REVIEW | Article in Press

Risk-guided CKM care through a kidney lens: an architecture for translating risk into action

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Received: 1 August 2026 / Accepted: 6 October 2026
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Abstract

Background Cardiovascular-kidney-metabolic (CKM) syndrome describes the clinical convergence of cardiovascular disease, chronic kidney disease (CKD), diabetes, and obesity. Through a kidney lens, CKM care requires more than disease classification; it requires a practical strategy to translate integrated risk assessment into timely and proportional guideline-directed medical therapy (GDMT).

Main body We propose a Risk-Guided Therapeutic Architecture for CKM care, represented as a house built from the foundation up. Lifestyle and risk-factor management form the foundation; integrated kidney and cardiovascular risk estimation occupies the first floor; risk-guided pharmacological therapy shapes the second floor; access, affordability, and health-system capacity act as load-bearing walls; and sustained clinical goals constitute the roof. The central innovation is housed on the first floor: proposed implementation thresholds that translate parallel risk assessments into priorities for the pace and intensity of eligible therapy. Rather than proposing another risk score, the architecture uses validated kidney and cardiovascular tools and applies a simple rule: the higher-risk axis governs the pace and intensity of implementing guideline- and phenotype-eligible therapies, rather than expanding pharmacological eligibility itself. These implementation thresholds are author-proposed, hypothesis-generating cut-points intended to synthesize existing evidence and guidelines into a practical framework, rather than new, prospectively validated, or formally guideline-endorsed thresholds in themselves.

Conclusion This framework is intended to complement existing guidelines by helping clinicians move from risk prediction to therapeutic action, reducing inertia while safeguarding individualized care. Because CKM science is still being built, we frame this architecture as a living, testable blueprint intended to evolve along the field's continuum of learning.

Keywords Cardiovascular Diseases · Renal Insufficiency, Chronic · Risk Assessment · Implementation Science · Guideline Adherence · Drug Therapy, Combination · Delivery of Health Care, Integrated

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https://doi.org/10.1186/s13098-026-02327-5

