	None	• Bluedrop* • Boehringer Ingelheim* • F. Hoffmann-La Roche • Merck*	
Scott Kahan	National Center for Weight and Wellness, George Washington University	• Currax Pharmaceuticals LLC • Eli Lilly and Company	None	None	None	None	• Plaintiff, Wegovy, 2025
Anuradha Lala	Yeshiva University Albert Einstein College of Medicine–Professor of Medicine	• AstraZeneca • Bayer* • Boehringer Ingelheim* • Merck* • Novo Nordisk*	None	None	None	• Heart Failure Society of America* • Sequana Medical (DSMB) • Zoll Medical Corporation	None
Melissa Magwire	Cardiometabolic Center Alliance, INC‡–Program Director		None	None	None	• Merck • Novo Nordisk	None
Michael Miller	University of Pennsylvania Hospital–Vice Chair of Medicine, Professor of Medicine	• Amarin Pharma Inc. • Boehringer Ingelheim • Ionis* Pharmaceuticals	None	None	None	None	None
Katie Moegenberg		None	None	None	None	None	None
Elif Oral	University of Michigan Medical School–Professor of Medicine	• Chiesi Farmaceutici • Regeneron Pharmaceuticals, Inc.*	None	None	None	• Amryt Pharma Holdings Ltd* • Chiesi Farmaceutici • Ionis Pharmaceuticals* • Morphic Therapeutic* • Novo Nordisk* • Regeneron Pharmaceuticals, Inc.*	None
Carl E. Orringer	Naples Comprehensive Health System–Vice President, Health Outcome Analytics	None	None	None	None	• American College of Physicians† • School of Medicine, Case Western Reserve University	None
Kershaw V. Patel	Houston Methodist Hospital–Physician	• Novo Nordisk • Roche Diagnostics Corporation	None	None	None	• Mineralys • NIH* • Novo Nordisk	None
Sonali Patel	UT Southwestern Medical Center–Physician	None	None	None	None	None	None
Jane E.B. Reusch	University of Colorado, Denver/Anschutz Medical Campus–Professor; Veterans Health Administration–Physician and Merit Investigator	• Medtronic	None	None	None	• Novo Nordisk* • NIH*	None

(*Continued*)

Appendix 2. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Philip Schauer	Pennington Biomedical Research Center–Bariatric Surgeon, Professor of Metabolic Surgery	• Eli Lily • Ethicon • GI Dynamics • Heron Therapeutics, Inc. • Medtronic • Novo Nordisk • Regeneron Pharmaceuticals, Inc.	None	• Mediflix* • Metabolic Health International, LTD* • SE Healthcare†	None	None	None
Daniel E. Weiner	Tufts Medical Center–Nephrologist, Attending Physician	None	None	None	None	• American Society of Nephrology† • National Kidney Foundation* • Vertex Pharmaceuticals	None

This table represents all reviewers' relationships with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

‡Acquired by American Heart Association, Inc., in October 2025 post–peer review.

ACC indicates American College of Cardiology; ACS, American Cancer Society; AHA, American Heart Association; DSMB, data and safety monitoring board; NCI, National Cancer Institute; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NYU, New York University; UCSF, The University of California San Francisco; and UT, University of Texas.