International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Treatment of Cardiometabolic Risk Factors in Adults with Cardiovascular-Kidney-Metabolic Syndrome: A Narrative Review of Evidence-Based and Real-World Observational Data: A Clinical Review for Practising Physicians

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Abstract: ***Background: Cardiovascular-kidney-metabolic (CKM) syndrome describes the mechanistic and clinical overlap between excess or dysfunctional adiposity, metabolic risk factors, chronic kidney disease (CKD), and cardiovascular disease (CVD). The American Heart Association formally defined and staged it (Stage 0 through Stage 4) in 2023,[1,2] and the AHA, American College of Cardiology (ACC), American Diabetes Association (ADA), and American Society of Nephrology (ASN) translated that framework into a full multi-society clinical practice guideline in 2026.[3] Objective: To synthesise published epidemiological, randomised-trial, and real-world observational evidence on the treatment of cardiometabolic risk factors in adults with CKM syndrome - with attention to data relevant to Indian clinical practice - and to summarise the safety and tolerability profile of guideline-recommended agents alongside their efficacy. Evidence synthesis: Large population cohorts confirm a graded, accelerating rise in all-cause and cardiovascular mortality across CKM stages,[4,5,6] while nationally representative Indian data (ICMR-INDIAB) document a very high underlying burden of the component risk factors.[11] Contemporary trial evidence supports a foundational, risk-based treatment architecture built on lifestyle and weight management, cardioprotective antihyperglycaemic therapy (SGLT2 inhibitors and GLP-1-based therapies), renin-angiotensin-system (RAS) blockade with a non-steroidal mineralocorticoid receptor antagonist for albuminuric CKD, and aggressive lipid and blood-pressure control.[3,15,21,23] Each pillar carries a distinct safety signal - GI intolerance with GLP-1-based agents, genital mycotic infection and rare euglycaemic ketoacidosis with SGLT2 inhibitors, hyperkalaemia with finerenone - that is clinically manageable but needs active monitoring, not passive prescribing.[37,39,40] Observational findings: Indian real-world data repeatedly document a wide gap between guideline recommendation and everyday prescribing - statin and antiplatelet use below 2% in individuals with a major cardiovascular risk factor, and LDLcholesterol goal attainment in only about one in four patients with established coronary disease, despite statin therapy.[31,32] Conclusion: Closing the treatment-implementation gap, not generating further efficacy data, is the principal unmet need in CKM care in India.***

Keywords: cardiovascular-kidney-metabolic syndrome, cardiometabolic risk, SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, chronic kidney disease, dyslipidaemia, India, treatment gap, safety and tolerability

Key Clinical Messages

- CKM syndrome (Stages 0-4) reframes cardiovascular disease, type 2 diabetes, obesity, and CKD as a single interconnected continuum. The 2026 AHA/ACC/ADA/ASN guideline provides a single-stage treatment architecture in place of separate single-organ pathways.
- Most adults already meet criteria for at least Stage 1-2. Mortality risk rises sharply - not linearly - from Stage 2 onward, which argues for early identification, not late intensification.
- SGLT2 inhibitors and GLP-1-based therapies now carry cardiorenal indications independent of glycaemic control. Finerenone is indicated for persistent albuminuria despite RAS blockade and an SGLT2 inhibitor.
- Each of these agents has a real, manageable but non-trivial safety profile - GI intolerance, genital mycotic infection and euglycaemic DKA, hyperkalaemia respectively. Specific counselling and monitoring are required, not blanket reassurance.
- India's principal evidence-practice gap is prescribing intensity, not drug availability. Statin and antiplatelet use below 2%, and LDL-C goal attainment near 25%, have been documented in Indian cohorts despite inexpensive, guideline endorsed therapy being on the market for decades.

A Note on Evidence Selection

This is a structured narrative synthesis, not a systematic review. Evidence was prioritised in this order: the 2023 AHA presidential advisory and the 2026 AHA/ACC/ADA/ASN joint guideline as the current authoritative staging and treatment framework; pivotal randomised controlled trials underpinning specific guideline recommendations; large observational cohorts (NHANES, Taiwanese and Chinese registries) describing CKM epidemiology; and Indian population-based and hospital-based observational studies describing real-world screening, prescribing, and safety patterns. Where Indianspecific data existed, it is presented in preference to extrapolation from Western cohorts. Where it

did not, that gap is flagged explicitly rather than filled by inference.

1. Introduction and Rationale

For decades, cardiovascular disease, type 2 diabetes, obesity, and chronic kidney disease were taught and managed as separate problems - separate specialists, separate guidelines, separate outcome measures. That model has become mechanistically indefensible. Excess and dysfunctional adiposity drives insulin resistance and hypertension, which damage the kidney, and kidney dysfunction in turn accelerates atherosclerosis and heart failure - a bidirectional, self-reinforcing loop that no single-organ clinic is designed to break.

In October 2023, the American Heart Association published a presidential advisory that gave this overlap a formal name and a staging framework: cardiovascular-kidney-metabolic (CKM) syndrome.[1,2] The explicit purpose was to correct fragmented, single-organ approaches to prevention and management.

