

# Optimal Management of Patients With Cardio-Kidney- Metabolic Syndrome

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## HIGHLIGHTS

- › An Overview of Cardiovascular Kidney Metabolic Syndrome
- › Diabetes, Cardiorenal, and Metabolic Multispecialty Practice Recommendations and Early Intensive Management of Cardio-Renal-Metabolic Disease
- › A Team-Based Approach to Type 2 Diabetes and Cardiovascular Care

# Optimal Management of Patients With Cardio-Kidney-Metabolic Syndrome

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## Optimal Management of Patients With Cardio-Kidney-Metabolic Syndrome

### OVERVIEW

This supplement to *The American Journal of Managed Care*<sup>®</sup> explores cardio-kidney-metabolic (CKM) syndrome, including its background, guidelines on the management of CKM syndrome, and subsequent translation of data into clinical practice using evidence from existing literature, consensus statements from multidisciplinary experts, and existing programs for coordinated care.

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**FACULTY**

**Keith C. Ferdinand, MD**

Professor of Medicine  
Department of Cardiology  
Tulane University School of Medicine  
New Orleans, LA

**Yehuda Handelsman, MD**

Medical Director and Principal Investigator  
Metabolic Institute of America  
Tarzana, CA

**Erin D. Michos, MD, MHS**

Associate Director of Preventative Cardiology  
Division of Cardiology  
Johns Hopkins University School of Medicine  
Baltimore, MD

**Ian J. Neeland, MD**

Associate Professor of Medicine  
Case Western Reserve University School of Medicine

Director of Cardiovascular Prevention  
Director of Center for Integrated and Novel Approaches in Vascular-Metabolic Disease  
Division of Cardiovascular Medicine  
University Hospitals Harrington Heart and Vascular Institute  
University Hospitals Cleveland Medical Center  
Cleveland, OH

**Sanjay Rajagopalan, MD**

Director  
Professor of Medicine  
Cardiovascular Research Institute  
Case Western Reserve University School of Medicine

Division Chief  
Cardiovascular Medicine  
University Hospitals Cleveland Medical Center  
Cleveland, OH

**FACULTY DISCLOSURES**

These faculty have disclosed the following relevant commercial financial relationships or affiliations in the past 12 months.

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# Introduction to Optimal Management of Patients With Cardio-Kidney-Metabolic Syndrome

Erin D. Michos, MD, MHS

**T**he link between cardiovascular and kidney health has been known since Robert Bright first described significant changes to the structure of the heart in patients with advanced kidney disease nearly 200 years ago.<sup>1</sup> The French pathologist Frédéric Justin Collet similarly utilized autopsy-based anatomical findings to describe passive renal (kidney) congestion secondary to heart dysfunction in 1903.<sup>2</sup> Yet, the term cardiorenal syndrome (CRS) was only classified in more recent years to encompass the bidirectional relationship between primary cardiac and kidney disorders.<sup>3-5</sup>

Originally, CRS was used to describe kidney injury that was secondary to heart failure (HF).<sup>6</sup> In 2004, investigators at the National Heart, Lung, and Blood Institute formally defined CRS as a state in which therapy to relieve HF symptoms is limited by declining kidney function.<sup>7</sup> In 2008, the definition of CRS was subsequently broadened by a consensus from the Acute Dialysis Quality Initiative, which established that cardiovascular and kidney diseases share similarities in pathophysiology and mutually aggravate worsening outcomes in the other organ class.<sup>4,5</sup> CRS was further classified into 5 subtypes according to whether the impairment of each organ was primary, secondary, or stemmed from coexisting cardiovascular and kidney dysfunction as a systemic disease.

Chronic kidney disease (CKD) induces a systemic, chronic, proinflammatory state that results in adverse vascular and myocardial remodeling processes including atherosclerosis, vascular calcification, valvular calcification, and myocardial fibrosis.<sup>8</sup> In other words, CKD promotes an accelerated aging of the cardiovascular system. It should be noted that patients with CKD are more likely to die from cardiovascular disease (CVD) than they are from progression to end-stage kidney disease.<sup>9</sup> Fortunately, therapies such as angiotensin receptor blockers, sodium glucose cotransporter 2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide 1 receptor antagonists have demonstrated improvement in both cardiovascular and kidney outcomes.<sup>10-13</sup>

Additionally, with the emergence of obesity as a driving force behind risk factors for cardiovascular and kidney disease, CRS was further expanded to cardio-renal-metabolic syndrome.<sup>14</sup> Research

has highlighted the strong association between obesity and the inflammatory, neurohormonal, vascular, and metabolic responses that converge in cardiovascular and renal impairment.<sup>15</sup> Prolonged obesity was found to induce pathological changes in renal blood flow (RBF), vasodilation, and glomerular hyperfiltration, which are later followed by declines in RBF and glomerular filtration rate, which affect kidney function.<sup>16,17</sup> Furthermore, patients with obesity were affected by greater metabolic demands resulting in risk factors for metabolic syndrome, including insulin resistance, hypertension, and dyslipidemia, which contributed to obesity-related HF.<sup>18,19</sup>

More recently, the American Heart Association (AHA) updated its classification and introduced the term cardio-kidney-metabolic syndrome (CKM) to reflect the multidirectional relationship between metabolic risk factors, CKD, and the cardiovascular system.<sup>20</sup> In a scientific statement from the AHA regarding the management of CKM syndrome, unique management considerations are recommended for individuals with established CVD, or who are at high risk for CVD with coexisting metabolic risk factors, CKD, or both.<sup>21</sup>

A disproportionate CKM burden exists in patients with adverse social determinants of health, family history, and concomitant inflammatory conditions.<sup>20</sup> Additionally, traditional risk factors for metabolic syndrome such as dyslipidemia, hypertension, obesity, insulin resistance, and hyperglycemia, as well as behavioral factors such as physical inactivity, smoking, and unhealthy eating patterns also increase the risk for worsened cardiovascular and kidney outcomes.<sup>22,23</sup> The current AHA advisory provides a holistic approach to prevention and care optimization within CKM syndrome, though it identifies an unmet need to move beyond subspecialty silos to collaborative interdisciplinary patient-centered care models to optimize CKM health outcomes.<sup>20</sup>

This supplement will address some of the existing gaps and challenges to our understanding of CKM syndrome, including early screening and prevention measures, comprehensive management strategies to facilitate targeted interventions, and the translation of evidence-based guidelines to an integrated and interdisciplinary approach to care.<sup>24</sup>

In the first article in this supplement,<sup>25</sup> Keith C. Ferdinand, MD, from the Tulane University School of Medicine, New Orleans, Louisiana, presents an overview of CKM syndrome and the recent AHA presidential statement on the classification and management of the CKM syndrome. Dr Ferdinand explores current evidence on the prevalence and pathophysiology of CKM syndrome, as well as considerations of comorbid conditions and social determinants of health.

Many treatment guidelines in this therapy area come from single specialty groups. Hence, in the second article,<sup>26</sup> Yehuda Handelsman, MD, from the Metabolic Institute of America, Tarzana, California summarizes the recommendations of a multispecialty group of experts in cardiology, endocrinology, diabetology, lipidology, coagulation, nephrology, hepatology, obesity, and primary care toward the management of diabetes, cardiorenal, and/or metabolic (DCRM) diseases. The recommendations are targeted toward nonspecialists and cover patient assessment and treatment, including lifestyle management and pharmacotherapy strategies.

Notably, both the AHA presidential statement and DCRM guidelines highlight the need for coordinated care for patients with CKM syndrome. In the final article,<sup>27</sup> Ian J. Neeland, MD, from Case Western Reserve University School of Medicine and Sanjay Rajagopalan, MD, from University Hospitals Cleveland Medical Center, both in Cleveland, Ohio, present an overview of the Center for Integrated and Novel Approaches in Vascular-Metabolic Disease (CINEMA) program, which utilizes a coordinated framework approach to patients with CKM syndrome. They describe the key features of the CINEMA program and the key outcomes over the 2 years that the program has existed. The authors also discuss the scalability of such a program and some of the major barriers to implementation and potential strategies to overcome them.

In conclusion, this supplement explores the background, guidelines, and subsequent translation of data into clinical practice of CKM syndrome using evidence from existing literature, consensus statements from multidisciplinary experts, and existing programs for coordinated care. ■

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**Author Affiliation:** Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD

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**Authorship Information:** Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

**Address Correspondence to:** Erin D. Michos, MD, MHS, Johns Hopkins University School of Medicine, Ballock 524-B, 600 N Wolfe St, Baltimore, MD 21287. Email: edonnell@jhmi.edu

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# An Overview of Cardiovascular-Kidney-Metabolic Syndrome

Keith C. Ferdinand, MD

## Introduction

Type 2 diabetes (T2D), chronic kidney disease (CKD), and cardiovascular disease (CVD) represent major health challenges. An estimated 700 million<sup>1</sup> and 523 million<sup>2</sup> people worldwide have CKD and/or CVD. Current estimates indicate that, of the 529 million people with diabetes globally, the vast majority (96%) have T2D.<sup>3</sup> Presence of these conditions leads to a substantial burden of morbidity and mortality, which disproportionately affects those in underrepresented racial and ethnic groups.<sup>4-7</sup> In the US, CVD alone resulted in an age-adjusted mortality rate of 224.4 per 100,000 people in 2020.<sup>8</sup> The US mortality rates for diabetes (*diabetes* refers to both type 1 and type 2 diabetes, unless otherwise specified) and CKD are estimated to be 12.9 per 100,000 people<sup>3</sup> and 14.6 per 100,000,<sup>9</sup> respectively. Furthermore, CVD, T2D, and CKD are now known to be more closely associated than previously thought, and this interconnection has been termed cardiovascular-renal-metabolic (CRM) syndrome. The American Heart Association (AHA) has recently redefined CRM syndrome as cardiovascular-kidney-metabolic (CKM) syndrome<sup>10</sup>; both terms are used interchangeably.

## Prevalence of Cardiovascular-Kidney-Metabolic Syndrome

CKM conditions are common. A cross-sectional survey of 11,607 participants in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2020 estimated that 25% of participants had at least 1 cardiac, renal, or metabolic condition.<sup>11</sup> The survey also showed that there is considerable overlap between CKM conditions, with 8% of participants (rising to 25% of participants aged  $\geq 65$  years) having more than 1 CKM condition.<sup>11</sup>

## Comorbid CKM Conditions

The increased risk of CVD in people with T2D is well known, and in 1 study in 13 countries approximately one-third of people with T2D also had CVD.<sup>12</sup> Increased hemoglobin A<sub>1c</sub> variability is associated with greater risk of incident CVD. Concomitant CKD is also common in patients with T2D with up to 40% of people with T2D also having CKD.<sup>13</sup> Comorbid CKM conditions are also common in people with

## ABSTRACT

Cardio-kidney-metabolic (CKM) syndrome is a term to describe the interconnection between cardiovascular disease, type 2 diabetes, and chronic kidney disease. The National Health and Nutrition Examination Survey from 1999 to 2020 estimated that 25% of participants had at least 1 CKM condition. It is proposed that CKM syndrome originates in excess and/or dysfunctional adipose tissue, which secretes proinflammatory and prooxidative products leading to damaged tissues in arteries, the heart, and the kidney, and reduction in insulin sensitivity. CKM syndrome is classified into 4 stages based on the presence of risk factors and clinical signs. Risk factors associated with progression of CKM syndrome include chronic inflammatory conditions, family history of diabetes or kidney disease, mental health and sleep disorders, increased levels of elevated high-sensitivity C-reactive protein, and sex-specific risk enhancers. There are substantial racial and ethnic differences, although they are likely due to social determinants of health (SDOH). The American Heart Association suggests that CKM syndrome screening should include both biological factors and SDOH. Interventions in patients with stages 0 to 3 CKM syndrome focus on preventing future cardiovascular events by management of excess adiposity, mainly through diet and exercise in the early stages, then through pharmacological treatment of metabolic syndrome components in later stages. There is a general acceptance that treatment of CKM syndrome should involve a holistic approach to prevention, screening, and management to improve outcomes and reduce long-term morbidity and mortality.

