

# International Society of Nephrology International Expert Forum: Exploring the Nexus of Cardiovascular-Kidney-Metabolic Health



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Received 27 March 2026; revised 24 May 2026; accepted 29 June 2026; published online 28 July 2026

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**The cardiovascular-kidney-metabolic framework recognizes the interconnected biological, clinical, and societal drivers of cardiovascular disease, chronic kidney disease, diabetes, and obesity. To advance an integrated perspective, aligned with the kidney community focus, the International Society of Nephrology convened an International Expert Forum, bringing together a global and multidisciplinary team of leaders in this field. This meeting report synthesizes key discussions spanning cardiovascular-kidney-metabolic risk stratification, lifestyle interventions, guideline-directed medical therapies, emerging late-stage therapeutics, and models of care delivery. Participants emphasized the importance of early, integrated case finding; long-term, joint kidney–cardiovascular risk assessment; and timely use of evidence-informed therapies to reduce kidney disease progression, kidney failure, and cardiovascular events. Persistent gaps, including therapeutic inertia, fragmented care, and global inequities in access to care, were highlighted, alongside promising multidisciplinary and system-level care models. Emerging therapies targeting residual risk further underscore the need for adaptive implementation strategies. Aligned with the International Society of Nephrology’s mission, this forum represents a foundational step toward connecting disciplines, bridging evidence-to-practice gaps, and building global capacity to improve equitable cardiovascular-kidney-metabolic outcomes.**

*Kidney International* (2026) **110**, 812–828; <https://doi.org/10.1016/j.kint.2026.06.044>

**KEYWORDS:** cardio-kidney-metabolic syndrome; cardiovascular disease; chronic kidney disease; diabetes; obesity

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The International Society of Nephrology (ISN) hosted the ISN International Expert Forum: Exploring the Nexus of Cardiovascular-Kidney-Metabolic (CKM) Health, in Amsterdam from October 16 to 18, 2025, bringing together a global multidisciplinary group of experts to examine the CKM framework as a model for integrated risk assessment, prevention, and treatment of cardiovascular, kidney, and metabolic diseases. The forum adds to a broader initiative (*Cardio-Kidney-Metabolic Initiative–International Society of Nephrology*)<sup>1</sup> designed to advance the field in alignment with ISN’s strategic vision: *connect* disciplines and regions through a shared CKM language; *bridge* conceptual, clinical, and guideline gaps spanning cardiovascular, metabolic, and kidney care; and lay the groundwork for *building capacity* via education, collaborative research, and implementation-driven dialogue. To advance an integrated perspective, aligned with the kidney community focus, the meeting brought together leaders from nephrology, cardiology, endocrinology, and primary care-oriented fields to build a common understanding of global CKM health, harmonize viewpoints, and establish priorities for clinical practice, knowledge dissemination, and effective implementation sensitive to differences in resources.

The opening session, “The CKM Framework: Three Lenses, One Vision,” introduced metabolic, cardiology, and nephrology perspectives, establishing CKM health as a shared language for integrated care. Preforum discussions had facilitated some shared understandings around CKM; thus, the session focused on practical interdisciplinary integration and framing future questions. Although the CKM framework aims to unify care across specialties, there is shared understanding of the need to further refine kidney-related staging, risks, and outcomes.

From a *metabolic perspective*, CKM health is driven by the global burden of obesity and diabetes, which act as upstream determinants of both kidney disease and cardiovascular disease (CVD). While CVD remains the leading cause of death worldwide, metabolic risk factors, particularly hyperglycemia, insulin resistance, and excess adiposity, are dominant contributors to disability and reduced life span. Lifestyle interventions were emphasized as foundational therapeutic strategies across the CKM continuum, but substantial residual risk remains even among individuals achieving guideline-recommended targets, underscoring the need for comprehensive approaches, including individualized risk stratification and use of evidence-informed therapies.

From a *cardiology perspective*, the CKM framework expands on past classifications of complex diseases, such as chronic kidney disease (CKD) staging and cardiorenal syndromes, illustrating how staging systems can influence clinical practice and research even before validation. CVDs include various disorders and processes, like coronary, cerebrovascular, and peripheral arterial disease, and heart failure. Although the CKM model integrates metabolic, kidney, and cardiovascular factors, it omits systemic inflammation, which is a major contributor to both cardiovascular and kidney disease risk. Evidence shows residual inflammatory risk predicts cardiovascular events despite optimal therapies, suggesting the CKM framework should address inflammatory pathways to improve disease management.<sup>2</sup>

From the *nephrology perspective*, discussions emphasized both the opportunities and challenges of embedding kidney disease within the CKM framework. Nephrology has a long-standing tradition of multidimensional risk stratification based on estimated glomerular filtration rate (eGFR), albuminuria, and disease etiology, integrating diagnostic evaluation, prognostic assessment, and management of CKD-specific complications into longitudinal care. Importantly, patients with diabetes or CVD may also have alternative or superimposed causes of kidney disease requiring specialized nephrology evaluation, with staging systems that directly inform prognosis, treatment decisions, and research design. Within current CKM staging, the automatic classification of all individuals with CKD as at least stage 2—regardless of etiology or disease trajectory—raises concerns about risk discrimination and clinical utility. Importantly, kidney-specific outcomes, such as kidney

failure, eGFR slope, and albuminuria reduction, established predictors of both kidney and cardiovascular events, have only recently been incorporated into risk equations and are not yet widely implemented. This underscores the need to refine CKM models to better capture disease heterogeneity, CKD etiology specificities, longitudinal risk, and patient-centered outcomes.

