Cardiovascular-Kidney-Metabolic Syndrome: What Providers Need to Know

Contributing authors on behalf of Team Best Practices:
Ian Neeland, MD, Case Western Reserve University
Jackson T. Wright, Jr., MD, PhD, Case Western Reserve University
Craig Nunemaker, PhD, Ohio University

Cardiovascular-kidney-metabolic (CKM) syndrome is a newly recognized health disorder characterized by interactions among heart disease, kidney disease, diabetes, and obesity, leading to poor health outcomes.1

CKM syndrome affects nearly all the organs in the body and has a very powerful impact on heart disease risk.2 New therapeutics are available to manage CKM syndrome more effectively than traditional ones, though they are also more costly. Their use requires thoughtful consideration and a greater emphasis on a multidisciplinary approach to treatment.

The American Heart Association (AHA) recently released new guidance to help clinicians define, assess, and treat CKM syndrome.1 The new term CKM syndrome:

1. Emphasizes the link between obesity, cardiovascular disease, chronic kidney disease, and diabetes outcomes.

2. Addresses the fact that chronic kidney disease is a very strong indicator of cardiovascular disease risk but has not been incorporated into traditional cardiovascular disease risk calculators. Chronic kidney disease is defined as an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73m² and/or a urine albumin-creatinine ratio (UACR) of ≥ 30 mg/g.

3. Promotes new therapies to manage the components of the disorder to prevent cardiovascular disease.

4. Highlights the need for an interdisciplinary approach for effective disease management, including social determinants of health (SDOH), which are critical to successful patient care.
Stages of Cardiovascular-Kidney-Metabolic Syndrome

There are five stages of CKM syndrome (stages 0 through 4, Table 1) defined by their correlation with adverse health outcomes at each stage. CKM syndrome stages can progress (get worse) or regress (get better) depending on prevention and treatment interventions. Using stages may help clinicians and patients recognize poor CKM health earlier than they otherwise would and make changes to the health plan to prevent or treat CKM syndrome.

### Table 1. CKM Syndrome Stage Definitions

<table>
<thead>
<tr>
<th>CKM Syndrome Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0: No CKM risk factors</strong></td>
<td>Individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD</td>
</tr>
<tr>
<td><strong>Stage 1: Excess or dysfunctional adiposity</strong></td>
<td>Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD³</td>
</tr>
<tr>
<td></td>
<td>■ BMI ≥25 kg/m² (or ≥23 kg/m² if Asian ancestry)</td>
</tr>
<tr>
<td></td>
<td>■ Waist circumference ≥88/102 cm in women/men (or if Asian ancestry ≥80/90 cm in women/men), or</td>
</tr>
<tr>
<td></td>
<td>■ Fasting blood glucose ≥100-124 mg/dL or HbA1c between 5.7% and 6.4%*</td>
</tr>
<tr>
<td><strong>Stage 2: Metabolic risk factors or CKD</strong></td>
<td>Individuals with metabolic risk factors (hypertriglyceridemia [135 mg/dL], hypertension, MetS,† diabetes), or CKD</td>
</tr>
<tr>
<td><strong>Stage 3: Subclinical CVD in CKM</strong></td>
<td>Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD</td>
</tr>
<tr>
<td></td>
<td>■ Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria)</td>
</tr>
<tr>
<td></td>
<td>■ Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs- troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk</td>
</tr>
<tr>
<td></td>
<td>Risk equivalents of subclinical CVD</td>
</tr>
<tr>
<td></td>
<td>■ Very high-risk CKD (stage G4 or G5 CKD or very high risk per KDIGO classification)</td>
</tr>
<tr>
<td></td>
<td>■ High predicted 10-y CVD risk</td>
</tr>
<tr>
<td><strong>Stage 4: Clinical CVD in CKM</strong></td>
<td>Clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD</td>
</tr>
<tr>
<td></td>
<td>■ Stage 4a: no kidney failure</td>
</tr>
<tr>
<td></td>
<td>■ Stage 4b: kidney failure present</td>
</tr>
</tbody>
</table>

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; HDL=high-density lipoprotein; HF=heart failure; hs-troponin=high-sensitivity troponin; KDIGO=Kidney Disease Improving Global Outcomes; MetS=metabolic syndrome; 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 or more of the following: (1) waist circumference ≥88 cm for women and ≥90 cm for men if Asian ancestry; (2) HDL 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 mmHg or diastolic blood pressure ≥80 mmHg and/or use of antihypertensive medications); and (5) fasting blood glucose ≥100 mg/dL.