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heart failure (HF). A meta-analysis of patients with HF across the spectrum of ejection fraction observed that 32% also had CKD.<sup>14</sup> Similarly, a US-based study found that 64% of patients hospitalized for HF had estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m<sup>2</sup>.<sup>15</sup> The prevalence of T2D is also common in patients with HF; an estimated 20% to 40% of people with HF have T2D<sup>16</sup> and 16% of people with HF have both T2D and CKD.<sup>16</sup> Approximately 35% of people with CKD also have diabetes<sup>17</sup> and 50% of people with stage 3 to 5 CKD have CVD.<sup>18</sup>

### Increasing Burden of CKM Conditions

The prevalence and burden of CKM conditions is increasing over time<sup>11</sup> and this may be linked to increasing age,<sup>19</sup> prevalence of T2D and obesity,<sup>20,21</sup> physical inactivity,<sup>22</sup> and poor control of hypertension.<sup>22,23</sup> The prevalence of overlapping CKM conditions is also increasing.<sup>11</sup> Ostrominski and colleagues observed a significant increase in the proportion of US adults with at least 2 CKM conditions between 1999 to 2000 and 2017 to 2020 and a doubling of the proportion of adults with all 3 CKM conditions in the same time periods.<sup>11</sup> Multiple CKM conditions are more common with older age, male sex, self-reported non-Hispanic Black race or ethnicity, and adverse socioeconomic circumstances.<sup>11</sup> Patients with multiple CKM conditions are at risk of increased mortality.<sup>24-27</sup> In patients with both diabetes and CKD, the adjusted risk difference for cardiovascular (CV) mortality was 16%, compared with the risks conferred by T2D (3%) or CKD alone (6%).<sup>26</sup> Although there has been a general decrease in CV mortality over the past 20 years,<sup>28</sup> the decline in CVD mortality rates reversed during the COVID-19 pandemic in 2020 and mortality rates have remained high.<sup>29</sup> Globally, overall CKD mortality is increasing despite decreasing mortality rates among patients with end-stage kidney disease.<sup>30</sup> There remains a considerable difference in outcomes between male and female patients with components of CKM syndrome including CVD,<sup>31</sup> CKD,<sup>32</sup> and HF.<sup>33</sup>

### Pathophysiology of Cardiovascular-Kidney-Metabolic Syndrome

The underlying pathophysiology of CKM syndrome is a result of the interrelationship among metabolic risk factors, CKD, and the CV system. Although there are a number of potential mechanisms underlying the relationships between CKM conditions (Figure 1),<sup>34</sup> it is proposed that this syndrome primarily originates in excess and/or dysfunctional adipose tissue, which secretes proinflammatory and prooxidative products leading to damage to tissues in arteries, the heart, and the kidney,<sup>4,35-37</sup> and reduction in insulin sensitivity.<sup>35,37</sup>

### Staging of Cardiovascular-Kidney-Metabolic Syndrome

The AHA has recently proposed that CKM syndrome is classified into 4 stages (Table) based on presence of risk factors (stage 0, no CKM risk factors; stage 1, excess or dysfunctional adiposity but

no evidence of subclinical or clinical CKD or CVD; stage 2, established metabolic risk factors or CKD; stage 3, subclinical CVD in CKM syndrome; stage 4, clinical CVD or Kidney Disease Improving Global Outcomes [KDIGO] stage 4 CKD).<sup>10</sup>

### Risk Factors for Cardiovascular-Kidney-Metabolic Syndrome

Notably, the definition of CKM syndrome given in the AHA presidential advisory in 2023 includes patients who do not have clinical CVD but do have risk factors for CVD due to the presence of metabolic risk factors, CKD, or both; and individuals with existing CVD that is potentially related to or that may complicate metabolic risk factors or CKD.<sup>10</sup>

Further to the risk inherent in each of the CKM conditions, there are several known risk factors for progression of CKM. The AHA estimates that 1 in 3 people have risk factors that contribute to CVD, metabolic disorders, and/or kidney disease.<sup>38</sup> In addition to the risk factors included in the staging system, these include chronic inflammatory conditions (eg, psoriasis, rheumatoid arthritis, lupus, HIV/AIDS), family history of diabetes or kidney disease, mental health and sleep disorders, increased levels of elevated high-sensitivity C-reactive protein, and sex-specific risk enhancers such as premature menopausal transition, adverse pregnancy outcomes, and polycystic ovary syndrome.<sup>10</sup> There are substantial racial and ethnic differences in a number of these risk factors, including the metabolic risk factors.<sup>39</sup> While some genetic factors underlie these differences (for example, people with South Asian ancestry are likely to have a higher proportion of ectopic body fat at any given body mass index [BMI]<sup>40</sup>), the primary driver of the racial and ethnic differences is the adverse effects of social determinants of health (SDOH).<sup>41,42</sup>

### Social Determinants of Health

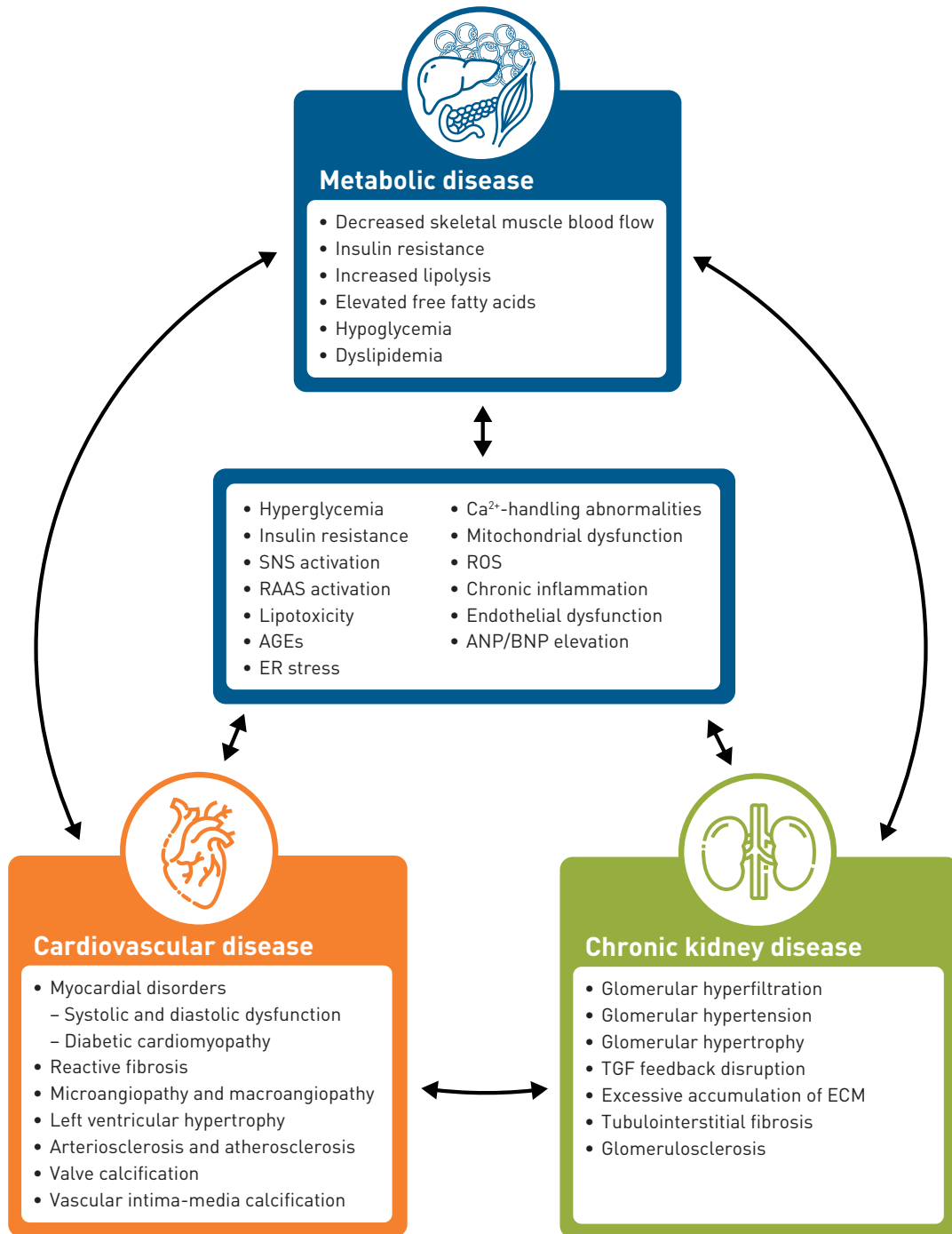
The impact of SDOH on incidence and outcomes in CVD, CKD, and diabetes has become increasingly apparent in recent years. In 1 analysis of the NHANES study, SDOH were completely responsible for the disparity in CV mortality between Black/African American and White American populations.<sup>43</sup> In the analysis of the NHANES survey by Ostrominski et al, the burden of comorbidities in people with CKM conditions was disproportionately high among participants who were unemployed, had lower socioeconomic status, and without a high school degree.<sup>11</sup> The AHA proposes that epigenetic factors predisposing an individual to CKM syndrome should be viewed in context of SDOH (Figure 2).<sup>44</sup>

### Screening for Cardiovascular-Kidney-Metabolic Syndrome

The AHA suggests that screening should include both biological factors and SDOH.<sup>10</sup> In adults, screening recommendations are based



**FIGURE 1.** Interactions Between CKM Conditions<sup>34</sup>



AGEs, advanced glycated end-products; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CKM, cardiovascular-kidney-metabolic; ECM, extracellular matrix; ER, endoplasmic reticulum; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TGF, tubuloglomerular feedback.

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on CKM stage and include measurement of adiposity via annual BMI and waist circumference measurements in all patients. Adults with stage 0 CKM should be screened for components of metabolic syndrome every 3 to 5 years. In adults with stage 1 CKM, this should be done every 2 to 3 years, and in adults with stage 2 or higher CKM, annual screening should be performed. Kidney function tests (urine albumin-creatinine ratio and eGFR) are proposed for accurate KDIGO staging and should be performed annually in stage 2 or higher CKM, and more frequently in those with higher KDIGO risk.

Risk calculations are available for CVD including the Framingham Risk Score for coronary heart disease,<sup>45</sup> the American College of

Cardiology (ACC)/AHA pooled cohort equations,<sup>46</sup> and the American Diabetes Association 2024 Standards of Care,<sup>47</sup> although none of these adequately account for SDOH. However, recognition of the impact of SDOH on CVD risk, changes in the prevalence of risk factors, and changes in available therapies has meant that newer predictive equations are warranted to include the effects of SDOH. This was the impetus for the AHA to develop a new risk prediction equation.<sup>10</sup> The PREVENT equation<sup>48</sup> provides 10- and 30-year risk estimates for total CVD and includes CKM factors and SDOH. Controversially, the calculation deliberately excludes race as a factor, and instead uses the social deprivation index. The equation has shown good

calibration among Black individuals but has not been extensively tested in other racial/ethnic groups. Most tools evaluate financial strain, education/literacy, personal safety, and whether the person requires assistance in addressing their social needs.<sup>49-52</sup> Tools that incorporate assessment of behaviors affected by SDOH, such as the Oregon Community Health Information Network<sup>53</sup> and Centers for Medicare & Medicaid Services,<sup>50</sup> may be of particular value.

## Management of Cardiovascular-Kidney-Metabolic Syndrome

Currently available treatment guidelines for CKM conditions are discussed in the other articles in this supplement.<sup>54,55</sup> It is known that having multiple CKM conditions is associated with increased mortality<sup>11</sup>; to address the increase in CV mortality, the totality of the CKM burden should be considered.

Interventions for people with stage 0 to 3 CKM syndrome focus on preventing future CV events by management of excess adiposity. This is mainly accomplished through diet and exercise in stage 1, and through pharmacological treatment of metabolic syndrome components in stage 2 (Figure 3).<sup>10</sup> In subclinical CVD (stage 3 CKM syndrome), patients should be treated to manage their CKM conditions. In more advanced disease (stage 4), patients should be treated according to the relevant guidelines to manage their CKM conditions (ADA, ACC/AHA/Heart Failure Society of America [HFSa], KDIGO).