A central contribution of the CKM framework is the establishment of a shared clinical language to facilitate collaboration across traditionally siloed specialties, alongside opportunities to rethink clinical trial design by moving away from single-disease indications toward composite CKM end points that better reflect real-world multimorbidity. However, limitations of the CKM framework as currently articulated were acknowledged, including the lack of incorporation of nonlinear disease trajectories and focus on successively more advanced CVD as the sole dimension of the outcome. These themes provided the basis for subsequent sessions addressing guideline harmonization, risk stratification, lifestyle interventions, guideline-directed medical therapy (GDMT) implementation, clinical development, and global disparities. Importantly, the forum was conceived as the starting point of a broader ISN-led effort, with anticipated follow-up outputs including consensus-informed guidance, implementation tools adaptable to diverse health systems, and regionally relevant initiatives aimed at translating CKM principles into equitable improvements in kidney health globally.

### Screening and risk stratification in the CKM framework

An integrated, interdisciplinary approach to CKM screening and risk stratification is essential to emphasize diagnostic precision for kidney disease and CVD, guide targeted therapies, and maximize opportunities for prevention and early intervention. We propose that screening for metabolic, kidney, or cardiovascular conditions should account for shared risk profiles and incorporate all parameters relevant to the CKM framework (summarized in [Table 1](#)), using a common minimum dataset from the outset.

CKD is often asymptomatic and detected through laboratory testing, making identification largely reliant on targeted case finding rather than population-based screening. Because many individuals with early CKM conditions are primarily managed in community and primary care settings, primary care physicians (PCPs) play a critical role in the routine assessment of eGFR, albuminuria, blood pressure, lipid profile, and glycemic status. While PCPs play a central role in CKM case finding and early management, nephrologists contribute essential expertise in the evaluation of CKD etiology, interpretation of albuminuria and eGFR trajectories, identification of nonmetabolic kidney diseases, and the assessment of kidney-specific complications and progression risk. Cardiologists bring specialized expertise in advanced cardiovascular risk stratification and interpretation of cardiac imaging and biomarkers. Within a CKM

Table 1 | Core screening measures across the CKM spectrum and their cross-specialty clinical relevance

| CKM domain                  | Core measure (screening)           | Informs risk of                         | Example risk tools                                               | Cross-specialty relevance                   |
|-----------------------------|------------------------------------|-----------------------------------------|------------------------------------------------------------------|---------------------------------------------|
| Adiposity/ metabolic health | Weight, BMI (±waist circumference) | Diabetes, CVD, CKD progression          | Clinical risk assessment; diabetes risk models                   | All specialties                             |
| Glycemic status             | HbA1c (or fasting glucose)         | CVD, CKD progression, HF                | Diabetes risk models; CV risk tools                              | All specialties                             |
| Kidney function             | Serum creatinine, eGFR             | CKD progression, CVD, HF                | KDIGO heat map, CKD-PC models, KFRE; KlinRisk                    | All specialties (primary focus: nephrology) |
| Kidney damage               | Urine albumin-to-creatinine ratio  | CKD progression, CVD, HF                | KDIGO heat map, CKD-PC models, KFRE, KlinRisk; CV risk modifiers | All specialties                             |
| Lipids                      | LDL-C, HDL-C, triglycerides        | ASCVD                                   | PREVENT; ASCVD risk models                                       | All specialties                             |
| Blood pressure              | Office BP (±home/ambulatory)       | CKD progression, ASCVD, HF              | CV risk models; clinical HF risk tools                           | All specialties                             |
| Electrolytes                | Sodium, potassium                  | Treatment safety, HF, CKD complications | Clinical decision support                                        | All specialties                             |

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CKD-PC, Chronic Kidney Disease Prognosis Consortium; CKM, cardiovascular-kidney-metabolic; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; KFRE, Kidney Failure Risk Equation; LDL-C, low-density lipoprotein cholesterol; PREVENT, Predicting Risk of Cardiovascular Disease Events.

framework, such risk-based case finding should be systematically extended to other high-risk groups, including individuals with hypertension and established CVD. The overlap in risk factors that drive CKM syndrome is mirrored by a convergence in adverse clinical outcomes. Individuals with CKD are at high risk of CVD, particularly heart failure, whereas patients with CVD face a substantial risk of progressive CKD. Importantly, CKD acts as a potent amplifier of cardiovascular risk.<sup>3</sup>

Although kidney and cardiovascular risk assessments are often separate and short-term, a CKM framework encourages integrated, long-term risk evaluation that captures cumulative disease burden and progression across outcomes and specialties. Effective screening relies on cross-disciplinary collaboration to identify high-risk individuals early and initiate therapies that address both cardiovascular and kidney risks. Despite the fact that there is a clear need for a broader uptake, nephrologists historically have used tools like the Kidney Disease: Improving Global Outcomes heat map, Chronic Kidney Disease Prognosis Consortium model, or Kidney Failure Risk Equation to predict CKD progression and in some regions the Klinrisk,<sup>4</sup> while cardiologists and diabetes specialists typically use Predicting Risk of Cardiovascular Disease Events (PREVENT) or other CVD risk models for cardiovascular risk assessment.<sup>3</sup> A collaborative CKM approach to risk stratification provides distinct benefits. Recognizing the overlapping cardio-kidney benefits requires moving beyond single-outcome prediction toward composite kidney and CVD outcomes across specialties to inform management.

