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CARDIO KIDNEY METABOLIC MEDICINE 2026

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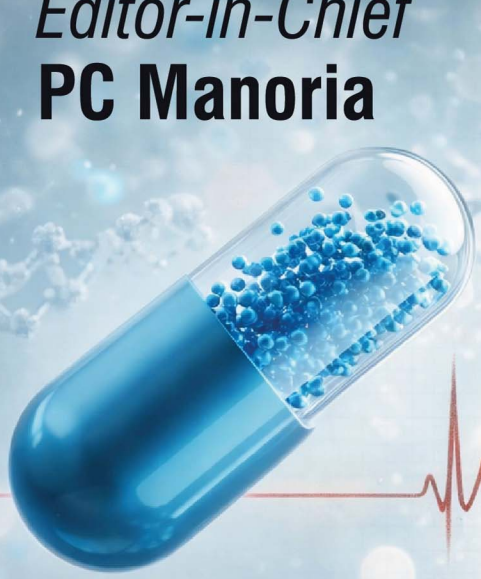

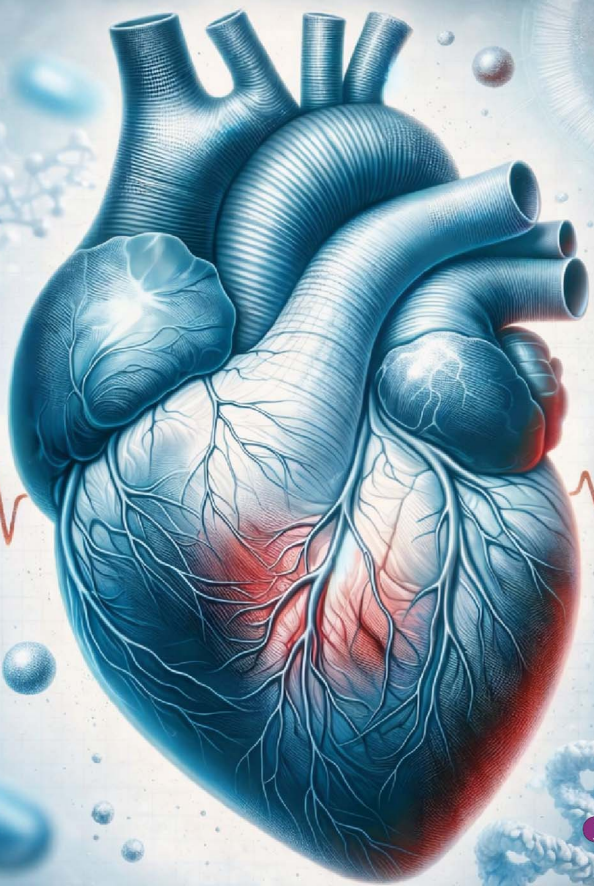

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CHAPTER 1

Cardio–kidney–metabolic Medicine: The Necessity for Adopting Globally

PC Manoria

ABSTRACT

The need for cardiovascular–kidney–metabolic (CKM) syndrome stems from recognizing that heart disease, kidney disease, and metabolic issues (like diabetes and obesity) are not separate problems but interconnected conditions, often starting with unhealthy lifestyles and excess fat, leading to severe multi-organ failure, if untreated. This framework promotes an integrated, holistic approach to early detection, risk reduction, and coordinated treatment (lifestyle and new drugs) for better outcomes, preventing severe complications such as heart failure, stroke, and kidney failure.