Aside from specific recommendations for treatment and management, there is acceptance that treatment of CKM syndrome should include a multispecialty team. This is recognized by

**TABLE.** American Heart Association Staging of CKM Syndrome<sup>10</sup>

CKM syndrome stages	Definition
<b>Stage 0:</b> No CKM risk factors	<ul style="list-style-type: none"> <li>• Normal BMI and waist circumference</li> <li>• Normoglycemia</li> <li>• Normotension</li> <li>• Normal lipid profile</li> <li>• No evidence of CKD or subclinical or clinical CVD</li> </ul>
<b>Stage 1:</b> Excess or dysfunctional adiposity	<ul style="list-style-type: none"> <li>• BMI <math>\geq 25</math> kg/m<sup>2</sup> (or <math>\geq 23</math> kg/m<sup>2</sup> if Asian ancestry)</li> <li>• Waist circumference <math>\geq 88/102</math> cm in women/men (or if Asian ancestry <math>\geq 80/90</math> cm in women/men)</li> <li>• Fasting blood glucose <math>\geq 100</math>-124 mg/dL or HbA<sub>1c</sub> between 5.7% and 6.4%<sup>a</sup></li> </ul>
<b>Stage 2:</b> Metabolic risk factors and CKD	<ul style="list-style-type: none"> <li>• Metabolic risk factors (hypertriglyceridemia <math>\geq 135</math> mg/dL, hypertension, metabolic syndrome,<sup>b</sup> diabetes), or CKD</li> </ul>
<b>Stage 3:</b> Subclinical CVD in CKM	<ul style="list-style-type: none"> <li>• Subclinical ASCVD (principally diagnosed by coronary artery calcification — subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria)</li> <li>• Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP <math>\geq 125</math> pg/mL, hs-troponin T <math>\geq 14</math> ng/L for women and <math>\geq 22</math> ng/L for men, hs-troponin I <math>\geq 10</math> ng/L for women and <math>\geq 12</math> ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk</li> <li>• Risk equivalents of subclinical CVD (very high-risk CKD [stage G4 or G5 CKD or very high risk per KDIGO classification; high predicted 10-year CVD risk])</li> </ul>
<b>Stage 4:</b> Clinical CVD in CKM	<ul style="list-style-type: none"> <li>• Clinical CVD (CHD, HF, stroke, PAD, AF) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD (KDIGO stage 4a or stage 4b)</li> </ul>

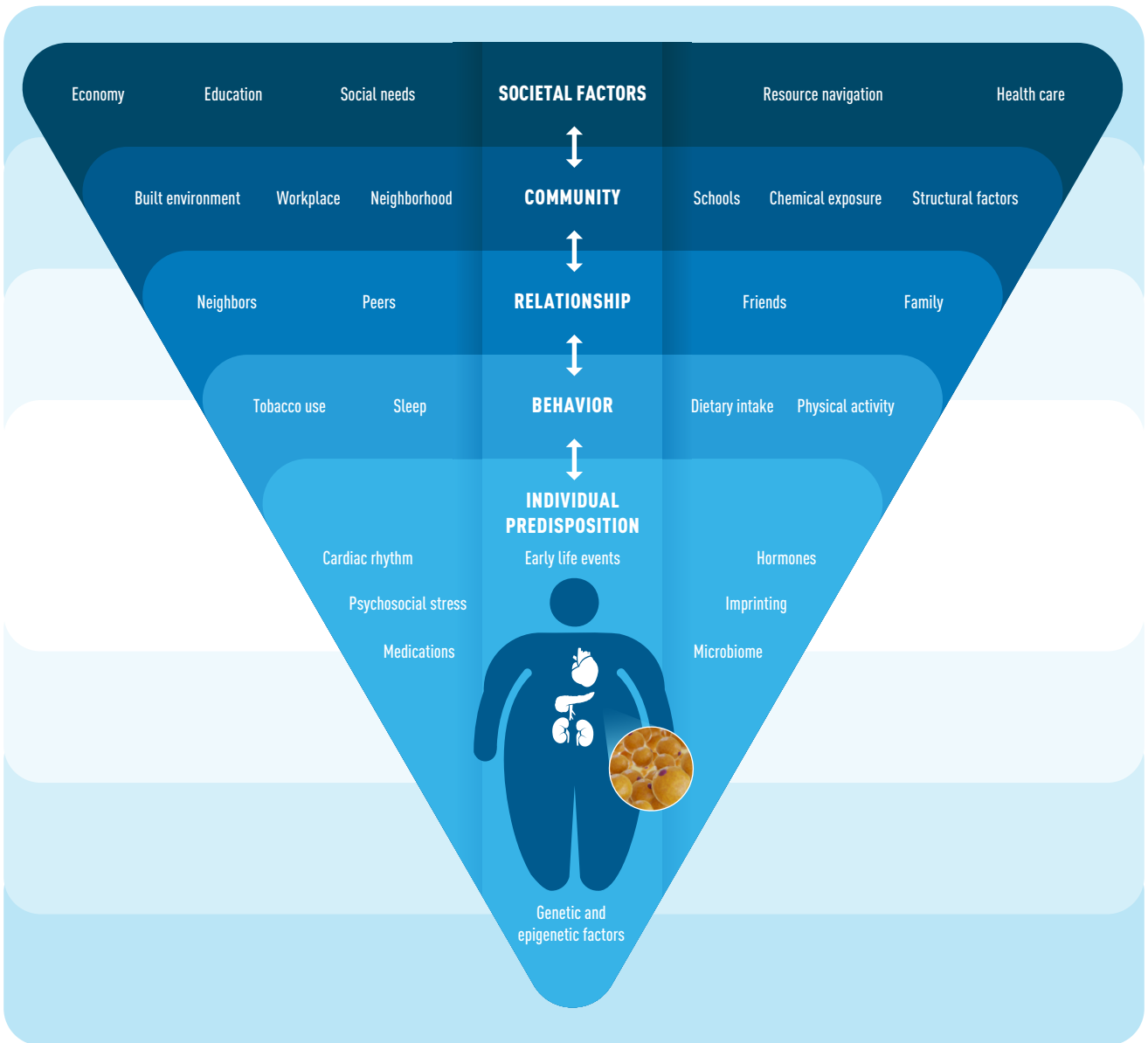
AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CT, computed tomography; CVD, cardiovascular disease; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; HF, heart failure; hs-troponin, high-sensitivity troponin; KDIGO, Kidney Disease Improving Global Outcomes; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral arterial disease.

<sup>a</sup>Individuals with gestational diabetes should receive intensified screening for impaired glucose tolerance after pregnancy.

<sup>b</sup>Metabolic syndrome is defined by the presence of  $\geq 3$  of the following: (1) waist circumference  $\geq 88$  cm for women and  $\geq 102$  cm for men ( $\geq 80$  cm for women and  $\geq 90$  cm for men if Asian ancestry); (2) HDL cholesterol  $< 40$  mg/dL for men and  $< 50$  mg/dL for women; (3) triglycerides  $\geq 150$  mg/dL; (4) elevated blood pressure (systolic blood pressure  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 80$  mm Hg and/or use of antihypertensive medications); and (5) fasting blood glucose  $\geq 100$  mg/dL.

Reproduced from Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. 2023; 148(20):1606-1635. doi:10.1161/CIR.0000000000001184

**FIGURE 2.** Societal Determinants of Health in CKM Syndrome<sup>64</sup>



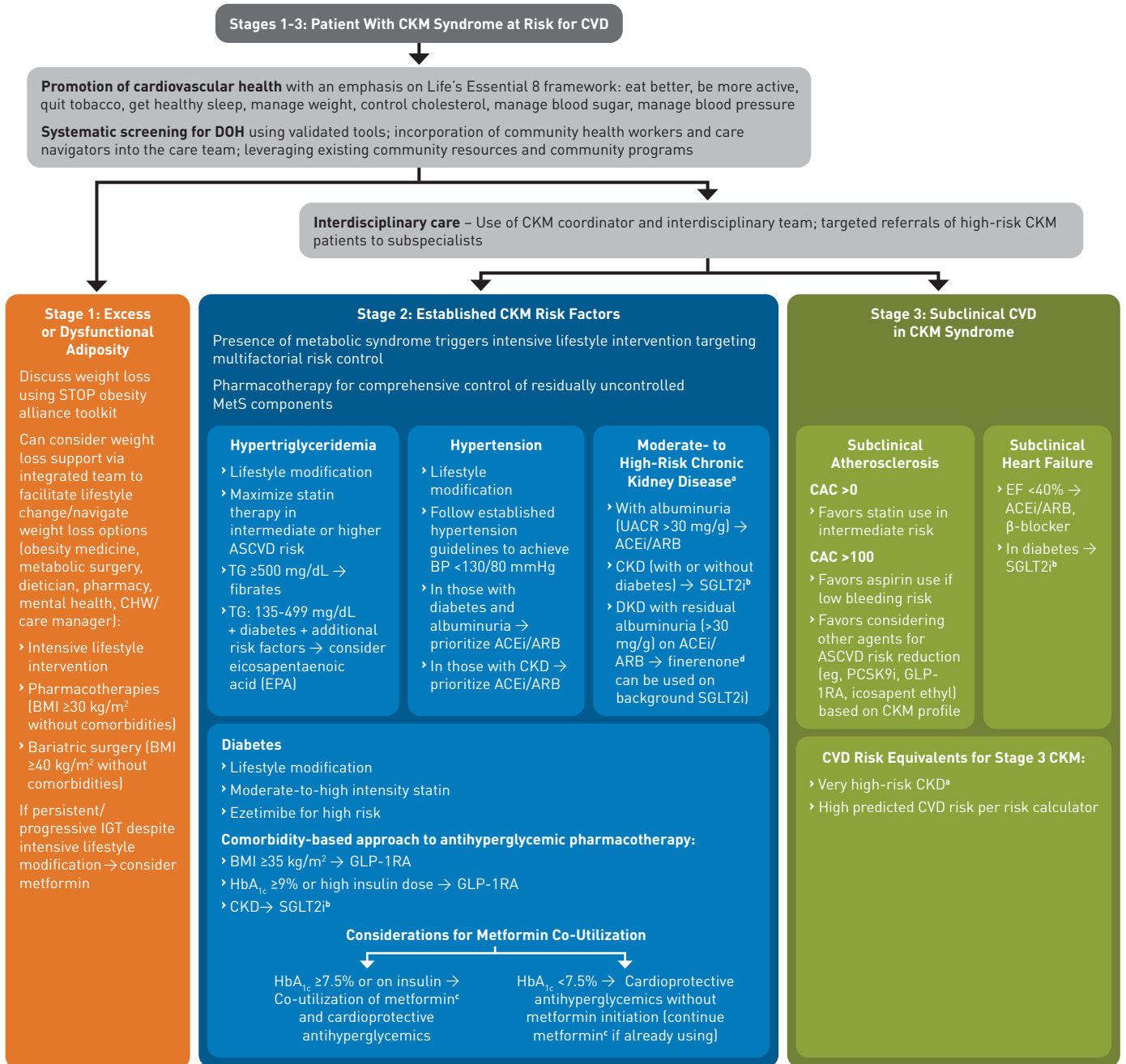
CKM, cardiovascular-kidney-metabolic.

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the AHA Life's Essential 8 construct,<sup>56</sup> which specifies the need to move beyond subspecialty silos to collaborative interdisciplinary care models. Studies have observed that a coordinated, multifaceted intervention increased prescription of evidence-based therapies in adults with T2D and atherosclerotic CVD.<sup>57,58</sup> This was irrespective of sex, race, or ethnicity.<sup>59</sup> Team-based care is crucial and time constraints should be considered for members of the multispecialty

team, including physicians, physician's assistants, nurse practitioners, nurses, pharmacists, dietitians, exercise therapists, mental health specialists, and social workers. Attention should also be paid to how the support structures around the patient can support implementation of CKD guidance, whether they be family, or community and religious groups.<sup>10</sup> Increasing health literacy is essential for people living with, or at risk of, CKM. This is particularly

**FIGURE 3.** Algorithm for the Management of CKM Syndrome Stages 1-3<sup>10</sup>



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CHW, community health worker; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes; EF, ejection fraction; EPA, eicosapentaenoic acid; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HF, heart failure; IGT, impaired glucose tolerance; MetS, metabolic syndrome; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; P2Y12i, P2Y12 inhibitor; SDOH, social determinants of health; SGLT2i, sodium-glucose transport protein 2 inhibitors; STOP, Strategies to Overcome and Prevent; TG, triglycerides; UACR, urine albumin-creatinine ratio.

<sup>a</sup>Per Kidney Disease Improving Global Outcomes heat map.

<sup>b</sup>SGLT2i can be safely initiated for patients with estimated glomerular filtration rate  $\geq 20$  mL/min/1.73 m<sup>2</sup>.

<sup>c</sup>Metformin can also be used in patients with eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>.

<sup>d</sup>Finerenone can likely be initiated on background SGLT2i for those with eGFR  $> 25$  mL/min/1.73 m<sup>2</sup> and potassium  $< 5$  mEq/L.

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important in people in different racial and ethnic populations or disadvantaged groups, who traditionally have a greater number of metabolic risk factors.

## Conclusions

The complexity of CKM syndrome as a multifaceted condition requires a holistic approach to prevention, screening, and management. Because of the high burden of CKM conditions, which is magnified in patients with multiple conditions, optimal prevention, screening, and management are required to improve outcomes and reduce long-term morbidity and mortality.

