The kidney in the middle: Kidney Disease: Improving Global Outcomes (KDIGO) guidelines address multiple key components of cardiovascular-kidney-metabolic syndrome

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Chronic kidney disease (CKD) is closely intertwined with obesity, diabetes, hypertension, dyslipidemia, and cardiovascular disease. In 2023, the American Heart Association formally recognized these interconnections as a unified entity, the cardiovascular-kidney-metabolic (CKM) syndrome. The CKM syndrome brings renewed attention to the importance of CKD in cardiovascular disease and reinforces the need for effective, evidence-based, interdisciplinary approaches to diagnose and prevent its intersecting components. The Kidney Disease: Improving Global Outcomes (KDIGO) organization has long led efforts to synthesize knowledge and translate evidence to practice in this area through the lens of the kidney. This review highlights KDIGO clinical practice guidelines and controversies conference publications that directly address the CKM syndrome. These include guidelines addressing CKD, blood pressure, diabetes, and lipids; an upcoming guideline addressing heart failure in CKD; and controversies conference reports addressing obesity and CKD prevention. Overarching themes include the importance of early detection and intervention; comprehensive, personalized management of kidney and cardiovascular risk; and multidisciplinary care. Through integrated, evidence-based, disease-specific guidelines and reports, KDIGO has established a robust framework for the management of people at risk for or with CKM syndrome as well as priorities for ongoing research.

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Strong links between metabolic diseases, chronic kidney disease (CKD), and cardiovascular disease (CVD) have been recognized for decades. Risk factors are shared across disease entities, and it is increasingly clear that prevention and treatment of organ-specific diseases requires consideration of related conditions.[1–8] The Kidney Disease: Improving Global Outcomes (KDIGO) organization has long led efforts to synthesize and translate knowledge across the intersecting domains of cardiovascular, kidney, and metabolic health, as evidenced in all the guidelines since 2004. In 2023, the American Heart Association formally recognized these interconnections as a unified entity, the cardiovascular-kidney-metabolic (CKM) syndrome.[9,10] The CKM syndrome includes well-established modifiable risk factors but frames them in light of an improved understanding of the complex interrelationships and pathways that are amenable to treatment, with the goal of simultaneously mitigating adverse kidney, metabolic, and cardiovascular outcomes (Figure 1a).[11] A related and important entity, metabolic dysfunction–associated steatotic liver disease (MASLD), is recognized as an amplifier of both CVD and CKD risks.[12–15]

The burden of the CKM syndrome is substantial, in terms of impact on both individual patients and the health economy. Obesity affects 16% of the world's adult population,[16] and metabolic syndrome (obesity, hypertension, dyslipidemia, and hyperglycemia) affects approximately 12.5%.[17] Worldwide, 588.7 million adults aged 20–79 years are living with diabetes,[18] 850 million are living with CKD,[19] and 640