Keywords: Cardiovascular–kidney–metabolic syndrome, cardiometabolic risk, chronic kidney disease, metabolic syndrome, lifestyle modification

INTRODUCTION

Cardiovascular–kidney–metabolic (CKM) medicine focuses on the widespread adoption of an integrated care framework to address the interconnected nature of these diseases, implementation barriers, and the use of novel therapeutics. CKM medicine represents a paradigm-shifting framework that unifies the battle against cardiovascular (CV), kidney, and metabolic epidemics, poised to save millions amid their explosive global surge. CMK poses alarming global crisis with over 1.5 billion people grapple with CKM risks, fueling 45% of worldwide mortality-equivalent to a major city vanishing daily. Stage 4 extremes ravage 1 in 4 adults, with low-resource hotspots like India facing three times higher CKD escalation, devouring $500B+ in avoidable costs yearly. Siloed care and training deficits block progress, despite guidelines [American Heart Association (AHA)/Kidney Disease: Improving Global Outcomes (KDIGO)] blueprints proving 60% risk slashing via sodium-glucose cotransporter 2 inhibitors (SGLT2i)/glucagon-like peptide-1 receptor agonist (GLP-1 RA) combos. Stigma and inequities sideline 70% of at-risk populations in low- and middle-income countries (LMICs), demanding bold steps.

CKM medicine integrates management of CV, kidney, and metabolic disorders, which share common pathways like inflammation and insulin resistance. Global adoption is crucial due to their synergistic risks, affecting over 1 billion people worldwide and driving 40% of global deaths.

CKM syndrome stages patients from 0 (no risks) to 4 (extreme risk), with Stage 3+ prevalent in 20–30% of adults in high-income nations. In low-resource areas such as India, undiagnosed cases exacerbate CKD progression to end-stage renal disease, costing billions annually. Integrated screening could prevent 50% of events through SGLT2 inhibitors and GLP-1 agonists.

EVOLUTION OF THE CONCEPT: FROM CARDIORENAL TO CARDIOVASCULAR–KIDNEY–METABOLIC SYNDROME

The concept builds upon earlier frameworks:

- *Metabolic syndrome:* Focused on CV risk, clustering hypertension, dyslipidemia, hyperglycemia, and abdominal obesity.

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- *Cardiorenal syndromes:* Classified (types 1–5) the bidirectional heart-kidney interactions in acute and chronic settings. CKM syndrome expands these by integrating metabolic dysfunction as a central, driving component that initiates and accelerates both cardiac and renal injury, creating a vicious and self-perpetuating cycle.

PATHOPHYSIOLOGICAL PILLARS OF CARDIOVASCULAR–KIDNEY–METABOLIC SYNDROME

The interconnection is driven by overlapping mechanisms:

- *Insulin resistance and hyperglycemia:* Chronic hyperglycemia and insulin resistance promote advanced glycation end-product (AGE) formation, oxidative stress, and endothelial dysfunction, damaging both the glomerular filtration barrier and coronary vasculature.
- *Chronic low-grade inflammation and immune dysregulation:* Adipose tissue, especially visceral fat, acts as an endocrine organ secreting proinflammatory adipokines (e.g., leptin and resistin) and cytokines [e.g., tumor necrosis factor-α (TNF-α) and interkeukin-6 (IL-6)]. This systemic inflammation accelerates atherosclerosis, promotes renal fibrosis, and worsens insulin resistance.
- *Neurohormonal activation renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS):* Overactivity of the RAAS and the SNS is a final common pathway. It drives hypertension, sodium retention, myocardial fibrosis, and progressive glomerulosclerosis.
- *Endothelial dysfunction and microvascular disease:* A hallmark of CKM syndrome, leading to impaired vasodilation, a prothrombotic state, and capillary rarefaction, affecting the heart, kidneys, and other organs.
- *Hemodynamic and fluid overload:* Kidney dysfunction leads to sodium/water retention, increasing preload and afterload, precipitating or worsening heart failure [especially heart failure with preserved ejection fraction (HFpEF)]. Conversely, reduced cardiac output in heart failure decreases renal perfusion, exacerbating chronic kidney disease (CKD).