CKM care should provide patients with clear and accessible information on how metabolic disorders serve as a root driver of disease, and how kidney and cardiovascular

risks evolve and react to treatment. Highlighting long-term risk in younger patients may increase engagement and support earlier prevention. Risk assessments using tools compatible with electronic records and artificial intelligence can enhance CKM care by dynamically updating risk profiles, provided transparency and equity are ensured.

The importance of lifestyle changes in CKM health

Lifestyle changes, especially regular physical activity and a healthy diet, are essential for preventing and managing CKM syndrome (Figure 1). These habits lower type 2 diabetes risk, reduce blood pressure, and decrease CKM risks, complementing medication management. Combined diet and exercise programs reduce body mass index and improve CKM health; however, evidence for other lifestyle strategies in primary prevention is still emerging. For individuals with excess adiposity but no established metabolic or kidney disease, caloric restriction, improved diet quality, and behavioral interventions yield clinically meaningful weight loss.<sup>5</sup> Long-term studies, including the Diabetes Prevention Program, demonstrate that combined dietary and physical activity interventions can reduce progression to type 2 diabetes by nearly 60%.<sup>6</sup> Early lifestyle modification also lowers the risk of developing hypertension, particularly through weight reduction and dietary sodium restriction.<sup>7</sup>

For these individuals with obesity, hypertension, or pre-diabetes but without CKD or CVD, interventions like the Dietary Approaches to Stop Hypertension (DASH) diet can delay or prevent progression to overt CKM.<sup>8</sup> Potassium-enriched salt substitutes are shown to lower blood pressure and reduce stroke and cardiovascular events in high-risk populations,<sup>9</sup> whereas healthy dietary patterns and regular