This review integrates the current staging framework, the pivotal RCT evidence underpinning current guideline recommendations, the safety and tolerability profiles of the agents that evidence supports, and real-world observational data describing how - and how imperfectly - this evidence is currently applied. Where data from Indian cohorts exist, they take priority over extrapolation from Western populations.

2. Epidemiology and Burden of CKM Syndrome

2.1 Global and US Cohort Data

Only a small minority of adults are free of any CKM risk factor. Across different NHANES cohorts (1999-2020), Stage 0 prevalence ranges from roughly 12-13%. Stage 2 - established metabolic risk factors, CKD, or both - is the largest single category, accounting for approximately 53-55% of the adult population. [7,9]

The mortality data are sobering. In a prospective NHANES cohort of 34,809 adults followed for a median of 8.3 years, the adjusted hazard ratio for all-cause mortality rose from 1.43 at Stage 2 to 3.02 at Stage 4, relative to Stage 0. Cardiovascular mortality hazard ratios climbed even more steeply - 2.96, 7.60, and 10.5 at Stages 2, 3, and 4 respectively - with population attributable fractions of 25.3% for all-cause mortality and 45.3% for cardiovascular mortality concentrated in Stages 3-4.[5] A large Taiwanese occupational health cohort of over 515,000 adults followed for a median of 16.5 years reported closely analogous findings, with Stage 2 again the modal category (approximately 65% of the cohort) and a population-attributable fraction for cardiovascular mortality of 55.0%.[6]

Two clinical points emerge from these converging datasets. First, CKM syndrome is the epidemiological norm, not the exception, among adults in most studied populations. Second, the mortality curve is not linear - it accelerates sharply from Stage 2 onward. That argues for identifying and treating patients at Stage 1-2, before subclinical or clinical cardiovascular disease appears, rather than concentrating treatment intensity only after an index event.

2.2 The Indian Burden: ICMR-INDIAB and Related Data

The nationally representative ICMR-INDIAB study (113,043 individuals, 2008-2020) reported weighted prevalences in Indian adults of 11.4% for diabetes, 15.3% for prediabetes, 35.5% for hypertension, 28.6% for generalised obesity, 39.5% for abdominal obesity, and 81.2% for dyslipidaemia.[11] Project those proportions onto 2021 national population estimates and you get approximately 101 million people with diabetes, 315 million with hypertension, and 351 million with abdominal obesity. Every one of those risk factors maps directly onto the AHA CKM staging construct.

Nearly all of those individuals already meet criteria for at least CKM Stage 1, and a substantial proportion for Stage 2 - before any cardiovascular endpoint has occurred. A pooled meta-analysis of Indian studies estimated overall metabolic syndrome prevalence at approximately 30%, higher in urban areas, older adults, and women.[13] Community-based data from Tamil Nadu corroborate a persistent urban-rural gradient.[14] A recent ICMR-INDIAB dietary analysis further linked India's characteristically carbohydrate-heavy, comparatively low-protein diet to higher odds of incident diabetes, prediabetes, and both generalised and abdominal obesity - a population-level mechanistic explanation for the scale of the underlying burden.[12]

The practical implication is direct: CKM risk-factor screening cannot wait for patients who present with overt cardiovascular symptoms. Systematic assessment of BMI and waist circumference, glycaemic status, blood pressure, lipid profile, eGFR, and UACR needs to be routine in general and family practice, because the 2026 joint guideline recommends staging every adult and using that stage to calibrate treatment intensity. [3]

3. Pathophysiological Basis of CKM Syndrome

The CKM construct isn't merely descriptive. It reflects a shared, bidirectional mechanistic pathway - and understanding it changes which interventions get prioritised.

Excess and dysfunctional visceral adipose tissue secretes pro-inflammatory adipokines and free fatty acids. These drive systemic insulin resistance and low-grade inflammation. Insulin resistance then promotes activation of the renin angiotensin-aldosterone system (RAAS) and sympathetic overactivity - both of which raise blood pressure and increase intraglomerular pressure, initiating albuminuria, often the earliest detectable marker of kidney involvement in this pathway. [1] Once kidney function starts to decline, even modestly, it independently accelerates atherosclerotic disease and left-ventricular remodelling. Kidney disease becomes a bidirectional driver of cardiovascular risk, not a passive downstream complication of diabetes. [3]

That interdependence is exactly why single-organ management - treating glucose without reference to

albuminuria, or blood pressure without reference to adiposity - has historically under-performed. And it's why the staging framework places adiposity (Stage 1) upstream of both metabolic risk factors and CKD (Stage 2), rather than treating them as parallel, independent tracks.

4. Defining and Staging CKM Syndrome

The AHA advisory and the 2026 AHA/ACC/ADA/ASN guideline define five stages of CKM syndrome, summarised in Table 1.[1],[3] The progression is typical, not obligatory.

