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AHA SCIENTIFIC STATEMENT

A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association

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ABSTRACT: A growing appreciation of the pathophysiological interrelatedness of metabolic risk factors such as obesity and diabetes, chronic kidney disease, and cardiovascular disease has led to the conceptualization of cardiovascular-kidney-metabolic syndrome. The confluence of metabolic risk factors and chronic kidney disease within cardiovascular-kidney-metabolic syndrome is strongly linked to risk for adverse cardiovascular and kidney outcomes. In addition, there are unique management considerations for individuals with established cardiovascular disease and coexisting metabolic risk factors, chronic kidney disease, or both. An extensive body of literature supports our scientific understanding of, and approach to, prevention and management for individuals with cardiovascular-kidney-metabolic syndrome. However, there are critical gaps in knowledge related to cardiovascular-kidney-metabolic syndrome in terms of mechanisms of disease development, heterogeneity within clinical phenotypes, interplay between social determinants of health and biological risk factors, and accurate assessments of disease incidence in the context of competing risks. There are also key limitations in the data supporting the clinical care for cardiovascular-kidney-metabolic syndrome, particularly in terms of early-life prevention, screening for risk factors, interdisciplinary care models, optimal strategies for supporting lifestyle modification and weight loss, targeting of emerging cardioprotective and kidney-protective therapies, management of patients with both cardiovascular disease and chronic kidney disease, and the impact of systematically assessing and addressing social determinants of health. This scientific statement uses a crosswalk of major guidelines, in addition to a review of the scientific literature, to summarize the evidence and fundamental gaps related to the science, screening, prevention, and management of cardiovascular-kidney-metabolic syndrome.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ diabetes, type 2 ■ heart diseases ■ kidney failure, chronic ■ metabolic syndrome ■ obesity ■ social determinants of health

Poor cardiovascular-kidney-metabolic (CKM) health is a major determinant of premature morbidity and mortality. Consequently, developing comprehensive strategies to augment CKM health across the life course is a key clinical and public health priority. There is a growing understanding of the science underlying the complex interplay among metabolic risk factors, chronic kidney disease (CKD), and the cardiovascular system. Accordingly, there has been an expansion of therapeutic approaches to prevent or mitigate metabolic risk factors, to delay kidney disease progression, and to reduce associated cardiovascular risk. The increasing number of agents with

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beneficial metabolic effects, kidney effects, or both that additionally improve cardiovascular disease (CVD) outcomes offers promise for the future of CKM care.

However, several fundamental gaps remain in our scientific insight into the mechanistic underpinnings of CKM health. There are also major gaps, as well as some conflicts, in current clinical guidelines with respect to the approach to screening, prevention, and management of the patient with CKM syndrome. Using a review of the literature and crosswalk of major guidelines, this scientific statement describes the current evidence and gaps in our knowledge in terms of the science, screening, and clinical care of CKM syndrome. The scientific statement concludes with charting a path forward for science and clinical care in relation to CKM health.

THE CURRENT SCIENTIFIC UNDERSTANDING OF CKM SYNDROME

As described in the CKM health presidential advisory,[1] CKM syndrome is defined as 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 CVD that is potentially related to or complicates metabolic risk factors or CKD. 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.

The pathophysiological consequences of CKM syndrome reflect multidirectional relationships among metabolic risk factors, CKD, and the cardiovascular system (Figure 1). CKM syndrome most commonly originates from excess or dysfunctional adipose tissue or both. Dysfunctional adipose tissue, particularly visceral adipose tissue, secretes proinflammatory and prooxidative products that damage arterial, cardiac, and kidney tissues.[2–6] Inflammatory processes reduce sensitivity to the action of insulin, resulting in impaired glucose tolerance.[3,6] The

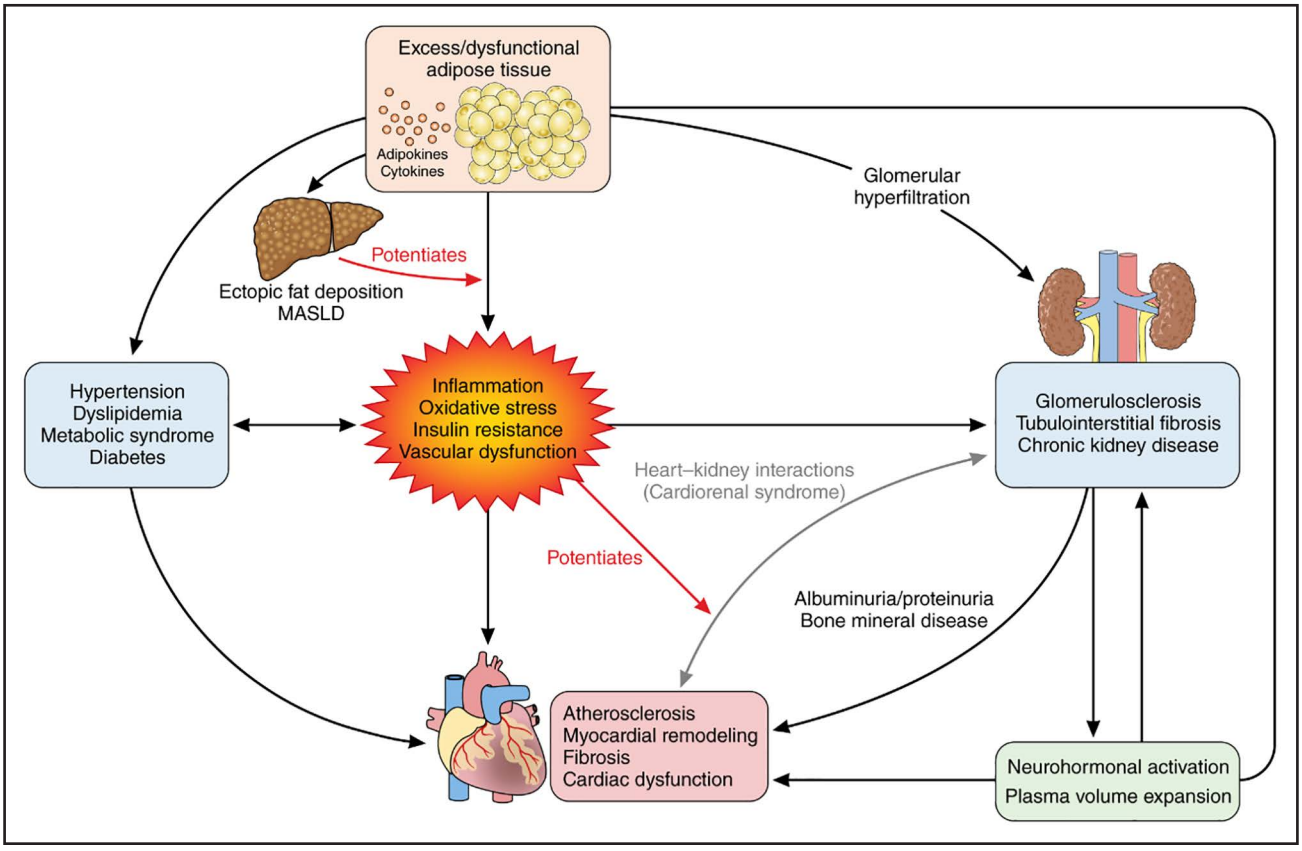

Figure 1. Conceptual diagram for CKM syndrome.
The image displays the pathophysiology underlying cardiovascular-kidney-metabolic (CKM) syndrome. CKM syndrome most commonly originates from excess adipose tissue, dysfunctional adipose tissue, or both. Multiple pathological processes related to dysfunctional adipose tissue result in insulin resistance and eventual hyperglycemia. Inflammation, oxidative stress, insulin resistance, and vascular dysfunction are highlighted as central processes leading to the development of metabolic risk factors, to the progression of kidney disease, to the potentiation of heart-kidney interactions, and to the development of cardiovascular diseases. Metabolic risk factors and chronic kidney disease further predispose to cardiovascular diseases through multiple direct and indirect pathways. MASLD indicates metabolic dysfunction–associated steatotic liver disease.

development of metabolic dysfunction–associated steatotic liver disease[7] (previously called nonalcoholic fatty liver disease) further amplifies systemic inflammation and insulin resistance. Beyond these systemic effects, metabolic dysfunction–associated steatotic liver disease has additionally become the leading cause of liver failure and need for liver transplantation.[8] When released into the systemic circulation, pro-oxidative and proinflammatory mediators exacerbate pathophysiological processes involved in atherosclerosis and myocardial injury; in glomerulosclerosis, kidney tubular inflammation, and kidney fibrosis; and in the development of metabolic risk factors. In addition to the systemic effects of adipose tissue, ectopic fat may be a local source of mediators and can produce compressive organ damage, especially when deposited in the epicardium and pericardium, promoting arrhythmogenesis, myocardial dysfunction, and coronary atherosclerosis, and within and around the kidney, contributing to hypertension and abnormal blood pressure variability.[3,5,6,9]

As one component of CKM syndrome, the constellation of risk factors making up metabolic syndrome (MetS)—abdominal obesity, dysglycemia, atherogenic dyslipidemia, and hypertension—has numerous pathophysiological consequences, including endothelial dysfunction, atherogenesis, thrombosis, myocardial injury, fibrosis, and cardiac remodeling. MetS thereby contributes to the development of all subtypes of CVD, including coronary heart disease, cerebrovascular disease, peripheral artery disease, cardiac arrhythmias, and heart failure (HF). Progression from MetS to type 2 diabetes (T2D) is common as a consequence of beta cell dysfunction in the context of chronic insulin resistance, which markedly amplifies risk for vascular and kidney disease.[10]

Mechanisms of vascular, heart, and kidney injury associated with these processes can be broadly classified as hemodynamic, metabolic, inflammatory, and fibrotic.[11–14] Hyperglycemia induces glomerular hyperfiltration and hypertension, which are hemodynamic mechanisms that have long been recognized to initiate and propagate kidney damage. Along with obesity and systemic hypertension, glomerular hemodynamic and arterial injury is promulgated by sheer stress and damage to the endothelium that contribute to both atherosclerosis and glomerulosclerosis.[11,15] Hypertension and obesity are also major etiologic factors underlying the development of left ventricular hypertrophy and HF.[16]

Hyperglycemia in T2D initiates a series of intracellular processes that promote kidney and vascular damage through inflammation and fibrosis.[11,15,17] Altered intracellular glucose metabolism generates advanced glycation end products, reactive oxygen species, and activation of protein kinase C and the Janus kinase–signal transducer and activator of transcription pathways.[11,15] These and various related intracellular signals lead to ongoing release of proinflammatory mediators, profibrotic factors, and immune cell recruitment.[15,18,19] Intensively controlling hyperglycemia only modestly reduces the risk of microvascular complications or progression in individuals with long-term diabetes.[20] Past hyperglycemia leads to long-lasting advanced glycation end products and epigenetic modifications, as well as subsequent upregulation of proinflammatory and profibrotic genes.[15,21] Consequently, pathways initially activated by metabolic disturbance may become self-perpetuating.[9,15,21]

CKD is a major amplifier of cardiovascular risk. The hallmarks of CKD, albuminuria, low glomerular filtration rate (GFR), or both, are associated with progressive increases in the risk of major atherosclerotic vascular and HF events and cardiovascular death.[22,23] Consequently, the most common causes of death for people with diabetes and CKD are HF and atherosclerotic CVD (ASCVD),[24–26] and only ≈10% of patients with CKD even survive to reach kidney failure.[27] As a result, greater numbers of individuals are affected by the constellation of risk factors and disease burden that encompasses CKM syndrome.