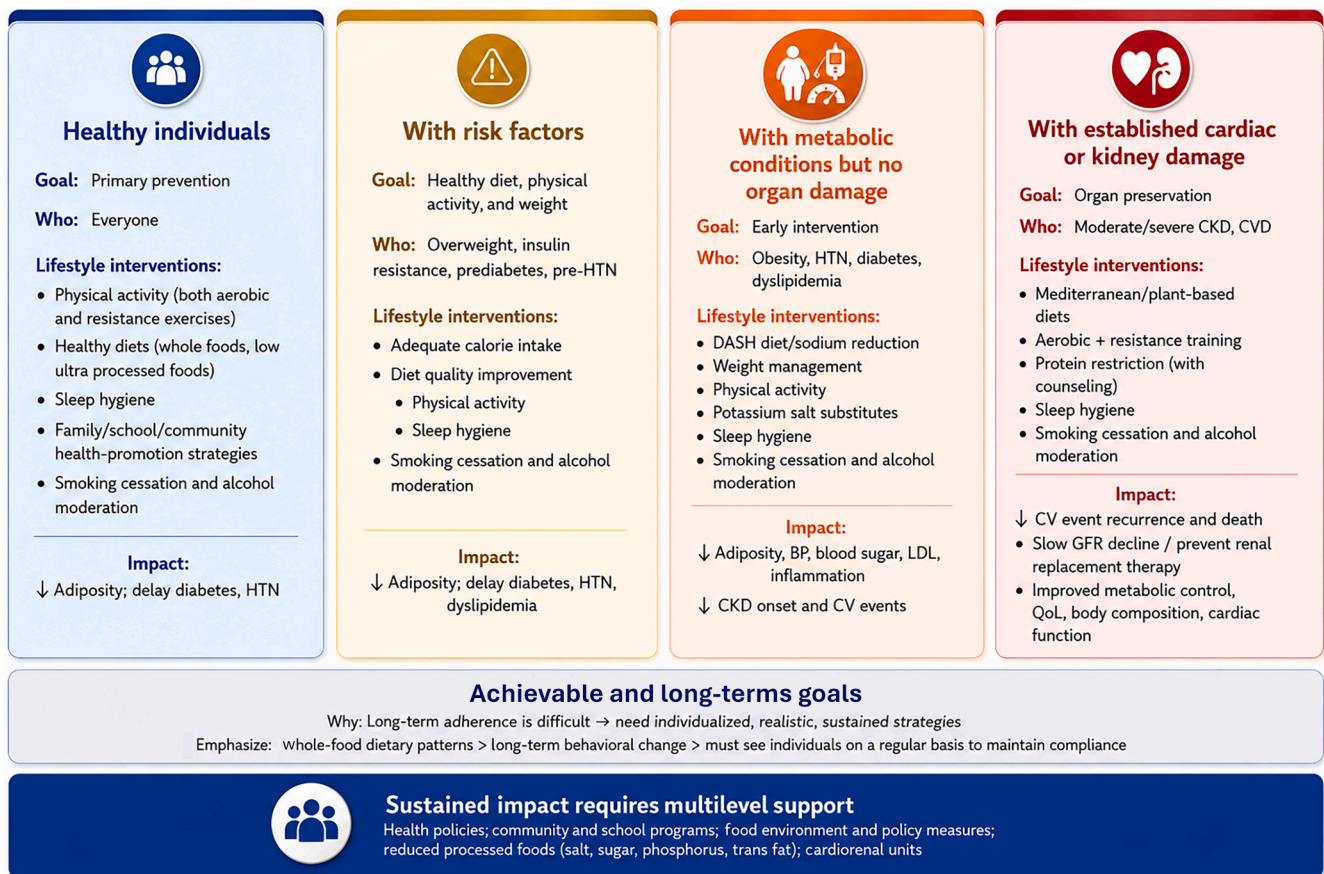


**Figure 1 | Lifestyle modifications across the cardiovascular-kidney-metabolic syndrome continuum.** BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; GFR, glomerular filtration rate; HTN, hypertension; LDL, low-density lipoprotein; QoL, quality of life.

moderate physical activity are associated with delayed CKD onset.<sup>10</sup>

Lifestyle changes addressing weight, cholesterol, blood pressure, and glycemia help preserve kidney and heart function in CKD or CVD.<sup>11</sup> Mediterranean plant-based diets are recommended for secondary CVD prevention, and lowering animal protein intake in moderate to severe CKD can delay dialysis but requires individualized nutritional counseling.<sup>11</sup> Regular aerobic and resistance exercise improves metabolic health, quality of life, body composition, and heart performance.<sup>11</sup>

Throughout the CKM continuum, lifestyle advice requires individualization, taking into account food availability and affordability, patient preferences, basal activity level, and willingness to change behaviors.<sup>11</sup> Trials show attenuation of benefits over time, with weight regain and return to pretrial habits. Multilevel support (such as behavioral counseling and policy measures to reduce ultraprocessed foods) is needed to translate trial effects into long-term population impact, with the potential to drive lasting improvements in CKM outcomes. PCPs are uniquely positioned to support longitudinal patient engagement, reinforce preventive strategies, and facilitate shared decision-making across the CKM continuum.

#### GDMTs across the CKM spectrum

The forum highlighted the significant impact of GDMTs on both kidney disease progression and cardiovascular events in CKD patients. This section reviews therapies proven to benefit kidney and cardiovascular outcomes, emphasizing treatments that influence both aspects of the CKM continuum (evidence summarized in Figure 2). It excludes GDMTs for cardiovascular risk when kidney-specific results are lacking. While many with heart or vascular conditions also have CKD, integrated CKM care remains important even without specific CKD data. Participants emphasized that PCPs would play a central role in operationalizing the CKM framework globally, particularly through early identification of at-risk individuals, longitudinal monitoring of kidney and cardiovascular risk factors, initiation of evidence-informed therapies, and coordination of multidisciplinary care pathways.

**Renin-angiotensin-aldosterone system-targeting therapies.** Renin-angiotensin-aldosterone system inhibitors remain essential in CKM management due to their effectiveness, cost, and long-term data. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers lower cardiovascular risk, slow the progression of proteinuric CKD, and reduce mortality in people with heart failure with reduced

|            | ACE  |      | ARB  |      | nsMRA |      | SGLT2i        |               | Incretin-based therapies |                          |
|------------|------|------|------|------|-------|------|---------------|---------------|--------------------------|--------------------------|
| Indication | G1-3 | G4-5 | G1-3 | G4-5 | G1-3  | G4-5 | G1-3          | G4-5          | G1-3                     | G4-5                     |
| HFrEF      |      |      |      |      |       |      |               |               |                          |                          |
| HFpEF      |      |      |      |      |       |      |               |               | With diabetes or obesity | With diabetes or obesity |
| CKD        |      |      |      |      |       |      |               |               |                          |                          |
| DKD        |      |      |      |      |       |      |               |               |                          |                          |
| CV risk    |      |      |      |      |       |      | With diabetes | With diabetes | With diabetes            | With diabetes            |
| Diabetes   |      |      |      |      |       |      |               |               |                          |                          |
| Obesity    |      |      |      |      |       |      |               |               | With CVD                 | With CVD                 |

Direct evidence
  Indirect evidence
  No evidence
  Evidence of absence of benefit

**Figure 2 | Color-coded strength of evidence for guideline-directed therapies, by indication, and by glomerular filtration rate (GFR).**

We called evidence direct when people with GFR in this range were included in randomized trials, or when people with GFR that fell into this range continued on active treatment and contributed to outcome assessment in randomized controlled trials. We called evidence indirect when there were supporting data from adjacent populations or from observational data, and when no biological rationale or clinical evidence exists supporting the presence of an important statistical interaction. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; DKD, diabetic kidney disease; G, grade; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

ejection fraction (HFrEF).<sup>12,13</sup> To achieve their best results, these drugs need to be utilized in the maximal tolerated dose. Angiotensin receptor–neprilysin inhibitors further decrease cardiovascular deaths and heart failure hospitalizations in people with HFrEF, and possibly in people with heart failure with preserved ejection fraction with reduced progression of kidney disease in these patients; though they do not produce additional kidney benefits in patients selected on the basis of CKD, they should be used only in patients with heart failure.<sup>14</sup> Stopping renin-angiotensin-aldosterone system inhibitors in advanced CKD does not help kidney outcomes and may increase mortality,<sup>15</sup> supporting ongoing treatment at doses adjusted for GFR. Angiotensin-converting enzyme inhibitors typically require a 50% dose reduction at GFR < 30 ml/min per 1.73 m<sup>2</sup>; angiotensin receptor blockers, with the exception of candesartan, require no dose adjustment. Hyperkalemia is a key obstacle to optimal dosing and should be managed.<sup>16</sup>