Disparities in prevalence of CKM conditions and outcomes are persistent and getting worse, not only based on race and ethnicity, but also sex, geography, socioeconomic status, ability, or disability. Targeted interventions are needed to identify and eliminate these disparities, and as health care professionals, we have a moral and a practical imperative to address them. ■

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**Author Affiliation:** Section of Cardiology, Tulane University School of Medicine, New Orleans, LA.

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**Address Correspondence to:** Keith C. Ferdinand, MD, Tulane University School of Medicine, 1430 Tulane Ave #8540, New Orleans, LA 70112. Email: kferdina@tulane.edu

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# Diabetes, Cardiorenal, and Metabolic Multispecialty Practice Recommendations and Early Intensive Management of Cardio-Renal-Metabolic Disease

Yehuda Handelsman, MD

## Rationale and Development Process for the Original Diabetes, Cardiorenal, and Metabolic Practice Recommendations

There is a strong overlap and interconnection between diabetes, cardiovascular (CV) disease, and chronic kidney disease (CKD).<sup>1</sup> Due to the interconnectivity between these conditions, there is a need for a holistic approach to the treatment of patients with cardio-renal-metabolic (CRM) disease.<sup>2</sup> Despite this and the known poorer outcomes in patients with multiple CRM conditions, until recently, there was an unmet need for comprehensive clinical recommendations specifically for the management of patients with CRM disease. While there are several major guidelines and scientific statements that have been produced for diabetes, CV disease, and CKD that cover some of the overlap between CRM diseases, each of these societies' recommendations have been somewhat limited in scope and focused mainly on their own disciplines. Examples of such guidelines include the American Diabetes Association (ADA) Standards of Care in Diabetes for managing patients with diabetes and its associated comorbidities including CV disease and CKD,<sup>3-5</sup> the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for managing CKD in patients with and without diabetic kidney disease,<sup>6,7</sup> and the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for preventing atherosclerotic cardiovascular disease (ASCVD) and managing heart failure (HF), with specific recommendations for patients with diabetes or CKD.<sup>8,9</sup>

In 2022, the Diabetes, Cardiorenal, and Metabolic (DCRM) multispecialty practice recommendations were published (hereafter referred to as *the DCRM*).<sup>10</sup> They were the first multispecialty consensus on the comprehensive management of patients with diabetes, cardiorenal, and/or metabolic diseases. The DCRM recommendations endorse a fundamental change in management, focusing on preventing the next ASCVD/HF/CKD event independent of patient risk, while continuing to manage conventional CV risk factors. Note that the DCRM has been using the term *cardiorenal and metabolic diseases* since 2021 in line with many other groups and organizations, whereas the recent 2023 AHA uses the term *cardiovascular-kidney-metabolic (CKM) syndrome*; however, the 2 terms

## ABSTRACT

In recent years, evidence has continued to mount showing a strong relationship between diabetes, cardiovascular disease, and chronic kidney disease. This, in turn, has driven a shift to a more integrated and holistic approach in the treatment of patients with cardio-renal-metabolic (CRM) disease. The 2022 Diabetes, Cardiorenal, and Metabolic (DCRM) multispecialty practice recommendations were the first multispecialty consensus on the comprehensive management of patients with diabetes, cardiorenal, and/or metabolic diseases, providing evidence-based recommendations that are simple to implement. The recommendations provide guidance on assessments and treatments, including both lifestyle therapy and pharmacotherapy, for patients across the DCRM spectrum, and are an invaluable tool for clinicians who need to develop treatment plans for complex patients with cardio-renal-metabolic disease. This article reviews the key elements of the DCRM recommendations and summarizes the updates included in the DCRM 2.0.

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For author information and disclosures, see end of text.

generally refer to the same collection of conditions.<sup>10,11</sup> The DCRM recommendations were developed by a group of 31 recognized experts in cardiology, endocrinology, diabetology, lipidology, coagulation, nephrology, hepatology, obesity, and primary care, with a focus on providing nonexperts (ie, primary care physicians, specialists from within the CRM spectrum who may lack expertise in areas other than their own specialty, and clinicians from other specialties) with the initial framework for diagnosis and a comprehensive treatment plan for patients with CRM diseases. A follow-up publication in 2023 updated the recommendations and emphasized the importance of early identification of these conditions and prompt intervention with intensive management.<sup>12</sup>

## Current Recommendations for the Management of CRM

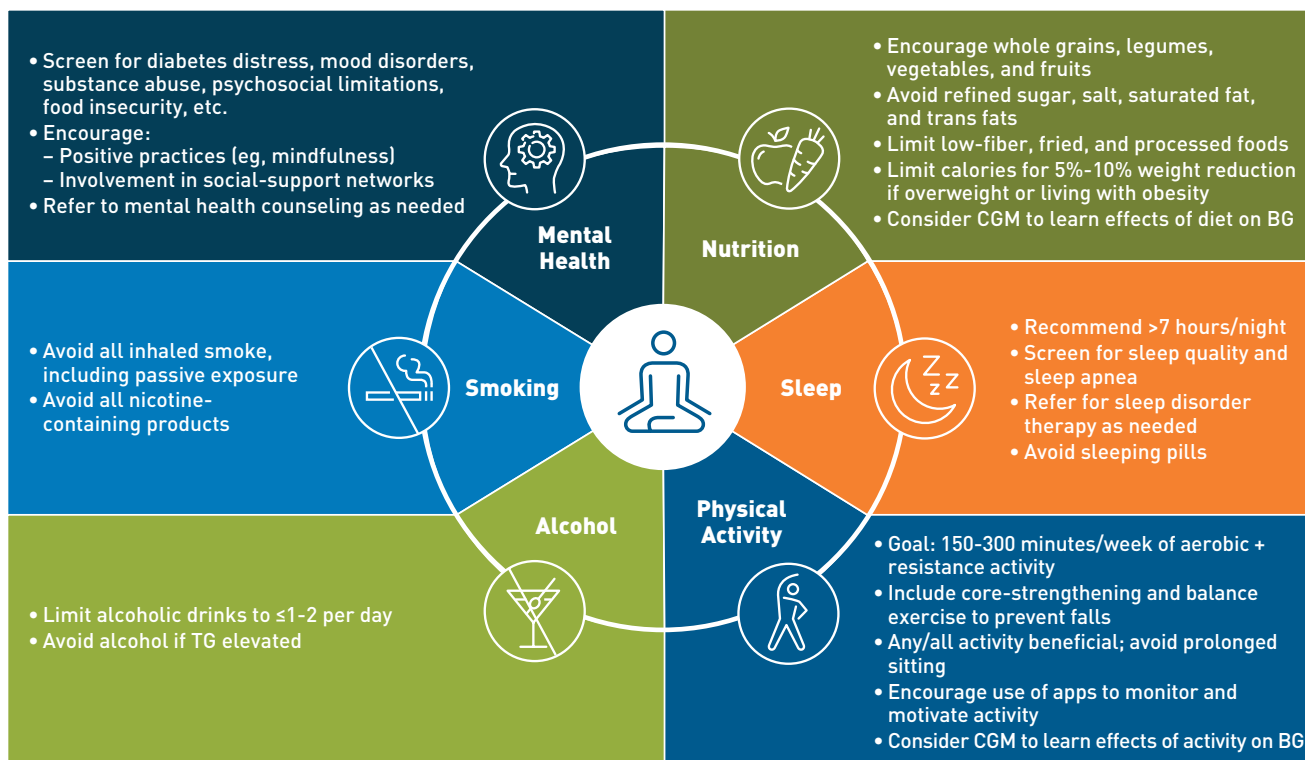
### General Health and Background Considerations

The DCRM makes recommendations regarding 6 elements of lifestyle therapy—nutrition, physical activity, sleep, alcohol, smoking, and mental health (Figure).<sup>13</sup> The mindset to be encouraged is that any effort the patient makes will be worthwhile, and clinicians

should support patients by educating them about the importance of adhering to medication and lifestyle interventions. This includes staying up-to-date with vaccinations, as patients with CRM diseases are at high risk of complications following infection.<sup>14,15</sup> The goal is for patients to know their numbers for the different tests used to monitor their conditions, appreciate the importance of a healthy lifestyle, and fully understand all aspects of their medication. This could include the use of validated apps and wearable fitness monitors to track the different elements of the patient's lifestyle routine, which have been shown to improve the level of physical activity and diet quality.<sup>16</sup> Similarly, patients with diabetes can be trained in the use of technology-based options for glucose monitoring and insulin delivery.<sup>17</sup> Early intervention is key in patients with obesity, metabolic syndrome, or prediabetes to prevent progression to type 2 diabetes (T2D) and promote a return to normoglycemia. The key factor is sustained weight loss, either through lifestyle changes and/or drug therapy and exercise.<sup>18</sup>

The DCRM also recommends that clinicians undertake a full assessment of each patient, including obtaining their medical history, completing a physical exam, and measuring their blood

**FIGURE.** Elements of Lifestyle Therapy<sup>13</sup>



BG, blood glucose; CGM, continuous glucose monitoring; TG, triglycerides.

DCRM 2.0: Multispecialty practice recommendations for the management of diabetes, cardiorenal, and metabolic diseases by Handelsman Y, Anderson JE, Bakris GL, et al. *Metabolism*. Published online June 4, 2024. doi:10.1016/j.metabol.2024.155931 is licensed under CC BY 4.0.

pressure (BP), lipids, and glycemia. Where suspected, the diagnosis of white-coat hypertension can be confirmed by measuring BP with ambulatory or home BP monitoring kits.<sup>19</sup> Patients with diabetes are at high risk not just for macrovascular disease but also for microvascular complications. Therefore, it is advisable to conduct an annual foot exam for these patients, and those with sensory loss or previous ulceration/amputation should be checked at every visit.<sup>20</sup> In addition, estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR) should be measured annually in patients with diabetes and in those with/at risk of CKD.<sup>6,7</sup> A yearly eye exam should be included to assess for retinopathy.<sup>20</sup>

### CV Risk Management

The DCRM recommends that lipid levels be monitored closely (ideally at least every 12 weeks, although some experts check every 6 weeks) until low-density lipoprotein cholesterol (LDL-C) levels are reduced by ≥50% from baseline or the patient reaches their risk-based goal, whichever is lower.<sup>21</sup> Clinicians should also aim for a BP of <130/80 mm Hg in patients with hypertension.<sup>22</sup> Assessments should be carried out both weekly at home and every 3 to 6 months in the office, as out-of-office BP measurements are important and are often more accurate than office measurements.<sup>23</sup>

Antithrombotic therapy selection should depend on the presence of risk factors and CV conditions such as chronic coronary artery disease and acute coronary syndrome. Recommended medications for primary and secondary prevention are shown in **Table 1**.<sup>13</sup>

Antihyperglycemic therapy should be tailored to each patient’s hyperglycemic goals. The goals may range from the ADA guideline recommendation of a hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level of <7.0% for most patients<sup>24</sup> with some less stringent HbA<sub>1c</sub> goals (eg, <8.0% recommended for frail patients with significant comorbidities) to the American Association of Clinical Endocrinology guidance, which recommends goals of <6.5% for most patients and as close to normoglycemia as possible for recently diagnosed healthy patients in the absence of comorbidities.<sup>25</sup> In addition, clinicians should consider prescribing a sodium-glucose cotransporter-2 inhibitor (SGLT2i) or glucagon-like peptide 1 receptor agonist (GLP-1 RA) independent of glycemic control in patients with T2D who are at risk of/or with established ASCVD,

CKD, and/or HF. These drug classes have been shown to reduce cardiorenal diseases and mortality independent of their glucose-lowering effects.<sup>26,27</sup> The risk of hypoglycemia should be minimized by prescribing antihyperglycemic agents from drug classes known not to induce hypoglycemia. For patients on insulin, insulin analogs should be used, and glucagon should be prescribed to treat severe hypoglycemic events as appropriate, with training provided for the patient and their family.<sup>3,28</sup>

### Contemporary Prevention of Comorbidities and Mortality

Clinicians should check for metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as nonalcoholic fatty liver disease or NAFLD) by monitoring transaminase levels and,