Adapted from Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association.
Prevention and Management of CKM Syndrome

Optimal CKM health can be achieved by providing education, assessing and addressing SDOH, improving obesity care and enlisting teams to support lifestyle change and weight management, increasing access to medications, and developing partnerships with important stakeholders and community leaders to support improved cardiovascular health across diverse communities.4

Screening

Early screening for cardiovascular disease risk factors and evidence of clinical/subclinical cardiovascular or kidney disease is necessary. Screening involves blood pressure assessment, lipid and glucose measurement, and evaluation of liver and kidney function.

Screening for SDOH is essential for all CKM stages.5 The health care team should document obstacles identified as impeding a patient’s health in the clinical record, and plans should be made to address and monitor the obstacles for resolution.

Managing CKM by Stage (Figure 1, Figure 2)

Stage 1. Major objective: support lifestyle and weight loss efforts
- Assure adequate resources are available within the practice or health care system, or that community resources and are coordinated with primary care provider(s).

Stage 2. Major objective: assure that all CKM risk factors are managed and controlled to recommended targets, including blood pressure, glycemic, lipid, and metabolic targets
- If more than one risk factor is present, management likely will require a team-based approach, coordinated by the primary care provider. This approach will incorporate multiple specialties and disciplines, with an agreed-upon protocol for prioritizing and managing risk factors.

Stage 3. Major objective: manage risk factors to prevent CKM progression
- If more than one risk factor is present, management likely will require a team-based approach, coordinated by the primary care provider and relevant specialists. This approach will incorporate multiple specialties and disciplines, with an agreed-upon protocol for prioritizing and managing risk factors.

Stage 4. Major objective: manage risk factors and end organ damage to prevent clinical outcomes/morbidity6
- Management will require a team-based approach coordinated by the primary care physician, incorporating multiple specialties and disciplines, with an agreed-upon protocol for prioritizing and managing risk factors.

Resources to address SDOH:5
1. Social Needs Screening Tools
   cardi-oh.org/resources/social-needs-screening-tools
2. Electronic Health Record Systems
   cardi-oh.org/resources/electronic-health-record-systems2
3. Using Social Determinants of Health Data to Achieve Policy Change
   epicshare.org/perspectives/using-sdoh-data-to-achieve-policy-change
   sciedirect.com/science/article/pii/S0735109723003613
**Figure 1. Algorithm for the Management of CKM Syndrome Stages 1–3**

**STAGES 1-3: Patient With CKM Syndrome at Risk for CVD**

**Promotion of cardiovascular health** with an emphasis on AHA’s Life’s Essential 8 framework: eat better, be more active, quit tobacco, get healthy sleep, manage weight, control cholesterol, manage blood sugar, manage blood pressure

**Systematic screening for SDOH** using validated tools; incorporation of community health workers and care navigators into the care team; leveraging existing community resources and community programs

**Interdisciplinary care** including use of CKM coordinator and interdisciplinary team; targeted referrals of high-risk CKM patients to subspecialists

---

**Stage 1: Excess or Dysfunctional Adiposity**
Discuss weight loss using STOP obesity alliance toolkit
Can consider weight loss support via integrated team to facilitate lifestyle change/navigate weight loss options (obesity medicine, metabolic surgery, dietician, pharmacy, mental health, CHW/care manager):
- Intensive lifestyle intervention
- Pharmacotherapies (BMI ≥30 kg/m² without comorbidities)
- Bariatric surgery (BMI ≥40 kg/m² without comorbidities)
If persistent/progressive IGT despite intensive lifestyle modification → consider metformin

---

**Stage 2: Established CKM Risk Factors**
Presence of metabolic syndrome triggers intensive lifestyle intervention targeting multifactorial risk control
Pharmacotherapy for comprehensive control of residually uncontrolled MetS components

- **Hypertriglyceridemia**
  - Lifestyle modification
  - Maximize statin therapy in intermediate or higher ASCVD risk
  - TG ≥500 mg/dL → fibrates
  - TG: 135-499 mg/dL + diabetes + additional risk factors → consider eicosapentaenoic acid (EPA)