Published online: 03 November 2026

https://doi.org/10.1186/s13098-026-02327-5

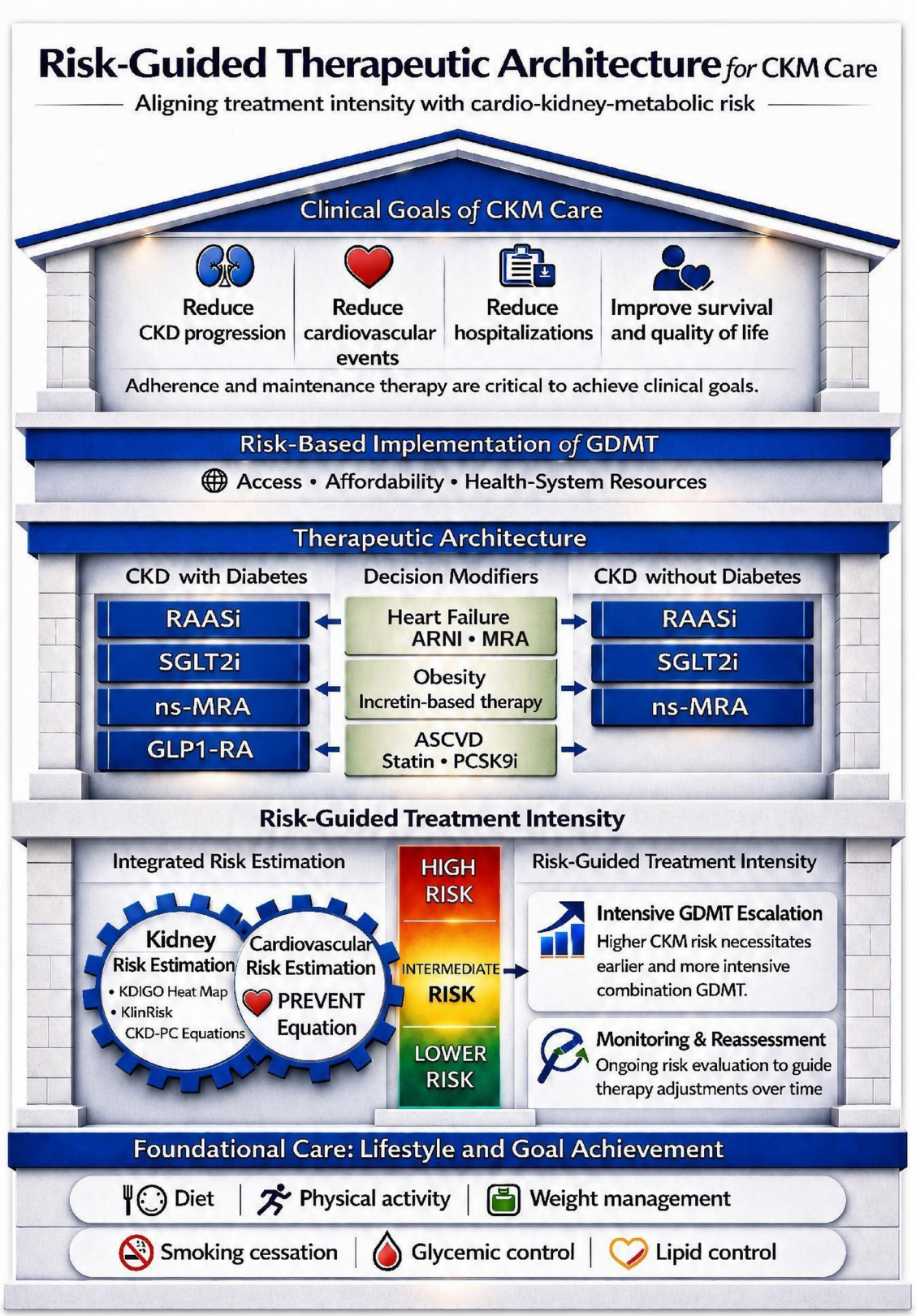


Fig. 1 Risk-Guided Therapeutic Architecture for CKM care through a kidney lens. The house places lifestyle and risk-factor control as the foundation, integrated risk estimation and treatment thresholds as the first floor, evidence-based pharmacological therapy as the second floor, access and affordability as load-bearing walls, and sustained clinical goals as the roof. ASCVD, atherosclerotic cardiovascular disease; GDMT, guideline-directed medical therapy; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor. KlinRisk denotes a validated, region/population-specific kidney risk tool. Figure reproduced, without adaptation, from the ISN International Expert Forum report [2], under a Creative Commons CC BY-NC-ND 4.0 license (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reuse of the work as published, without adaptation, provided it is fully attributed

Introduction

The cardiovascular-kidney-metabolic (CKM) framework has changed how clinicians, other health care professionals, and health systems understand the overlapping burden of cardiovascular disease, CKD, diabetes, and obesity [1]. It has also created a common language for specialties that have traditionally approached the same patient through separate clinical lenses. To advance this integrated perspective through a kidney-community lens, the International Society of Nephrology (ISN) convened the International Expert Forum on Cardiovascular-Kidney-Metabolic Health in Amsterdam in October 2025, bringing together a global, multidisciplinary group of leaders [2].

The Forum report emphasized early integrated case-finding, joint long-term kidney and cardiovascular risk assessment, timely use of evidence-informed therapies, and multidisciplinary models of care, while highlighting therapeutic inertia, fragmented care, and global inequities in access [2]. This Perspective was developed by authors who participated in the Forum. Building on its multidisciplinary discussions and implementation priorities, we developed a "Proposed Risk-Guided Therapeutic Architecture for CKM care (Fig. 1). The framework represents the authors' synthesis of one strand of those discussions, translating integrated risk into therapeutic action and is intended to complement the broader Forum report. The concept is deliberately architectural: patients with CKD need a house that clearly indicates what comes first, what supports the structure, where treatment thresholds reside, and how evidence-based therapies can be layered without losing cardiovascular and metabolic integration.

The CKM construct was largely formalized by the cardiovascular community through the 2023 AHA Presidential Advisory [1]. Subsequent multisociety efforts have reinforced the need for integrated cardiovascular, kidney, and metabolic care. Recently, the AHA/ACC, in collaboration with the ADA and ASN, published a Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome, providing a formal clinical practice framework for CKM staging, risk assessment, prevention, treatment, and monitoring [3]. Yet, further operational work is needed to define how kidney risk should guide therapeutic intensity at the point of care. A focus through a kidney lens is therefore not a narrowing of CKM care but a practical entry point: it keeps care integrated while making explicit what nephrology adds [2, 4]. CKD identifies patients at high cardiovascular risk, modifies drug eligibility and safety, and provides measurable markers such as eGFR and albuminuria that can guide therapeutic intensity.

This architecture and definition of GDMT is intended for adults with CKD not on dialysis, with or without diabetes, across the CKM continuum. It is not intended for patients receiving dialysis, kidney transplant recipients, pregnant patients, or those with kidney diseases requiring disease-specific therapy (for example, glomerulonephritis requiring immunosuppression), for whom disease-specific guidelines should take precedence. It also does not address GDMT that is specific to comorbidities other than CKD, which are approached in the architecture as decision modifiers (Fig. 1).

At the same time, CKM care from a kidney perspective has entered a therapeutic era in which RAAS inhibition, SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and incretin-based therapies can slow CKD progression and reduce cardiovascular events across overlapping populations [5–20]. The current challenge is implementation. Many eligible patients receive therapies late, sequentially, or not at all. The Forum

report and real-world data show that gaps in guideline-directed medical therapy (GDMT) remain substantial even when evidence is strong [2, 21, 22]. This gap motivates a practical structure to help clinicians translate integrated risk assessment into timely implementation of indicated therapy.