**TABLE 1.** Principles of Anticoagulation and Antiplatelet Therapy<sup>13</sup>

	Condition	Risk consideration	Recommended medication
Primary prevention	No known ASCVD but ≥2 RF	Low bleeding risk	• Aspirin, 75-100 mg daily
	CAC ≥100 or CAC ≥75th percentile for age and gender	Low bleeding risk	• Aspirin, 75-100 mg daily
Secondary prevention	ACS within 1 year of event		• Aspirin, 75-100 mg daily + P2Y12i
	Stable CAD with history of PCI or ≥12 months after ACS	High ischemic risk AND low bleeding risk	• Aspirin, 75-100 mg daily + ticagrelor, 60 mg BID • Rivaroxaban, 2.5 mg BID + aspirin, 75-100 mg • Aspirin, 75-100 mg + clopidogrel, 75 mg
		Low ischemic risk OR high bleeding risk	• Clopidogrel, 75 mg daily • Aspirin, 75-100 mg daily
	Stable CAD, no PCI	High ischemic risk AND low bleeding risk	• Rivaroxaban, 2.5 mg BID + aspirin, 75-100 mg
		Low ischemic risk OR high bleeding risk	• Clopidogrel, 75 mg daily • Aspirin, 75-100 mg daily
	PAD	Without limb revascularization	• Rivaroxaban, 2.5 mg BID + aspirin, 75-100 mg • Clopidogrel, 75 mg daily
	After limb revascularization	• Rivaroxaban, 2.5 mg BID + aspirin, 75-100 mg	

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

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more importantly, using the FIB-4 (fibrosis 4) calculation annually in patients with obesity and/or T2D. This will help identify the disease before it progresses into metabolic dysfunction-associated steatohepatitis (MASH, formerly known as nonalcoholic steatohepatitis or NASH).<sup>29,30</sup> Note that early fatty liver disease cannot be detected using liver function tests, hence the need for FIB-4 and/or imaging. Patients with MASLD should be managed primarily with lifestyle changes coupled with control of CV and renal risks. However, pioglitazone should be considered for patients with MASH or hepatic fibrosis (regardless of the presence of T2D), unless contraindicated, along with lifestyle and risk factor changes.<sup>31</sup> Standard therapies should also be used to control lipids, hypertension, anticoagulation therapy, and hyperglycemia in patients with or at risk for ASCVD. Further primary and secondary risk reduction strategies are detailed in [Table 2](#).<sup>13</sup>

Clinicians should aim to reduce the risk of HF using lifestyle changes, BP and glucose control, and ASCVD interventions as needed. An angiotensin II receptor blocker (ARB)/angiotensin-converting enzyme inhibitor (ACEi) and SGLT2i should be considered for high-risk patients with and without diabetes and CV risk factors. Patients with elevated natriuretic peptides who are at high clinical risk, and/or with the signs and/or symptoms of HF, should be referred to a cardiologist or multidisciplinary disease management program. In cases of suspected HF, clinicians should characterize left ventricular ejection fraction using an echocardiogram with Doppler flow studies.<sup>32</sup> Patients who have HF with preserved ejection fraction (HFpEF, EF  $\geq 50\%$ ) should be treated with an SGLT2i with proven efficacy such as empagliflozin and dapagliflozin.<sup>33</sup> Quadruple therapy is indicated for patients with HF with reduced ejection fraction (HFrEF, EF  $< 40\%$ ) (ie, an angiotensin receptor neprilysin inhibitor [ARNI], beta blocker, mineralocorticoid receptor antagonist [MRA], and SGLT2i) and, if needed, with a diuretic for congestion.<sup>34</sup> Patients with HF who have a mildly reduced ejection fraction (HFmrEF, EF 41%-49%) should be considered for treatment with an SGLT2i and additional elements of the quadruple therapy, if needed.

CKD should be diagnosed by measuring both eGFR and UACR and reassessed at least annually. Regular risk assessments are very important as CKD is associated with ASCVD, HF, end-stage kidney disease, hypertension, arrhythmia, and hypoglycemia.<sup>35,36</sup> Clinicians should aim to reduce CKD risk through lifestyle changes and goal-directed therapies to lower BP, glucose, and lipid levels.<sup>6,7</sup> First-line drug therapy for patients with CKD includes controlling elevated lipids with statins and blood pressure with a renin-aldosterone system inhibitor (ACEi/ARB) in patients with hypertension, and SGLT2is (irrespective of T2D status).<sup>37</sup> Additionally, the nonsteroidal MRA finerenone and the GLP-1 RA semaglutide have also demonstrated CV and kidney benefits in patients with diabetic kidney disease.<sup>38,39</sup>

HF and CKD frequently occur together and require special consideration of their high risk of progression and mortality. Due to this high risk, SGLT2is should be prescribed as indicated, as they have demonstrated efficacy beyond reducing glucose levels in the treatment of comorbid HF and CKD and are suitable to initiate in patients with an eGFR of  $\geq 20$  mL/min per 1.73 m<sup>2</sup> (and can be continued

**TABLE 2.** Management of ASCVD<sup>13</sup>

	MI/CAD	Stroke/TIA	PAD
Standard of care	See lipid, hypertension, anticoagulation, and antihyperglycemic recommendations, depending on comorbidities		
Add for primary prevention in persons with diabetes	LA GLP-1 RA IPE <sup>a</sup> SGLT2i	LA GLP-1 RA IPE <sup>a</sup>	
<b>Add for secondary prevention</b>			
Without diabetes	Aspirin IPE <sup>a</sup>	Aspirin IPE <sup>a</sup>	
	Rivaroxaban + aspirin <sup>b</sup>	PCSK9i	PCSK9i
	PCSK9i	Pioglitazone <sup>c</sup>	Rivaroxaban + aspirin <sup>b</sup>
	GLP1-RA (obesity only)	Clopidogrel + aspirin	
	Colchicine		
With diabetes	Aspirin Rivaroxaban + aspirin <sup>b</sup>	Aspirin PCSK9i	PCSK9i
	PCSK9i	GLP1-RA	Rivaroxaban + aspirin <sup>b</sup>
	GLP1-RA	Clopidogrel + aspirin	GLP1-RA
	SGLT2i	Pioglitazone	
	Pioglitazone Clopidogrel + aspirin		

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist (ie, dulaglutide, liraglutide, semaglutide); IPE, icosapent ethyl; LA GLP-1 RA, long-acting glucagon-like peptide 1 receptor agonist (ie, dulaglutide, liraglutide, semaglutide); MI, myocardial infarction; PAD, peripheral artery disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RF, major risk factors (ie, advancing age, elevated non-high-density lipoprotein cholesterol [HDL-C], elevated low-density lipoprotein cholesterol, low HDL-C, diabetes, hypertension, chronic kidney disease, cigarette smoking, family history of ASCVD); SGLT2i, sodium-glucose co-transporter-2 inhibitor; TG, triglyceride; TIA, transient ischemic attack.

<sup>a</sup>In patients with TG, 135-499 mg/dL + ASCVD or diabetes + 2 RFs.

<sup>b</sup>Rivaroxaban, 2.5 mg, twice daily + aspirin, 75-100 mg.

<sup>c</sup>In patients with insulin resistance.

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even when eGFR falls below this threshold until renal replacement therapy or transplantation is required).<sup>40</sup> In cases where the patient is congested, diuretics should be initiated, in addition to the agents from the 4 therapeutic classes recommended for management of HFrEF (beta-blockers, ARNIs [or ACEi/ARBs], SGLT2is, and MRAs). These patients should also be monitored for eGFR decline, as a modest decline is expected with initiation of ACEi/ARBs, MRAs, and SGLT2is (in the case of SGLT2is, this decline is known to return to baseline within a few months) and should not be a reason to discontinue therapy, as ultimately these medications facilitate eGFR stabilization and slow long-term eGFR decline. They should also be monitored for hyperkalemia as a result of treatment with ACEi/ARBs, and especially MRAs. UACR and natriuretic peptides should be used to evaluate disease progression. Patients with HFpEF will benefit from SGLT2is, GLP-1 RA when body mass index is 30 kg/m<sup>2</sup> or higher, and ARNI (or ACEi/ARBs) and MRAs for patients with an ejection fraction up to 55% to 60%.

In addition to the more well-known complications and comorbidities, there are other effects that may be ameliorated or prevented by proper management of the risk factors for CRM diseases (eg, cognitive dysfunction).

It is important to note that while lifestyle changes can play a significant role in any treatment plan, they are generally not sufficient to address the multiple conditions needing management in patients with CRM. As a result, pharmacotherapy is usually required; medication should be prescribed based on patients' needs and using the latest clinical practice guidelines, taking all relevant factors into account (eg, patient characteristics and products' attributes and contraindications; see [Table 3](#)).<sup>13</sup>

SGLT2is are recommended for patients with HF and CKD with and without T2D, due to beneficial effects on weight, BP, prevention of HF hospitalization, prevention of CKD deterioration, as well as reductions in mortality.<sup>10,37</sup> However, they are not indicated to initiate for patients with eGFR <20 mL/min per 1.73 m<sup>2</sup>. Potential adverse effects may include genital mycotic infections (GMI) and ketoacidosis. However, it should be noted that GMIs are generally mild and can be treated with topical agents or a single dose of oral fluconazole, and the risk of ketoacidosis is infinitely small in people with HF and CKD; GMIs do not impact patients who do not have diabetes.<sup>10,37</sup> GLP-1 RAs are recommended for patients with T2D with established or who are at high risk for ASCVD to prevent myocardial infarction, stroke, and mortality. They improve hyperglycemia, help with weight loss, and improve diabetic CKD and quality of life in people with HFpEF. The GLP-1 RA semaglutide has also been shown to reduce major adverse cardiovascular events in persons with preexisting CVD and overweight or obesity but without diabetes.<sup>41</sup> Potential adverse effects include mild-to-moderate gastrointestinal adverse events.<sup>1,3,39,42,43</sup> GLP-1 RAs do not cause hypoglycemia; however, if patients are receiving insulin,

sulfonylureas, or glinides, hypoglycemia is possible. Such patients should be monitored, and if hypoglycemia occurs, the doses of insulin, sulfonylureas and glinides should be reduced or stopped if possible.<sup>3</sup> Lipid-lowering medications are essential in patients with diabetes and/or cardiorenal and metabolic diseases (the DCRM patient) to prevent or reduce the risk of ASCVD. Nonstatin lipid-lowering therapy in combination with statins can be used to reach risk-based LDL-C goals. Nonstatins should be used in people with statin intolerance.<sup>44</sup> MRAs and ARNIs are recommended for patients with HF, and nonsteroidal MRAs are indicated for patients with diabetic kidney disease. Patients who receive MRAs should be monitored for the risk of hyperkalemia.

### Summary of Updates in DCRM 2.0

An updated version of the DCRM (DCRM 2.0) has been recently published, accompanied by a revised slide deck.<sup>13</sup> Since the original DCRM practice recommendations were published, the scope of conditions thought to play a role in CRM diseases has expanded, with heightened recognition of the role of inflammation; sleep and breathing disturbances; lung disorders; and especially increased understanding of the impact of obesity on heart, lung, and kidney diseases. Therefore, the DCRM 2.0 updated the original recommendations with a special focus and recommendations on obesity and inflammation. Unlike the original DCRM, which was US-based, the DCRM 2.0 is extended globally with the contribution of top experts from Europe and Canada. The DCRM 2.0 further features novel medications, new indications for existing medications, and advanced management of DCRM diseases. In addition, the DCRM 2.0 highlights early intervention and intensified management with increased focus on implications for clinical practice. It includes a revised summary of medications to help clinicians choose the most relevant therapies with CV outcomes for their patients based on efficacy and potential adverse effects. New evidence will be evaluated for inclusion in the update based on scientific strength, clinical relevance, and ultimately, benefit to patients.

As mentioned, due to intense international interest, the DCRM 2.0 has been transformed from a US perspective to a global outlook so it can be easily adopted worldwide. This has been achieved by cooperation with international experts addressing the DCRM topics and their relevance to different populations, allowing local adoption. Approximately 60% of the authors are from the original DCRM, and the remaining 40% are international leaders, primarily from Europe and Canada.