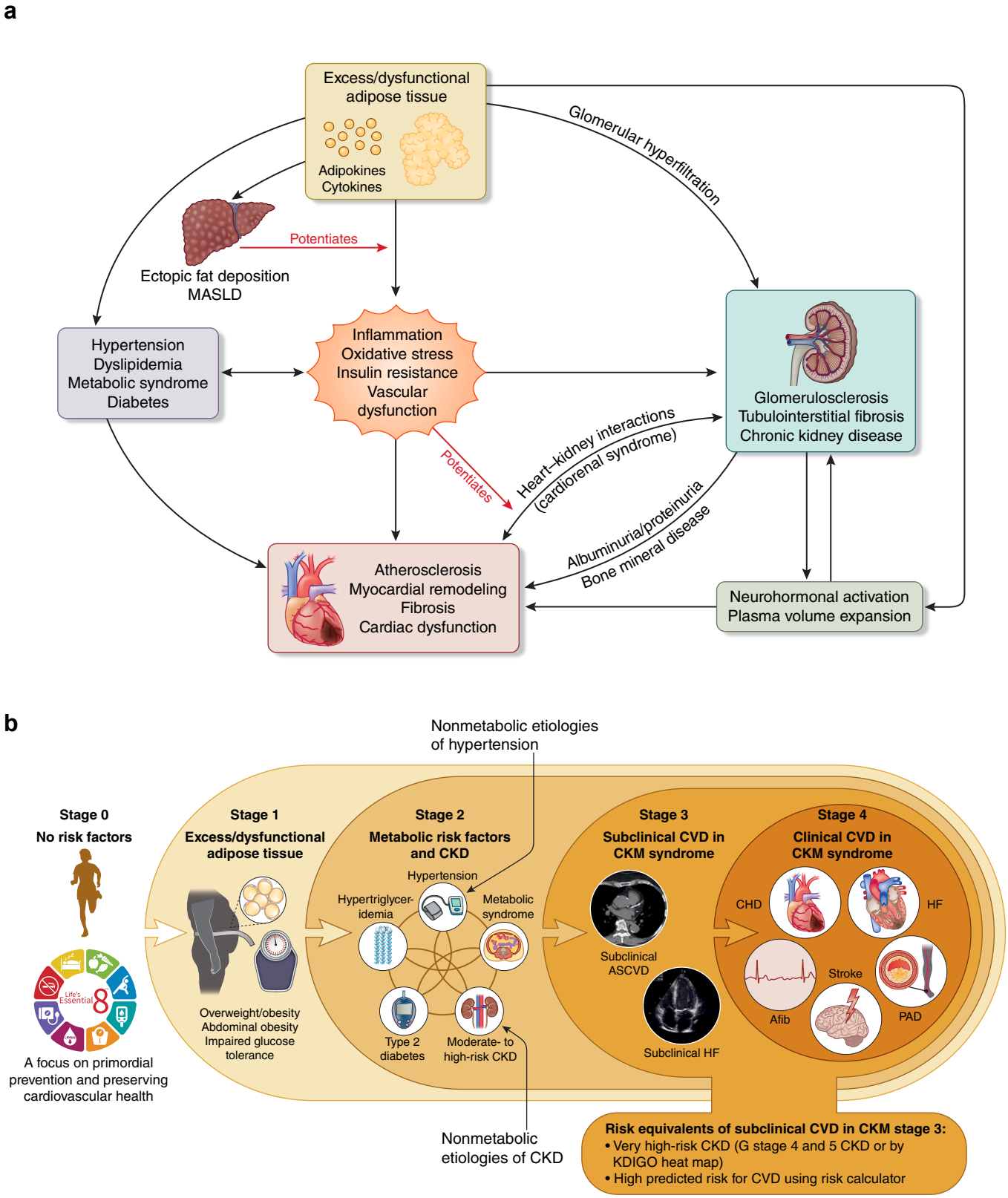

Figure 1 | (a) Conceptual diagram for the cardiovascular-kidney-metabolic (CKM) syndrome and (b) proposed CKM stages from the American Heart Association. (**a**) The image displays the pathophysiology underlying CKM syndrome. CKM syndrome most commonly originates from excess adipose tissue, dysfunctional adipose tissue, or both. Multiple pathological processes related to dysfunctional adipose tissue result in insulin resistance and eventual hyperglycemia. Inflammation, oxidative stress, insulin resistance, and vascular (continued)

million people are living with heart and circulatory diseases.[20,21] The prevalence of MASLD has increased by >50% in the past 3 decades.[17,22,23] CKM is a leading cause of mortality and disability-adjusted life-years. Heart and circulatory diseases cause nearly 1 in 3 deaths globally.[24,25] Obesity and overweight, diabetes, and CKD together contribute a third of the attributable burden related to deaths due to heart and circulatory diseases.[26] In 2017, CKD was estimated to account for 35.8 million disability-adjusted life-years, rising to 44.5 million in 2021.[27–29] Kidney disease is the third fastest-growing cause of death globally and the only noncommunicable disease with a sustained rise in age-adjusted mortality.[30]

The CKM syndrome brings renewed attention to the importance of CKD in CVD and reinforces the need for effective, evidence-based, interdisciplinary approaches to diagnose and prevent its intersecting components. Obesity, diabetes, and hypertension are important causes of CKD, and CKD can promote and amplify CVD through multiple mechanisms: retention of cardiotoxic metabolites, systemic inflammation, anemia, mineral and bone abnormalities, accelerated atherosclerosis, and impaired regulation of body water content, electrolytes, and acid-base status, among other processes. This review highlights KDIGO clinical practice guidelines and controversies conference reports that directly address the components of the CKM syndrome, demonstrating the existing guidance for those with CKD across all stages, and the elevated risk and challenges in treatment that CKD brings to the management of CKM.

KDIGO foundational role in CKM health

The KDIGO guideline portfolio—spanning hypertension, dyslipidemia, diabetes, and obesity—highlights the key components of the current CKM framework across stages (Figure 1b).[31–44] Recognizing the biological and clinical interconnected nature of these diseases, KDIGO promotes integrated, patient-centered care beginning in primary care and coordinated across specialties. Guideline Work Groups, controversies conference attendees, and patient partners are all multidisciplinary to foster coherent messaging and collaboration across disciplines. Importantly, the recognition and diagnosis of CKD in high-risk populations is emphasized.[31,38,45,46] Guidance for prevention and management of MASLD to date has been beyond the remit of KDIGO, but detailed guidance is available from other international associations.[12,47,48]

The specific KDIGO recommendations relevant to CKM health are presented in Figure 2, Table 1, and Supplementary Table S1. The recommendations for lifestyle, management of obesity, and control of comorbidities (arterial hypertension, type 2 diabetes [T2D], and dyslipidemia) apply equally in MASLD and are critical for reducing cardiovascular risk. Central to the KDIGO mission are rigorous evaluation of evidence to inform recommendations, global reach, and an emphasis on patient-focused care throughout the full life course. Supporting alignment of health policies and resource prioritization worldwide are also highlighted.

Summary of relevant KDIGO guidelines and reports

KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. When clinical suspicion is high, a diagnosis can be made without waiting for 3 months. Importantly, the definition is inclusive of various markers of kidney damage (e.g., hematuria, abnormalities of tubular function, and structural abnormalities seen on imaging or biopsy) and is not determined solely by glomerular filtration rate (GFR) and urinary albumin-to-creatinine ratio (UACR). The classification of CKD considers 3 dimensions: cause, GFR category (G1–G5), and albuminuria category (A1–A3). The 3 components of the classification system are each critical in assessing CKD and determining severity and risk (Figure 3).[49] The CKM framework does not emphasize this, but identifying CKD as an important modifier of risk offers an excellent opportunity