Discussion

Three lenses, one patient

CKM health can be read through three clinical lenses. Metabolically, obesity and diabetes drive insulin resistance, chronic inflammation, mitochondrial dysfunction, lipid dysregulation, hemodynamic stress, albuminuria, vascular injury, and organ damage. From the cardiovascular (CV) perspective, CKM extends a tradition of absolute-risk estimation, prevention thresholds, and phenotype-guided treatment. From nephrology, CKD places the kidney in the middle: as an early signal of systemic disease, a risk amplifier, and a central organ that modifies cardiovascular (CV) prognosis, therapeutic eligibility, drug safety, and long-term outcomes, including kidney failure [2, 4, 5].

The same patient cannot be managed by three disconnected algorithms. A person with reduced eGFR, marked albuminuria, obesity, heart failure, and type 2 diabetes does not have five isolated problems. This patient with CKD has one integrated CKM risk state. The architecture proposed herein makes their risk state visible and actionable.

Why an architecture, and not a set of pillars?

Clinical guidelines increasingly define what should be prescribed. They are less explicit about how treatment intensity should be matched to the integrated CKM risk in patients with CKD. Existing frameworks classify disease; existing prediction models estimate prognosis; existing guidelines recommend therapies. An unresolved implementation question is how discordant kidney and cardiovascular assessments should jointly inform the pace and sequencing of already indicated therapies [2, 3].

The four-pillar paradigm in heart failure has been useful because it simplifies implementation, particularly in heart failure with reduced ejection fraction (HFrEF), where the phenotype and very high-risk profile are defined a priori and a standardized approach is appropriate [23]. CKM care is more complex. It crosses specialties, prognostic timeframes, and organ-specific outcomes, and it involves therapies whose absolute benefit depends heavily on baseline risk. A lower-risk patient may reasonably undergo sequential treatment; a patient with advanced CKD, severe albuminuria, established atherosclerotic cardiovascular disease (CVD), or heart failure should not wait years for the same therapeutic combination to be implemented.

Architecture is therefore more than a metaphor. It is a way of ordering clinical decisions. In the house architecture framework (Fig. 1), lifestyle and risk-factor control form the foundation; integrated risk assessment precedes therapeutic intensity; the therapeutic floor layers pharmacological therapy according to risk and phenotype, with decision modifiers guiding drug selection, sequencing, and the pace of treatment intensification; access, affordability, and health-system capacity serve as structural support; and long-term clinical goals form the roof.

The architecture: building ckm care floor by floor

Figure 1 depicts CKM care through a kidney lens as a house. We walk through the architecture from the foundation upward because each level provides structural support for the one above. The perspective is nephrological, but the structure remains multidisciplinary.

Foundation floor: lifestyle and goal achievement

Every structure needs a foundation. In CKM care, that foundation is lifestyle and risk-factor assessment and control. Dietary quality, physical activity, smoking cessation, weight management, blood-pressure control, lipid management, and glycemic optimization remain essential at every stage [2, 3, 24]. These interventions are not a replacement for pharmacological therapy. They support it.

This framing is useful because it avoids treating lifestyle and risk-factor control as a preliminary step that ends when medication begins. Foundation work persists throughout CKM care, influencing albuminuria, blood pressure, adiposity, glycemic exposure, heart failure symptoms, and cardiovascular risk. It is the foundation on which all subsequent risk assessment and therapeutic decisions are built.

First floor: integrated risk estimation and treatment thresholds

The first floor is the intellectual core of the architecture: the level at which risk assessment triggers therapeutic action. Prediction alone does not improve outcomes; implementation guided by risk assessment does.

First, kidney and cardiovascular risks should be estimated in parallel, with tools matched to the outcome, the patient's stage, and the population. Across the broader population, including people with preserved eGFR, with or without diabetes, the KDIGO heat map provides categorical staging, and CKD Prognosis Consortium (CKD-PC) equations estimate the absolute risk of a significant eGFR decline or kidney failure over 2–3 years [5, 25]. As disease advances into CKD stages G3–G5, the Kidney Failure Risk Equation (KFRE) adds a guideline-endorsed estimate of kidney failure risk well suited to timing combination therapy, nephrology referral, and preparation for kidney replacement therapy [26, 27]. Cardiovascular risk can be estimated with the PREVENT-CVD calculator, which incorporates CKM-relevant variables and provides absolute risk for total CVD, including heart failure and ASCVD [28, 29]. This approach is consistent with the 2026 AHA/ACC/ADA/ASN CKM guideline, which uses PREVENT-based risk estimation to inform CKM staging and the prioritization of preventive treatment [3]. Our architecture extends this logic by explicitly linking integrated kidney and cardiovascular risk to therapeutic intensity through a kidney lens. In specific settings, locally validated or population-specific cardiovascular risk tools may also be considered [30]. These tools should not be forced into a single composite score; they answer different questions across different time horizons and, in doing so, help define clinical priorities and specific management rather than collapse into a single label. In the original ISN Forum source figure reproduced as Fig. 1, KlinRisk appears alongside the KDIGO heat map and CKD-PC as a further example of a validated, region/population-specific kidney risk tool; KDIGO, CKD-PC, KFRE, and tools such as KlinRisk are complementary and stage-specific rather than alternatives to one another [2, 5, 25, 26].