Steroidal mineralocorticoid receptor antagonists (spironolactone, eplerenone) further reduce cardiovascular events and heart failure hospitalizations in people with HFrEF but do not prevent CKD progression in people with CKD.<sup>17,18</sup> In

contrast, the nonsteroidal mineralocorticoid receptor antagonist, finerenone, provides kidney and cardiovascular benefit in people with CKD and type 2 diabetes, significantly reducing CKD progression and cardiovascular events; and reduces cardiovascular outcomes in people with heart failure with preserved ejection fraction.<sup>19–21</sup> Combination therapy with finerenone and sodium-glucose cotransporter 2 (SGLT2) inhibitors enhances albuminuria reduction while attenuating hyperkalemia risk.<sup>22</sup> The FIND-CKD trial<sup>23,24</sup> ([ClinicalTrials.gov Identifier: NCT05047263](https://clinicaltrials.gov/ct2/show/study/NCT05047263)) extends the evidence base for finerenone to nondiabetic CKD, demonstrating a significant slowing of kidney function decline as measured by eGFR slope. These results, together with regulatory discussions around eGFR slope as an accepted surrogate end point, are expected to support label expansion and inform future guideline updates for nonsteroidal mineralocorticoid receptor antagonist use beyond diabetic CKD.

**SGLT2 inhibitors.** SGLT2 cardiovascular outcome trials revealed substantial clinical benefits, particularly reductions in heart failure events, and suggested favorable effects on kidney outcomes. These were followed by 3 landmark trials that provided robust evidence of kidney protection in

persons with CKD across the full spectrum and independent of type 2 diabetes or albuminuria status.<sup>25–27</sup> Meta-analyses of large cardiovascular and kidney outcome trials demonstrate large absolute benefits when all the different benefits are combined across a wide range of baseline eGFR and albuminuria levels, irrespective of diabetes status.<sup>25–27</sup> SGLT2s also reduce cardiovascular and kidney outcomes in people with HFrEF,<sup>28</sup> and people with heart failure with preserved ejection fraction.<sup>29,30</sup>

**Incretin-based therapies.** Incretin-based therapies provide complementary benefits across the CKM spectrum. These agents improve glycemic control, induce substantial and sustained weight loss, and reduce major atherosclerotic cardiovascular events, cardiovascular mortality, and heart failure hospitalizations, with benefits observed in populations with and without diabetes.<sup>31</sup> The FLOW trial<sup>32</sup> ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT03819153)—the first to evaluate CKD progression as a primary outcome—demonstrated a significant reduction in major adverse kidney disease events with semaglutide, accompanied by reductions in major adverse cardiovascular events and all-cause mortality.<sup>33</sup> Meta-analysis confirms class-wide reductions in preservation of kidney function and reduced kidney failure risk, with gastrointestinal tract adverse effects that are typically dose dependent and manageable.<sup>34,35</sup>

#### **Additional guideline-directed therapies aiming reduction of cardiovascular risk in patients with CKD**

**Statins.** Statins reduce cardiovascular events and mortality in CKD patients not on dialysis, but dedicated dialysis trials show no benefit in these populations. Guidelines advise statins ( $\pm$ ezetimibe) for adults with CKD aged  $\geq 50$  years or younger patients at high atherosclerotic CVD risk (e.g., by virtue of diabetes), but not for new initiation once on dialysis.<sup>4,36</sup> However, lipid management now extends beyond statins and ezetimibe. Recent guidelines endorse risk-based low-density lipoprotein cholesterol lowering, incorporating nonstatin therapies in the context of clinical atherosclerotic CVD when targets are not achieved with maximally tolerated statins or alternative agents, that is, proprotein convertase subtilisin/kexin type 9 (PCSK9i).<sup>37</sup> Evidence indicates that patients with CKD derive comparable cardiovascular benefit from these agents, supporting a broader, goal-directed approach to low-density lipoprotein cholesterol reduction using all evidence-based therapies.

**Antiplatelet therapy.** In people with CKD, antiplatelet agents lower myocardial infarction risk but do not reduce overall mortality and increase major bleeding. Data do not support routine primary prevention; for secondary prevention after myocardial infarction, stroke, or percutaneous coronary intervention, low-dose aspirin or a P2Y<sub>12</sub> inhibitor is recommended, with bleeding risk defining duration of the therapy.<sup>38</sup>

#### **CKD-specific risk factors**

CKD presents distinct cardiovascular risks—such as anemia, altered iron metabolism, and mineral and bone disease—as well as changes in dyslipidemia and platelet function, which affect the efficacy and safety of cardiovascular treatments, particularly in advanced stages.<sup>39</sup> This section reviews strategies for managing CKD-specific risks (Table 2),<sup>4,38,40–57</sup> noting that supporting evidence for these interventions is often limited or varies by stage and should be tailored to individual patients.