In addition to their various impacts on vascular disease, MetS and diabetes are predisposing conditions for CKD, with three-quarters of kidney failure cases attributed to diabetes and hypertension in the United States.[28,29] Although the prevalence of other diabetes complications has fallen substantially, the number of people with diabetes who develop kidney failure has progressively risen over time.[28,30–32] Moreover, deaths attributed to CKD in diabetes increased by 106% worldwide between 1990 and 2013.[32]

Although the mechanisms of kidney-heart interactions for reciprocal risk amplification are not fully elucidated, it is clear that many risk factors are shared. CKD, especially when present with diabetes, is a proinflammatory state, with elevated systemic inflammatory markers strongly associated with high cardiovascular risk.[33,34] Vascular calcification is a common complication of CKD that is associated with ischemic complications, including myocardial infarction and peripheral artery disease.[35] In addition, CKD and diabetes are more likely to precipitate peripheral artery disease below the knee, which is often more difficult to revascularize and is associated with more ischemic injury.[36,37] CKD also leads to anemia and bone and mineral metabolism disorders that exacerbate CVD.[38] Lower oxygen-carrying capacity increases myocardial demand and may worsen HF.[16] Conversely, CVD, particularly HF, is associated with the development of CKD.[16] HF may reduce GFR as a result of impaired cardiac output, high venous pressure, and activation of the renin-angiotensin-aldosterone system and sympathetic nervous system.[16,39] In turn, low estimated GFR (eGFR) can exacerbate fluid retention, which increases vascular congestion, forming an interlocking cycle of organ failure between the heart and kidney. Last, atherosclerosis can affect the kidney vasculature, which, when associated with critical ischemia, can cause both resistant hypertension and kidney failure.[40,41]

In summary, CKM syndrome represents a multidirectional pathophysiology leading to increased morbidity and mortality that goes beyond the simple sum of its components.

MAJOR GAPS IN SCIENTIFIC UNDERSTANDING OF CKM

Although the scientific understanding of the determinants and pathophysiological consequences of CKM syndrome is increasing, several key gaps persist in our knowledge, as detailed in the following sections (Table 1).

Table 1. Key Gaps in the Scientific Understanding of CKM Syndrome

Topic area	Key gaps
Mechanisms of CVD development in CKM	Elucidating mechanisms underlying the development of ASCVD Demographic differences, particularly by sex, and regional differences in CVD risk related to CKM syndrome Genetic underpinnings of CVD and role for genetic testing Mechanisms of endothelial dysfunction Elucidating mechanisms underlying the development of HF and arrhythmias Molecular mechanisms of HFpEF development Determinants of progression from subclinical to clinical CVD Interactions between extracardiac dysfunction and cardiac dysfunction
Understanding the heterogeneity within CKM syndrome	Elucidating key aspects of CKM heterogeneity Heterogeneity in degree and subtypes of metabolic risk factors among individuals with excess weight Heterogeneity in progression across CKM stages Clarifying biological factors predisposing to CKM risk, social determinants of CKM risk, and their interrelationships Understanding the effect of risk-enhancing factors in those susceptible to CKM syndrome
Need for longitudinal studies of competing risk	Need for Accurate estimations of risk for CVD and CKD in the context of CKM syndrome considering competing risks Strategies for prioritizing clinical outcomes in longitudinal CKM risk modeling
Understanding bidirectional cardiovascular-kidney relationships	Clarifying aspects of cardiovascular-kidney interactions Pathways linking CVD to the development of CKD and those potentiating cardiovascular-kidney interactions Subtypes of CVD most linked to CKD Most appropriate markers for tracking CKD development in CVD

ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; HF, heart failure; and HFpEF, heart failure with preserved ejection fraction.

Mechanisms of CVD Development in CKM

Although epidemiological studies have described clear associations of CKM components, including hallmark features of visceral adiposity and insulin resistance, with risk of ASCVD, the exact mechanisms remain incompletely understood. When present, CKM syndrome appears to accelerate the pathophysiology of atherosclerosis by augmenting inflammation, dyslipidemia, hypertension, and insulin resistance, each central contributors to the development of atherogenesis.[2] With the changing landscape of atherosclerosis that has shifted to developing countries, women, and younger individuals, current knowledge gaps include an incomplete understanding of (1) sex differences in CVD in CKM syndrome, (2) genetic underpinnings of disease that may account for some regional differences and clinical applications of genetic testing, (3) mechanisms of endothelial dysfunction in CKM syndrome (accelerated in the presence of CKD[42]) as an early harbinger of CVD, and (4) environmental and community-level risk factors in the development of CVD.[43]

In contrast to atherosclerosis, mechanisms by which CKM syndrome leads to HF and arrhythmias (and, in particular, atrial fibrillation [AFib]) are less well described. Adiposity itself leads to hemodynamic changes. Additionally, adipose depots, including pericardial and myocardial fat accumulation, may exert direct effects on cardiac remodeling through activation of inflammatory and fibrosis pathways, in addition to abnormal myocardial energetics. The role of metabo-inflammation is increasingly recognized as an important mechanism leading to HF with preserved ejection fraction (HFpEF).[44] Key knowledge gaps that remain include (1) molecular mechanisms of HFpEF in the setting of substantial phenotypic heterogeneity; (2) determinants of disease progression from subclinical to overt CVD, including HFpEF and AFib; and (3) interactions between extracardiac organ dysfunction, particularly kidney disease,[16] and cardiac dysfunction.

Understanding the Heterogeneity Within CKM Syndrome

Another key gap relates to understanding the factors underlying the marked heterogeneity within CKM syndrome. There is significant heterogeneity in metabolic disease within weight categories, with some individuals having few or no metabolic risk factors beyond excess weight and others having multiple metabolic risk factors despite having only modest degrees of excess weight or even being within a normal weight range. It is important to note that the absence of metabolic risk factors among individuals with obesity is still associated with increased CVD risk relative to individuals with normal weight without metabolic risk factors.[45] This is due to direct adverse cardiovascular effects of obesity and the fact that many

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individuals develop metabolic risk factors over time.[45] However, there is limited understanding of the reasons for this heterogeneity in metabolic risk factors, with the distribution of ectopic fat and the metabolic activity of adipose tissue thought to play key roles.[46]

In addition, there are significant racial and ethnic differences in the propensity for metabolic risk factors at a given weight.[47] Much of this is related to social determinants of health (SDOH), which primarily drive the higher burden of metabolic risk factors within historically disenfranchised populations.[48,49] SDOH can be conceptualized within a socioecological framework in which societal factors, community, and interpersonal relationships affect each other and strongly influence individual health behaviors (Figure 2).

Individual biological predisposition also plays a key role; as an example, the higher burden of metabolic risk factors among people of South Asian ancestry is likely related to a higher degree of ectopic fat deposition at a given body mass index (BMI).[50] However, individual biological predisposition is likely best conceptualized within a social context, with adverse SDOH and unfavorable biological factors being interrelated and leading to worse CKM outcomes when jointly present. Epigenetic changes, resulting from interconnections among genetic, environmental, social, and lifestyle factors, may help to elucidate the biological basis for heterogeneous manifestations of CKM syndrome.[51] A better understanding is also needed regarding multiple MetS subtypes (eg, insulin resistance dominant, lipid dominant, vascular dominant) and the variability in the end organ–related manifestations of CKM syndrome.

There is also heterogeneity in the speed and extent of progression across CKM stages. Progression along CKM stages is associated with increased relative and absolute risk for CVD, kidney failure, and mortality. Altering the trajectory of CKM syndrome requires a deeper understanding of metabolic-inflammatory interplay accompanied by an integration of bio-socio-ecological pathways. Factors such as genetics, behavioral and environmental factors, and SDOH may collectively influence the progression of CKM syndrome across its stages. Indeed, in the CKM health presidential advisory, we identified risk-enhancing factors for progression along CKM stages, including sex-specific factors such as early menopausal transition, adverse pregnancy outcomes, and polycystic ovarian disease; mental health and sleep disorders; chronic inflammatory conditions; and family history of diabetes or kidney

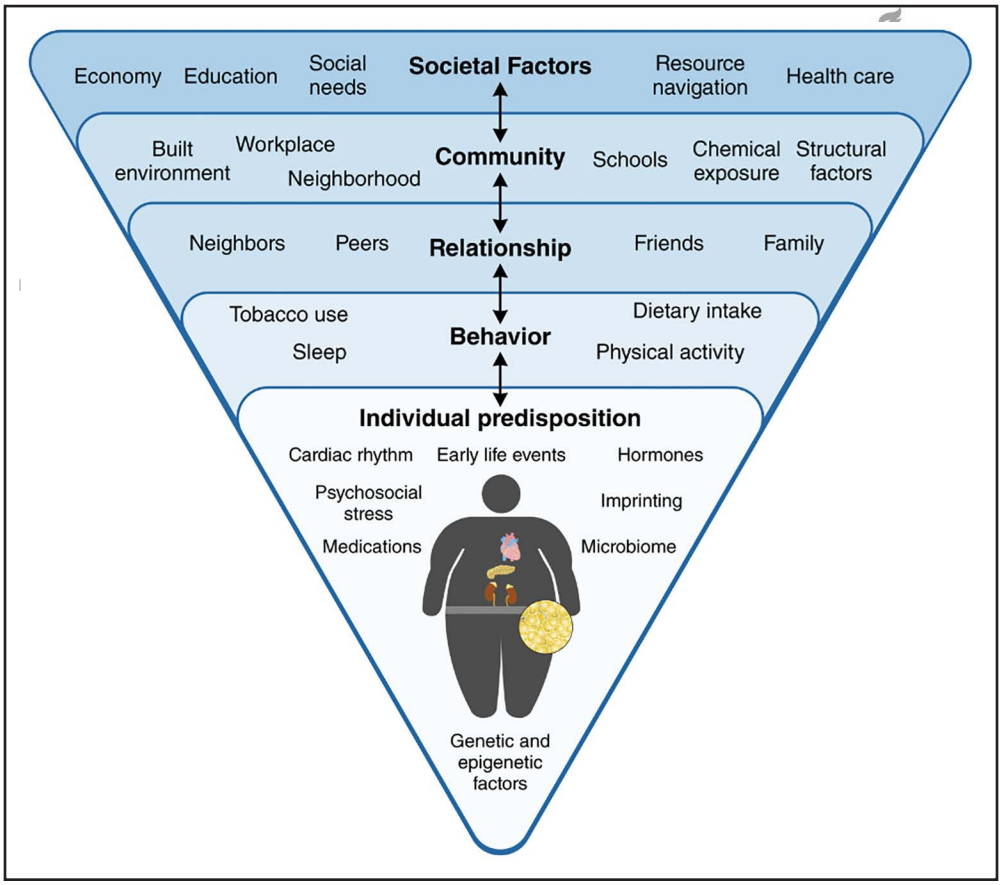

Figure 2. Socioecological framework for CKM syndrome.
Social determinants at multiple levels of influence, including at societal, community, interpersonal and individual behavioral levels, affect the likelihood of cardiovascular-kidney-metabolic (CKM) syndrome and of consequent adverse outcomes. Individual biological predisposition, nested within these multiple levels of social influence, further affects CKM syndrome development and related outcomes.

failure. However, there is limited understanding of the relative importance of these factors and how they interact to influence transitions from excess and dysfunctional adiposity to the emergence of metabolic risk factors and progressive kidney disease to subclinical and eventual clinical CVD. There is a key need for such outcomes data from diverse populations, including groups traditionally underrepresented in clinical studies and trials, to maximize our understanding of CKM syndrome heterogeneity. In addition, the development of animal or cellular models would be beneficial in understanding the molecular mechanisms that mediate the development and progression of CKM syndrome. Obtaining a deeper understanding of the factors linked to the variability in CKM and progression along CKM stages may inform novel strategies for predicting and positively influencing CKM health in the population.