### Conclusions

Cardiorenal and metabolic diseases comprise many conditions and diseases, including obesity, T2D, CKD, ASCVD, HF, and fatty liver disease. Because cardiorenal and metabolic diseases share pathophysiology, 2 or more conditions are often present in the



**TABLE 3.** Summary of Medications for Diabetes, Lipid, and Kidney Disorders<sup>13</sup>

	ASCVD	HF	Kidney	GI	Liver	GU	Bone
<b>Weight-reducing medications</b>							
GLP1-RA	++	+	++	↑↑	+		
GIP/GLP1-RA				↑↑	+		
Phentermine/topiramate			↑ creatinine				
Naltrexone/bupropion				↑			
Orlistat				↑↑			
Phentermine							
<b>Glucose-lowering medications</b>							
Metformin			eGFR <30 <sup>a</sup>	↑			
GLP1-RA	++	+	++	↑↑	+		
GIP/GLP1-RA				↑↑			
SGLT2i	+	++	++ Dialysis			↑ Mycotic infections	
TZD	+	↑			++		↑
DPP4i		↑ HF hospitalizations <sup>b</sup>	Dose adjust <sup>c</sup>				
Insulin		↑ HF risk <sup>d</sup>	↑↑ Hypoglycemia risk				
SU			↑ Hypoglycemia risk				
GLN			↑ Hypoglycemia risk				
AGI				↑↑			
Colesevelam	+			↑			
BCR-QR	+			↑↑			
Pramlintide				↑↑			

++ Strong benefit	+ Modest benefit	Mild benefit	↑ Increased value or incidence	↓ Decreased value or incidence	Mild risk	Modest risk and/or precaution/warning	Contraindicated
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(continued »)

same individual. Evidence supports the benefits of some agents on several of the cardiorenal-metabolic diseases. The complexity of the DCRM patient who typically displays more than 1 disease requires a multispecialty approach for the diagnosis and management of their conditions. The needed holistic approach generally incorporates the involvement of several specialists. Because of this, the DCRM 2.0 practice recommendations combine expertise from

multiple specialties into a comprehensive standalone document designed for use by nonexpert physician specialists and primary care physicians alike. The recommendations are based on strong evidence, represent the consensus of top experts, are clinically relevant, and most importantly, are simple to follow and implement. These recommendations provide an invaluable tool for clinicians who do not have the support of a specialists' network and who need



DIABETES, CARDIORENAL, AND METABOLIC MULTISPECIALTY PRACTICE RECOMMENDATIONS

Eye	Weight	BP	Glucose	Hypoglycemia	DKA	LDL-C	TG	Other
Weight-reducing medications								
	↓↓↓	↓	↓			↓	↓	
	↓↓↓	↓	↓			↓	↓	
Glaucoma	↓↓	↓				↓	↓	↑ Mood/cognition disorders Paresthesia
↑ Glaucoma	↓						↓	↑ Mental/mood disorders ↑ Seizures
	↓	↓				↓	↓	
Glaucoma	↓							
Glucose-lowering medications								
			↓↓					
	↓↓	↓	↓↓↓			↓	↓	
	↓↓	↓	↓↓↓			↓	↓	
	↓	↓	↓↓		↑ <sup>b</sup>	↑	↓	↓ Hyperkalemia ↓ Uric acid ↑ Mg <sup>+</sup>
	↑	↓	↓↓				↓	
			↓↓↓					
	↑↑		↓↓↓	↑↑↑				
	↑		↓	↑↑				
	↑		↓	↑				
			↓					
			↓			↓	↑	
			↓					
	↓		↓	↑				

++ Strong benefit

+ Modest benefit

Mild benefit

↑ Increased value or incidence

↓ Decreased value or incidence

Mild risk

Modest risk and/or precaution/warning

Contraindicated

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

<sup>a</sup>Contraindicated if eGFR <30 mL/min/1.73 m<sup>2</sup> due to increased risk of lactic acidosis

<sup>b</sup>Possible increased HF hospitalizations with saxagliptin and alogliptin.

<sup>c</sup>Except linagliptin.

<sup>d</sup>Due to fluid retention.

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to develop treatment plans for complex cases of patients with CRM diseases. Ultimately, the DCRM 2.0 aims to help improve the health and well-being of patients with DCRM. ■

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**Authorship Information:** Acquisition of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

**Address Correspondence to:** Yehuda Handelsman, MD, Metabolic Institute of America, 18372 Clark St #212, Tarzana, CA 91356. Email: yhandelsman@gmail.com

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# A Team-Based Approach to Type 2 Diabetes and Cardiovascular Care

Ian J. Neeland, MD; and Sanjay Rajagopalan, MD

## Introduction

Historically, cardiovascular (CV), kidney, and metabolic diseases have been managed in silos, which has often resulted in fragmented care, treatment delays, and increased health care delivery costs. As highlighted by the American Heart Association (AHA) Presidential Advisory on cardiovascular-kidney-metabolic (CKM) health, provision of optimum care for patients with CKM syndrome requires a multidisciplinary team approach involving high levels of stakeholder collaboration to reduce fragmentation of care.<sup>1</sup>

The Center for Integrated and Novel Approaches in Vascular-Metabolic Disease (CINEMA) program is a patient-centered, team-based intervention developed and implemented at the University Hospitals Harrington Heart and Vascular Institute and Research Education Institute, in Cleveland, Ohio, for patients with type 2 diabetes (T2D) or prediabetes, with a high risk for CKM.<sup>2-4</sup> The program aims to reduce CV risk factors and increase utilization of evidence-based therapies to improve deficiencies in diabetes care and lower the risk for CV and kidney events in this high-risk population. Here we review the main features of the CINEMA program, the outcomes observed, and the next steps in expanding the program.<sup>2,3</sup>

## CINEMA Program and Participants

The CINEMA program was funded through an investment by the Research Education Institute in 2019. It began enrollment in May 2020, was initially offered at 4 sites in the Cleveland metroplex, and expanded to 3 additional sites in 2024 (Figure 1).<sup>2,3</sup> It comprises a multidisciplinary team of 4 cardiologists and 1 advanced practice provider with special interest/training in T2D management and prevention, 2 nurse navigators, 2 registered dietitians, 3 certified diabetes care and education specialists (CDCESs), a dedicated pharmacist, a program coordinator, a community health worker (CHW), and a program administrator. There is also mandated communication and care coordination with primary care, endocrinology, nephrology, and bariatric surgery providers when needed (ie, these were not included routinely in CINEMA care visits).<sup>3</sup>

Patients could be referred to the CINEMA program by internal/family medicine practitioners, cardiologists, endocrinologists,

## ABSTRACT

The Center for Integrated and Novel Approaches in Vascular-Metabolic Disease (CINEMA) program is an innovative, patient-centered system of care developed by the University Hospitals Harrington Heart and Vascular Institute in Cleveland, Ohio in the US for the management of high-risk patients with type 2 diabetes (T2D) and prediabetes at high risk for cardiovascular-kidney-metabolic (CKM) syndrome and its consequences. At its core, CINEMA is a multidisciplinary team of care experts, working together outside of traditional silos. The patient meets with the entire team up to 4 times each year to address all aspects of cardiovascular (CV) and T2D care. At the first visit, the team formulates a personalized approach that is evidence based and centered on optimal strategies to improve the patient's lifestyle, reduce their risk of CV and kidney disease events, and increase their access and adherence to guideline-directed pharmacologic therapies. A community health worker is utilized to address social determinants of health as needed. The program has a substantial research component, with the intent of developing evidence for novel care paradigms. The multiyear results of the CINEMA program indicate that a multidisciplinary approach to management of high-risk patients is highly effective in reducing CKM syndrome risk factors and increases use of guideline-directed therapies. The aim of this review is to describe the structure, operation, and eligibility criteria for admission to the CINEMA program, provide an overview of how CKM syndrome risks are determined and managed for each patient, and discuss how the integrated approach to care is supported by current recommendations from professional societies and results from other coordinated care/multidisciplinary programs. Lastly, the scalability challenges of a wider rollout of the CINEMA program are considered.

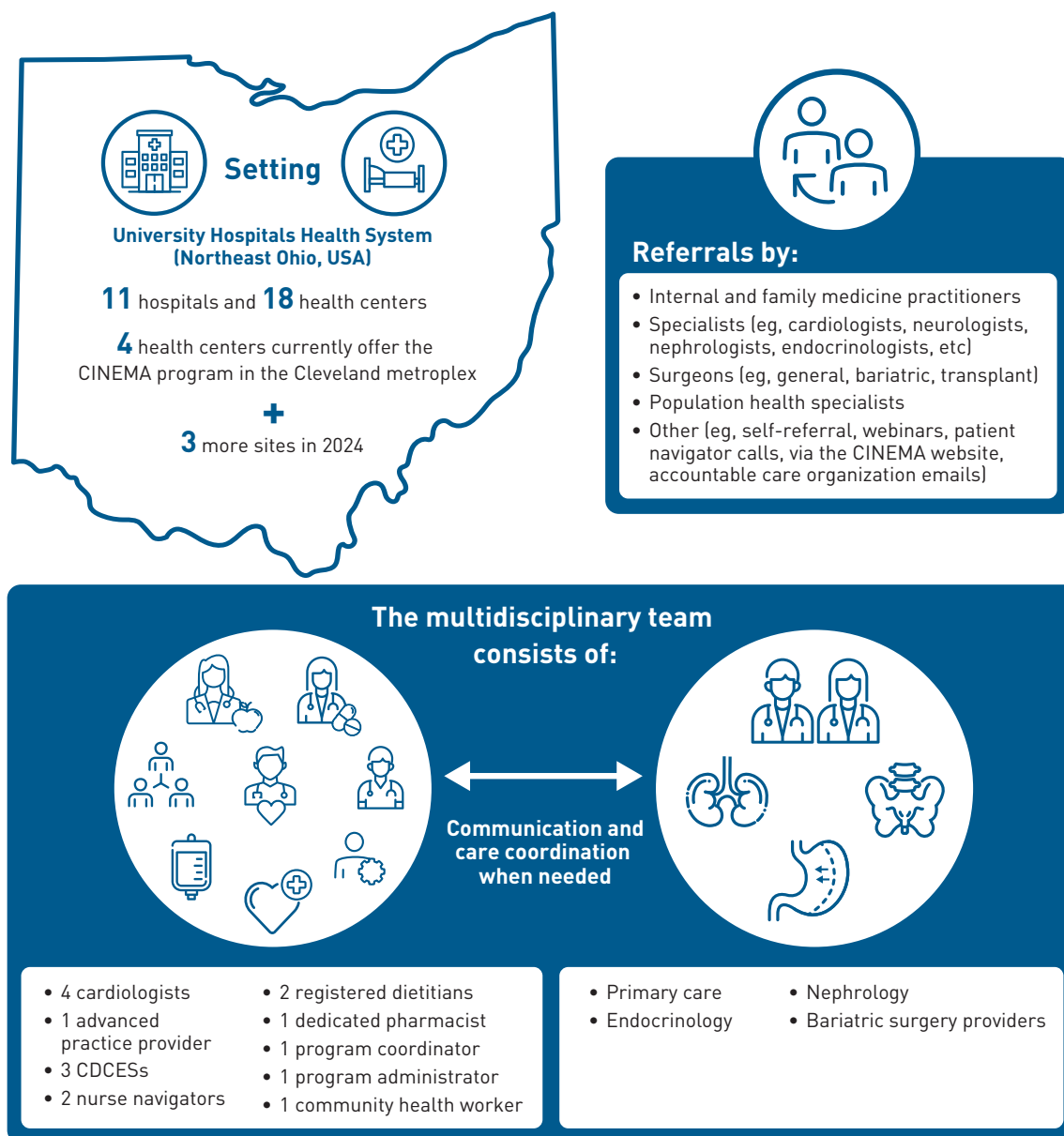
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For author information and disclosures, see end of text.

nephrologists, neurologists, bariatric and other surgeons, and population health specialists, or via webinars, patient navigator calls, CINEMA website referrals, accountable care organization referrals, or self-referrals. In year 1, individuals were included with either (1) self- or physician-reported T2D (with medical care and/or hemoglobin A<sub>1c</sub> [HbA<sub>1c</sub>] ≥6.5%), and/or (2) established or high risk for atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and/or chronic heart failure (HF) with reduced ejection

fraction (HFrEF), per the 2021 American Diabetes Association (ADA) Professional Practice Committee pathway.<sup>2,5</sup> Patients with type 1 diabetes or HbA<sub>1c</sub> <5.7% without a diagnosis of T2D were excluded. In year 2, due to high demand and patient interest, the inclusion criteria were expanded to include individuals with prediabetes (defined as HbA<sub>1c</sub> ≥5.7% and <6.5%) and those with T2D or prediabetes and concomitant metabolic syndrome and/or a coronary artery calcium (CAC) score ≥100 Agatston units.<sup>3</sup>

**FIGURE 1.** Overview of the CINEMA Program<sup>2,3</sup>



CDCES, certified diabetes care and education specialist; CINEMA, Center for Integrated and Novel Approaches in Vascular-Metabolic Disease.