Figure 1 | (continued) dysfunction are highlighted as central processes leading to the development of metabolic risk factors, the progression of kidney disease, the potentiation of heart-kidney interactions, and the development of cardiovascular diseases (CVDs). Metabolic risk factors and chronic kidney disease (CKD) further predispose to CVD through multiple direct and indirect pathways. Reprinted with permission Ndumele CE, Neeland IJ, Tuttle KR, et al. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation*. 2023;148:1636–1664.[9] https://www.ahajournals.org/doi/10.1161/CIR.0000000000001186. © 2023 American Heart Association, Inc. (**b**) The CKM staging construct reflects the progressive pathophysiology and increasing absolute CVD risk along the spectrum of CKM syndrome. Stage 0 CKM includes individuals with normal weight, normal glucose, normal blood pressure, normal lipids, normal kidney function, and no evidence of subclinical or clinical CVD; the focus in stage 0 CKM is primordial prevention and preserving cardiovascular health. Stage 1 CKM includes individuals with excess adipose tissue, dysfunctional adipose tissue, or both. Excess adiposity is identified by either weight or abdominal obesity, and dysfunctional adipose tissue is reflected by impaired glucose tolerance and hyperglycemia. Stage 2 includes individuals with metabolic risk factors (hypertriglyceridemia, hypertension, metabolic syndrome, or type 2 diabetes), moderate- to high-risk CKD, or both. Although hypertension and CKD are usually downstream of metabolic risk factors, the curved arrows represent individuals with nonmetabolic causes of these conditions; the risk implications and treatment approaches are similar. Stage 3 includes individuals with subclinical CVD with overlapping CKM risk factors (excess/dysfunctional adipose tissue, metabolic risk factors, or CKD) or those with the risk equivalents of very high-risk CKD or high predicted risk using the forthcoming CKM risk calculator. Stage 4 includes individuals with clinical CVD (coronary heart disease [CHD], heart failure [HF], stroke, peripheral artery disease [PAD], or atrial fibrillation [Afib]) overlapping with CKM risk factors. Reprinted with permission from Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. 2023;148:1606–1635.[15] https://www.ahajournals.org/doi/10.1161/cir.0000000000001184. ©2023 American Heart Association, Inc. ASCVD, atherosclerotic cardiovascular disease; KDIGO, Kidney Disease: Improving Global Outcomes; MASLD, metabolic dysfunction–associated steatotic liver disease.

Figure 2 | Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines and controversies conference reports addressing key components of the cardiovascular-kidney-metabolic framework. CKD, chronic kidney disease.

for nephrology to demonstrate the added value of more granular diagnosis. The creatinine-based estimated GFR category of ≥105 ml/min per 1.73 m^2 has been omitted from Figure 3 to avoid potential confusion caused by the "J"-shaped relationship with creatinine-based estimated GFR for the 8 outcomes that are not influenced directly by changes in creatinine, as hyperfiltration is a known concern in obesity and early diabetic nephropathy within the CKM syndrome construct.

Early identification of CKD is key, as many people may be asymptomatic at early stages. Case finding in high-risk populations requires an accurate assessment of GFR and UACR with thorough evaluation of cause, followed by appropriate staging and management. The importance of albuminuria testing cannot be overstated: albuminuria is central to CKD diagnosis and staging, strongly associated with kidney and cardiovascular outcomes, included in risk calculators for these outcomes, and modifiable with therapy. Unfortunately, for the majority of people at risk for CKD, albuminuria is currently not measured as recommended, even in high-income settings. When laboratory albuminuria measurements are not available, point-of-care testing may facilitate access to earlier diagnosis and care, and it can be implemented in rural and remote locations. The CKM

Table 1 | Summary of select KDIGO-graded recommendations related to CKM mapped to the proposed staging from the AHA

Recommendation	KDIGO guideline recommendation			Applicable to AHA CKM stage[a]				
	CKD	BP	Diabetes	0	1	2	3	4
Evaluation, staging, and monitoring								
Test people at risk for and with CKD using both urinary albumin measurement and assessment of GFR.	PP			✓	✓	✓	✓	✓
After incidental detection of an elevated urinary ACR), hematuria, or low eGFR, repeat tests to confirm the presence of CKD.	PP			✓	✓	✓	✓	✓
In adults at risk for CKD, we recommend using eGFRcr. If cystatin C is available, the GFR category should be estimated from the combination of creatinine and cystatin C (eGFRcr-cys) (*1B*).	1.1.2.1			✓	✓	✓	✓	✓
We suggest performing a kidney biopsy as an acceptable, safe, diagnostic test to evaluate the cause and guide treatment decisions when clinically appropriate (*2D*).	1.1.4.1					✓	✓	✓
We recommend using eGFRcr-cys in clinical situations when eGFRcr is less accurate and GFR affects clinical decision making (*1C*).	1.2.2.1			✓	✓	✓	✓	✓
We recommend using a validated GFR-estimating equation to derive GFR from serum filtration markers (eGFR) rather than relying on the serum filtration markers alone (*1D*).	1.2.4.1			✓	✓	✓	✓	✓
We suggest that POCT may be used for creatinine and urinary albumin measurement where access to a laboratory is limited or providing a test at the point of care facilitates the clinical pathway (*2C*).	1.4.1			✓	✓	✓	✓	✓
In people with CKD G3–G5, we recommend using an externally validated risk equation to estimate the absolute risk of kidney failure (*1A*).	2.2.1					✓	✓	✓
We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (*1B*).		1.1		✓	✓	✓	✓	✓
We suggest that out-of-office BP measurements with ABPM or HBPM be used to complement standardized office BP readings for the management of high BP (*2B*).		1.2				✓	✓	✓
We suggest that adults with high BP and CKD be treated with a target SBP of <120 mm Hg, when tolerated, using standardized office BP measurement (*2B*).	3.4.1	3.1.1				✓	✓	✓
We suggest that in children with CKD, 24-hour MAP by ABPM should be lowered to ≤50th percentile for age, sex, and height (*2C*).	3.4.2	5.1				✓	✓	✓
We recommend using HbA1c to monitor glycemic control in patients with diabetes and CKD (*1C*).			2.1.1			✓	✓	✓
We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (*1C*).			2.2.1			✓	✓	✓
Lifestyle management								
We recommend that people with CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 min/wk or to a level compatible with their cardiovascular and physical tolerance (*1D*).	3.2.2.1			✓	✓	✓	✓	✓
We suggest that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 min/wk or to a level compatible with their cardiovascular and physical tolerance (*2C*).		2.2.1		✓	✓	✓	✓	✓
We suggest maintaining a protein intake of 0.8 g/kg body weight/d for adults with CKD G3–G5 (*2C*).	3.3.1.1					✓	✓	✓
We suggest maintaining a protein intake of 0.8 g protein/kg body weight/d for those with diabetes and CKD not treated with dialysis (*2C*).			3.1.1			✓	✓	✓
We suggest that sodium intake be <2 g sodium/d (or <90 mmol sodium/d or <5 g sodium chloride/d) for people with CKD (*2C*).	3.3.2.1			✓	✓	✓	✓	✓
We suggest that sodium intake be <2 g sodium/d (or <90 mmol sodium/d or <5 g sodium chloride/d) for patients with high BP and CKD (*2C*).		2.2.1		✓	✓	✓	✓	✓
We suggest that sodium intake be <2 g sodium/d (or <90 mmol sodium/d or <5 g sodium chloride/d) for patients with diabetes and CKD (*2C*).			3.1.1	✓	✓	✓	✓	✓
Recommendation 1.5.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products (*1D*).			1.5.1	✓	✓	✓	✓	✓
Pharmacological management								
We recommend starting RASi (ACEi or ARB) for people with CKD and severely increased albuminuria (stages G1–G4 and A3) without diabetes (*1B*).	3.6.1					✓	✓	✓
We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and severely increased albuminuria (stages G1–G4 and A3) without diabetes (*1B*).		3.2.1				✓	✓	✓
	3.6.2					✓	✓	✓