Need for Longitudinal Studies of Competing Risk

Accounting for competing risk in longitudinal analyses not only allows more accurate risk prediction but also adds contextual dimensions and insights, especially when conducted over longer periods of time.[52,53] CKM syndrome represents a complex interplay of conditions that are individually associated with high cardiovascular and kidney disease event rates such as myocardial infarction, stroke, HF, kidney failure, and death. However, high-quality studies focused on describing and assessing risks in CKM syndrome are scarce; thus, a longitudinal approach to studying competing risks of the various components of CKM syndrome provides an opportunity for new insights into mechanisms that affect or modify each factor over time. In the context of CKM syndrome, using competing-risk methodology to identify the first adverse outcome resulting from multiple interacting factors can guide the prioritization of preventive therapies, with the goal of averting primary (eg, myocardial infarction) and subsequent secondary (eg, HF or recurrent myocardial infarction) events.

Individually, the components of CKM have been modeled with competing-risk methodologies in multiple studies to avoid biased estimates of the risk for disease outcomes, as described previously.[54] In CKD and kidney failure, competing-risk models have demonstrated higher concordance with observed outcomes than standard Cox regression modeling.[55–57] Establishing adequate modeling methodologies will be important in consistent risk estimation. Such modeling methodologies will be important in accurately estimating future outcomes for the purposes of trial design and resource allocation in health care settings. The challenge for future analyses with the broad CKM syndrome will be the selection of outcomes to consider. For example, a patient with CKD G4 may be at risk for and experience kidney failure, a cardiovascular event, or death not related to CKM disease. On the other hand, individuals with earlier stages of CKD but with components of MetS may have higher risks of death or cardiovascular events in the short term and progressive kidney disease in the long term. Therefore, there is a great need to prioritize outcomes in risk modeling with CKM and to develop the appropriate modeling strategies to answer important questions related to long-term CKM syndrome consequences.

Understanding Bidirectional Cardiovascular-Kidney Relationships

The importance of considering cardiovascular and kidney disease in a singular framework stems from the frequent co-occurrence of these entities and the bidirectional organ cross talk that perpetuates organ damage. CKD is an important risk factor for CVD. The heightened risk begins at the earliest stages of kidney disease, most easily recognized by the presence of albuminuria.[58] This biomarker reflects global vascular endothelial dysfunction and early kidney disease,[59] further amplified by traditional metabolic risk factors such as elevated blood pressure and hyperglycemia. In addition, this heightened cardiovascular risk in kidney disease is recognized even in young individuals with congenital kidney diseases and in primary glomerular or tubulointerstitial diseases.[60]

The causal relationship between CVD and subsequent kidney disease is less understood (type 2 cardiorenal syndrome).[16] Although kidney benefits have been shown in data from cardiovascular trials with agents such as angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and finerenone,[61] the global kidney trajectory in CVD has not received as much attention and needs further clarification. Questions that remain include the types of CVD most associated with future kidney disease (ie, ischemia, HF, valvular disease, arrhythmias), appropriate biomarkers for tracking kidney disease development in CVD, and age-specific variations in this risk.

METHODS FOR THE CROSSWALK OF GUIDELINES RELATED TO CKM SCREENING, PREVENTION, AND MANAGEMENT

To review the evidence related to the clinical management of CKM syndrome, the American Heart Association convened a science advisory group with broad transdisciplinary expertise. The science advisory group included representation from pediatrics, primary care, nephrology, endocrinology, cardiology, neurology, nursing, and pharmacology, with additional expertise in basic, clinical, epidemiologic, and interventional research. Regular meetings were held among the science advisory group and among a complementary CKM health patient advisory group to provide a lay perspective.

The science advisory group conducted a comprehensive review of the latest guidelines related to screening for

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CKM risk factors and the prevention and management of ASCVD, HF, and AFib in patients with CKD, T2D, obesity, and other cardiometabolic conditions (Table 2). We compared recommendations across guidelines using a systematic approach and identified the discrepancies in recommendations, the areas that were not adequately addressed in current clinical guidelines, and the gaps in the literature requiring further investigation. In our evaluation of the major guidelines, we classified the recommendations into 3 main categories: lifestyle, pharmacotherapy, and other considerations, including SDOH, interdisciplinary care, and patient-centered approaches. Prevention guidelines provided additional recommendations on screening individuals at risk of developing CVD or progressive kidney disease related to CKM risk factors.

The most recent guidelines from American (led primarily by American Heart Association/American College of Cardiology, with involvement of other subspecialty organizations) and European (primarily led by the European Society of Cardiology) cardiology societies for the management and prevention of ASCVD and HF served as the backbone for our crosswalk. Because ASCVD and HF guidelines from American societies referenced the hypertension[65] and cholesterol[66] guidelines for specific population subgroups and comorbidities such as recommendations for individuals with diabetes or CKD, hypertension and cholesterol guidelines were used as the primary reference for these specific patient populations. It is notable that the major guideline for the management of overweight and obesity in adults was published in 2013.[67] Therefore, we incorporated recommendations related to weight management using more up-to-date guidelines and scientific statements within the CKM framework. The American Diabetes Association's Standards of Care 2023 served as the primary source for CKM-related recommendations in patients with diabetes, and the Kidney Disease Improving Global Outcomes guidelines were used for therapeutic considerations related to CKD and diabetic kidney disease.[75]

To identify gaps in the recommendations, we additionally used information provided in scientific statements. This allowed us to incorporate the current evidence base and expert opinion into our advisory while also highlighting areas that necessitate further research. The guideline crosswalk was further supported by an extensive review of the scientific literature by members of the writing group. The complete list of guidelines used for the crosswalk exercise can be found in Table 2.

Table 2. Major Guidelines and Scientific Statements Used in the CKM Health Crosswalk

Prevention and Management of ASCVD
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease[62]
2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice[63]
2023 Standards of Medical Care in Diabetes[64]
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults[65]
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[66]
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults[67]
2022 AHA Scientific Statement: Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes[61]
2021 AHA Scientific Statement on Weight-Loss Strategies for Prevention and Treatment of Hypertension[68]
2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease[69]
2013 KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease[70]
Prevention and Management of HF
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure[71]
2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure[72]
2023 Standards of Medical Care in Diabetes[64]
2022 AHA Scientific Statement: Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes[61]
2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease[69]
Prevention and Management of AFib
2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration With the EACTS[73]
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation[74]
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure[71]
2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure[72]
Management of CKM Health in CKD
2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease[69]
2023 Standards of Medical Care in Diabetes[64]
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure[71]
2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure[72]

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AFib, atrial fibrillation; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; HF, heart failure; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; KDIGO, Kidney Disease Improving Global Outcomes; NLA, National Lipids Association; NMA, National Medical Association; PCNA, Preventive Cardiovascular Nurses Association; and TOS, The Obesity Society.

EVIDENCE SUPPORTING CKM-RELATED SCREENING

The ability to detect, at an early stage, conditions with significant negative clinical consequences remains an urgent preventive public health opportunity, especially when multiple effective therapeutics are available. The CKM staging construct provides a framework for identifying

Table 3. Definitions of CKM Health Stages

CKM health stages	Definition
Stage 0: No CKM health risk factors	Individuals without overweight/obesity, metabolic risk factors (hypertension, hypertriglyceridemia, MetS, diabetes), CKD, or subclinical/clinical CVD
Stage 1: Excess and/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) and/or Fasting blood glucose ≥100–124 mg/dL or HbA1c between 5.7% and 6.4%*
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia (≥135 mg/dL), hypertension, MetS†, diabetes) or CKD
Stage 3: Subclinical CVD in CKM	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, high-sensitivity troponin T ≥14 ng/L for women and ≥22 ng/L for men, high-sensitivity troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with combination indicating highest HF risk. Risk equivalents of subclinical CVD Very high-risk CKD (G4 or G5 CKD or very high risk per KDIGO classification) High predicted 10-y CVD risk
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, AFib) among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present

AFib indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CT, computed tomography; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Individuals with gestational diabetes should receive intensified screening for impaired glucose tolerance after pregnancy.

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

individuals at early stages of CKM syndrome to prevent progression to CVD (Table 3). Assessment and early management of modifiable risk factors is a cornerstone of cardiovascular prevention, with the recommended intensity of preventive interventions typically linked to the absolute risk of the individual and expected net benefit of the intervention. Major organizations support screening for hypertension, diabetes, and dyslipidemias, all key CKM risk factors, with early management of these conditions recommended to potentially improve clinical outcomes.[62,63,69,76,77] Obesity confers greater risk with longer severity and duration, supporting the concept of addressing excess weight at early points in the life course.[78] Traditionally, the components of CKM syndrome have been evaluated and measured separately, but there is a need to consider collective assessments for closely interrelated risk factors to facilitate holistic approaches to prevention.

MetS is strongly linked to the development of diabetes and CVD, and the MetS construct underscores the connectivity of several metabolic risk factors. Both the diagnostic components of MetS and additional pathophysiological features such as inflammation, endothelial dysfunction, a prothrombotic milieu, and a higher low-density lipoprotein (LDL) particle concentration confer CVD risk. Therefore, addressing the root causes of MetS through lifestyle modification, in addition to pharmacological risk factor control, is key to fully address both diagnostic and typically unmeasured MetS components and their associated CVD risk.