**Anemia therapies: erythropoiesis-stimulating agents and hypoxia-inducible factor–prolyl hydroxylase inhibitors.** Targeting higher hemoglobin with erythropoiesis-stimulating agents, especially when using high doses, does not improve cardiovascular outcomes and instead increases stroke and thrombosis risk. Hypoxia-inducible factor–prolyl hydroxylase inhibitors also do not appear to mitigate the risk of major cardiovascular events in specific populations. Therapy is generally recommended at hemoglobin 9 to 10 g/dl, avoiding levels above 11.5 g/dl, with individualization based on symptoms, transfusion needs, and history.<sup>45</sup> Note that all these studies were conducted in earlier eras, in the absence of any of the current therapeutic advances discussed earlier.

**Iron supplementation.** In dialysis, and in people with CKD and HFrEF (either transferrin saturation  $< 20\%$  or ferritin  $< 100 \mu\text{g/L}$ <sup>58</sup>), high-dose i.v. iron reduces heart failure hospitalizations, cardiovascular events, and erythropoiesis-stimulating agent needs. Data are less robust in non-dialysis-dependent CKD, but meta-analyses suggest fewer heart failure hospitalizations and no mortality harm.<sup>46</sup> Iron therapy should be tailored (oral vs. i.v.), keeping ferritin  $\leq 700 \mu\text{g/L}$  and transferrin saturation  $\leq 40\%$ , and withheld during active infection.<sup>45</sup>

**Phosphate binders and mineral metabolism therapies.** Evidence on phosphate binders reducing mortality or cardiovascular events is inconclusive. Non-calcium-based binders, like sevelamer, are often preferred, but their benefits are unclear.<sup>49</sup> Vitamin D analogues and calcimimetics improve biochemical parameters without clear survival or cardiac advantages. Current guidelines prioritize biochemical targets and avoiding hypercalcemia or calcium excess.<sup>53</sup>

#### **Implementation and sequencing of GDMT in CKM care**

A major challenge in CKM care is ensuring timely and coordinated use of effective treatments. Despite clear guidelines, real-world adoption of GDMT remains inconsistent because of therapeutic inertia, fragmented care, and barriers like access, monitoring, pill burden, and cost. Three strategies for implementation of multiple agents directed at mitigating CVD and CKD risks were reviewed:

- The traditional stepwise approach optimizes renin-angiotensin-aldosterone system therapy first, then adds other agents later. While familiar, this may lead to

**Table 2 | Summary of interventions for CKD-specific risk factors in patients with CKD**

| Therapeutic class    | Effects on mortality/CV outcomes/safety                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Guideline recommendations                                                                                                                                                                                                          |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ESAs/HIF-PHIs        | <ul style="list-style-type: none"> <li>Higher Hb → ↑ stroke, AVF thrombosis; no mortality benefit<sup>40–42</sup></li> <li>HIF-PHIs noninferior to ESAs for MACE in dialysis<sup>43,44</sup></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <ul style="list-style-type: none"> <li>Initiate if Hb &lt;10 g/dl (ND-CKD) or 9–10 g/dl (dialysis)</li> <li>Avoid Hb &gt;11.5 g/dl</li> <li>Apply same thresholds for HIF-PHIs<sup>45</sup></li> </ul>                             |
| Iron supplementation | <ul style="list-style-type: none"> <li>Iron therapy vs. usual care/placebo in ND-CKD and DD-CKD: fewer HF hospitalizations (RR, 0.77; 95% CI, 0.61–0.96); CV death (RR, 0.81; 95% CI, 0.65–1.02); all-cause mortality neutral; effects consistent across CKD stages<sup>46</sup></li> <li>High-dose i.v. iron vs. lower dose/no iron in DD-CKD only: no significant differences in CV mortality or cardiac adverse events; improved iron indexes without higher infection risk<sup>47</sup></li> <li>Safety of i.v. iron in DD-CKD: higher vs. lower dose (or i.v. vs. oral/no iron) showed no increase in mortality, CV events, infections, or hospitalizations<sup>48</sup></li> </ul> | <ul style="list-style-type: none"> <li>Choose i.v. vs. oral based on tolerance and logistics</li> <li>Maintain ferritin ≤700 µg/L, TSAT ≤40%</li> <li>Withhold during infections<sup>45</sup></li> </ul>                           |
| Phosphate binders    | <ul style="list-style-type: none"> <li>In DD-CKD: sevelamer vs. calcium-based binders: lower mortality; sucroferric oxyhydroxide and lanthanum vs. calcium: slower progression of CAC<sup>49,50</sup></li> <li>In ND-CKD: unclear effect on clinical outcomes and intermediate cardiovascular end points (scant data)<sup>51</sup></li> <li>In ND-CKD and DD-CKD: no clear mortality benefit vs. placebo; mixed signals vs. calcium salts (possible advantage for sevelamer)<sup>49,52</sup></li> </ul>                                                                                                                                                                                  | <ul style="list-style-type: none"> <li>Treat persistent hyperphosphatemia</li> <li>Limit calcium-based binders</li> <li>Avoid aluminum</li> <li>Agent choice guided by calcium load and calcification risk<sup>53</sup></li> </ul> |
| Vitamin D analogues  | <ul style="list-style-type: none"> <li>No effect on all-cause death (RR, 1.04; 95% CI, 0.84–1.24) and CV death (RR, 0.73; 95% CI, 0.31–1.71); short-term follow-up periods, small sample size, and suboptimal quality of RCTs<sup>54</sup></li> <li>No effect on all-cause death (RR, 1.26; 95% CI, 0.77–2.05)<sup>55</sup></li> </ul>                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Use for biochemical indications</li> <li>Avoid routine use for mortality prevention</li> <li>In ND-CKD, reserve for progressive SHPT<sup>4,53,56</sup></li> </ul>                           |
| Calcimimetics        | <ul style="list-style-type: none"> <li>No difference in mortality (RR, 0.97; 95% CI, 0.90–1.05) or CV mortality (RR, 0.69; 95% CI, 0.36–1.31)<sup>57</sup></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>Base use on biochemical PTH control</li> <li>No proven mortality benefit</li> <li>Combine with vitamin D if needed</li> <li>Monitor for hypocalcemia<sup>4,53,56</sup></li> </ul>           |