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Table 1 | (Continued) **Summary of select KDIGO-graded recommendations related to CKM mapped to the proposed staging from the AHA**

Recommendation	KDIGO guideline recommendation			Applicable to AHA CKM stage[a]				
	CKD	BP	Diabetes	0	1	2	3	4
We suggest starting RASi (ACEi or ARB) for people with CKD, and moderately increased albuminuria (stages G1–G4 and A2) without diabetes (*2C*).								
We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (stages G1–G4 and A2) without diabetes (*2C*).		3.2.2				✓	✓	✓
We recommend starting RASi (ACEi or ARB) for people with CKD and moderately to severely increased albuminuria (stages G1–G4, A2, and A3) with diabetes (*1B*).	3.6.3					✓	✓	✓
We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately to severely increased albuminuria (stages G1–G4, A2, and A3) with diabetes (*1B*).		3.2.3				✓	✓	✓
We recommend that treatment with an ACEi or an ARB be initiated in patients with diabetes, hypertension, and albuminuria and that these medications be titrated to the highest approved dose that is tolerated (*1B*).			1.2.1			✓	✓	✓
We recommend avoiding any combination of ACEi, ARB, and DRI therapy in patients with CKD, with or without diabetes (*1B*).	3.6.4	3.3.1				✓	✓	✓
We recommend treating patients with T2D, CKD, and eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (*1A*).	3.7.1		1.3.1			✓	✓	✓
We recommend treating adults with CKD with an SGLT2i for the following (*1A*): • eGFR ≥20 ml/min per 1.73 m^2 with urinary ACR ≥200 mg/g (≥20 mg/mmol) or • heart failure, irrespective of level of albuminuria.	3.7.2					✓	✓	✓
We suggest treating adults with eGFR 20–45 ml/min per 1.73 m^2 with urinary ACR <200 mg/g (<20 mg/mmol) with an SGLT2i (*2B*).	3.7.3					✓	✓	✓
We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, eGFR >25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite the maximum tolerated dose of RASi (*2A*).	3.8.1		1.4.1			✓	✓	✓
In adults with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment or who are unable to use those medications, we recommend a long-acting GLP-1 RA (*1B*).	3.9.1		4.2.1			✓	✓	✓
In adults aged ≥50 years with eGFR <60 ml/min per 1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5), we recommend treatment with a statin or statin/ezetimibe combination (*1A*).	3.15.1.1					✓	✓	✓
In adults aged ≥50 years with CKD and eGFR ≥60 ml/min per 1.73 m^2 (GFR categories G1 and G2), we recommend treatment with a statin (*1B*).	3.15.1.2					✓		
In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (*2A*): • known coronary disease (myocardial infarction or coronary revascularization), • diabetes mellitus, • prior ischemic stroke, or • estimated 10-yr incidence of coronary death or nonfatal myocardial infarction >10%.	3.15.1.3					✓	✓	✓
We recommend oral low-dose aspirin for prevention of recurrent ischemic cardiovascular disease events (i.e., secondary prevention) in people with CKD and established ischemic cardiovascular disease (*1C*).	3.15.2.1							✓
We suggest that in stable stress test–confirmed ischemic heart disease, an initial conservative approach using intensive medical therapy is an appropriate alternative to an initial invasive strategy (*2D*).	3.15.3.1							✓
We recommend use of NOACs in preference to vitamin K antagonists (e.g., warfarin) for thromboprophylaxis in atrial fibrillation in people with CKD G1–G4 (*1C*).	3.16.1							✓
We recommend treating patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m^2 with metformin (*1B*).			4.1.1			✓	✓	✓
Systems approach								
Enable access to a patient-centered multidisciplinary care team consisting of dietary counseling, medication management, education, and counseling about different KRT modalities, transplant options, dialysis access surgery, and ethical, psychological, and social care for people with CKD.	PP					✓	✓	✓
			5.1.1			✓	✓	✓

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Table 1 | (Continued) **Summary of select KDIGO-graded recommendations related to CKM mapped to the proposed staging from the AHA**

Recommendation	KDIGO guideline recommendation			Applicable to AHA CKM stage[a]				
	CKD	BP	Diabetes	0	1	2	3	4
We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (*1C*).								
We suggest that policymakers and institutional decision makers implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD (*2B*).			5.2.1			✓	✓	✓

ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor(s); ACR, albumin-to-creatinine ratio; AHA, American Heart Association; ARB, angiotensin receptor II blocker; BP, blood pressure; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; DRI, direct renin inhibitor; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcr-cys, creatinine and cystatin C–based estimated glomerular filtration rate; GFR, glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HBPM, home blood pressure monitoring; KDIGO, Kidney Disease: Improving Global Outcomes; KRT, kidney replacement therapy; MAP, mean arterial pressure; NOAC, non–vitamin K antagonist oral anticoagulant; POCT, point-of-care testing; PP, practice point; RASi, renin-angiotensin system inhibitor(s); SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor(s); T2D, type 2 diabetes.
[a]CKM stages from the AHA are defined as follows: stage 0: no risk factors; stage 1: excess/dysfunctional adipose tissue; stage 2: metabolic risk factors and CKD; stage 3: subclinical cardiovascular disease in CKM syndrome; stage 4: clinical CKM in CKM syndrome.

framework does identify both GFR and albuminuria as components to identify CKD, but falls short of specifying the need for albuminuria to truly assess risk.

The relative risks of kidney failure, CVD, and mortality are increased for all people with CKD (Figure 3). Among 27.5 million people participating in the CKD Prognosis Consortium, both lower estimated GFR and higher UACR were independently associated with adverse outcomes, including all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, heart failure (HF), atrial fibrillation, peripheral vascular disease, kidney failure with kidney replacement therapy, acute kidney injury, and hospitalization.[50]

KDIGO recommends applying risk prediction scores to inform estimation of absolute individual risk and to help tailor the frequency of visits, bloodwork, timing of educational activities, and escalation of care. At the time of publication, the most commonly used predictive tools are the Kidney Failure Risk Equation to predict 2- and 5-year risk of kidney failure[51,52] and the validated prediction models for CKD progression and CVD risk prediction from the CKD Prognosis Consortium.[50,53]

The CKM framework importantly highlights CKD in both early and late stages. The presence of CKD itself places a person in at least stage 2 CKM, and CKM stage is higher with more advanced CKD stage or clinical CVD. The CKM framework also incorporates risk equations developed to predict risk of specific CVD events (e.g., atherosclerotic CVD, HF, myocardial infarction, and stroke).[54] The newer models (such as Predicting Risk of Cardiovascular Disease EVENTs [PREVENT]) improve on previous equations by explicitly incorporating GFR and (optionally) UACR in addition to traditional risk factors. These models attempt to estimate risks across the range of cardiovascular outcomes, giving a more integrated holistic perspective. They rely on data obtained in routine clinical care and from electronic medical records and may therefore be limited in their applicability worldwide. We note that the precise diagnosis of CKD is not included in any of the CKM frameworks, which again calls out the need for nephrology input into these care paradigms to ensure accurate diagnoses, so that potentially disease-specific care can be implemented, in addition to CVD risk management.

KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Hypertension is defined as persistently raised arterial pressure. Blood pressure (BP) is normally distributed in the population, and there is no natural definitive cutoff point. The KDIGO 2021 Clinical Practice Guidelne for the Management of Blood Pressure in Chronic Kidney Disease uses the term "high BP" to denote BP above the target for subpopulations (adults with CKD, children and adolescents with CKD, and kidney transplant recipients).[36] Any increase in BP may be associated with an increase in CVD risk. The American Heart Association recommends measurement of BP across the age span to screen for early CKM. In addition, presence of hypertension places an individual in stage 2 CKM, concurrent with CKD (Figure 1b).

For adults with CKD not treated with dialysis or kidney transplantation, KDIGO recommends a systolic BP target for adults of <120 mm Hg (using standardized BP measurement) irrespective of age, UACR, or diabetes status, based on results from randomized trial data.[36,55–57] However, evidence supporting the systolic BP target of <120 mm Hg is less certain in those with advanced CKD (G4 and G5), significant proteinuria (>1 g/d), baseline systolic BP 120–129 mm Hg, younger age (<50 years), or very old age (>90 years). The KDIGO guideline advises considering less intensive BP-lowering therapy in people with frailty, high risk of falls and fractures, very limited life expectancy, or symptomatic postural hypotension. In children with CKD, the guideline suggests that mean arterial pressure measured by ambulatory BP monitoring be lowered to ≤50th percentile for age, sex (biological attributes), and height.

KDIGO 2020 and 2022 Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease. Diabetes, growing in prevalence worldwide, is the most common cause of CKD and a strong risk factor for kidney failure and cardiovascular events. The KDIGO 2020 and 2022 Guidelines for