CVD and kidney diseases are currently treated as separate health conditions. However, the increasing recognition that these 2 conditions are closely linked through shared biological and social risk factors warrants updated considerations in the context of CKM syndrome. Historically, screening for kidney diseases has had variable support from the medical community. In the strongest argument against screening, the US Preventive Services Task Force issued a statement that routine screening for CKD among the general adult population lacked sufficient evidence for benefit.[79] However, this guidance must be revisited with the advent of several classes of medications now demonstrating benefit in slowing the progression of CKD (eg, ACE inhibitors/ARBs, SGLT2 inhibitors, and nonsteroidal mineralocorticoid receptor antagonists), preventing CVD events, and reducing cardiovascular mortality. Most specialty organizations have now embraced the importance of identifying CKD, especially in high-risk adult populations such as those with diabetes.[58,61] Screening for CKD has historically been centered around the eGFR. The challenges with relying solely on the eGFR are numerous, including inconsistent reporting with some systems not reporting granular values >60 mL·min^{-1}·1.73 m^{-2} and imprecision related to higher eGFR estimations. There are alternative categorizations to define kidney disease, including a rubric that relies on albuminuria (>30 mg/g creatinine in a spot urine specimen). Albuminuria is an independent risk marker for future CVD events below the standard threshold for CKD criteria and is an important screening tool for patients with diabetes.[58,69,80] The Kidney Disease Improving Global Outcomes CKD staging system combines eGFR and albuminuria to provide a broad risk estimate for CKD progression, CVD events, and overall mortality.[81] Including kidney parameters as

part of comprehensive CKM screening will enhance the potential to predict and prevent clinically relevant and patient-reported outcomes.

GAPS IN APPROACHES TO SCREENING

Review of the literature and major guidelines revealed key gaps and conflicts with regard to screening for children, metabolic risk factors and CKD in adulthood, subclinical CVD, and SDOH closely linked to CKM health (Table 4).

Gaps in Early Life Screening

Indicators of cardiovascular health such as those in Life's Essential 8[82] present an important paradigm for prevention of disease, but the age at which to begin screening and prevention efforts has been controversial. The vascular and myocardial pathology underlying CVD begins early in life and progresses through childhood and adolescence into adulthood. The most direct evidence for prevention would come from studies linking screening and prevention efforts initiated during childhood to a clear reduction of cardiac outcomes in adulthood. Unfortunately, such studies are impractical because of the necessary duration and cost. From this lack of direct evidence, the US Preventive Services Task Force has concluded that there is insufficient evidence to assess the benefits and harms of screening for most cardiovascular risk factors in children and adolescents.[83–86] However, some pediatric organizations, including the American Academy of Pediatrics, have recommended early-life screening on the basis of multiple lines of indirect evidence suggesting an association among childhood cardiovascular risk factor onset, preservation of ideal cardiovascular health, tracking of risk factors into adulthood, and the likelihood of long-term CVD events.[87–91] Pediatric obesity and pediatric CKD precede the development of other CKM risk factors.[92,93] Pediatric CKD is associated with increased CVD mortality risk that is often arrhythmic in pathogenesis.[60,94] In addition, blood pressure control in pediatric patients with CKD reduces CKD progression.[95] Additional evidence of the benefits of screening early in life and the impact of early identification of modifiable risk factors is needed.

Table 4. Key Gaps in the Screening Approaches for CKM Syndrome

Topic area	Key gaps
Early-life screening	Need for clarity on early life screening for CKM factors Not currently recommended by USPSTF because of limited evidence on outcome, but recommended by other pediatric organizations
Screening for metabolic risk factors and CKD in adulthood	Obesity: limited focus on waist circumference measurements and race- and ethnicity-specific cut points in current guidelines MetS components: suboptimal identification of MetS in clinical practice, which should trigger lifestyle change and multifactorial risk factor control Optimal frequency for MetS screening undefined CKD: significant underuse of urine albumin-creatinine ratio measurement in concert with eGFR to fully characterize CKD-associated risk
Subclinical CVD diagnosis	Subclinical HF: optimal strategy for identifying in the population not fully defined Possible targeted cardiac biomarker measurements based on combination of age/CKM risk factors/risk algorithms Next diagnostic/therapeutic steps after the finding of elevated cardiac biomarkers not yet defined CKD systematically underemphasized in current HF staging despite high HF risk with CKD CKD not among risk conditions in HF guidelines; CKD excluded from biomarker definition for subclinical HF because of elevated biomarker levels with kidney dysfunction; alternative approach for defining and addressing risk in CKD remains undefined
SDOH screening	Approach to and utility of systematic screening for SDOH Optimal tools for SDOH screening (may differ by setting) Strategies for incorporating SDOH screening into EHR and clinical workflows Impact of addressing SDOH identified by screening on clinical outcomes

CKD indicates chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HF, heart failure; MetS, metabolic syndrome; SDOH, social determinants of health; and USPSTF, US Preventive Services Task Force.

Gaps in Screening for Metabolic Risk Factors and CKD in Adulthood

The foundations of metabolic risk factor screening include measurements of blood pressure, lipids, blood glucose, and the anthropometric measures of BMI and waist circumference. Assessments of kidney function provide complementary prognostic information and guide therapeutic approaches. However, there is limited and conflicting guidance on the recommended frequency, age of inception, and modalities for screening for CKM risk factors, which need to be addressed within the paradigm for CKM screening.

Screening for traditional risk factors is recommended in healthy young adults every 4 to 6 years. Obesity is at the core of CKM syndrome, and annual assessments of BMI are widely recommended.[62,63] Because BMI does not reflect body composition, the addition of waist circumference measurements enhances the identification of increased cardiometabolic risk, particularly in overweight and grade I obesity, but the utility of widespread waist circumference assessments is debated. Assessments for prediabetes and diabetes may inform dietary and physical activity counseling and are recommended by American Diabetes Association and US Preventive Services Task Force every 3 years in adults with overweight or obesity

on the basis of modeling of diabetes incidence. Those with gestational diabetes are at high risk for diabetes, and timely interventions prevent diabetes development.[96] Evidence further suggests that glycemic assessments in the overall population, regardless of BMI, increase equity in prediabetes and diabetes diagnosis.[97] Blood pressure screening is recommended every 3 to 5 years in those 18 to 39 years of age and annually in those >40 years of age.[98] Approximately half of individuals with obesity but without metabolic risk factors develop metabolic risk factors over 6 to 7 years of follow-up.[99] The Endocrine Society recommends assessment for MetS every 3 years for individuals with risk factors and yearly diabetes assessments in those with prediabetes.[100] Because of the close relationship between metabolic risk factors and metabolic dysfunction–associated steatotic liver disease, the American Association for the Study of Liver Diseases recommends screening for liver fibrosis every 1 to 2 years among individuals with established metabolic risk factors. The Kidney Disease Improving Global Outcomes recommends CKD assessments, including eGFR and albuminuria, to provide the most prognostic information for kidney and cardiovascular risk,[75] with the greatest utility in those with CKD and established metabolic risk factors such as diabetes and hypertension.[80] Overall, current evidence, although limited, supports the most frequent assessments of CKM risk profiles for those with established metabolic risk factors, moderate-frequency CKM risk factor screening in those with excess weight or prior gestational diabetes, and less frequent but systematic screening in healthy adults to support equitable identification of CKM risk factors.[97] However, there is need for prospective clinical data to validate the utility of this approach.

Gaps in Subclinical CVD Diagnosis

Subclinical CVD is associated with increased absolute risk for CVD events. However, in the general primary prevention population, routine testing for the diagnosis of subclinical CVD in asymptomatic individuals is not recommended.[62] The presence of coronary artery calcium (CAC), a marker of subclinical atherosclerosis, identifies individuals likely to have the greatest net clinical benefit from statin therapy.[101] Although carotid intima-media thickness is also associated with ASCVD, the magnitude of association is diminished compared with CAC, and the relationship of carotid intima-media thickness to treatment remains controversial.[102] Therefore, American Heart Association guidelines endorse selective use of CAC scoring to help guide decisions on statin therapy for those in the borderline to intermediate range as quantified by the Pooled Cohort Equations. Emerging data further suggest that CAC testing may help with targeting the intensification of preventive therapies beyond statins.[103,104]

The optimal approach for identifying subclinical HF in the population is less clear. Elevated cardiac biomarkers (BNP [brain natriuretic peptide] or high-sensitivity cardiac troponins) and abnormal cardiac function or structure by cardiac imaging now make up the diagnostic criteria for subclinical HF, with the presence of both associated with greatest HF risk.[71,105] The 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines for HF management support BNP-based measurements[71] on the basis of data from STOP-HF (St. Vincent's Screening to Prevent Heart Failure Study)[106] and PONTIAC (NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients),[107] which were randomized controlled trials that demonstrated benefit and cost-effectiveness of BNP-based assessments for the prevention of HF.[108] An American Diabetes Association consensus statement supports BNP measurements in older adults with diabetes. However, there is limited clarity on how best to target cardiac biomarker measurements in the population, the frequency of such testing, and appropriate next diagnostic steps (eg, echocardiograms) when elevated cardiac biomarkers are identified. Potential strategies may include measurement strategies based on risk factors (eg, diabetes[109,110]), age (eg, ≥65 years[111,112]), or an intermediate risk threshold based on 10-year risk of HF.

Individuals with CKD are systematically underemphasized in current HF staging approaches. Despite being strongly linked to HF risk, CKD is not among the HF risk factors in stage A HF.[71] In addition, because of elevated cardiac biomarker levels with kidney dysfunction, individuals with CKD are excluded from the biomarker-based definition for subclinical HF (stage B HF). Alternative strategies are needed to quantify and address HF risk in CKD.

Gaps in SDOH Screening

SDOH play a critical role in CKM health; however, several evidence gaps exist about screening for social needs among patients with CKM syndrome.[113,114] The effectiveness of routine social needs screening and referral to resources for improving CKM health behaviors such as nutrition and physical activity and outcomes must be further elucidated. Interventions for social needs screening and referral must account for CKM-related health behavior and outcome disparities and promote health equity. Effective interventions should be identified for geographic areas where structural racism and other adverse SDOH serve as barriers to health care and healthy behaviors (ie, food deserts[115]), without stigmatizing patients or adding undue clinician burden. Moreover, SDOH are intrinsically linked to access to CKM therapies, particularly cardioprotective glucose-lowering therapies. Therefore, we must better understand the effects of addressing social needs on CKM therapeutic access and use. Social needs screening tools must also be harmonized across electronic health record platforms to reach diverse patient populations. In addition,

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workflow pathways should be developed in health care systems to address social needs among patients with CKM syndrome by identifying, evaluating, using, and referring to existing community resources. Last, multilevel support across health care systems is critical for the implementation of care models that reflect a SDOH focus. The composition of interdisciplinary care teams should include care navigators, social workers, or community health workers who can connect patients to necessary social need resources that protect against the effects of adverse social conditions.