Table 1: AHA/ACC/ADA/ASN Staging of Cardiovascular-Kidney-Metabolic Syndrome

Stage	Definition
Stage 0	No CKM risk factors present.
Stage 1	Excess or dysfunctional adiposity (elevated BMI and/or waist circumference), with or without prediabetes, in the absence of other metabolic risk factors.
Stage 2	Metabolic risk factors present (hypertension, hypertriglyceridaemia, metabolic syndrome, diabetes) and/or CKD.
Stage 3	Subclinical cardiovascular disease (e.g., coronary artery calcification, elevated natriuretic peptides) in a patient with CKM risk factors, or very high-risk CKD, or high predicted 10-year CVD risk.
Stage 4	Clinical cardiovascular disease (coronary heart disease, heart failure, stroke, peripheral arterial disease) in a patient with CKM risk factors; subdivided by presence (4b) or absence (4a) of kidney failure.

A key innovation is the dedicated 10- and 30-year risk calculator (the PREVENT equations). Unlike older pooled-cohort equations, PREVENT incorporates eGFR and UACR directly into cardiovascular risk estimation rather than treating kidney disease as an unrelated comorbidity.[3] the 2026 guideline is clear: quantify cardiovascular risk using PREVENT, not informal estimation, and check both eGFR and UACR routinely - not only in patients with known diabetes - because albuminuria is frequently undetected in primary care and materially changes both risk stratification and drug choice.[3],[15]

One acknowledged limitation of the current staging construct is that it doesn't yet incorporate hepatic biomarkers, despite evidence that hepatic steatosis (metabolic dysfunction-associated steatotic liver disease, MASLD) commonly precedes overt insulin resistance by several years and is disproportionately prevalent at higher CKM stages.[10] A cross-sectional NHANES-based analysis found MASLD prevalence rising from roughly 8% at CKM Stage 1 to over 40% at Stages 3-4, with insulin-resistance-driven cardiovascular mortality risk concentrated in the MASLD subgroup.[4] This is a recognised gap, not a settled feature of the framework - and a reasonable area for Indian clinicians to monitor as the guideline literature matures, particularly given the high regional prevalence of metabolic fatty liver disease in South Asian metabolic phenotypes.

5. Treatment of Cardiometabolic Risk Factors: The Evidence Base

The 2026 AHA/ACC/ADA/ASN guideline organises management around a small number of high-yield interventions applied according to CKM stage and coexisting conditions (CKD, heart failure, obesity, atherosclerotic cardiovascular disease [ASCVD]), rather than a single glucose-centric or lipid-centric algorithm. [3] Table 2 summarises the landmark trials underlying these recommendations.

Table 2: Landmark Randomised Controlled Trials Underpinning CKM Treatment Recommendations

Trial	Agent/Class	N	Population and Key Finding
SELECT	Semaglutide (GLP-1RA)	17,604	Overweight/obesity + established CVD, no diabetes. 20% reduction in MACE; 73% reduction in incident diabetes.[15]
STEP-HFpEF / -DM	Semaglutide (GLP-1RA)	1,145	Obesity-phenotype HFpEF, without/with diabetes. Improved KCCQ symptom score, 6-min walk distance, body weight.[19],[20]
FLOW	Semaglutide (GLP-1RA)	3,533	Type 2 diabetes + CKD. 24% reduction in composite kidney outcome; 18% reduction in CV events; 20% reduction in all-cause mortality. Stopped early for efficacy.[21]
FIDELIO-DKD / FIGARO-DKD (FIDELITY)	Finerenone (nsMRA)	13,026	Type 2 diabetes + CKD on RASi. ~18% reduction in kidney composite; ~14% reduction in CV composite; 31% UACR reduction at 4 months.[23],[25]
DAPA-CKD / EMPAKIDNEY / CREDENCE	SGLT2 inhibitors	>15,000 combined	Diabetic and non-diabetic albuminuric CKD. Consistent reduction in progression to kidney failure and cardiovascular death across trials.[27],[29]
DPP	Intensive lifestyle vs. metformin	3,234	Adults at high risk of type 2 diabetes. 58% relative reduction in incident diabetes over 2.8 years with lifestyle intervention.[34]
Look AHEAD	Intensive lifestyle intervention	5,145	Adults with established type 2 diabetes. Improved weight, fitness, risk factors; no reduction in primary CV composite endpoint over 9.6 years; stopped for futility.[35]
ASCEND	Aspirin 100 mg/day	15,480	Adults with diabetes, no known vascular disease. 12% reduction in serious vascular events, offset by a 29% increase in major bleeding.[41]

5.1 Lifestyle Modification and Weight Management

Lifestyle intervention is the foundation of CKM prevention and Stage 1-2 management. The 2026 guideline frames weight management as capable of promoting regression - not merely slowing progression - of CKM stage.[3] But the evidence here is more nuanced than often assumed.