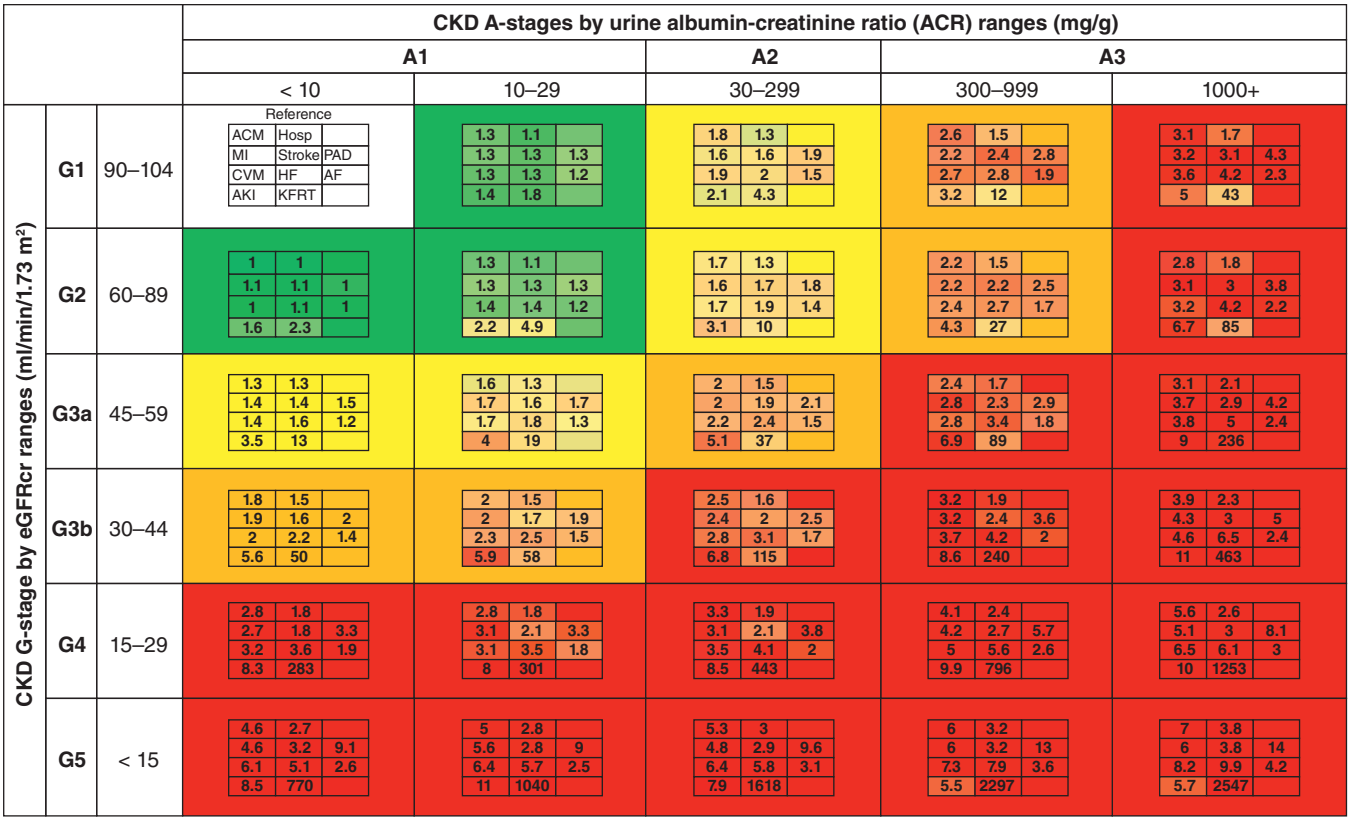

Figure 3 | Associations of chronic kidney disease (CKD) stages by creatinine-based estimated glomerular filtration rate (eGFRcr) and albumin-to-creatinine ratio. Adjusted hazard ratios for 10 outcomes as a function of CKD eGFR (G) and albuminuria (A) stages by heatmap colors of risk stages (green = low risk, yellow = moderately increased risk, orange = high risk, and red = very high risk). Numbers reflect the adjusted hazard ratio compared with the reference cell in a separate analysis for each of the 10 outcomes. Adjustment variables included age, sex, smoking status (current, former, or never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, use of antihypertensive medications, and a history of diabetes, coronary heart disease, stroke, heart failure (HF), atrial fibrillation (AF), peripheral artery disease (PAD), cancer, and chronic obstructive pulmonary disease when relevant. The cohorts used in these analyses are the general population and electronic health record cohorts (the CKD cohorts did not have sufficient individuals in this reference cell). Sample sizes include individuals who are missing a measure of albuminuria. The percentile shaded the darkest green color corresponds to the proportion of cells in the grid without CKD, and the percentile shaded the darkest red color corresponds to the proportion expected to be at the highest risk for adverse outcomes. In this manner, the numbers of green and red cells are consistent across outcomes, but the patterns are allowed to differ. We omitted the eGFRcr category of ≥105 ml/min per 1.73 m^2 from this figure because this category displays an increased risk of some outcomes. Figure depicts data from Writing Group for the CKD Prognosis Consortium, Grams ME, Coresh J, et al. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. *JAMA*. 2023;330:1266–1277.[49] ACM, all-cause mortality; AKI, acute kidney injury; CVM, cardiovascular mortality; Hosp, hospitalization; KFRT, kidney failure with replacement therapy; MI, myocardial infarction.

Diabetes Management in Chronic Kidney Disease advise a comprehensive approach to reducing risks of CKD progression and CVD experienced by people with diabetes and CKD.[40,58]

The 13 graded recommendations in the KDIGO 2022 Guideline for Diabetes Management in Chronic Kidney Disease include 3 lifestyle recommendations that directly affect both kidney and cardiovascular outcomes (physical activity, dietary sodium restriction, and smoking cessation), 5 recommendations for pharmacological therapies that improve both kidney and cardiovascular outcomes (renin-angiotensin system inhibitors [RASi], sodium-glucose cotransporter-2 inhibitors [SGLT2i], glucagon-like peptide-1 receptor agonists [GLP-1 RAs], nonsteroidal mineralocorticoid receptor antagonists [nsMRAs], and metformin), and 2 recommendations for holistic self-management and integration of care (Table 1).[40]

The presence of both diabetes and CKD indicates stage 2 CKM or greater, highlighting the importance of this combination of diseases in the CKM paradigm. Consistent with approaches to CKM staging and treatment offered by cardiology and diabetes professional organizations, KDIGO provides guidance for selecting interventions according to individual comorbidities and kidney and cardiovascular risks, integrated with known risks and benefits of evidence-based interventions. For example, glycemic targets should be individualized, balancing the benefit of strict glucose control with the risk of hypoglycemia, which increases with lower GFR. A consensus statement published in collaboration with the American Diabetes Association specified areas of agreement,[59] emphasizing the inherent interdisciplinary nature of caring for this population.