## Determining CKM Syndrome Risk and Optimizing Health

The CINEMA program is structured around up to 4 visits per year, with additional follow-up as needed.<sup>2,3</sup> Unlike the traditional model of care, where the patient travels to different providers in several locations over multiple time points in the hope of receiving a comprehensive evaluation, CINEMA is unique in that the care team comes to the patient via an in-person or virtual platform in a single initial visit that attempts to address all aspects of CV and T2D care. The traditional model is well known to have a high probability of defects in care, meaning critically important aspects of care are not acted upon promptly. There is extensive empirical evidence of physician inertia in multiple diabetes-related end points including glycemic control, lipid management, and initiation of treatments known to have cardiorenal benefit.<sup>6-9</sup> A substantial component of CINEMA is dedicated to patient education about T2D and its complications including knowledge around pharmacologic and lifestyle approaches, by nonphysician CINEMA personnel.<sup>2,3</sup> This empowers the patient, builds confidence, and reduces the likelihood of patient and physician inertia.<sup>10</sup>

At the outset, providers in CINEMA seek to determine the patient's overall risk for long-term CKM outcomes and then formulate an evidence-based, personalized care plan. The plan is centered upon T2D lifestyle and pharmacologic strategies for reducing CKM events by weighing additional personal and precision factors. Providers use baseline measurements to determine the patient's overall risk for future CV and kidney events, including multiple novel measures. They recommend both lifestyle modification and a pharmacologic strategy including use of sodium glucose co-transporter 2 inhibitors (SGLT2is) and/or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (as recommended by the ADA and the European Association for the Study of Diabetes).<sup>11</sup> Patients on Medicaid and those without access to insurance are referred for visits with a CHW who evaluates social determinants of health and directs patients to appropriate resources. Prior studies have suggested that CHW models increase adherence to medical care.<sup>12,13</sup> Patient well-being is emphasized with utmost attention to lifestyle, diet, and sleep including periodic assessment of target organ complications through visits to ophthalmology, podiatry, endocrinology, nephrology, and other specialties, if warranted.

All patients undergo a standardized assessment of body weight, height, and laboratory testing including chemistries, lipids, HbA<sub>1c</sub>, and urine albumin-to-creatinine ratio (UACR), using standard assays. Laboratory studies are performed for the initial visit and for each subsequent follow-up visit (as applicable). In addition, CINEMA assesses CKM risk including precision measures of cardiovascular risk such as University Hospitals No-Cost Coronary Artery Calcium Score Test.<sup>14</sup> This allows early initiation of therapies in many patients and also increases patient understanding of the

health implications of T2D and CKM risk. Other precision measures for CKM risk include use of continuous glucose monitoring (CGM) and circulating- and/or imaging-based markers of CKM risk. These are used extensively to assemble a comprehensive portrait of each patient's risk.<sup>15,16</sup>

The team works with insurance, pharmacy, and assistance programs to obtain patients' medication in the most affordable way.<sup>2,3</sup> This involves working around insurance barriers and identifying prescription assistance for patients otherwise unable to obtain these medications. This approach enables initiation of novel agents and continuation of these therapies in the CINEMA program. A CHW is involved early on if social determinants of health needs are identified and/or patients are on Medicaid or are dual eligible. A pathways hub model available in the state of Ohio is used to open pathways that can lead to reimbursement.<sup>17,18</sup>

During the CINEMA journey, the nurse navigator and dietitian/CDCES provide continued support, coordination of care, and education (including weekly podcast-type educational sessions with video broadcast over a virtual meeting platform and peer-led support groups), and additional resources between physician visits. All patients requiring initiation and dose escalation of therapies, such as GLP-1 RAs, are contacted by a pharmacist working with CINEMA for a virtual appointment to review the use and anticipated adverse effects with treatments as well as treatment goals. The pharmacy team coordinates medication adjustments in conjunction with the CINEMA team with documentation of these visits in the electronic medical record. The University Hospitals pharmacy services provide direct delivery of prescriptions for the majority of patients, obviating the need for a visit to the pharmacy. Moreover, for patients with economic barriers, the pharmacy team attempts to alleviate cost considerations through corporate incentives and discounts from pharmacy benefit managers.

Patients return approximately 3 months later, following repeat clinical and laboratory testing, to discuss their progress, review medical events that may have occurred between visits, and discuss laboratory results. Every 3 to 6 months the patient contacts their nurse coordinator, dietitian/CDCES, and physician using a combination of telephone and/or a virtual video telehealth platform to ensure continued support, engagement, and metabolic recovery. Patients continue their routine follow-up appointments with primary care and specialty physicians during this time. CINEMA physicians and support staff partner closely with primary care providers to ensure continuity of care, prevent fragmentation, and overcome barriers to communication.

To further foster patient engagement, optional patient-oriented virtual activities are available to all study participants. These include weekly podcast-type educational sessions and peer/patient-led support group discussions about diabetes, the patient journey, CV disease, and lifestyle optimization. There are also cooking classes



and grocery store tours to educate patients about nutrition, a weekly home or office-based exercise session, CINEMA Studio (a patient advocacy group of volunteers discussing how to improve CINEMA), and a monthly CINEMA Blockbuster series open to medical professionals, patients, and lay people, where world-renowned experts discuss various topics.

## Key Findings of the CINEMA Program

A total of 426 patients were enrolled in the CINEMA program from 2020 through 2022: 206 patients in year 1 and 220 in year 2. The mean age was 60 years, 47% of patients were women, and White and Black patients constituted 58% and 37% of the study population, respectively. In year 1, most referrals were from cardiologists (53%) and internal/family medicine practitioners (26%), with <1% from endocrinologists (0.5%) and nephrologists (0.2%).<sup>2</sup> In year 2, cardiologists and internal/family medicine practitioners were still responsible for most of the referrals (85%), but there was an increase in referrals from endocrinologists (9%).<sup>3</sup>

Overall, 85% of patients (n = 363/426) had prevalent T2D, 48% (n = 204/426) had established ASCVD, 29% (n = 125/426) had HF/rEF, and 27% (n = 113/426) had CKD. The mean baseline 10-year estimated risk of ASCVD was 25.1%. ASCVD risk factors were improved after the first year and continued to improve in year 2 (Figure 2).<sup>3</sup> There were statistically significant changes from baseline in body weight, body mass index, systolic and diastolic blood pressure (BP), HbA<sub>1c</sub>, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides ( $P < .05$  for each risk factor). Trends over time for changes in high-density lipoprotein cholesterol and UACR were favorable but not statistically significant. Stratified analyses provided similar findings when the model was adjusted by factors such as single vs multiple follow-up visits, and the baseline prevalence of ASCVD, T2D, CKD, or HF. In total, the absolute 10-year predicted risk of ASCVD decreased by 2.4% ( $P < .001$ ) with the CINEMA program intervention.<sup>3</sup>

Year 1 data showed an increase in guideline-directed cardiometabolic medication prescriptions, which continued into year 2 (Figure 3).<sup>3</sup> The largest increases were in use of SGLT2is and GLP-1 RAs, with an approximately 3-fold increase from baseline to follow-up (SGLT2is: 21%-57%,  $P < .001$ ; GLP-1 RAs: 18%-65%,  $P < .001$ ). As the follow-up duration and overall program timeline was relatively brief (median: 4 months), no inference could be made on associations with event-related outcomes, such as myocardial infarction, stroke, or CV death.<sup>3</sup>

## Discussion

The patient-centered, team-based approach utilized in the CINEMA program resulted in reductions in ASCVD risk factors and increased use of guideline-directed medical therapy (GDMT; eg, SGLT2is and GLP-1 RAs). These improvements were maintained over the

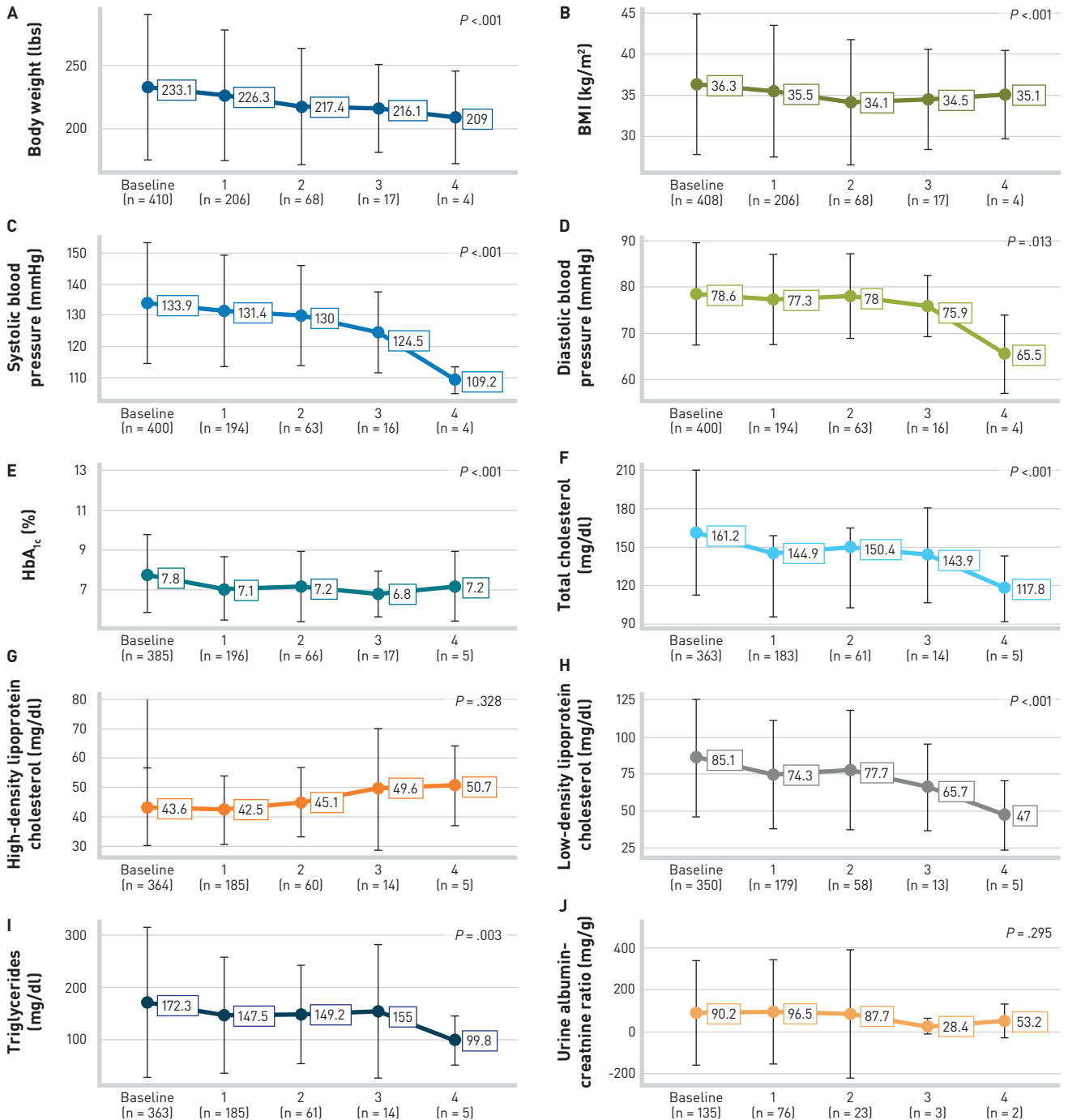
course of the 2-year study period and were applicable across the spectrum of CKM conditions, regardless of baseline T2D, ASCVD, HF, or CKD status.<sup>3</sup>

The approach taken by the CINEMA program is supported by current recommendations from professional societies. For example, the ADA Standards of Care recommend alignment of approaches in diabetes management with the Chronic Care Model, emphasizing person-centered team care, integrated long-term treatment of diabetes and comorbidities, and ongoing collaborative communication and goal setting.<sup>19</sup> The AHA has also stated that the management of CKM conditions should involve a multidisciplinary team led by a coordinator.<sup>16</sup> However, who should act as care coordinator is less well defined. In one US survey, primary care physicians (PCPs) self-identified as a patient's coordinator of care in 54% of cases for CKD and 59% for ASCVD (59%), whereas only 25% and 9% of patients viewed their PCP as their care coordinator for CKD and ASCVD, respectively.<sup>20</sup> One approach is to appoint a nonphysician, such as a nurse navigator with CDCES certification, as the care coordinator. A registered nurse with specialty training in diabetes care is well positioned to be the coordinator and provide education, counseling, and medical advice to patients (with the assistance of the physician when needed), and to form a long-term relationship with patients for continuity of care. Additionally, the use of pharmacists in the CINEMA program to educate, initiate, and help adjust medications such as GLP-1 RAs is critical to the rapid attainment of goals as seen in this program. This approach prevents therapeutic inertia and helps adjudicate the time of the CINEMA staff in addressing other needs including scaling the operation to reach more patients. The CHW model is also important in addressing social determinants of health needs that are often barriers in optimizing CKM health. The results of the CINEMA program are in line with those observed in other multidisciplinary/coordinated care programs in T2D and non-T2D populations. For example, in a 5-year prospective cohort study in patients with T2D in China, Wan and colleagues evaluated a multidisciplinary risk assessment and management program with initial risk assessment and review by specialist nurses who also provide individual care advice. Information was then shared among the multidisciplinary health care team (doctors, nurses, optometrists, podiatrists, dietitians, physiotherapists).<sup>21</sup> There was a risk reduction of 40.6% (HR, 0.594;  $P < .001$ ) in CVD/microvascular complications and a 66.1% (HR, 0.339;  $P < .001$ ) risk reduction in all-cause mortality in patients in the coordinated care group vs the usual care group.<sup>21</sup>

In the COORDINATE trial (NCT03936660) in 43 US cardiology clinics, patients with T2D and ASCVD, who were not taking all 3 classes of evidence-based therapies (statins; angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; SGLT2i or GLP-1 RAs), entered a multidisciplinary program where their care was managed by a cardiologist, endocrinologist, and implementation specialist. At the last follow-up visit (12 months for 97.3% of the participants),



**FIGURE 2.** Changes in Key ASCVD Risk Factors Over Time Among Eligible Patients Participating in the CINEMA Program<sup>3,a</sup>



ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CINEMA, Center for Integrated and Novel Approaches in Vascular-Metabolic Disease; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

<sup>a</sup>The model is adjusted for age, sex, and race/ethnicity. Linear mixed effect model *P* values are for trends of change over time. **A.** body weight; **B.** BMI; **C.** systolic blood pressure; **D.** diastolic blood pressure; **E.** HbA<sub>1c</sub>; **F.** total cholesterol; **G.** high-density lipoprotein cholesterol; **H.** low-density lipoprotein cholesterol; **I.** triglycerides; **J.** urine albumin-creatinine ratio.