CLINICAL STAGING AND RISK STRATIFICATION

A proposed staging system adapted from the AHA[1] facilitates risk assessment and guides preventive actions:

- *Stage 0 (At risk):* No CKM risk factors. *Focus:* Healthy lifestyle.
- *Stage 1 (Excess adiposity):* Overweight/obesity, or dysfunctional adipose tissue (e.g., elevated waist circumference). *Focus:* Weight management.
- *Stage 2 (Metabolic risk factors):* Includes type 2 diabetes mellitus (T2DM), hypertension, hypertriglyceridemia, and metabolic syndrome. *Focus:* Risk factor control.
- *Stage 3 (Subclinical CKM):* Evidence of end-organ damage without symptoms: e.g., high CV risk (by calculators), left ventricular (LV) hypertrophy, albuminuria (≥30 mg/g), estimated glomerular filtration rate (eGFR) 30–59 mL/min/1.73 m^2. *Focus:* Disease-modifying therapies.
- *Stage 4 (Clinical CKM):* Symptomatic disease: Cardiovascular disease (CVD) (heart failure, coronary artery disease, atrial fibrillation, and stroke), CKD (eGFR <30), or both. Subclassified by kidney function (a–d). *Focus:* Multidisciplinary specialty care.

KEY CURRENT ISSUES AND FOCUS AREAS IN 2025

- *Integrated care and breaking down silos:* A primary issue is moving away from traditional, organ-specific "siloed" care models (e.g., separate cardiologists, nephrologists, and

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endocrinologists) toward a multidisciplinary and integrated approach. Professional societies like the AHA and the International Society of Nephrology (ISN) are collaborating to provide resources and roadmaps to facilitate this change in clinical practice.

- *Early detection and risk assessment:* There is a strong emphasis on early screening and risk assessment, often starting at younger ages (e.g., 30 years old), to prevent disease progression.
  - The 2025 CKM framework encourages using the new *AHA PREVENT™ Online Calculator* which includes eGFR in its base model and removes race as a factor to promote more equitable care.
  - Routine screening for urine albumin-creatinine ratio (UACR) is recommended in patients with diabetes, hypertension, or metabolic syndrome to fully characterize kidney and CV risk.
- *Implementation barriers:* Despite robust evidence for improved outcomes with certain therapies, the uptake of guideline-directed medical therapies (GDMT), such as SGLT2 inhibitors and GLP-1 receptor agonists, remains low. Barriers include clinical inertia, provider lack of awareness, and system-level issues like inequitable access to medications and fragmented care systems.
- *Role of novel therapeutics:* The benefits of new pharmacological agents are a major focus, specifically:
  - *SGLT2 inhibitors* and *GLP-1 RAs* have shown robust benefits across multiple CKM conditions and are often prioritized for patients with specific risk factors.
  - *Mineralocorticoid receptor antagonists (MRAs),* like finerenone, are also key components of contemporary management strategies for kidney and CV protection.
- *Social determinants of health (SDOH):* There is growing recognition that adverse social determinants of health significantly impact CKM outcomes. Integrating SDOH screening and addressing these factors is a key recommendation for improving equitable care.
- *Lifestyle interventions:* Lifestyle modifications (diet, exercise, smoking cessation, and sleep) remain central to prevention and management. However, 2025 research highlights that for patients with established disease, lifestyle interventions alone may be insufficient and must be combined with intensive pharmacotherapy.
- *Expanding the framework to the liver:* Emerging research in 2025 suggests the need to integrate metabolic dysfunction-associated steatotic liver disease (MASLD) into the CKM framework, recognizing the liver's critical role in this interconnected system, potentially moving toward a cardio-renal-hepatic-metabolic paradigm.

THERAPEUTIC PARADIGM SHIFT: FROM ORGAN-SPECIFIC TO ORGAN-PROTECTIVE

Management transcends simple risk factor control to include agents with proven multiorgan benefits:

- *SGLT2 inhibitors (e.g., empagliflozin and dapagliflozin):* These are a cornerstone therapy. They reduce CV mortality and heart failure hospitalizations, slow progression of CKD (reducing albuminuria and eGFR decline), and modestly improve glycemic control and weight.
- *GLP-1 receptor agonists (e.g., semaglutide and liraglutide):* Provide superior glycemic and weight control, with proven CV benefits (reduced MACE) and emerging evidence for renal protection (primarily through reduction in albuminuria).
- *Nonsteroidal MRAs (e.g., finerenone):*[2] Demonstrated specific benefit in reducing

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CKD progression and CV events in patients with T2DM and CKD, independent of blood pressure control, by targeting inflammation and fibrosis.