KDIGO 2013 Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Dyslipidemia is a common feature of CKD associated with CVD and mortality, and CKD is considered a high-risk condition for the development of CVD. In general, the benefit of treating elevated cholesterol with statins applies in CKD as in other populations. Thus, in people with CKD aged ≥50 years but not treated with chronic dialysis or with kidney transplantation, it is recommended to treat with statins or statins/ezetimibe. This recommendation also applies when age is 18–49 years for people with atherosclerotic CVD, an estimated 10-year incidence of coronary death or nonfatal myocardial infarction >10%, or diabetes.[34] Data are mixed for people on dialysis, where trials failed to document a benefit of statins on CVD outcomes.[60–63]

The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease now also suggests consideration of prescribing proprotein convertase subtilisin/kexin type 9 inhibitors to people with CKD who have an indication for their use (e.g., very high-risk atherosclerotic CVD or when low-density lipoprotein cholesterol remains above a threshold for secondary prevention).[38] A plant-based "Mediterranean-style" diet can also be considered in addition to lipid-modifying therapy to reduce cardiovascular risk.[38]

KDIGO Clinical Practice Guideline for the Management of Heart Failure in Chronic Kidney Disease. KDIGO has recently announced their first guideline on HF in CKD. The upcoming KDIGO guideline will provide practical guidance on the diagnosis and management of HF in people with CKD. The report of the KDIGO 2024 Controversies Conference on "Kidney Disease and Heart Failure: Recent Advances and Current Challenges: Conclusions From a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference" copublished in *Kidney International* and *JACC: Heart Failure* in April 2026.[64,65] HF, regardless of ejection fraction, is highly prevalent in people with CKD (estimated between 10% and 40%), and ∼50% of people with HF have concomitant CKD.[66,67]

Both HF and CKD commonly result from pathophysiological mechanisms such as endothelial dysfunction, inflammation, and atherosclerosis (Figure 1a).[9,15,68] In a recently proposed update to the HF staging system, all people with CKD are considered at risk for HF.[69] The diagnosis of HF can be challenging in people with CKD because of overlapping symptoms and difficulty in interpreting diagnostic tests such as natriuretic peptide levels. However, people with HF and CKD are commonly undertreated with guideline-directed medical therapies.[70,71] Multiple therapies, such as SGLT2i and RASi, are indicated for both diseases, highlighting the shared mechanisms between HF and CKD. Optimal care of the person with HF and CKD requires an integrated care approach between the cardiologist and the nephrologist.

KDIGO 2024 Controversies Conference on the Relationship Between Obesity and Chronic Kidney Disease: Pathophysiology, Prognosis, and Management. In the CKM paradigm, obesity is an inciting condition that defines stage 1 CKM and initiates pathological processes that can lead to clinical CKM manifestations, including CKD. At the conference, participants examined the evidence regarding the epidemiology, pathophysiology, and treatment of obesity and CKD.[72] The importance of increasing awareness of obesity-related CKD was emphasized. Long-term, early-onset obesity as well as prolonged exposure to obesity carry the highest risk of developing CKD, which is of particular concern with the increase in childhood obesity. Assessment of GFR is a challenge in obesity and with large changes in body weight, but refining assessment methods in the context of obesity could provide opportunities for preventing loss of kidney function. We note that the linear nature of the CKM paradigm may not highlight the potential causal relationship here between obesity and CKD.

The foundation for managing obesity in CKD includes modifications to diet and physical activity. Pharmacotherapies such as GLP-1 RAs are effective in weight reduction and have kidney-protective and cardiovascular benefits. Metabolic and bariatric surgery is also effective in weight reduction and can reduce the likelihood of obesity-related complications and has been demonstrated to reduce albuminuria, a marker of kidney damage. Choice of prescribed treatment will vary depending on age and comorbidities and may change over time. Multidisciplinary collaboration is important both for optimizing patient care and advancing research.

KDIGO 2023 Controversies Conference on Preventing Chronic Kidney Disease and Maintaining Kidney Health. Recognition of the CKM syndrome draws attention to the evolution of CKM risk factors and disease over the lifespan and highlights opportunities to prevent advanced clinical manifestations of disease. In this context, prevention of CKD offers an opportunity to both preempt kidney failure and forestall the long-term adverse effects of CKD on CVD. Risk factors for CKD include obesity, hyperglycemia, and hypertension, among other modifiable and nonmodifiable risk factors. In 2023, KDIGO convened a controversies conference to focus on opportunities for CKD prevention, identifying multiple potential approaches to maintain kidney health before CKD develops.[45] After this, KDIGO is partnering with the American Diabetes Association, the European Association for the Study of Diabetes, and the American College of Cardiology to generate a consensus report with a systematic review of interventions to prevent CKD among people living with diabetes.

Overarching themes across KDIGO clinical practice guidelines and controversies conference reports

Early detection and intervention. Early detection and treatment optimization of CKD generally occurs in primary care. Options for optimizing the first-line approach include integrating CKD management into existing care pathways (e.g., diabetes and hypertension) and using skills and competencies from other healthcare professionals such as pharmacists to manage CKM in integrated clinics.[73] Within the CKM framework, we further emphasize the need for

nephrology consultation to establish the etiology of CKD, given the diverse possibilities, which may further inform treatment strategies.

Comprehensive, personalized management of kidney and cardiovascular risk. Individually and collectively, published KDIGO guidelines and guideline statements promote a comprehensive approach to mitigating the high risks of adverse kidney and cardiovascular outcomes associated with CKD (Table 1). Implementing recommended management of hypertension and diabetes, delaying CKD progression, managing its complications, and preventing/delaying CVD complications begins with addressing lifestyle factors common to all components of the CKM syndrome (weight management, diet, physical activity, and cessation/avoidance of tobacco) and continues with monitoring and targeted management of BP, diabetes, and lipids.