EVIDENCE FOR PREVENTION AND MANAGEMENT IN CKM SYNDROME

A growing body of evidence supports the overarching considerations of facilitating interdisciplinary care and assessing or addressing SDOH in CKM care. There is also substantial evidence supporting approaches for individual CKM stages, including those without CKM risk factors or subclinical or clinical CVD (stage 0); with excess/dysfunctional adiposity (stage 1); with metabolic risk factors, moderate- to high-risk CKD, or both (stage 2); with subclinical CVD overlapping with CKM risk factors or risk equivalents (stage 3); and with clinical CVD overlapping with CKM risk factors (stage 4). A summary of the evidence supporting the approach to management for each stage of CKM syndrome is provided in Figure 3.

Interdisciplinary Care

Individuals navigating multiple comorbid conditions face unique challenges related to fragmented care across several health care professionals. Models supporting interdisciplinary care demonstrate promise for providing harmonized and holistic care and supporting adherence to recommended therapies.[116–118] Patients attending cardiometabolic clinics that include representation from cardiology, endocrinology, pharmacy, and nutrition, aided by nurse navigators, have increased use of cardiometabolic therapies and achieve more favorable metabolic risk profiles.[119] A recent randomized trial demonstrated increased use of cardiometabolic therapies with the engagement of a multidisciplinary team and an implementation specialist.[120] A combination of value- and volume-based interdisciplinary care models has the potential to increase feasibility and scalability across diverse clinical settings with disparate health care resources.

Incorporation of SDOH

Interventions that incorporate social need screening and connect patients to services have demonstrated reductions in social need prevalence.[114] A limited number of interventions have examined health outcomes in the setting of addressing social needs, and few studies have shown improvement in CKM health–related factors. For instance, obtaining resources for social needs related to food, housing, medication, and transportation after screening was associated with reductions in blood pressure and LDL cholesterol (LDL-C) but not hemoglobin A1c (HbA1c).[71] Screening for and addressing social needs has also been linked to a reduction in emergency room visits. Other interventions have shown higher smoking cessation rates or greater fruit and vegetable consumption for those who gained resources to address social needs.[121] More data are needed that examine the impact of interventions that address social needs on CKM health risk factors and outcomes.

Screening to Support CKM Staging

A critical element of the CKM framework is active screening in the population and clinical settings to identify individuals at different stages of CKM syndrome. Screening involves assessing for biological factors and screening for SDOH, which can powerfully affect the development of CKM syndrome and influence its outcomes and management. The goal is to identify CKM syndrome in its earliest phases to avert the development of clinical CVD and kidney failure. Currently, for both children and adults, there is a lack of consensus on timing, frequency, and components for screening approaches to CKM syndrome (Table 4). A detailed discussion of recommendations for CKM screening can be found in the CKM health presidential advisory.[1]

Evidence for Stage 0 CKM Approach

The stage 0 approach is focused on primordial prevention in those with optimal cardiovascular health, including the absence of CKM risk factors and subclinical or clinical CVD. CKM risk factors in childhood such as obesity, hypertension, and diabetes frequently persist into adulthood and are linked to long-term vascular disease.[90,122,123] The Life's Essential 8 framework provides a holistic approach for attaining and preserving cardiovascular health,[82] with Life's Essential 8 health metrics of weight, blood pressure, glycemia, and lipids also being components of CKM syndrome. Studies indicate that sustaining healthy lifestyle practices from childhood through young adulthood is critical for maintaining ideal cardiovascular health through middle age.[82] Among children, school-based programs promoting healthy eating and physical activity by targeting students, staff, and families or enhancing the school environment are shown to reduce weight and increase the likelihood of achieving ideal cardiovascular health.[124,125] Among young adults, the avoidance of weight gain with aging reduces the likelihood of developing CKM risk factors such as MetS and prediabetes/diabetes over time.[126]

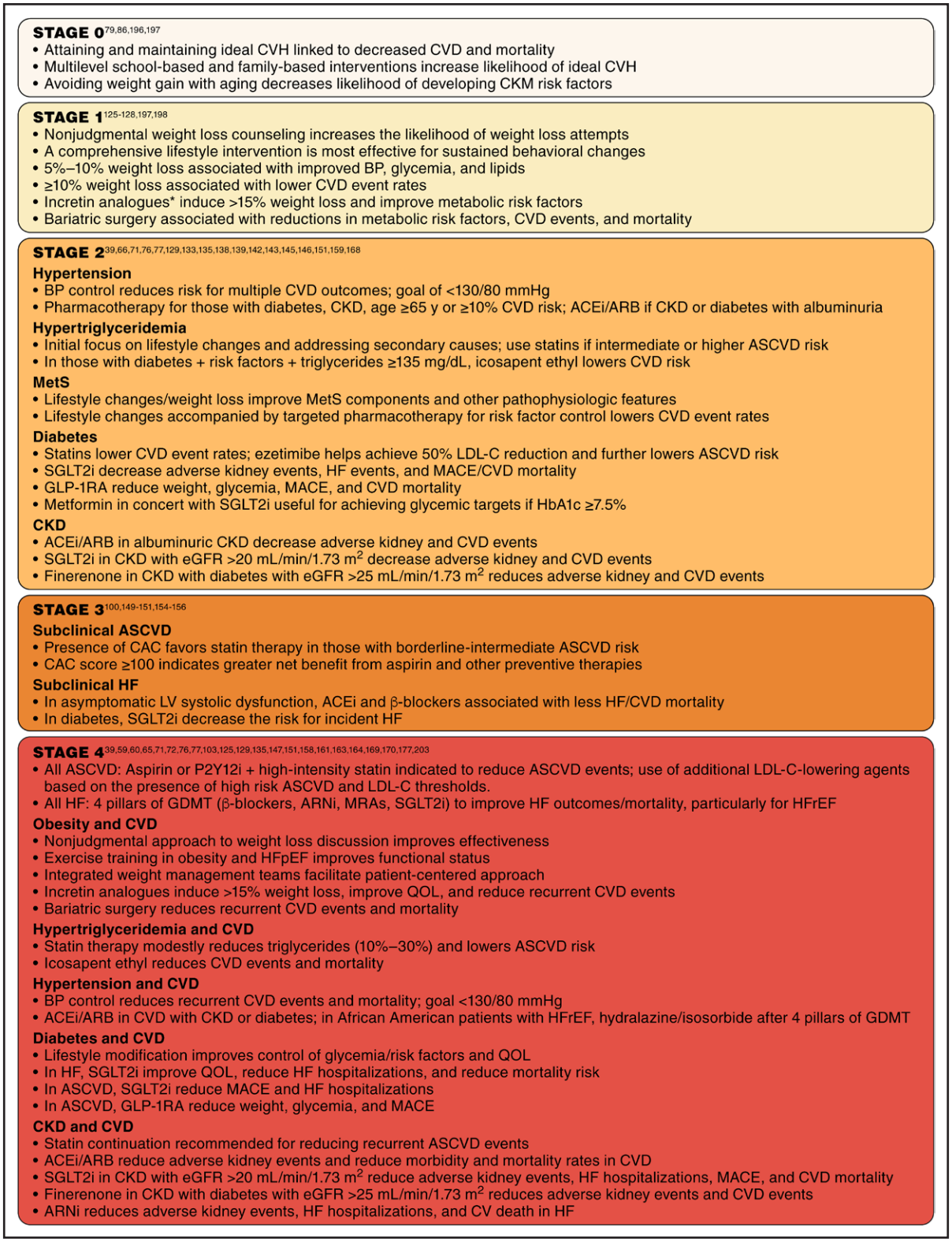

Figure 3. Summary of the evidence for recommended approaches and treatments at each stage of CKM syndrome.
ACEi indicates angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNi, angiotensin receptor/neprilysin inhibitors; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density cholesterol; LV, left ventricle; MACE, major adverse cardiac event; MetS, metabolic syndrome; MRA, mineralocorticoid receptor antagonist; P2Y12i, P2Y12 inhibitor; QOL, quality of life; and SGLT2i, sodium-glucose cotransporter-2 inhibitor. *Incretin analog indicates GLP1-RA, GLP1/GIP-RA, and GLP1/GIP/glucagon-RA.

Evidence for Stage 1 CKM Approach

The stage 1 approach is focused on the prevention of metabolic risk factor development in those with excess or dysfunctional adiposity. Although weight loss is highly desirable at this CKM stage for cardiometabolic benefits, adopting a heart-healthy diet and increasing levels of physical activity and fitness confer several clinical benefits that are independent of weight loss and should be encouraged. Although providing weight loss counseling is strongly linked to patients' likelihood of attempting weight loss, patients are more likely to achieve clinically significant weight loss if they do not perceive judgment during the weight loss discussion.[127] Therefore, it is important to use patient-centered approaches such as those outlined in toolkits from the STOP Obesity Alliance when engaging in weight loss discussions.[128] For patients with excess weight, intentional weight loss reduces the likelihood of developing metabolic risk factors in a dose-response fashion, with clinically significant benefits seen at ≥5% weight loss.[129] More marked weight loss may be associated with lower risk for incident CVD. Intentional weight loss through lifestyle modification is best achieved through a comprehensive lifestyle intervention of ≥6 months' duration. Obesity pharmacotherapies and bariatric surgery are effective adjunctive approaches to lifestyle change, with bariatric surgery linked to lower CVD and mortality rates in matched observational studies.[130,131] In navigating the various therapeutic options for supporting weight loss, integrated multidisciplinary weight loss teams can facilitate patient-centered approaches to achieving weight reduction goals. In assessing metabolic risk and the need for lifestyle change, it is important to consider both anthropometric and glycemic measures to capture individuals with dysfunctional adiposity despite nonelevated anthropometric measures.[132,133] Notably, non-White adults develop prediabetes or diabetes in normal weight categories more commonly than White adults,[47] illustrating the importance of such an approach for identifying metabolic risk equitably. Among individuals with impaired glucose tolerance, including those with prior gestational diabetes, both lifestyle modification and metformin reduce progression to diabetes.[95,134]

Evidence for Stage 2 CKM Approach

The stage 2 approach is focused on CVD prevention in those with at least 1 established metabolic risk factor or moderate- to high-risk CKD.