- *Foundational support:* RAAS inhibition [angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blocker (ARB)], GDMT for heart failure [including angiotensin receptor-neprilysin inhibitors (ARNI)], and statins remain critical. Lifestyle intervention (nutrition and exercise) is the bedrock of management at all stages.

IMPERATIVE FOR INTEGRATED CARE MODELS[3]

Effective CKM management requires dismantling specialty silos. Proposed models include:

- *Multidisciplinary CKM clinics:* Colocating or closely integrating cardiology, nephrology, endocrinology, dietetics, and pharmacy.
- *Shared digital health records:* Enhancing communication between primary care and specialists.
- *Patient-centered education:* Empowering patients to understand the systemic nature of their condition.

STRATEGIES FOR GLOBAL ROLLOUT

- *Policy advocacy:* Mandate CKM staging in national health programs, as piloted by ISN initiatives.
- *Education campaigns:* Train 10 million providers via online modules on risk calculators.
- *Tech integration:* Deploy artificial intelligence (AI)-driven apps for remote monitoring in rural areas like Bhopal.
- *Equity focus:* Subsidize therapies for LMICs to achieve 80% coverage by 2030.

PROJECTED IMPACT

Widespread adoption could avert 10 million CV events yearly, slashing dialysis demand by 30% and aligning with sustainable development goal (SDG) 3.0 goals.

BOLD STRATEGIES FOR WORLDWIDE TRIUMPH

- *Revolutionary policies:* Embed CKM staging in every national health blueprint, mirroring ISN's high-impact pilots.
- *Massive education surge:* Arm 15 million clinicians with AI-powered modules and risk simulators by 2028.
- *Tech-powered equity:* Roll out free AI apps for rural screening, hitting 90% coverage.
- *Therapy revolution:* Slash prices 80% via generics, targeting zero-access gaps in underserved zones.

TRANSFORMATIVE HORIZON

Universal CKM rollout could avert 15 million CV catastrophes annually, crater dialysis needs by 40%, and propel SDG 3.0 to victory-redefining medicine's greatest comeback story.

FUTURE DIRECTIONS

- *Research gaps:* Need for deeper understanding of CKM phenotypes, biomarkers for early detection, and the impact of novel therapies [e.g., glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 coagonists] on the full CKM spectrum.
- *Public health implications:* CKM syndrome underscores the need for population-level strategies addressing obesity and metabolic health to prevent downstream cardiac and renal complications.

CONCLUSION

CKM syndrome represents a fundamental reframing of the interplay between the heart, kidneys, and metabolism. Its adoption into clinical practice through unified staging, the use of multiorgan protective therapies, and integrated

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care pathways is essential to improve the prognosis and quality of life for a vast population of patients globally. Embracing this holistic paradigm is the next critical step in combating interconnected noncommunicable diseases.

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CARDIO KIDNEY METABOLIC MEDICINE 2026

Salient Features

- This comprehensive book on *Cardio Kidney Metabolic Medicine 2026* underscores the global necessity for an integrated care models to combat interconnected threats like obesity—a looming cardiometabolic crisis extending from childhood phenotypes to overlooked sarcopenic obesity and epicardial fat as key biomarkers
- It explores antiobesity medications' evolution, bariatric surgery advances, and the reality of diabetes remission, bolstered by CGM breakthroughs in glycemic control
- Innovations in hypertension management, metabolic dysfunction-associated steatotic liver disease (MASLD) link to atherosclerotic cardiovascular disease (ASCVD), and strategies against HF in diabetes—from HFpEF perspectives to hyperkalemia roadblocks—are demystified alongside SGLT2 inhibitors' blockbuster impact and 2025 antihypertensive drugs
- Cutting-edge chapters on digital twins, AI in clinics, and 2026 digital diabetes care herald personalized, tech-driven futures.

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