Lifestyle management. KDIGO suggests maintaining a protein intake of 0.8 g/kg body weight/d and a sodium intake of <2 g/d in the absence of sodium wasting (Table 1). Although not a graded recommendation, a diet higher in plant-based foods than in animal-based foods and a lower consumption of processed foods is beneficial in reducing acidosis, hyperkalemia, hyperphosphatemia, and risk of protein-energy wasting. Weight control and physical activity are key and again central to all components of CKM syndrome, together with avoidance of tobacco products.

Pharmacological management. Recommended targeted treatment includes agents shown to significantly reduce CKD progression and CVD complications (Table 1). Therapeutic recommendations include RASi, nsMRAs, SGLT2i, and GLP-1 RAs, which all address key processes thought to be central to the CKM syndrome, such as inflammation, fibrosis, oxidative stress, and hemodynamic factors.

Specifically, KDIGO guidelines recommend RASi for people with CKD, albuminuria, and hypertension, with and without diabetes; SGLT2i for adults with CKD who have T2D, albuminuria (UACR ≥200 mg/g, with a lower-level recommendation for lower levels of albuminuria), and/or HF; nsMRA for adults with T2D, CKD, and albuminuria; and GLP-1 RAs for adults with T2D and CKD who have a need for improved glycemic control. Importantly, there are safety considerations for people with more advanced CKD for some of these agents, and during acute illnesses, when the risk of acute kidney injury may impair excretion of metabolites. Meta-analysis of SGLT2i trials identified no increased risk of serious acute kidney injury, even among those with CKD G4.[74,75] Moreover, there was an overall reduction in serious acute kidney injury, reduction in hospitalization, and reduction in death. Note also that the absolute risks of adverse events remain quite modest (e.g., SGLT2i and mycotic genital infections). Drug-drug interactions are also more common in people with CKD, and polypharmacy and pill burden are major issues. It is beyond the scope of this paper to address these in depth, and the reader is referred to the specific guidelines for in-depth discussion.

Since the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease and 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease were published, additional clinical trials demonstrated kidney and cardiovascular benefits of GLP-1 RAs. In addition, GLP-1 RAs have shown significant benefits for CVD and CKD outcomes in people without diabetes who are overweight or obese.[76,77] This expanding evidence base was reviewed in a subsequent commentary and will likely lead to expanded indications for GLP-1 RAs in the future as existing guidelines are updated.[78] Current guidelines also suggest to address RASi- and/or nsMRA-associated hyperkalemia, such as dietary modifications, diuretics, and potassium binders, to avoid decreasing the dose or stopping these agents. Evidence suggests that outcomes are worse in people with CKD who have these agents titrated down or stopped than in matched people maintaining treatment unaltered.[79,80] Specific details regarding potassium-lowering strategies are beyond the remit of this review.

Multidisciplinary care. People living with CKD and other components of the CKM syndrome often require expertise from multiple specialists, including nephrologists, cardiologists, endocrinologists, hepatologists, and primary care physicians. Given the interconnected nature of these conditions, there is a need for a more integrated approach to care, especially as the onset or progression of one disease often exacerbates another (Table 1). Guidelines and care pathways tend to be siloed by organ or disease, though we describe here that KDIGO guidelines to date have incorporated many aspects of CVD and metabolic syndromes, aligned with those of CKM. Aligning practice and policies with the realities of patient care should improve outcomes for those living with these complex conditions.

Moving forward

CKM syndrome: implications for the nephrology community. Although CKM health has historically been a central focus of nephrology practice, the conceptualization and recent socialization of the CKM syndrome framework brings renewed attention to the importance of kidney disease to the broader community. The CKM syndrome may help strengthen nephrology partnerships with cardiology and endocrinology, moving beyond management of individual risk factors to a more integrated diagnosis, prevention, and management framework. In particular, the emphasis on the value of measuring UACR and GFR (e.g., as in the PREVENT equation) may lead to earlier CKD identification, which in turn will help facilitate greater implementation of CVD therapies in people with kidney disease.[9,15,81] Better and earlier identification and monitoring of kidney disease also enables our focus to move from prevention of progression of CKD with guideline-directed medical therapy to possible remission, not just in glomerular disease but also in diabetic and nondiabetic CKD.[82]

There will be a need to more overtly emphasize preventive and curative concepts in nephrology training programs, which have traditionally focused on dialysis, transplantation, and rarer causes of CKD, such as glomerulonephritis. All these patient populations will benefit from an integrated CKM approach as well, and many people with CKD will need a diagnosis, if identified by primary care, cardiology, or endocrinology.

KDIGO role in leading next steps in CKM health. KDIGO has published numerous guidance documents and controversies conference reports in support of the management of people at risk for or with CKM syndrome. The new framework serves to improve the relevance of those guidelines and the importance of CKD. The organization is well-positioned to continue advancing the promotion of CKM health through an integrated, evidence-based approach, which combines clinical guidance and supports ongoing research. KDIGO hosts many educational meetings and conferences that focus on nephrology while acknowledging the interrelationship with the CKM framework. KDIGO also traditionally ensures that key insights from relevant KDIGO guidelines reach a broad audience including patients, endocrinologists, cardiologists, and primary care physicians. Looking ahead, and in keeping with the holistic approach to evidence-informed care, KDIGO will ensure the adoption of key aspects of the CKM paradigm into guideline updates and support research using the framework. We encourage healthcare professionals within and beyond the nephrology community to apply the wealth of evidence-based KDIGO guidelines to deliver high-quality care to people with or at risk for CKM.

DISCLOSURE

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