Hypertension, Hypertriglyceridemia, and MetS

Improving blood pressure control markedly reduces risk for multiple CVD outcomes in a dose-response fashion. Guidelines support a blood pressure goal of <130/80 mm Hg for all, with the addition of pharmacological therapy to lifestyle change recommended for those with diabetes, CKD, age ≥65 years, or a predicted 10-year ASCVD risk of ≥10%. Although thiazide-type diuretics and calcium channel blockers are similarly effective, ACE inhibitors/ARBs should be prioritized in those with diabetes and albuminuria or those with other CKD given their impact on preventing worsening kidney function.[65,135,136]

Hypertriglyceridemia is causally related to ASCVD. Guidelines support addressing lifestyle factors and medications often linked to hypertriglyceridemia as the initial approach for lowering triglycerides.[66] In those at intermediate ASCVD risk or greater, statin therapy modestly reduces triglycerides and lowers ASCVD risk. In those with modest hypertriglyceridemia (135–499 mg/dL), diabetes, and concomitant risk factors, icosapent ethyl lowers risk for CVD events.[137] Marked hypertriglyceridemia (≥500 mg/dL) is associated with increased pancreatitis risk. Guidelines support fibrate therapy to reduce pancreatitis risk if triglycerides remain markedly elevated after lifestyle change and addressing secondary causes, with fenofibrate associated with least side effects with concomitant statin therapy.[66]

The MetS construct includes the interrelated metabolic risk factors of hypertension, atherogenic dyslipidemia, abdominal obesity, and impaired glucose tolerance. MetS is found among the majority of individuals with diabetes, and collective metabolic risk factor control is strongly linked to CVD risk in diabetes.[138] An approach of lifestyle modification with additional pharmacological therapy as needed to achieve multifactorial risk factor control is associated with reduced CVD event rates.[139]

Diabetes

Among individuals with T2D with overweight or obesity, weight loss through intensive lifestyle intervention improves risk factor control and functional status.[140] Several randomized controlled trials support the utility of moderate- to high-intensity statin therapy for preventing ASCVD events in individuals with diabetes, with more intensive statin therapy indicated for those with higher baseline risk. For individuals with diabetes and high estimated ASCVD risk, the addition of ezetimibe can help achieve the desired goal of ≥50% LDL-C reduction.[141,142]

The use of cardioprotective antihyperglycemic therapies such as SGLT2 inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1RAs) reduces CVD events and mortality and is indicated for patients with diabetes and significant comorbidities on the basis of inclusion criteria from randomized clinical trials. Because of the differential physiological effects of SGLT2 inhibitors and GLP-1RAs, data support a comorbidity-based approach for selecting agents.[143] SGLT2 inhibitors reduce the risk of worsening kidney function and are likely preferred for those with CKD.[69,80,144] Because American Diabetes Association guidelines support achieving an HbA1c <7% in diabetes, GLP-1RAs may be preferred in those with marked hyperglycemia (HbA1c ≥9%) or on high insulin doses because of a stronger impact on glycemia

than SGLT2 inhibitors.[145] In addition, GLP-1RAs may be preferred for those with severe obesity (BMI ≥35 kg/m^2) given their potent impact on weight loss. Data suggest that risk estimation may help guide the targeting of cardioprotective antihyperglycemic therapies.[146] SGLT2 inhibitors may have greatest utility in those with high HF risk given their beneficial impact on reducing HF hospitalizations. GLP-1RAs may be particularly useful in those with high ASCVD risk. Metformin improves glycemic control and is associated with significantly less financial burden than newer cardioprotective antihyperglycemic therapies. For individuals with uncontrolled hyperglycemia (eg, HbA1c, ≥7.5%), co-utilization of metformin with cardioprotective antihyperglycemic therapies (particularly with SGLT2 inhibitors) can help to achieve glycemic targets with less financial burden for patients.

Chronic Kidney Disease

ACE inhibitor/ARB use in proteinuric CKD regardless of diabetes status is linked to decreased kidney disease progression and rates of adverse cardiovascular events.[77] Better blood pressure control leads to CVD risk reduction in CKD regardless of diabetes status.[65,77,147] Consistent benefits have been demonstrated with SGLT2 inhibitors with respect to reduction in CKD progression or need for kidney replacement therapies and incident CVD, with the largest impact on rates of incident HF.[39] GLP-1RAs also have established CVD benefits,[39] with ongoing studies examining kidney outcomes.[148] In the FIDELITY (Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis) pooled analysis, among patients with T2D and CKD on maximally tolerated ACEI/ARB use, finerenone led to reduced risk of kidney disease progression and CVD events, with a particularly potent impact on HF hospitalizations.[149] In the SHARP trial (Study of Heart and Renal Protection), among patients with CKD (almost half of whom were on dialysis) with no known history of ASCVD, patients randomized to simvastatin plus ezetimibe compared with placebo had a significant reduction in first major atherosclerotic events.[150]

Evidence for Stage 3 CKM Approach

The Stage 3 approach is focused on intensified lifestyle change and preventive therapies for those individuals with evidence of subclinical ASCVD or HF overlapping with CKM risk factors or with the risk equivalents of very high-risk CKD or high predicted CVD risk.

Subclinical HF

Elevations of cardiac biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide] or high-sensitivity troponin) and the presence of myocardial structural or functional abnormalities on cardiac imaging identify individuals with subclinical cardiac dysfunction who are at greatest risk for clinical HF. Among patients with asymptomatic systolic dysfunction, ACE inhibitors have been shown to reduce progression to clinical HF or CVD mortality.[151] In post hoc analyses of clinical trials, the addition of β-blocker therapy to ACE inhibitors for those with asymptomatic left ventricular dysfunction was associated with lower rates of the combined outcome of death or HF hospitalization.[152] As a result, ACE inhibitors and β-blockers are recommended in guidelines for individuals with subclinical systolic dysfunction.[71] Among individuals with diabetes, SGLT2 inhibitors reduce the likelihood of incident hospitalized HF or cardiovascular mortality.[153] SGLT2 inhibitors are expected to have the greatest absolute reduction in HF events in those with diabetes and subclinical cardiac dysfunction given their high baseline HF risk.[154] Trials of HF prevention efforts guided by natriuretic peptide screening demonstrate some promise for reducing progression to clinical HF.

Subclinical ASCVD

Extensive data validate CAC scores as a powerful discriminator of ASCVD risk. In the MESA study (Multi-Ethnic Study of Atherosclerosis), a CAC score of 0 was associated with 10-year ASCVD rates <5% among individuals at less than high predicted ASCVD risk, whereas CAC scores ≥100 are linked to 10-year ASCVD rates ≥7.5% (intermediate risk or higher).[155] CAC scores provide the most prognostic information in those estimated to be at intermediate risk, with significant reclassification, improvement in discrimination, and greater estimated absolute risk reduction from statins in those with elevated CAC.[156,157] Current guidelines therefore support selective CAC scoring to guide decisions about statin use in those estimated to be at borderline to intermediate risk for ASCVD events.[62] A growing body of data support the use of CAC, as an indicator of absolute ASCVD risk, for identifying individuals likely to have greatest net benefit from the use of aspirin, as well as from proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, GLP-1RAs, icosapent ethyl for hypertriglyceridemia, and antihypertensive therapy.[158] However, clinicians should be mindful that these studies represent simulated data from randomized controlled trials applied to epidemiological cohorts with significant drop-in of preventive therapies over time, making assessment of absolute event rates difficult.

Risk Equivalents and Overarching Considerations in Stage 3 CKM

Individuals with very high-risk CKD by the Kidney Disease Improving Global Outcomes risk classification or with high predicted CVD risk also represent subgroups of individuals with high absolute risk for whom preventive therapies may have the greatest net benefit, if contraindications to therapy are not present and after competing risk is considered. Several of the preventive therapies described previously might have the largest effect on event rates in this population, and additional preventive approaches may be considered. For example, observational

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data suggest that combination therapy with SGLT2 inhibitors and GLP-1RAs may have a greater impact on major adverse cardiac events and HF events than one of the agents alone.[159] Optimal targeting for such an approach is undefined but could be considered in the stage 3 CKM population at higher absolute CVD risk.

Evidence for Stage 4 CKM Approach

The stage 4 approach is focused on the management of patients with CVD overlapping with CKM risk factors. In addition to a general emphasis on healthy lifestyle practices, guidelines are largely aligned on approaches to guideline-directed medical therapy (GDMT) for patients with HF, with a focus on the 4 pillars of management: β-blockers, angiotensin receptor/neprilysin inhibition, mineralocorticoid receptor antagonists, and SGLT2 inhibitors in HF with reduced ejection fraction (HFrEF).[71,72] Similarly, guidelines generally agree on the use of aspirin or P2Y12 inhibitor and high-intensity statins for patients with ASCVD, with additional LDL-lowering therapy as needed according to LDL-C levels, LDL-C reduction goals, and the presence of accompanying high-risk features.[62,63] Additional evidence supporting therapeutic approaches for those with overlapping CKM risk factors is described in the next section.

Obesity, MetS Components, and CVD

Despite the finding of an obesity paradox among individuals with CVD in which individuals with overweight and grade I obesity have slightly longer survival than those with normal weight, intentional weight loss is linked to clinical benefit among patients with obesity and CVD. A patient-centered and nonjudgmental approach to initiating the weight loss discussion is most effective,[127] with the STOP Obesity Alliance toolkit serving as a useful framework for clinicians.[128] Weight loss through lifestyle modification is linked to improved risk factor control among patients with obesity and ASCVD.[129] In patients with obesity and HFpEF, lifestyle modification, including exercise training, improves functional status.[160] In terms of adjunctive obesity pharmacotherapies, high-dose glucagon-like peptide 1 receptor agonists (GLP-1RAs) and glucose-dependent insulinotropic polypeptide-receptor agonists (GLP-1/GIP-RAs) induce marked weight loss (12%–18% compared with placebo) and improve cardiometabolic risk factors, functional status, and quality of life in individuals with obesity and CVD. GLP-1RAs reduce myocardial infarction, stroke, and cardiovascular mortality in individuals with diabetes.[161] Initial results from the SELECT trial (Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity) indicate that high-dose GLP-1RA causes a reduction in major adverse cardiovascular events in those with obesity and CVD, and the STEP-HFpEF trial (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) will evaluate their effects in HFpEF.[162] Bariatric surgery reduces major adverse cardiac events and mortality rate by >50% in individuals with prior ASCVD and HF.[163] Integrated weight loss teams best facilitate patient-centered approaches to weight loss and may improve clinical outcomes.

The presence of MetS should trigger intensified lifestyle modification, with pharmacological therapy as needed to achieve risk factor control and improve cardiovascular outcomes. In those with hypertriglyceridemia and CVD, icosapent ethyl reduces CVD events and mortality and may be considered after statin therapy.[66] In hypertension, a therapeutic goal for all patients is <130/80 mm Hg. ACE inhibitors/ARBs should be prioritized in patients with CVD and CKD or diabetes for cardiovascular and renal benefits.[62] In HFrEF, calcium channel blockers for hypertension should be avoided. If residual elevated blood pressure persists in Black patients with HFrEF after the 4 pillars of GDMT, hydralazine/isosorbide should be considered for both hypertension control and improved HF morbidity and mortality.[71]

Diabetes and CVD

In patients with T2D and CVD, lifestyle modification improves risk factor control and quality of life. For all patients with HF, SGLT2 inhibitors are a fundamental component of GDMT. Across several randomized clinical trials of HF patients, SGLT2 inhibitor therapy improved quality of life and lowered the risk of hospitalized HF, cardiovascular mortality, and all-cause mortality.[164–166] Despite SGLT2 inhibitor therapy being an antihyperglycemic therapy, similar results are seen in those with and without diabetes. Benefits are also seen in both HFpEF and HFrEF.[167] GLP-1RA data in HF currently are relatively limited. In addition to favorable effects on weight and glycemia, mechanistic studies suggest potential benefits of GLP-1RAs in HFpEF on cardiac function and quality of life, but definitive trial data are pending.[168] There are some concerns about potential deleterious effects of GLP-1RAs in HFrEF due to increases in heart rate and cAMP levels in cardiac myocytes, but data are inconclusive.[169] Agents within the dipeptidyl peptidase 4 inhibitor and thiazolidinedione classes of antihyperglycemic agents have been linked to adverse effects in patients with HR; therefore, these medications are contraindicated in HF patients.