Discordance between the kidney and cardiovascular axes is therefore expected. A patient may carry a high kidney-failure risk with a lower predicted total cardiovascular risk in the presence of less advanced CKD. The architecture treats this discordance as clinically useful rather than inconvenient: in CKM care, the higher-risk axis should govern the urgency, pace, and intensity with which guideline- and phenotype-eligible therapies are implemented, rather than determining pharmacological eligibility itself.

This higher-risk-axis rule is primarily a rule of global intensity rather than a purely risk-specific one. Because RAAS inhibitors, SGLT2 inhibitors, ns-MRA, and GLP-1 receptor agonists have overlapping kidney and cardiovascular benefit, the higher-risk axis sets the overall pace and combination intensity of GDMT. Within that intensified pace, however, agent selection and sequencing remain phenotype- and axis-informed: kidney-specific evidence is prioritized when kidney risk dominates, and heart-failure- or ASCVD-specific agents are prioritized when cardiovascular risk dominates.

This is where thresholds matter. Clinical decisions rarely change continuously across the risk spectrum; clinicians intensify therapy when patients cross meaningful thresholds, such as blood pressure, LDL cholesterol, HbA1c, albuminuria, eGFR, or estimated cardiovascular risk. We propose the same logic for CKM management through the kidney lens: thresholds do not replace continuous risk prediction, CKM staging, or clinical judgment;

they identify proposed points at which expected absolute benefit justifies earlier and more intensive GDMT, which improves outcomes (both kidney and CV) in patients with CKD. CKM care is thus organized into three pragmatic tiers that align kidney and cardiovascular assessment with action: lower-risk patients may undergo indicated treatment with individualized sequencing and planned reassessment; intermediate-risk patients receive prioritized optimization of foundational therapies and phenotype-guided additions; and high- or very-high-risk patients should be considered for early combination GDMT, and closer monitoring without unnecessary delays (Fig. 2).

To make these tiers concrete, Fig. 2 presents three proposed implementation tiers, defined using eGFR/CKD-PC and KDIGO categories (stages G1–G2), the Kidney Failure Risk Eq. (5-year risk, applied from CKD stage G3–G5 onward, consistent with the Class I recommendation for KFRE use in "CKD categories G3–5" in the newly published 2026 ESC/ERA CVD-CKD guideline), the PREVENT-CVD 10-year total cardiovascular disease risk, and urine albumin-to-creatinine ratio: lower risk corresponds approximately to CKD-PC/KFRE < 5%, PREVENT < 5%, and UACR < 30 mg/g; intermediate risk to CKD-PC/KFRE 5–15%, PREVENT 5% to < 20%, and UACR 30 to < 300 mg/g; and high/very-high risk to CKD-PC/KFRE > 15%, established ASCVD or heart failure or PREVENT ≥ 20%, and UACR ≥ 300 mg/g. Because KFRE, CKD-PC, and PREVENT estimate different outcomes over different time horizons, these tiers should be read as clinical prioritization categories built by aligning tool outputs ordinally, not as a claim that the underlying absolute risks are mathematically equivalent across tools. For the same reason, the specific cut-points shown in Fig. 2 are illustrative, hypothesis-generating implementation thresholds selected by the author group from populations enrolled in landmark trials, validated risk-prediction tools, and expert interpretation, rather than validated or guideline-endorsed decision points in themselves.

The CKM construct is still being built and, as the AHA emphasized from the outset, should advance as data and evidence accrue. The thresholds proposed here should be interpreted in that spirit. Importantly, they are pragmatic rather than trial-derived. They are not the product of randomized controlled trials (RCTs) that tested threshold-based treatment intensification against usual care; rather, they are informed by populations enrolled in landmark trials, validated risk-prediction tools, and expert interpretation, and are then extrapolated to the point of care. We therefore offer them as an explicit, testable hypothesis rather than a standard, a first scaffold, not a finished wall and expect them to be challenged, moved, and refined as knowledge accrues. Confirming, relocating, or discarding a given threshold will require a continuum of evidence that mirrors the continuum of learning itself. Pragmatic implementation trials, together with real-world evidence and target-trial emulation, are likely to be the most feasible and informative approaches [2, 22]. They can test whether threshold-guided care changes prescribing, persistence on therapy, and patient outcomes at scale. Until such evidence matures, the thresholds proposed here are best understood as a shared kidney-lens starting point for calibration and study: a living reference intended to evolve with the field, not a set of fixed cutoffs.

Second floor: the therapeutic core

Once treatment intensity has been defined by assessments conducted on the first floor, the second floor becomes the place where evidence-based therapies are layered. Decision modifiers should be explicit from the start: phenotypes like HF, obesity, diabetes, established atherosclerotic CVD and dyslipidemia all influence which therapies are selected, prioritized, and how quickly they are combined [3]. Greater CKM risk accelerates the pace and combination of therapies for which a patient is already guideline- and phenotype-eligible; it does not, by itself, expand pharmacological eligibility or select otherwise non-indicated drug classes. Throughout this architecture, "GDMT" refers to the kidney specific, individual, trial- and guideline-supported drug classes themselves; the pathway linking risk tier to the pace and combination of these therapies is the authors' own proposed implementation logic, and we use "guideline-supported" or "evidence-based therapies" where this distinction matters.