The Diabetes Prevention Program showed that an intensive lifestyle intervention targeting approximately 7% weight loss and 150 minutes per week of activity reduced incident type 2 diabetes by 58% over 2.8 years in high-risk adults, an effect that persisted - attenuated, but real - over 10-year follow-up.[34] That's a convincing signal for prevention. But Look AHEAD tells a different story: the same style of intensive lifestyle

intervention applied to adults who already had established type 2 diabetes achieved better weight loss and fitness, with fewer medications, yet failed to reduce the primary composite cardiovascular endpoint over 9.6 years, and was stopped early for futility on that endpoint.[35]

The lesson isn't that lifestyle doesn't matter once diabetes is established. It does - for quality of life, for risk-factor control, for how patients feel day to day.

But lifestyle intervention alone should not be presented to patients with established diabetes as a substitute for cardioprotective pharmacotherapy once cardiovascular risk is elevated. The RCT evidence doesn't support that.

The 2026 guideline additionally supports adjunctive obesity pharmacotherapy and metabolic/bariatric surgery when lifestyle measures alone are insufficient, reflecting maturing evidence that GLP-1-based agents themselves confer disease modifying cardiovascular and kidney benefits beyond weight loss.[3],[17]

5.2 Cardioprotective Antihyperglycemic Therapy: SGLT2 Inhibitors and GLP-1-Based Therapies

The single largest shift in CKM pharmacotherapy over the past decade has been the repositioning of two drug classes - SGLT2 inhibitors and GLP-1 receptor agonists - as cardiovascular- and kidney-protective agents selected on the basis of cardiorenal risk, independent of HbA1c targets. The 2026 guideline states this directly: among patients with type 2 diabetes and established cardiovascular disease or elevated cardiovascular risk, cardioprotective guideline-directed medical therapy - an SGLT2 inhibitor, a GLP-1-based therapy, or both - is recommended to improve cardiovascular and kidney outcomes, with the specific agent selected according to coexisting CKD, heart failure, obesity, or established atherosclerotic disease.[3]

Then SELECT extended the logic to patients without diabetes at all. In 17,604 adults with established cardiovascular disease and overweight or obesity but no diabetes, once-weekly semaglutide 2.4 mg reduced major adverse cardiovascular events by 20% relative to placebo over approximately 3 years.[15] Prespecified SELECT analyses added a 73% relative reduction in incident diabetes and a 22% reduction in a composite kidney outcome,[18] alongside weight loss that continued for up to four years (mean 10.2% versus 1.5% with placebo at 208 weeks).[16] Taken together, those findings have led investigators to describe semaglutide as a disease-modifying cardiometabolic therapy - not just a glycaemic or weight-loss agent.[16]

In heart failure with preserved ejection fraction and obesity - a phenotype now recognised as intrinsically cardiometabolic - STEP-HFpEF and STEP-HFpEF DM showed that semaglutide produced clinically meaningful improvements in heart failure symptoms (KCCQ score), six-minute walk distance, and body weight, in patients without and with type 2 diabetes respectively.[19],[20] A prespecified analysis of SELECT itself, in patients with prevalent heart failure at baseline, showed consistent benefit on major adverse cardiovascular events, heart-failure composite outcomes, and all-cause mortality regardless of heart-failure subtype.[19]

For kidney outcomes specifically, FLOW randomised 3,533 adults with type 2 diabetes and established CKD to once weekly semaglutide 1.0 mg or placebo on top of standard RAS blockade; it was stopped early for efficacy, showing a 24% reduction in the primary composite kidney outcome, an 18% reduction in major cardiovascular events, and a 20% reduction in all-cause mortality, together with a slower annual eGFR decline of 1.16 mL/min/1.73 m² compared with placebo.[21] These benefits were broadly consistent across the range of baseline eGFR, UACR, and KDIGO risk categories studied, and were not modified by concomitant SGLT2 inhibitor use - suggesting the two drug classes act through complementary rather than redundant mechanisms.[22]

SGLT2 inhibitors bring a longer track record of dedicated kidney-outcome trials: CREDENCE (canagliflozin), DAPACKD (dapagliflozin), and EMPA-KIDNEY (empagliflozin) each demonstrated reductions in progression to kidney failure and cardiovascular death across diabetic and non-diabetic CKD populations with albuminuria.[27],[28],[29] In heart failure, empagliflozin and dapagliflozin are now established first-line guideline-directed therapy across the full ejection-fraction spectrum, with the 2026 guideline explicitly recommending SGLT2 inhibitors as first-line therapy in HFmrEF/HFpEF and as part of quadruple foundational therapy in HFrEF, with GLP-1-based agents added where obesity or additional CKM risk factors are present.[3]

5.3 Kidney-Protective Therapy: RAS Blockade and Non-Steroidal Mineralocorticoid Receptor Antagonism

ACE inhibitors or angiotensin receptor blockers remain foundational, first-line therapy for albuminuric CKD in the presence of type 2 diabetes.[3] Where albuminuria persists despite optimised RAS blockade and an SGLT2 inhibitor, the 2026 guideline recommends adding the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone, or a GLP1-based therapy, for further kidney and cardiovascular protection.[3]