AVF, arteriovenous fistula; CAC, coronary artery calcification; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; DD-CKD, dialysis-dependent chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HF, heart failure; HIF-PHI, hypoxia-inducing factor–prolyl hydroxylase inhibitor; MACE, major adverse cardiovascular event; ND-CKD, non–dialysis-dependent chronic kidney disease; PTH, parathyroid hormone; RCT, randomized controlled trial; RR, relative risk; SHPT, secondary hyperparathyroidism; TSAT, total iron saturation.

treatment inertia and less frequent use of beneficial therapies and leave patients exposed to ongoing cardiovascular and kidney risk during implementation.

- Concurrent initiation of combination therapies may introduce multiple beneficial therapies quickly to reduce risk early but may not be appropriate for all patients and could increase cost and adverse effects, ultimately leading to lower adherence over time.
- An accelerated, risk-based method uses tools described in [Table 1](#) to identify high-risk patients for early and quick combination GDMT, whereas others follow a gradual path. This personalizes treatment intensity and supports efficient, patient-centered care.

Effective implementation and sequencing of GDMT are crucial for translating advances into better outcomes. A risk-based approach can balance urgency, safety, and feasibility to achieve meaningful improvements in cardiovascular and kidney health. Notably, the forum participants considered the accelerated, risk-based method to guide early initiation of combination therapies in high-risk patients as the preferred strategy for optimizing care delivery and patient outcomes, challenging the concept of a pillared approach and

introducing the therapeutic architecture ([Figure 3](#)). Participants emphasized that timely and scalable CKM implementation will require pragmatic collaboration between specialists and PCPs.

### Emerging therapies in clinical development

The forum stressed the importance of future emergence of therapies aimed at addressing residual risk beyond established GDMT. Several therapies, summarized in [Table 3](#), are in late-stage clinical development. They aim to address this gap by targeting complementary pathways (aldosterone excess, inflammation, obesity-related mechanisms, and endothelin signaling) and are intended to be layered onto established CKM therapies. Outcome and safety data will determine the clinical impact of these agents.

### Regional disparities, equity, and population dimensions of CKM health

Equity and population-level disparities are central drivers of CKM risk, care access, and outcomes. In many low-resource settings, PCPs and community-based health care workers