RAAS inhibitors and SGLT2 inhibitors form the structural core for many patients with CKD because their kidney and cardiovascular benefits are consistent across broad CKM populations [6–8, 17]. Nonsteroidal

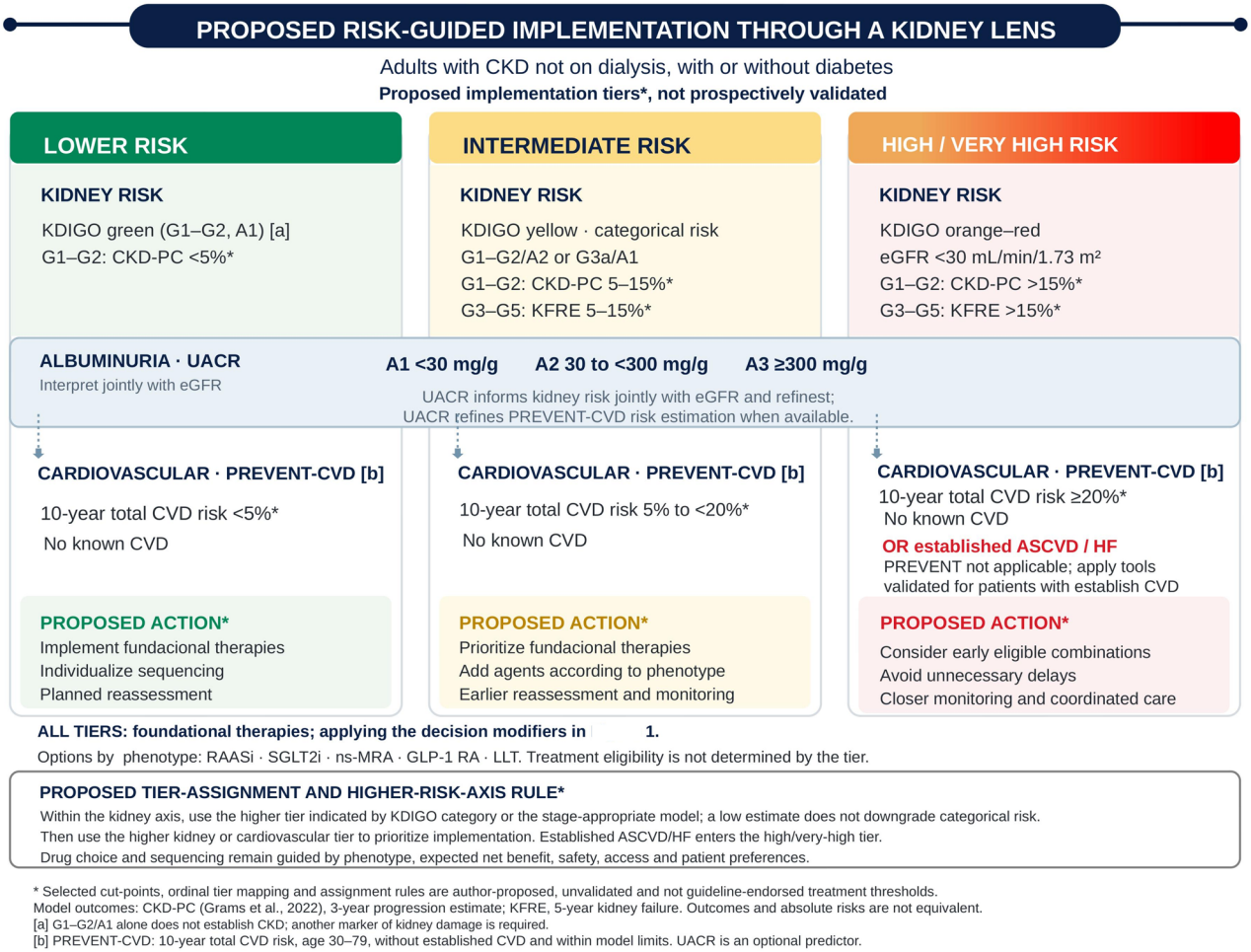


Fig. 2 Proposed risk-guided implementation tiers for CKM care through a kidney lens. The figure operationalizes the risk-assessment floor of Fig. 1 for adults with confirmed CKD not receiving dialysis, within the manuscript's stated exclusions. KDIGO eGFR/UACR categories and the stage-appropriate CKD-PC or KFRE estimate inform kidney priority. Within that axis, the higher categorical or model-derived tier is used; a low model estimate does not downgrade categorical risk. The higher kidney or cardiovascular tier then determines implementation priority. Established ASCVD or HF provides a separate route to the high/very-high tier. PREVENT-CVD is validated for adults 30–79 years without known cardiovascular disease and is not intended for use in patients with established disease. UACR is interpreted jointly with eGFR and may refine PREVENT-CVD when available. Model outputs are aligned ordinally, not mathematically: CKD-PC uses a 3-year progression estimate and KFRE a 5-year kidney-failure estimate, whereas PREVENT-CVD estimates 10-year total CVD risk. Selected cut-points, tier-assignment rules, and tier-to-action mapping are author-proposed and unvalidated; the PREVENT-CVD ≥ 20% threshold itself is a guideline-recognized CKM stage-3 risk equivalent [3]. These tiers do not replace CKM staging, establish drug eligibility, or justify delaying indicated therapy. Treatment choice and sequencing depend on phenotype, expected net benefit, safety, access, and patient preferences. Foundational care applies throughout, with Supplementary Table 1 (submitted as a separate supplementary file) listing the source and basis - guideline-established, validated-tool-derived, or author-proposed - for each input and cut-point used in this figure, ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CKD-PC, Chronic Kidney Disease Prognosis Consortium; CKM, cardiovascular–kidney–metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; KFRE, Kidney Failure Risk Equation; LLT, lipid-lowering therapy; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PREVENT, Predicting Risk of Cardiovascular Disease EVENTs; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2i, sodium–glucose cotransporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

mineralocorticoid receptor antagonist (ns-MRA) therapy now has evidence in albuminuric CKD associated with diabetes and in CKD without diabetes, whereas GLP-1 receptor agonist therapy is particularly relevant in patients with CKD and type 2 diabetes, obesity, or established cardiovascular disease [9–16, 18–20]. Statins and other lipid-lowering medications remain essential components of CKM risk reduction in patients with ASCVD, high predicted cardiovascular risk, and/or CKD [31, 32]. Heart failure therapies should be selected according to phenotype, while recognizing the central role of SGLT2 inhibitors and the emerging role of finerenone in HFmrEF and HFpEF [33–35].