In patients with ASCVD, adding LDL-lowering therapies beyond maximally tolerated statin therapy may have a more powerful clinical effect in those with than those without T2D.[141] Multiple clinical trials demonstrate that both GLP-1RA and SGLT2 inhibitors reduce risk for major adverse cardiovascular outcomes in patients with T2D and ASCVD.[153,161] SGLT2 inhibitors additionally reduce the risk for HF hospitalization and worsening kidney function in patients with ASCVD, whereas GLP-1RAs have more potent effects than SGLT2 inhibitors on weight and HbA1c.[170] These data support a comorbidity-based approach for selecting a cardioprotective antihyperglycemic therapy in those with diabetes

and ASCVD, favoring GLP-1RA in those with severe obesity or marked hyperglycemia and SGLT2 inhibitors in those with CKD or coexisting HF.

Metformin is helpful for achieving glycemic targets but should be avoided in decompensated/unstable HF or for eGFR <30 mL·min^{-1}·1.73 m^{-2} because of increased risk for lactic acidosis. Combination therapy with SGLT2 inhibitors and GLP-1RA, associated with lower CVD risk in observational studies, could be considered for combined HF and ASCVD or CVD with multiple or severely uncontrolled CKM risk factors.[159]

CKD and CVD

In patients with HF, SGLT2 inhibitors causes reductions in kidney disease progression, as well as HF hospitalizations and cardiovascular death.[39,171,172] These outcomes are consistent regardless of diabetes status and ejection fraction.[171,172] ACE inhibitors/ARBs are well known to reduce morbidity and mortality in HFrEF[71]; concomitantly, various trials have shown efficacy for preventing worsening renal function.[173–175] Use of ACE inhibitors/ARBs and mineralocorticoid receptor antagonists may be complicated in CKD because of concerns about hypotension, hyperkalemia, and worsening renal function.[176] An analysis of 6 randomized trials revealed that concomitant SGLT2 inhibitor use reduced the risk of serious hyperkalemia.[177] Studies of angiotensin receptor/neprilysin inhibitor use revealed significantly decreased risk of death resulting from cardiovascular causes and hospitalization for HF, especially in HFrEF,[178,179] while lowering the risk of worsening renal function and serious hyperkalemia.[179,180] Additional data demonstrate that the renal benefits of angiotensin receptor/neprilysin inhibitor use are extended to HFpEF.[181] The addition of potassium binders to combined use of SGLT2 inhibitor and angiotensin receptor/neprilysin inhibitor may be considered to optimize GDMT use in CKD, although evidence on clinical outcomes is uncertain.[176,179] On the basis of hemodynamic responses to renin-angiotensin-aldosterone system inhibitors and SGLT2 inhibitors, there can be an expected 10% to 30% drop in eGFR when these medications are started, and reflexive discontinuation of these agents based on minor fluctuations of serum creatinine should be avoided.[182,183]

In patients with ASCVD, CKD is linked to higher risk. There is no evidence of significant adverse effects with higher doses of statins in CKD,[184] and continuation of statins for ASCVD is recommended for cardiovascular risk reduction. ACE inhibitors/ARBs reduce morbidity and mortality in patients after acute coronary syndrome with left ventricular dysfunction[185] and prevent worsening kidney function.[173–175] Various trials have also shown cardiovascular and renal benefits for SGLT2 inhibitors with predominantly cardiovascular benefits for GLP-1RA reported at this time.[39] Among patients with diabetic kidney disease optimized on renin-angiotensin system inhibition, finerenone has been shown to reduce both adverse cardiovascular and kidney events.[149]

AFib in CKM Syndrome

Extensive data link the CKM risk factors of obesity, hypertension, dyslipidemia, MetS, diabetes, and CKD to a greater risk for AFib and higher AFib burden. Consequently, guidelines generally recommend comprehensive control of these risk factors as part of AFib management. Because the CKM risk factors of hypertension and diabetes increase stroke risk in AFib, their presence favors the use of anticoagulation for stroke prophylaxis. Growing data and guidance support the use of dual oral anticoagulants in nonvalvular AFib, even in those with severe obesity or CKD, although dose reductions are typically needed in the latter because of decreased drug clearance. Lifestyle modification, particularly weight loss, and regular physical activity are associated with decreased AFib burden. In addition, preprocedural weight loss and treatment for obstructive sleep apnea may be linked to a lower risk for recurrent AFib after catheter ablation.[186,187]

Kidney Failure

Despite markedly elevated risk for CVD for patients with kidney failure on maintenance dialysis, evidence for CVD management in this population is scarce because of their limited inclusion in clinical trials. Given the high burden of HF in patients on maintenance dialysis, consideration should be given to more frequent dialysis (hemodialysis or peritoneal dialysis) as a result of beneficial effects demonstrated with respect to left ventricular mass, blood pressure control, and pill burden for antihypertensive medications. Peritoneal dialysis may be preferable in patients with HF, especially in those with lower blood pressure, given the ability to achieve volume control without significant intradialytic hypotension.[188,189] In patients on hemodialysis, factoring in the dialyzability of GDMT therapies such as ACE inhibitors, β-blockers, and other antihypertensives is essential for optimal medical management.[190] For patients on dialysis, statin initiation does not reduce the risk of future ASCVD events.[191,192] However, in a post hoc analysis of patients with diabetes on dialysis, rosuvastatin use was associated with lower risk of adverse cardiovascular outcomes.[193] Moreover, among individuals who are already on statins, statin continuation when transitioning to dialysis is associated with reduced risk of cardiovascular and all-cause mortality,[194] with greater risk reduction seen when statins are combined with ezetimibe.[195]

GAPS IN CKM PREVENTION AND MANAGEMENT

A large body of evidence supports prevention and management approaches for individuals with CKM syndrome, as described previously. Nonetheless, several key gaps persist in the evidence for caring for the patient with CKM (Table 5).

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Table 5. Gaps in the Prevention and Management Approaches for CKM Syndrome

Topic area	Gaps
Interdisciplinary care approach	Defining optimal approaches for collaborative and harmonized CKM care Optimal structure of the interdisciplinary team and roles of CKM coordinators in interprovider communication and patient navigation Optimal strategies for enhancing collaboration between primary providers and subspecialists Benefits of complementary value- and volume-based interdisciplinary care models Approaches to supporting interdisciplinary care across diverse clinical/geographic settings Impact of collaborative care approaches on CKM-related outcomes
Early-life prevention	Optimal approaches for early life prevention Impact of maternal health interventions Impact of multilevel and family interventions Thresholds for starting advanced therapies (including obesity pharmacotherapies and metabolic surgery) Long-term clinical outcomes related to screening and prevention efforts in early life
Strategies to support weight loss	Optimal strategies to support weight loss in clinical settings Targeting of obesity pharmacotherapies and associated impact on CVD outcomes Long-term approaches for obesity pharmacotherapies, including strategies for successful discontinuation Need for clinical trials of bariatric surgery in patients with CVD Utility and optimal deployment of integrated weight loss teams for supporting patient-centered approach to achieving weight reduction goals
Use of cardioprotective antihyperglycemic therapies in those with diabetes at risk for CVD	Clarifying approach to using SGLT2 inhibitors and GLP-1RAs in those with diabetes and without CVD Defining thresholds for use of cardioprotective antihyperglycemic therapy Prioritizing SGLT2 inhibitors vs GLP-1RA; need to validate the utility of a comorbidity-based approach for agent selection Establishing the utility and indications for co-utilization of SGLT2 inhibitors and GLP-1RA in the population at risk for CVD
Use of cardioprotective antihyperglycemic therapies in those with diabetes and existing CVD	Prevalent ASCVD: both GLP-1RA and SGLT2 inhibitors recommended in guidelines; understanding which to prioritize and how Impact of using comorbidities (CKD, severe obesity, marked hyperglycemia) and concomitant HF to guide prioritization Prevalent HF: when to consider adding GLP-1RA to SGLT2 inhibitors Impact of using comorbidities and coexisting ASCVD Defining efficacy and safety of GLP-1RA in HFpEF and HFrEF Co-utilization of GLP-1RA and SGLT2 inhibitors: effectiveness and optimal targeting of co-utilization approach
Lipid-lowering therapies beyond statins in diabetes and high CKM risk	When and how to use nonstatin therapies Statin+ezetimibe agreed on in high-risk primary prevention population; are there high-risk primary prevention subgroups in whom additional LDL-C lowering therapy is indicated? Use of icosapent ethyl may be considered for hypertriglyceridemia; need to define effective approaches for addressing residual ASCVD risk linked to elevated triglycerides
Management of CVD in patients with CKD	Limited evidence regarding several aspects of GDMT in HF with eGFR <30 mL·min^{-1}·1.73 m^{-2} due to limited inclusion in clinical trials Use of SGLT2 inhibitors and ARN inhibitors Interpretation of fluctuations in kidney function with GDMT Approach to GDMT titration and use of concurrent agents Criteria for multidisciplinary involvement for HF and high-risk CKD and impact on outcomes

ASCVD indicates atherosclerotic cardiovascular disease; ARN, angiotensin receptor/neprilysin; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; GLP-1RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; and SGLT2, sodium-glucose cotransporter-2.

Interdisciplinary Care

Although there is a clear need for care models that support interdisciplinary collaboration in order to reduce care fragmentation for patients navigating a confluence of health conditions, the evidence for the impact of such approaches on clinical outcomes is just beginning to emerge. In addition, it is important to better understand how such models can be applied across diverse clinical and geographic settings with differing availability of health care resources, including subspecialists to accommodate patient referrals. Optimal strategies for supporting partnerships with primary care clinicians and patient-centered approaches to coordinating care also need to be better defined.

Early-Life Prevention

Prenatal exposures are known to influence offspring CKM health.[196] However, the impact of interventions to improve maternal health on CKM profiles among children is not yet fully defined. Once CKM risk factors are present, management during childhood and adolescence can be challenging because the child, their community, and their environment need to be considered for optimally effective therapeutic interventions.[197] This suggests that multimodal approaches to prevention and treatment should be considered.[198] Family-based approaches may be protective against the development of obesity in young adulthood. Other multilevel interventions targeting

the food and physical activity environments in addition to children and their support networks may enhance effectiveness, but further data are needed. Developing prevention and management strategies in childhood that are effective across diverse settings remains a key need. Although recent guidelines endorse the adjunctive use of obesity pharmacotherapies and bariatric surgery for children with obesity,[91] the optimal targeting of such therapies in childhood remains unclear. It is also critical to acquire data on the long-term clinical outcomes related to CKM screening, staging, and therapeutic approaches in childhood, adolescence, and young adulthood.