- **Hypertension**
  - Lifestyle modification
  - Follow established hypertension guidelines to achieve BP <130/80 mmHg
  - In those with diabetes and albuminuria → prioritize ACEi/ARB
  - In those with CKD prioritize ACEi/ARB

- **Moderate- to High-Risk Chronic Kidney Disease**
  - With albuminuria (UACR >30 mg/g) ACEi/ARB
  - CKD (with or without diabetes) → SGLT2i
  - DKD with residual albuminuria (>30 mg/g) on ACEi/ARB → finerenone (can be used on background SGLT2i)

**Diabetes**
- Lifestyle modification
- Moderate-to-high intensity statin
- Ezetimibe for high risk

**Comorbidity-Based Approach to Antihyperglycemic Pharmacotherapy**
- **BMI ≥35 kg/m² → GLP-1RA**
- **HbA1c ≥9% or high insulin dose → GLP-1RA**
- **DKD → SGLT2i**

**Considerations for Metformin Co-Utilization**

<table>
<thead>
<tr>
<th>HbA1c ≥7.5% or on insulin → Co-utilization of metformin® and cardioprotective antihyperglycemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt;7.5% → Cardioprotective antihyperglycemics without metformin initiation (continue metformin® if already using)</td>
</tr>
</tbody>
</table>

---

**Stage 3: Subclinical CVD in CKM Syndrome**
Subclinical Atherosclerosis
- CAC >0
  - Favors statin use in intermediate risk
  - Favors aspirin use if low bleeding risk
  - Favors considering other agents for ASCVD risk reduction (e.g., PCSK9i, GLP-1RA, icosapent ethyl) based on CKM profile

Subclinical Heart Failure
- EF <40% → ACEi/ARB, β-blocker
- In diabetes → SGLT2i

CVD Risk Equivalents for Stage 3 CKM
- Very high-risk CKD*
- Highly predicted CVD risk per risk calculator

---

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; CVD=cardiovascular disease; CVD in CKM Syndrome Subclinical Atherosclerosis
- CAC >0
  - Favors statin use in intermediate risk
  - Favors aspirin use if low bleeding risk
  - Favors considering other agents for ASCVD risk reduction (e.g., PCSK9i, GLP-1RA, icosapent ethyl) based on CKM profile

Subclinical Heart Failure
- EF <40% → ACEi/ARB, β-blocker
- In diabetes → SGLT2i

CVD Risk Equivalents for Stage 3 CKM
- Very high-risk CKD*
- Highly predicted CVD risk per risk calculator

---

*Per Kidney Disease Improving Global Outcomes (KDIGO) heat map.
†SGLT2i can be safely initiated for patients with estimated glomerular filtration rate (eGFR) ≥20 mL·min⁻¹·1.73 m⁻².
††Metformin can also be used in patients with eGFR ≥30 mL·min⁻¹·1.73 m⁻² and potassium <5 mEq/L.
‡FInerenone can likely be initiated on background SGLT2i for those with eGFR >25 mL·min⁻¹·1.73 m⁻² and potassium <5 mEq/L.

Adapted from Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association.¹
Adapted from Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association.§

The full results of the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity), high-dose GLP-1RA may become frontline therapy in patients with cardiovascular-kidney-metabolic health.

Finorenone can likely be initiated on background SGLT2i for those with eGFR > 25 mL∙min−1∙1.73 m−2 and potassium < 5 mEq/L.

Metformin can be also be used in patients with estimated glomerular filtration rate (eGFR) ≥ 20 mL∙min−1∙1.73 m−2.

*SGLT2i can be safely initiated for patients with estimated glomerular filtration rate (eGFR) ≥ 20 mL∙min−1∙1.73 m−2.

†Metformin can be also used in patients with eGFR ≥ 20 mL∙min−1∙1.73 m−2 and without unstable or decompensated HF.

‡Finorenone can likely be initiated on background SGLT2i for those with eGFR > 25 mL∙min−1∙1.73 m−2 and potassium < 5 mEq/L.

§Pending the full results of the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity), high-dose GLP-1RA may become frontline therapy in patients with obesity and established CVD.
References


The Ohio Cardiovascular & Diabetes Health Collaborative is funded by the Ohio Department of Medicaid and administered by the Ohio Colleges of Medicine Government Resource Center. The views expressed in this document are solely those of the authors and do not represent the views of the state of Ohio or federal Medicaid programs.