This floor should not be read as a rigid sequence. Its purpose is to align treatment intensity with risk while ensuring that therapy, once initiated, is sustained over time. Higher-risk patients should be considered for earlier initiation of combination GDMT, provided tolerability, reassessment, kidney function, potassium levels, patient preferences, and access are addressed. Clinical reassessment should be distinguished from drug-specific safety monitoring after initiation or titration; a routine follow-up interval must not postpone necessary kidney-function, potassium, or blood-pressure checks [5]. Because benefit accrues only with sustained therapy, treatment persistence (not just initiation) should be an explicit target from the outset.

A high baseline risk identifies patients more likely to have a large absolute prognostic risk, but prognostic risk and expected therapeutic net benefit are not necessarily equivalent. Frailty, multimorbidity, competing risks, hemodynamic and electrolyte tolerability (including hypotension and hyperkalemia), kidney function trajectory, life expectancy, treatment burden, and patient preference can all modify the expected net benefit of intensified therapy. Shared decision-making is therefore a cross-cutting requirement of the architecture at every floor, not only at the roof, and individualized net benefit and safety must still be determined through clinical judgment before therapy is intensified.

Load-bearing walls: access, affordability, and health-system capacity

A house cannot stand without walls. Access, affordability, and health-system capacity are the load-bearing walls of CKM care. Even optimal evidence fails when medicines are unavailable, unaffordable, or unsupported by healthcare systems. This is particularly important in low- and middle-income countries and for healthcare systems where public and private access to newer CKD therapies may differ substantially [2, 36].

The architecture should therefore support both clinical and policy decisions. It can help clinicians prioritize high-risk patients when resources are constrained and help health systems determine which therapies require earlier incorporation into care pathways. Risk-guided implementation is not a luxury. It is a strategy for making limited resources more clinically meaningful. In resource-limited settings, absolute risk can also help prioritize which interventions are extended first, not only which patients are prioritized for care.

Different guidelines endorse different validated cardiovascular risk tools by region: the 2026 [3] CKM guideline (United States) endorses PREVENT, while the newly published 2026 ESC Guidelines for the management of cardiovascular disease and chronic kidney disease [37], developed in collaboration with the European Renal Association, instead endorse SCORE2 with a CKD Add-On, SCORE2-OP, and SCORE2-Diabetes. This underscores that the architecture's logic, integrating kidney and cardiovascular risk into tiered implementation intensity is intended to be tool-agnostic, and should be operationalized with whichever regionally validated, and ideally locally recalibrated, risk tool is appropriate, rather than being tied specifically to PREVENT. Separately, the 2026 ACC/AHA/Multisociety Guideline on the Management of Dyslipidemia [38] defines four categorical 10-year PREVENT-ASCVD risk bands (low < 3%, borderline 3% to < 5%, intermediate 5% to < 10%, and high ≥ 10%) specifically to guide lipid-lowering therapy initiation. Our architecture's PREVENT CVD - based tiers (lower risk < 5%, intermediate 5% to < 20%, high/very high ≥ 20%) are proposed for a different purpose - the pace and intensity of combination GDMT across the CKM spectrum - and are not intended to replace those dyslipidemia-guideline categories.