That recommendation rests on FIDELIO-DKD and FIGARO-DKD and their prespecified pooled analysis (FIDELITY, n=13,026), where finerenone reduced the composite kidney outcome by approximately 18% and the composite cardiovascular outcome by approximately 14% relative to placebo, alongside a 31% UACR reduction at four months.[23],[25] A mediation analysis of the pooled FIDELITY dataset found that finerenone's UACR-lowering effect accounted for 84% of its kidney-outcome benefit and 37% of its cardiovascular-outcome benefit - reinforcing albuminuria reduction as a meaningful, trackable treatment target in routine practice, not merely a trial endpoint.[27]

A pooled participant-level analysis spanning FIDELIO-DKD, FIGARO-DKD, and the heart-failure trial FINEARTS-HF (FINE-HEART, n=18,991) extended these benefits across the cardiovascular-kidney-metabolic spectrum, supporting finerenone as a therapy relevant to CKM syndrome as an integrated entity rather than to diabetic kidney disease alone.[26] The CONFIDENCE trial, examining simultaneous initiation

of finerenone and empagliflozin, is testing whether combined rather than sequential therapy produces additive albuminuria reduction - reflecting the four-pillar model of CKD care in type 2 diabetes now described in nephrology literature: RAS blockade, SGLT2 inhibition, non-steroidal MRA therapy, and GLP-1-based therapy.[24],[22],[30]

5.4 Lipid Management

Statin therapy remains the backbone of atherosclerotic cardiovascular risk reduction across all CKM stages once risk crosses guideline-defined thresholds. The 2026 guideline continues to recommend risk-stratified statin intensity as part of first-line ASCVD prevention. The comparative challenge in India is not an absence of trial evidence - which is as robust here as anywhere globally - but a well-documented gap between recommendation and real-world attainment, discussed in Section 7.

5.5 Blood Pressure Control

Blood-pressure management follows established hypertension-guideline thresholds and is treated in the 2026 CKM guideline as inseparable from kidney and cardiovascular protection, given that RAS-inhibitor and SGLT2-inhibitor regimens used for kidney protection concurrently lower blood pressure, and given the strong mechanistic link between uncontrolled hypertension and CKM stage progression.[3] As with lipid management, the principal Indian challenge is treatment intensity in routine practice rather than absence of an evidence base.

5.6 Antiplatelet Therapy: A More Nuanced Role Than Often Assumed

Aspirin is standard for secondary prevention in patients with established atherosclerotic disease. Its role in primary prevention - patients with CKM risk factors such as diabetes but no prior cardiovascular event - is a different matter. The ASCEND trial randomised 15,480 adults with diabetes but no known vascular disease to aspirin 100 mg/day or placebo; over 7.4 years, aspirin reduced serious vascular events by 12% but increased major bleeding by 29%, with no significant effect on all-cause mortality or cancer incidence.[41] A meta-analysis pooling this and other primary-prevention trials in diabetes found a modest reduction in major adverse cardiovascular events (relative risk 0.89) with a number needed to treat of 95 over five years - without a clear net safety margin once bleeding risk is weighed in.[42]

Aspirin should not be added reflexively because a patient has diabetes or other CKM risk factors. Reserve it for patients with established atherosclerotic disease (Stage 4), or individualise based on bleeding risk in earlier stages - it's not an automatic component of cardiometabolic risk reduction.

6. Safety and Tolerability Considerations

Guideline endorsement of SGLT2 inhibitors, GLP-1-based therapies, and finerenone is sometimes communicated as though these agents were free of meaningful downside. They're not. Each class carries a specific, generally manageable but real safety signal that should change how a physician initiates, counsels, and monitors these therapies.

6.1 GLP-1-Based Therapies: Gastrointestinal Intolerance

Nausea, vomiting, diarrhoea, and constipation - these are the dominant tolerability issues with GLP-1-based agents, and they're dose- and titration-dependent. Across the STEP trial programme, GI adverse events led to treatment discontinuation in 3.4-4.5% of participants on semaglutide, versus 0-0.8% on placebo.[36] A systematic review across 38 phase III/IV placebo-controlled trials reported nausea in 19.3% of actively treated participants versus 6.5% on placebo, and vomiting in 7.6% versus 2.0%, with an overall discontinuation-for-adverse-event rate of 6.5% versus 3.6% on placebo.[37] Symptoms are most prominent during dose escalation and typically settle with time. Slower up-titration - not early discontinuation - is the right first response to tolerable GI symptoms; reserve dose reduction or a drug switch for more severe or persistent intolerance.[38]

6.2 SGLT2 Inhibitors: Genital Mycotic Infection and Euglycaemic Ketoacidosis

SGLT2 inhibitors carry approximately a three- to four-fold increase in genital mycotic infection risk relative to comparators - a mechanistically predictable consequence of induced glycosuria - and approximately a three-fold increase in diabetic ketoacidosis, which may present atypically as euglycaemic ketoacidosis (blood glucose <250 mg/dL with significant acidosis), risking delayed recognition.[39] In a single-centre Indian cohort of 270 patients with type 2 diabetes on SGLT2 inhibitors, genital infection was documented in approximately 13% of patients, similar in those with and without concomitant coronary artery disease, and required treatment discontinuation in only around 2.7% of cases when managed with topical antifungal therapy and hygiene counselling.[43]

Practical mitigation: proactive counselling on genital hygiene at initiation; prompt topical antifungal treatment rather than reflex discontinuation for uncomplicated mycotic infection; and temporary withholding of therapy during acute illness, prolonged fasting, peri-operative periods, or reduced oral intake - the circumstances that predispose to euglycaemic ketoacidosis.