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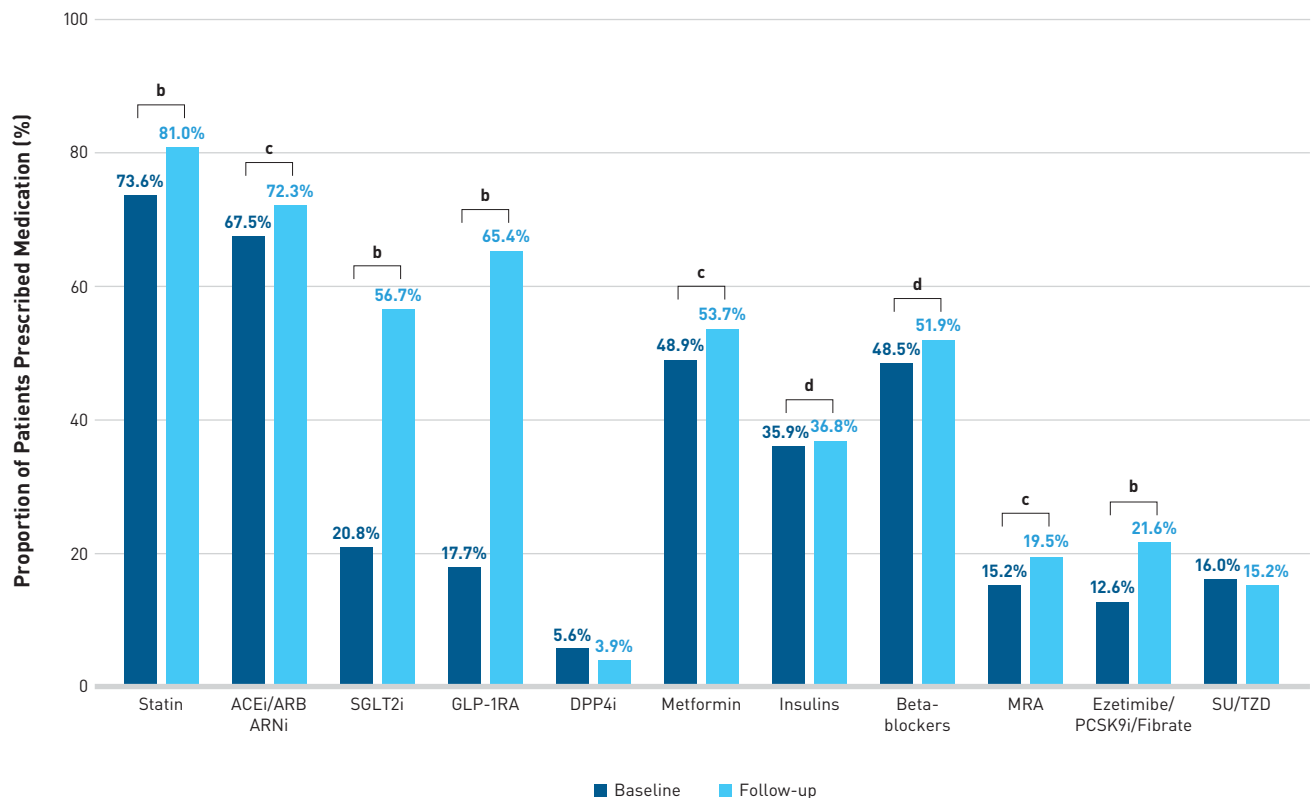
those in the intervention group were more likely to be prescribed all 3 therapies (173/457 [37.9%]) vs the usual care group (85/588 [14.5%]), with a difference of 23.4% (adjusted odds ratio [OR], 4.38 [95% CI, 2.49-7.71];  $P < .001$ ). However, unlike the CINEMA program, this intervention was not associated with changes in ASCVD risk factors, and was not powered to detect clinical events.<sup>22</sup>

Lastly, initial reports from the Cardiometabolic Center Alliance (CMCA) site at Saint Luke's Mid America Heart Institute demonstrated that the use of guideline-directed medical therapies for eligible patients ( $N = 129$ ) was improved using the cardiometabolic clinic model compared with usual care, including higher rates of SGLT2i and/or GLP-1 RA use.<sup>23</sup> A follow-up report from the CMCA in 2023 evaluated 606 individuals with T2D and CVD/CKD from 6 sites. Patients were a mean age of 64 years, 44% were female, 78% were White, and the median follow-up time was 6 months. After initiation

of care at CMCA sites, large improvements in GDMT and reductions in weight, HbA<sub>1c</sub>, BP, total cholesterol, LDL-C, triglycerides, and insulin requirements were observed. The authors concluded that CMCA-directed implementation of coordinated team-based care produced rapid and large improvements in GDMT and quality of care across multiple sites.<sup>24</sup>

To address the concern that a specialist-driven cardiometabolic clinic care model may devalue the role of PCPs in managing comorbid T2D and ASCVD, the CINEMA program works closely with primary care colleagues and seeks to directly address the fragmentation of care and management of multiple health conditions by working as a partnership. A key element of this partnership is to improve ASCVD prevention by increasing utilization of evidence-based therapies for the intensification of care, which appears to be both efficacious and cost effective. As the experience of the

**FIGURE 3.** Changes in Rates of Guideline-Directed Cardiometabolic Medication Prescriptions in CINEMA Between Baseline and Follow-Up in Eligible Patients<sup>3,a</sup>



ACEi/ARB/ARNi, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor; CINEMA, Center for Integrated and Novel Approaches in Vascular-Metabolic Disease; DPP4i, dipeptidyl peptidase 4 inhibitor; GLMEM, generalized linear mixed-effect model; GLP1 RA, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

<sup>a</sup>Comparisons between baseline and follow-up were assessed using a GLMEM;  $P$  values are for trends of change in prescriptions over time from baseline to follow-up: <sup>b</sup> $P < .001$ , <sup>c</sup> $P < .01$ , <sup>d</sup> $P < .05$ .

Reprinted from *American Journal of Preventive Cardiology*, 17, Neeland IJ, Arafah A, Bourges-Sevenier B, et al. Second-year results from CINEMA: A novel, patient-centered, team-based intervention for patients with Type 2 diabetes or prediabetes at high cardiovascular risk. 100630. Copyright (2023), with permission from Elsevier.

CINEMA program and other programs demonstrates, use of GDMTs in patients with T2D and ASCVD continues to be relatively low, despite routine primary and endocrinology specialist care. This demonstrates an unmet need for aggressive prevention, which can be provided by cardiometabolic specialty programs. A key component of CINEMA is the ability to risk-stratify patients with prediabetes and T2D appropriately. In this regard, the availability of the no-charge CAC score program helps risk stratification and early initiation of CKM therapies in patients with subclinical ASCVD, many of whom would not otherwise be identified. The Community Benefit of No-Charge Calcium Score Screening (CLARIFY) program established at University Hospitals provides free CAC testing for all patients within CINEMA and those with multiple risk factors, and this is an important part of the success of the CINEMA program.<sup>25-28</sup>

Challenges remain for the successful implementation and scalability of this multifaceted, integrated, patient-centered, team-based intervention for patients with T2D or prediabetes and high CV risk. Although several prior implementation strategies have been effective in single-system settings, scalability and dissemination of programs like CINEMA to other health systems and settings may prove difficult due to a lack of system-cohesiveness, infrastructure, and funding. Coordination of care is fundamental to the success of programs like CINEMA, and is facilitated by a strong network of outpatient sites, an integrated electronic medical record, important synergistic initiatives such as CLARIFY, presence of a CHW to address social determinants of health, and value-based care through the accountable care organization. Furthermore, incentives to join CINEMA, such as no-copay visits for employees at University Hospitals and institutional-led patient assistance programs, increase patient attendance and adherence to lifestyle and pharmacologic therapies.<sup>2,3</sup>

The use of precision measures for risk assessment such as CAC score is a unique facet of the CINEMA program. The availability of this diagnostic at no charge to the patient greatly simplifies decision-making and allows early initiation of pharmacologic approaches in patients with elevated CAC, which is akin to established coronary artery disease.<sup>25,26,29</sup>

Additional precision measures such as CGM and other remote monitoring devices can be effective tools to increase adherence to lifestyle and medical interventions and assist with patient self-monitoring and behavioral modification. The CINEMA program found that when the Dexcom G6 CGM system was used as an adjunct to a healthy meal plan, increased physical activity, and optimized medical therapy, it resulted in significantly improved glycemic control and reduced CV risk within 90 days in a cohort of adults with T2D who were not using insulin.<sup>15</sup> There was a significant reduction in average glucose levels and an increase in time in range, with a trend toward less glycemic variability. When users of the Dexcom system were surveyed, they reported significant

reductions in several cardiometabolic risk factors including HbA<sub>1c</sub>, triglycerides, BP, and cholesterol, as well as less diabetes distress. Furthermore, CGM use was associated with a reduced absolute 10-year predicted risk for ASCVD of ~8% and a significant increase in GDMT for diabetes and CV disease. The Dexcom system was well tolerated with no serious adverse events and no episodes of hypoglycemia during the study. To our knowledge, this is the first study to assess the impact of the Dexcom G6 CGM system on glycemic control and CV risk in a cohort of individuals with T2D who are not using insulin. It demonstrates the feasibility and effectiveness of CGM use for this patient population at high risk for adverse CV outcomes. Additional remote monitoring devices for BP, weight, sleep, activity, etc, can also assist patients in their health journey, and are planned for inclusion in CINEMA in the next year.

## Conclusion

The integrated, team-based, patient-centered approach to managing patients with T2D/prediabetes at high risk for CKM syndrome utilized in the CINEMA program resulted in improvements in patient outcomes and use of GDMT. Implementation of a team-based approach is critical to enhancing patient understanding, buy-in, and ultimately, treatment adherence. CINEMA utilizes novel approaches including deployment of a CHW to address social determinants of health, targeted use of remote monitoring such as CGM devices, and precision assessment with imaging and biomarker-based measures to further refine CKM risk. Further research is in progress to evaluate the scalability of the CINEMA program and dissemination to other health care settings. Multidisciplinary teams of specialists in CKM conditions, with the addition of other disciplines such as primary care, pharmacy, and nurse practitioners, should be the standard of care for patients with CKM syndrome to optimize the management of these high-risk patients. ■

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**Author Affiliations:** Case Western Reserve University School of Medicine and Division of Cardiovascular Medicine, University Hospitals Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center (IHN), Cleveland, OH; Cardiovascular Research Institute, Case Western Reserve University School of Medicine and University Hospitals Cleveland Medical Center (SR), Cleveland, OH.

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**Address Correspondence to:** Ian J. Neeland, MD. University Hospitals Harrington Heart and Vascular Institute, 11100 Euclid Ave, Cleveland, OH 44106. Email: ian.neeland@uhhospitals.org

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