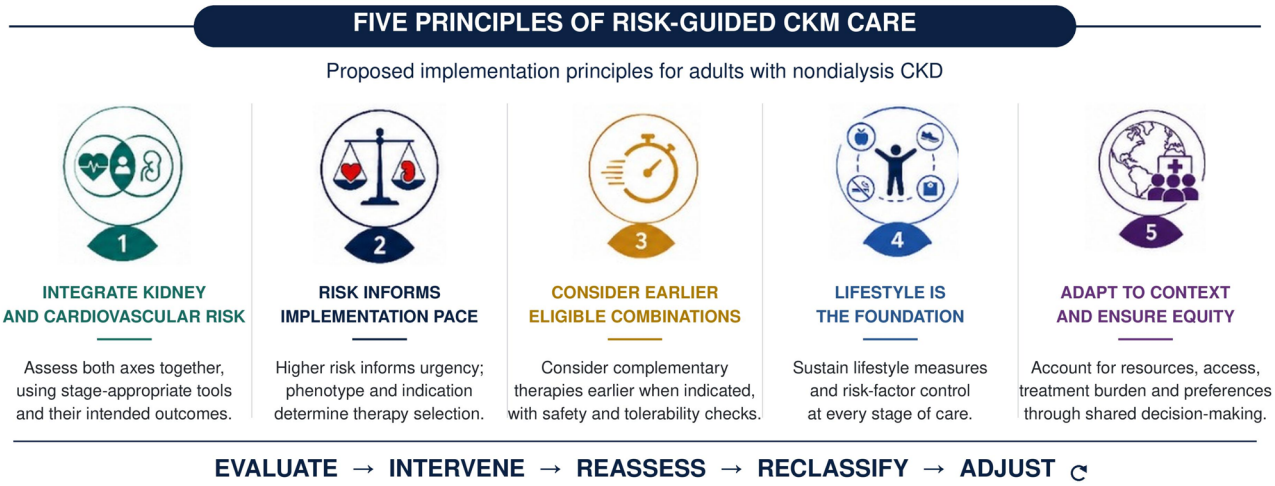


Fig. 3 Five principles of risk-guided CKM care through a kidney lens

Roof: clinical goals sustained by adherence and maintenance therapy

The roof represents the purpose of the entire structure: slower CKD progression, fewer cardiovascular events and hospitalizations, better quality of life, and improved survival. A roof protects the house only if it stays in place. Adherence, persistence, adverse-event management, shared decision-making, and longitudinal reassessment are therefore essential parts of the architecture [3].

This final level reminds us that CKM care is not a single prescribing event. It is a long-term protective strategy as risk, kidney function, symptoms, and patient priorities evolve.

Risk assessment within this architecture is not a single time-point decision. Kidney and cardiovascular risk change after interventions and with clinical evolution, so the architecture is best understood as a recurring cycle: evaluate, intervene, reassess, reclassify, and adjust therapy (Fig. 3). This cycle, rather than a one-time tier assignment, is what sustains the longitudinal nature of CKM care.

Five principles that hold the architecture together

Five principles run through every floor (Fig. 3). First, kidney and cardiovascular risk should be estimated together. Second, treatment intensity should be proportional to absolute CKM risk in patients with CKD. Third, complementary therapies should be initiated earlier in higher-risk patients. Fourth, lifestyle and risk-factor control remain foundational at all stages. Fifth, implementation must be adapted to local healthcare resources without abandoning equity [2, 3].

These principles are intentionally simple. Their purpose is to make the architecture usable by nephrologists, cardiologists, endocrinologists, primary care physicians, and health systems, while clarifying what a kidney lens adds to CKM care. The kidney lens refers to strategies specifically relevant to patients with CKD, prioritizing earlier combination therapy when kidney risk amplifies cardiovascular risk. Such care will improve when physicians and health systems share a common framework for determining who needs earlier action, which therapies to prioritize, and how to sustain treatment over time [2, 3]

Future perspectives

The next frontier in CKM care through a kidney lens will not come from GDMT alone. It will come from better implementation: optimization of electronic health records, automated risk calculators, decision support,

real-world evidence, multidisciplinary pathways, and reimbursement models that recognize absolute-risk reduction rather than isolated disease labels [2, 3, 22]. The proposed risk-based architecture is compatible with these tools because it does not require a new score. CKM care is a field still under construction, and this architecture is intended to advance along the continuum of learning and to be revised as new evidence and implementation experience accrue. It provides a disciplined way to use existing risk estimates and translate them into standardized clinical care.

This architecture aligns with the 2026 CKM guideline's emphasis on interdisciplinary care, longitudinal assessment, and coordinated delivery of GDMT, while extending it through a kidney lens by translating integrated kidney and cardiovascular risk into prioritized therapeutic intensity [2, 3].