6.3 Finerenone: Hyperkalaemia

Hyperkalaemia is the principal safety concern with finerenone. In FIDELIO-DKD, investigator-reported hyperkalaemia occurred in 18.3% of finerenone-treated patients versus 9.0% on placebo, though permanent discontinuation for hyperkalaemia was low in absolute terms (2.3% versus 0.9%), and no hyperkalaemia-related deaths were reported.[23] In the pooled FIDELITY analysis, permanent discontinuation for hyperkalaemia was similarly low (1.7% versus 0.6% with placebo) over a median three-year follow-up.[40]

Risk mitigation, reflected in the trial protocols themselves: confirm a baseline serum potassium ≤5.0 mmol/L before initiation, recheck within one month of starting or up-titrating

the dose, and withhold or discontinue if potassium exceeds 5.5 mmol/L. Potassium-binding agents are available as an adjunct where ongoing therapy is clinically warranted despite borderline levels.[40] Asian-subgroup analyses have suggested a somewhat higher hyperkalaemia signal in this population - a reason for closer monitoring in Indian patients with CKD who otherwise meet the indication, not a reason for avoidance.

7. The Observational Evidence: Treatment Gaps in Real-World Indian Practice

Here the document needs to depart from trial evidence and examine what actually happens in Indian practice. The gap is unusually well-documented, and unusually large.

A population-based Indian study assessing cardiovascular risk-factor treatment found that only 1.7% of individuals with at least one major cardiovascular risk factor were taking a statin, and only 0.5% were taking aspirin - despite these being inexpensive, widely available, guideline-endorsed therapies.[32] The same study found that although 58% of people with diabetes were on some antidiabetic treatment, only 1% were on insulin, and that among those treated for hypertension, the mean number of antihypertensive agents used was only 1.2. The authors attributed this in part to clinical inertia and inadequate treatment intensification, not to lack of drug availability.[32]

That pattern isn't confined to primary care. A study of physicians managing patients with established stable coronary heart disease across primary, secondary, and tertiary care levels in Rajasthan found suboptimal use of aspirin, beta-blockers, statins, and ACE inhibitors - the standard four-drug secondary-prevention regimen - even in a population where the diagnosis of coronary disease was already established and the indication for these drugs was, in guideline terms, unambiguous.[33] More recently, a nationwide Indian study of patients with confirmed coronary artery disease already receiving statin therapy found that only around one in four achieved guideline LDL-cholesterol targets, attributing the shortfall to low uptake of combination lipid-lowering therapy (ezetimibe or bempedoic acid add-on) and continued clinician inertia toward treatment intensification.[31]

Taken together across three decades of study, these data describe a consistent pattern: the principal barrier to better CKM outcomes in India is not a shortage of efficacious, affordable, low-cost therapy. It's under-prescription and under intensification in routine practice, compounded by inconsistent patient follow-up and, in certain settings, concerns about medication quality and continuity of supply.[32],[33] Newer, guideline-preferred agents - SGLT2 inhibitors, GLP-1-based therapies, finerenone - are more costly and less uniformly accessible across the Indian health system than statins or generic antihypertensives, which is likely to widen, not narrow, this observed treatment gap unless deliberately addressed through pricing, insurance coverage, and prescriber education. That's an implementation problem the trial literature cannot resolve.

Table 3: Practical Considerations for Applying CKM Guideline Recommendations in Indian Practice

Domain	Practical Consideration for Indian Practice
Screening threshold	Given South Asian body-composition phenotype (higher visceral adiposity at lower BMI), consider waist circumference and metabolic screening at lower BMI cut-offs than Western guideline defaults, consistent with ICMR-INDIAB observations on abdominal obesity prevalence.[11]
Cost and access	Statins, RAS inhibitors, and metformin are inexpensive and widely available; SGLT2 inhibitors, GLP-1-based therapies, and finerenone are costlier and less uniformly covered by insurance, which may concentrate the newest evidence-based options among patients who can self-pay unless addressed at a system level.
Treatment inertia	Repeated Indian observational data show under-intensification (e.g., mean 1.2 antihypertensive agents per treated patient) rather than drug unavailability as the dominant gap; audit and feedback on treatment intensification may be higher-yield than further access expansion alone.[32]
Monitoring on initiation	SGLT2 inhibitors: counsel on genital hygiene and mycotic infection symptoms (Indian single-centre data show ~13% incidence); avoid initiation during acute illness/fasting states to reduce euglycaemic DKA risk. Finerenone: check serum potassium before and after initiation; avoid if baseline potassium >5.0 mmol/L.[43],[40]
Interdisciplinary coordination	Where cardiology, endocrinology, and nephrology operate as separate practices without a shared record, a single physician (often the primary/family physician) should be explicitly designated to track eGFR, UACR, LDL-C, blood pressure, and HbA1c longitudinally.