Strategies to Support Lifestyle Changes and Weight Loss

Although options to support successful weight loss are expanding, many gaps remain. Newer obesity pharmacotherapies, particularly high-dose GLP-1RA and GLP1/GIP-RA agents, induce marked weight loss and improve metabolic risk factors,[199,200] but the optimal targeting of these agents as adjuncts to lifestyle modification in the broad population with obesity is unclear. The impact of these obesity pharmacotherapies for reducing major adverse cardiac events in patients with obesity and CVD, but without diabetes, is being evaluated.[162] Studies are also evaluating the impact of GLP-1RAs on symptoms, physical limitations, and exercise function in HFpEF.[168] If these trials have positive results, patients with obesity and prevalent CVD might be prioritized for these agents. The long-term impact of these pharmacotherapies is unclear. In addition, the discontinuation of these agents is associated with weight regain,[201] and strategies for successful weight maintenance with reductions or discontinuation of newer obesity pharmacotherapies are undefined. In controlled prospective studies, bariatric surgery markedly reduced major adverse cardiac events and mortality in those with and without CVD,[163,202] but interventional trials are needed among those with CVD to confirm efficacy and to assess safety. Integrated multidisciplinary teams improve patient-centered approaches to lifestyle change and weight loss support, but more data are needed on the optimal structure and deployment of these teams and their impact on clinical outcomes. As part of this integrated approach, more effective engagement with stakeholders such as insurance companies and employers is needed to expand incentives for supporting positive lifestyle changes to positively affect clinical outcomes.

Cardioprotective Antihyperglycemic Therapies in Those at Risk for CVD

The cardioprotective therapies SGLT2 inhibitors and GLP-1RAs have revolutionized preventive care for individuals with diabetes. However, more clarity is needed on the targeting and prioritization of these antihyperglycemic agents in individuals with diabetes at risk for CVD. Although guidelines generally agree that these agents are indicated for those at high risk for CVD, the criteria for meeting this threshold are unclear. Approaches across guidelines are inconsistent and include the presence of comorbidities,[145] the presence of diabetes-related complications or long diabetes duration,[62,63,145] and the use of CVD risk calculators to define high risk[62,63,71]; further clarity and validation are needed. Furthermore, strategies for prioritizing the selection of SGLT2 inhibitors or GLP-1RAs in the at-risk population are not well defined. Prioritization based on comorbidities such as obesity for GLP-1RA or CKD for SGLT2 inhibitors is reasonable on the basis of the physiological effects of these agents, but this also requires validation. Risk calculators hold promise to further refine the selection, with high HF risk, for example, potentially favoring use of SGLT2 inhibitors.[203] Subclinical ASCVD and HF could similarly guide selection of therapies. As the science related to pharmacogenomics matures further, it is possible that in the future knowledge of genetic variants may help refine the selection of antihyperglycemic therapies.

Co-utilization of SGLT2 inhibitors and GLP-1RA is recommended to decrease risk in high-risk patients,[145] but the approach to delineating this subset of patients is unclear, and interventional trials demonstrating the cardiovascular benefits of combined SGLT2 inhibitors and GLP-1RAs in those at risk for CVD are lacking.[204] Further data are urgently needed to guide prioritization of antihyperglycemic agents in individuals with diabetes at risk for CVD.

Cardioprotective Antihyperglycemic Therapies in Those With CVD

Cardiovascular outcome trials of SGLT2 inhibitors and GLP-1RAs demonstrate that individuals with existing CVD derive the greatest clinical benefit from these therapies.[165,205] In individuals with diabetes and ASCVD, the approach to prioritizing selection of SGLT2 inhibitors versus GLP-1RAs is unclear because these therapies have not been directly compared in clinical trials. It is possible that individuals with coexisting severe obesity or uncontrolled hyperglycemia may benefit most from GLP-1RAs, whereas those with CKD or concomitant HF will benefit most from SGLT2 inhibitors, but the clinical utility of such an approach needs to be verified. Furthermore, the approach to selecting the best antihyperglycemic agent in patients with diabetes and ASCVD but without such comorbidities is unclear. Although co-utilization of SGLT2 inhibitors and GLP-1RA has been associated with improved clinical outcomes in observational studies and is suggested in clinical guidelines,[62,63,76] interventional data are lacking, and the group who benefits most from such an approach is undefined. Among individuals with HF, for whom SGLT2 inhibitors are standard therapy, the optimal criteria for adding

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GLP-1RAs such as coexisting ASCVD, multiple comorbidities, or high levels of excess weight/glycemia should be further investigated and clarified. Further data are also needed on whether GLP-1RA use is similarly safe and effective in patients with HFpEF and HFrEF.

Lipid-Lowering Therapies Beyond Statins in Diabetes and High CKM Risk

Management of dyslipidemia is at the heart of ASCVD reduction for people with CVD and diabetes, who frequently fall into a very high-risk category because of high event rates. For individuals with diabetes and ASCVD, high-intensity statins are recommended first-line lipid-lowering therapy. Based on clinical trial data, both American and European guidelines support the addition of ezetimibe, followed by PCSK9 inhibitors when needed, as reasonable for very high-risk patients with diabetes and ASCVD on maximally tolerated statins who have not achieved a 50% reduction of LDL-C or with an LDL-C >70 mg/dL.[62,63] American and European guidelines differ on the use of PCSK9 inhibitors for primary prevention; European guidelines support consideration of PCSK9 inhibitors in very high-risk patients without familial hypercholesterolemia not meeting LDL-C goals.[63] In the primary prevention population, there are key questions about the value and net benefit of adding PCSK9 inhibitors or other novel LDL-lowering therapies to statins and ezetimibe.[63] Further research is needed to delineate whether there are subgroups of very high-risk primary prevention patients for whom such an approach could be both beneficial and cost-effective.

Hypertriglyceridemia is commonly encountered in diabetes, is a component of MetS, and is linked to greater ASCVD risk. For patients with hypertriglyceridemia in the setting of ASCVD or diabetes with additional comorbidities, data support considering the addition of icosapent ethyl (also known as eicosapentaenoic acid) to statin therapy for further lowering ASCVD risk.[137] There have been conflicting results from trials of fish oil supplementation, and there are questions about the extent to which harm from the use of mineral oil in the control arm of the REDUCE-IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl—Intervention Trial) contributed to the favorable results observed for eicosapentaenoic acid in that study. However, consistent differences between studies of eicosapentaenoic acid and eicosapentaenoic acid/docosahexaenoic acid suggest that physiological differences between these supplements likely primarily account for disparate outcomes of clinical trials. In addition, it is unclear why lesser or no risk reduction is seen in fibrate trials in patients with hypertriglyceridemia despite greater impact on triglycerides than icosapent ethyl.[206] It has been speculated that this may be linked to greater reduction of apolipoprotein B concentrations with icosapent ethyl,[207] but more research on this topic is needed.

Management of CVD in Patients With CKD

Most trials for GDMT in HF and CKD do not have adequate representation, especially for patients in the more advanced stages of CKD (eGFR<30 mL·min^{-1}·1.73 m^{-2}).[176] Hence, evidence for most GDMT for HF in patients with advanced CKD is limited.[71,208] There is also limited guidance with respect to interpretation of fluctuation of kidney function changes seen with decongestion and initiation/titration of GDMT in HF,[183] with considerable misinterpretation of expected fluctuations in markers of glomerular filtration as acute kidney injury. This results in the reflexive de-escalation of GDMT for HF, especially in the setting of CKD stage 4 and 5. Last, given concerns about hyperkalemia and the perception of worsening kidney function in CKD, there is no standard approach to the initiation and titration of GDMT in HF with CKD.[71] Comparative-effectiveness data for multidisciplinary involvement of subspecialty services and allied health personnel for GDMT optimization compared with usual care in patients with HF and CKD remain understudied at this time.[209] Data on the management of ASCVD in CKD are also lacking because of the underrepresentation of patients with CKD in CVD trials. Therefore, evidence for continued use of various components of guideline support care for ASCVD in advanced CKD stages is lacking.[210]

CONCLUSIONS

CKM syndrome reflects the impact of multisystem pathophysiological interrelationships, nested within multilevel SDOH, the confluence of which determines clinical outcomes. To achieve new frontiers in our understanding of CKM syndrome, our scientific approach will need to reflect this fundamental interdependence. Research efforts must involve collaboration across specialties, ensuring that perspectives from pediatrics, adult primary care specialties, nephrology, cardiology, and endocrinology are equitably incorporated. It is important that clinical research studies include the full spectrum of patients with CKM syndrome, with a particular need for inclusion of patients with CKD who have traditionally been underrepresented in cardiovascular trials. It is also critical that research studies include greater proportions of underrepresented racial and ethnic groups and postmenopausal women to ensure greater generalizability of investigative findings. Cross-disciplinary research is critical, with basic, translational, clinical, and epidemiological investigations having potential to provide complementary insights into mechanistic pathways, populations at risk, prediction strategies, and novel therapeutic approaches.

Many of the key considerations for CKM syndrome care moving forward relate to where, when, and how to deploy an increasing array of cardioprotective therapies with multisystem effects. In navigating these decisions, it is important

to consider short- and long-term risk, net clinical benefit, the anticipated duration of therapies, access to care, cost-effectiveness, and patient preferences and values. Risk algorithms that reflect the multiple adverse cardiovascular and kidney outcomes that occur with increased frequency among patients with CKM syndrome can help to better target therapies to subpopulations in whom they will have the greatest impact. With the present low rates of control of individual CKM risk factors, there is a need to define optimal strategies for prioritizing and managing multiple risk factors at various stages of CKM syndrome. Real-world effectiveness and implementation studies, with both quantitative and qualitative components, will be needed to refine CKM care models in the population.

In addition to ongoing efforts to optimize CKM care, it is crucial that there are concurrent efforts to address the historic influx of patients with CKM syndrome, driven by epidemics of obesity and diabetes. This necessitates enhanced approaches to preserving ideal cardiovascular health across the life course and across diverse populations. Enhanced CKM screening strategies across the life course, particularly for those at highest risk, will facilitate early interventions to avoid the progression of CKM syndrome and to mitigate risk for CVD events and kidney failure. Prevention efforts must extend beyond clinical settings to consider the social context in which individuals live, work, eat, and play. There is also a need to address the interplay between SDOH and biological predisposing factors, which can, in combination, have a profound impact on CKM-related risk. Holistic approaches to both prevention and management are needed to fully and equitably address the population impact of CKM syndrome, with the goal of advancing cardiovascular health for all.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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