Relative to the 2026 AHA/ACC/ADA/ASN CKM guideline [3], this architecture's incremental contribution is not a new risk score but four specific, kidney-lens additions: an explicit rule for resolving discordant kidney and cardiovascular risk (the higher-risk axis governs intensity); three-tier, cross-domain implementation thresholds that integrate kidney and cardiovascular risk with albuminuria ifnorming both; integration of kidney-specific tools (KFRE, CKD-PC) alongside PREVENT rather than PREVENT alone; and an explicit implementation and validation research agenda. This agenda could compare risk-guided implementation with contemporary guideline-based care using outcomes such as time to initiation of indicated therapies, the proportion of patients achieving appropriate GDMT, therapeutic persistence, adverse events, renal progression, heart-failure hospitalization, major cardiovascular events, mortality, quality of life, cost-effectiveness, and equity in access, tested through pragmatic implementation trials, real-world evidence, and target-trial emulation.

Relative to the earlier ISN International Expert Forum report (Kidney International, 2026) [2], reproduced as Fig. 1, this manuscript's specific new contribution is the operationalization of the architecture into explicit, tool-linked implementation thresholds (Fig. 2); the discordance rule by which the higher-risk axis governs intensity; the integration of specific kidney (KFRE, CKD-PC) and cardiovascular (PREVENT, or regionally appropriate equivalents such as SCORE2) tools into a single point-of-care framework; and the accompanying implementation and validation research agenda, none of which were operationalized in the original Forum report.

Limitations

This architecture has several limitations. First, the framework as a whole has not been prospectively validated; its implementation thresholds are author-proposed and hypothesis-generating rather than derived from a dedicated outcomes trial. Second, the risk tools used in Fig. 2 - KFRE (5-year kidney failure risk), CKD-PC (2–3-year progression estimate), and PREVENT-CVD (10- and 30-year risk) operate on different time horizons and predict different outcomes, so the resulting tiers are ordinal prioritization categories rather than mathematically equivalent absolute risks. Third, calibration and transportability of these tools, and of the specific thresholds proposed here, may vary across populations and health systems; locally validated or recalibrated tools should be used where available. Fourth, applying a risk tier without adequate attention to phenotype, tolerability, competing risks, and patient preference could lead to overtreatment; risk identifies patients more likely to have high absolute benefit, but it does not by itself establish individualized net benefit. Finally, pragmatic implementation studies are needed before these thresholds can be considered for routine clinical use.

Conclusion

The Risk-Guided Therapeutic Architecture is offered as a shared blueprint rather than a rigid protocol for CKM care through a kidney lens. Its foundation is lifestyle and risk-factor control; its first floor converts cardiovascular and kidney risk into implementation thresholds; its second floor layers GDMT according to risk, phenotype, and context; its walls represent access, affordability, and health-system capacity; and its roof is sustained

by adherence, persistence, and outcomes. Progress will depend less on knowing which therapies work than on delivering them earlier, more consistently, and first to the highest-risk patients. With effective therapies already in hand, the decisive task is no longer discovery alone but implementation: risk-guided, kidney-anchored care is a testable strategy for translating proven therapeutic efficacy into population-level benefit, helping ensure that the patients most likely to benefit become the patients actually treated in time, and, ultimately, supporting efforts to protect kidneys, hearts, and lives.

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CKD-PC	Chronic Kidney Disease Prognosis Consortium
CKM	Cardiovascular–kidney–metabolic
CVD	Cardiovascular disease
eGFR	estimated glomerular filtration rate
UACR	Urine albumin-to-creatinine ratio
GDMT	Guideline-directed medical therapy
RAASi	Renin-angiotensin-aldosterone system inhibitor
SGLT2i	Sodium-glucose cotransporter 2 inhibitor
ns-MRA	Nonsteroidal mineralocorticoid receptor antagonist
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
KFRE	Kidney Failure Risk Equation
PREVENT	Predicting Risk of Cardiovascular Disease Events
LLT	Lipid-lowering therapy

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1186/s13098-026-02327-5.

Acknowledgements The authors acknowledge the International Society of Nephrology (ISN) International Expert Forum on CKM Health (Amsterdam, October 2025), whose multidisciplinary discussions informed the development of this manuscript. The proposed Risk-Guided Therapeutic Architecture reflects the authors' interpretation and synthesis of concepts discussed during the Forum and does not represent a formal ISN guideline or consensus statement.

Author contributions Conceptualization: RPF, ACB; Methodology: ACB, RPF; Writing - original draft: ACB; Writing - review and editing: ACB, RPF, MLC, JFKS, MEFC, VCS; Visualization (prepared Figs. 1 and 2): ACB, RPF; Supervision: ACB; Project administration: ACB. All authors contributed intellectual content, critically reviewed the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Funding This study received no specific funding. No external sponsor had any role in the conception, writing, review, or decision to submit this manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable. This article did not involve human participants, human data, human tissue, or animals.

Consent for publication Not applicable. This article does not contain identifiable individual data, images, or videos.

Scientific meeting International Society of Nephrology International Expert Forum on Cardiovascular-Kidney-Metabolic Health; Amsterdam, the Netherlands; October 2025.

Use of generative AI and AI-assisted technologies Generative artificial intelligence tools were used to support language editing, reference organization, and figure preparation. No artificial intelligence tool was used to generate data or make scientific decisions. All outputs were reviewed and verified by the authors, who take full responsibility for the content.

Competing interests The authors declare no competing interests.

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