8. Interdisciplinary Care Models and Implementation

CKM syndrome by definition spans cardiology, endocrinology, nephrology, and primary care. The 2026 guideline assigns a Class 1 recommendation to interdisciplinary, team-based care for patients with CKM Stages 2-4, including designation of a coordinating point person to prevent the care fragmentation that has historically characterised management of these overlapping conditions.[3] The advisory that preceded the guideline had already flagged reduction of care fragmentation - through volume- and value-based strategies - as an explicit priority, alongside attention to social determinants of health given the disproportionate CKM burden observed among socioeconomically disadvantaged populations.[1]

For Indian health systems, where cardiology, diabetology, and nephrology services are frequently delivered by independent specialists without a shared record or protocol, this recommendation implies a practical need for structured referral pathways and shared risk-factor targets (eGFR, UACR, LDL-cholesterol, blood pressure, HbA1c) that any treating physician - regardless of specialty - can act on consistently.

9. Evidence Gaps and Limitations

Several limitations of the current evidence base and of this review merit acknowledgement. The pivotal SGLT2 inhibitor, GLP-1 receptor agonist, and finerenone trials cited here were conducted predominantly in North American, European, and East Asian populations. South Asian and Indian-specific representation within these global trials is comparatively limited, and extrapolation of absolute risk reductions to Indian populations - who differ in bodycomposition phenotype (higher visceral adiposity at lower BMI) and age of disease onset - should be made cautiously.[3]

Most of the mortality and staging data summarised in Section 2 are cross-sectional or registry-based, not derived from prospective Indian cohorts explicitly designed around the CKM staging construct. Indian-specific CKM staging and outcome data are still emerging.[8]

The current AHA/ACC/ADA/ASN staging framework doesn't yet formally incorporate hepatic steatosis biomarkers, despite accumulating evidence of their prognostic relevance - a limitation acknowledged in recent commentary, not a settled feature of the model.[10],[4]

This review itself is a narrative rather than systematic synthesis: evidence was purposively selected around the guideline architecture and Indian observational literature rather than identified through an exhaustive, reproducible search protocol.

And most importantly for Indian practice: the observational literature reviewed in Section 7 is now several decades deep and remarkably consistent in showing a treatment-implementation gap. The priority for Indian medical education and health-system design is arguably no longer generating further efficacy evidence. It's structured, physician-level and systemlevel interventions to close that gap.

10. Conclusion

Cardiovascular-kidney-metabolic syndrome reframes cardiometabolic risk as a single, staged, interconnected continuum rather than a set of independent diagnoses. The 2026 AHA/ACC/ADA/ASN guideline now provides a reasonably complete, risk-stratified treatment architecture: systematic staging using eGFR, UACR, and the PREVENT risk equations; lifestyle modification and weight management as the preventive foundation; cardioprotective antihyperglycaemic therapy with SGLT2 inhibitors and GLP-1-based agents selected by coexisting condition; RAS blockade with non-steroidal MRA addon for persistent albuminuria; judicious rather than reflexive use of antiplatelet therapy; and coordinated, interdisciplinary follow-up.[3] Each pillar comes with a specific, manageable safety profile that needs active monitoring, not passive reassurance.

India carries an unusually large share of the underlying risk-factor burden that defines this syndrome.[11] But the data in this review indicate something more uncomfortable than a drug-access problem: the therapies that would most immediately reduce cardiovascular mortality in Indian patients - statins, RAS inhibitors, adequately intensified antihypertensive regimens - are already available, already inexpensive, and already under-prescribed. Fixing that is the work. Progressively extending access to the newer cardiorenal-protective agents, with appropriate monitoring, where indicated and affordable, is the next priority - not the first.

References

[1] 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.
[2] American Heart Association Newsroom. Heart disease risk, prevention and management redefined [news release]. Dallas, TX: American Heart Association; October 9, 2023.
[3] American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, in collaboration with the American Diabetes Association and the American Society of Nephrology. 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-KidneyMetabolic Syndrome. J Am Coll Cardiol. 2026.
[4] Prevalence and Cumulative Incidence of Mortality Associated with Cardiovascular-Kidney-Metabolic Syndrome in the United States. medRxiv 2024.03.01.24303630 [preprint].
[5] Association of cardiovascular-kidney-metabolic syndrome with all-cause and cardiovascular mortality: a prospective cohort study (NHANES 1999-2018, n=34,809).
[6] Cardiovascular-kidney-metabolic syndrome and all-cause and cardiovascular mortality: a retrospective cohort study (Taiwan health-screening cohort, n=515,602). PLOS Med.
[7] The Associations of Anthropometric Indices With Stages and Mortality in Cardiovascular-Kidney-Metabolic Syndrome: Insights From NHANES.
[8] Epidemiology of cardiovascular-kidney-metabolic syndrome. Nat Rev Nephrol. 2026.
[9] Associations of Cardiovascular-Kidney-Metabolic Syndrome with Premature Mortality and Life Expectancies in US Adults: A Cohort Study.
[10] Cai X, Huang H, Li T. Cardiovascular-kidney-metabolic: hype or a focus on front-line health? J Transl Int Med. 2025.
[11] Anjana RM, Unnikrishnan R, Deepa M, et al (ICMR-INDIAB Collaborative Study Group). Metabolic noncommunicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023;11(7):474-489.
[12] Dietary profiles and associated metabolic risk factors in India from the ICMR-INDIAB survey-21. Nat Med. 2025.
[13] Association Between Anthropometric Risk Factors and Metabolic Syndrome Among Adults in India: A Systematic Review and Meta-Analysis of Observational Studies. Prev Chronic Dis. 2022.

[14] Prevalence and Determinants of Metabolic Syndrome Among Adults (18-60 Years) in Urban and Rural South India: A Community-Based Cross-Sectional Study.
[15] Lincoff AM, Malhotra A, Bays HE, et al; SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023; 389: 2221-2232.
[16] Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. Nat Med. 2024.
[17] Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial.
[18] U.S. Eligibility and Preventable Cardiovascular, Diabetes, and Kidney Outcomes from Semaglutide in the SELECT Trial.
[19] Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity (STEP-HFpEF). N Engl J Med. 2023; 389: 1069-1084.
[20] Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes (STEP-HFpEF DM). N Engl J Med. 2024; 390: 1394-1407.
[21] Perkovic V, Tuttle KR, Rossing P, et al; FLOW Trial Committees and Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024; 391: 109-121.
[22] Mahaffey KW, Tuttle KR, Arici M, et al. Cardiovascular outcomes with semaglutide by severity of chronic kidney disease in type 2 diabetes: the FLOW trial. Eur Heart J. 2024. doi:10.1093/eurheartj/ehae613.
[23] Bakris GL, Agarwal R, Anker SD, et al; FIDELIO-DKD Investigators. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD). N Engl J Med. 2020; 383: 2219-2229.
[24] COmbinatioN effect of FInerenone and EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint (CONFIDENCE) trial: baseline clinical characteristics. Nephrol Dial Transplant. 2025.
[25] Finerenone in Patients with Chronic Kidney Disease and Type 2 Diabetes by Sodium-Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis. Diabetes Care. 2022; 45: 2991-3001.
[26] Finerenone in heart failure and chronic kidney disease with type 2 diabetes: FINE-HEART pooled analysis of cardiovascular, kidney and mortality outcomes (FIDELIO-DKD, FIGARO-DKD, FINEARTS-HF; n=18,991).
[27] Impact of Baseline GLP-1 Receptor Agonist Use on Albuminuria Reduction and Safety with Simultaneous Initiation of Finerenone and Empagliflozin in Type 2 Diabetes and Chronic Kidney Disease (CONFIDENCE Trial). Diabetes Care. 2025.
[28] Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-1446.
[29] SGLT2 inhibitors and finerenone in non-diabetic CKD: a step into the (near) future? Clin Kidney J. 2024.
[30] A dose of CONFIDENCE: Building evidence for finerenone-empagliflozin synergy in diabetic kidney disease. NephJC. 2025.
[31] Low-Density Lipoprotein Cholesterol Goal Attainment in Indian Patients With Coronary Artery Disease: A Nationwide Study. 2026.
[32] Prevalence and pattern of cardiovascular risk factors in a population in India. BMJ Open (statin use 1.7%, aspirin use 0.5% among those with ≥1 major risk factor).
[33] Sharma KK, et al. Low use of statins and other coronary secondary prevention therapies in primary and secondary care in India. Vasc Health Risk Manag. 2009; 5: 1007-1014.
[34] Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009; 374: 1677-1686.
[35] Wing RR, et al; Look AHEAD Research Group. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. N Engl J Med. 2013; 369: 145-154.
[36] The societal implications of using glucagon-like peptide-1 receptor agonists for the treatment of obesity (STEP programme GI adverse event and discontinuation rates). 2025.
[37] The science of safety: adverse effects of GLP-1 receptor agonists as glucose-lowering and obesity medications. J Clin Invest. 2026.
[38] GI Adverse Effects of Glucagon-Like Peptide-1 Receptor Agonists. US Pharmacist. 2025.
[39] Sodium-Glucose Transport 2 (SGLT2) Inhibitors. StatPearls. Treasure Island, FL: StatPearls Publishing; 2025.
[40] Finerenone: Will It Be a Game-changer? CFR Journal. 2024 (FIDELITY hyperkalaemia-related discontinuation 1.7% vs 0.6%).
[41] ASCEND Study Collaborative Group (Bowman L, et al). Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med. 2018; 379: 1529-1539.
[42] Aspirin has potential benefits for primary prevention of cardiovascular outcomes in diabetes: updated literature-based and individual participant data meta-analyses of randomized controlled trials.
[43] Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors and Genital Infections in Patients with Diabetic Mellitus and Concomitant Coronary Artery Disease: A Single-Center Experience (India). PMC9788992.