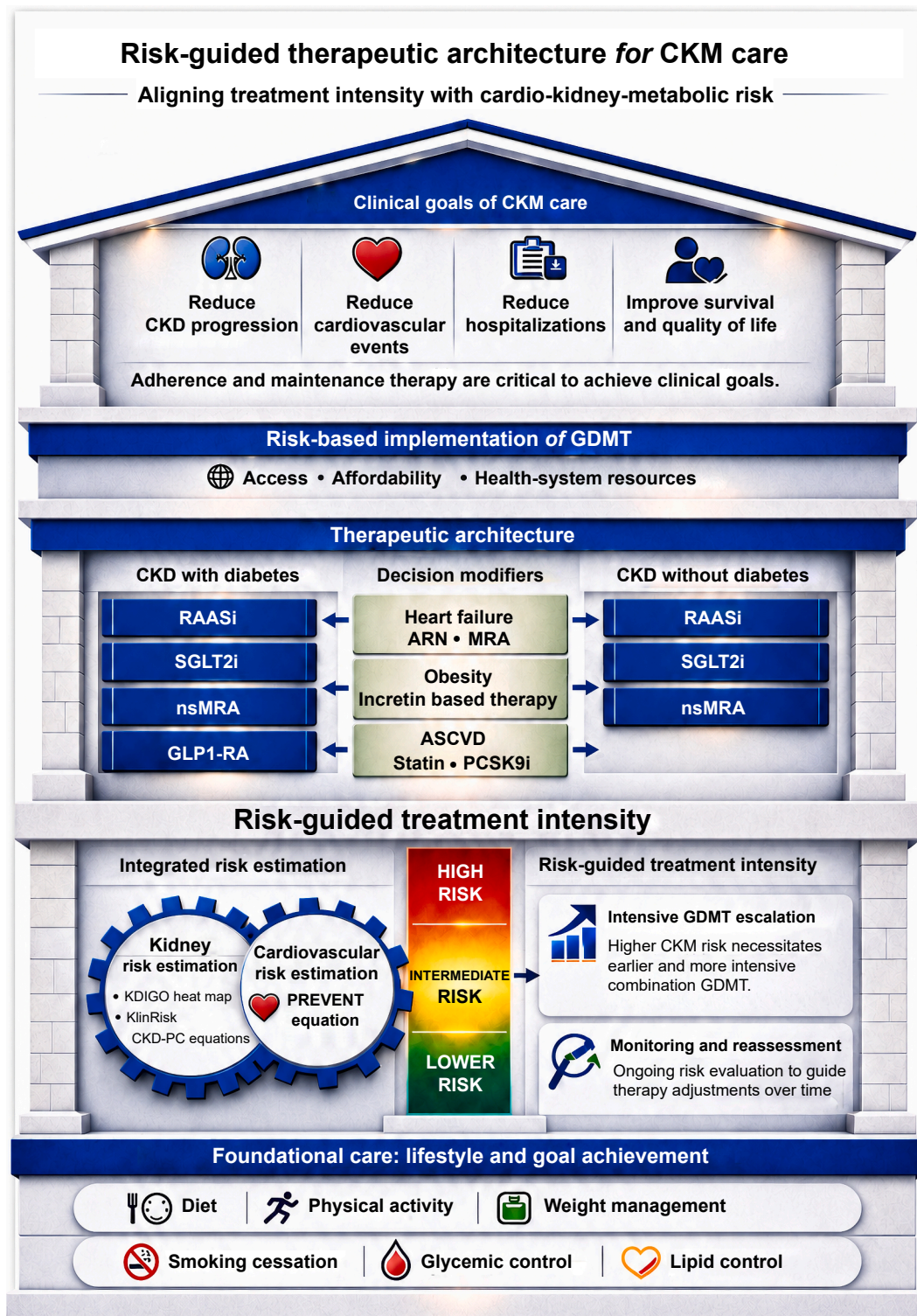


**Figure 3 | Risk-guided therapeutic architecture for cardiovascular-kidney-metabolic (CKM) care.** This framework illustrates a risk-based approach to implementing guideline-directed medical therapy (GDMT) in CKM care. Foundational lifestyle and risk factor management underpin all stages. Kidney and cardiovascular risk are estimated using validated tools (e.g., Kidney Disease: Improving Global Outcomes [KDIGO] heat map, KlinRisk, Chronic Kidney Disease Prognosis Consortium [CKD-PC] equations, and Predicting Risk of Cardiovascular Disease Events [PREVENT]), with higher risk supporting earlier and more intensive combination therapy. Core therapies include renin-angiotensin-aldosterone system inhibitors (RAASi), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and nonsteroidal mineralocorticoid receptor antagonist (nsMRA) across CKD populations. In CKD with diabetes, glucagon-like peptide-1 receptor antagonist (GLP1-RA) is typically incorporated. Comorbidities (heart failure, obesity, and atherosclerotic cardiovascular disease [ASCVD]) act as decision modifiers. Overall, treatment intensity is aligned with individual risk to optimize outcomes. ARN, angiotensin receptor/neprilysin inhibitor; PCSK9i, proprotein convertase subtilisin/kexin type 9.

**Table 3 | Emerging therapies targeting residual CKM risk: late-stage development**

| Therapeutic class                                                             | Primary mechanism                                              | Target CKM population                           | Key effects observed                                              | Key safety/practical issues                           | Expected outcome readout <sup>a</sup> |
|-------------------------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------|
| Aldosterone synthase inhibitors (e.g., vircadostat, baxdrostat, lorundrostat) | Selective inhibition of aldosterone synthesis                  | CKD ± diabetes; resistant hypertension; HF risk | ↓ BP; ↓ albuminuria (~40%) when added to RAASi/SGLT2i             | Mild ↑ potassium; requires monitoring                 | 2028–2029                             |
| IL-6 pathway inhibitors (e.g., ziltivekimab)                                  | Targeted anti-inflammatory signaling                           | CKD with ASCVD and elevated hsCRP               | Reduction in inflammatory biomarkers; CV benefit under evaluation | Infection risk; cost; patient selection               | 2026–2027                             |
| Antiobesity/incretin-based therapies                                          | Weight loss; metabolic, hemodynamic, anti-inflammatory effects | CKD with obesity ± diabetes                     | ↓ CV events; ↓ albuminuria; slower eGFR decline                   | GI tract tolerability; long-term kidney data evolving | 2026–2027                             |
| Endothelin receptor antagonists (e.g., atrasentan, zibotentan)                | ETA receptor blockade                                          | Proteinuric CKD (diabetic and nondiabetic)      | Large ↓ albuminuria; slowed CKD progression                       | Fluid retention; HF risk                              | 2026–2028                             |

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ETA, endothelin A; GI, gastrointestinal; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

<sup>a</sup>Timelines reflect anticipated primary outcome readouts from ongoing phase 3 trials.

may represent the only consistent point of contact for patients with early CKM disease. The burden is uneven across regions, populations, and the life course, varying by demographics. In the United States, nearly 90% of adults meet CKM stage  $\geq 1$  criteria and 15% are in advanced stages—predominantly older adults, men, and Black individuals.<sup>59</sup> Asian studies report prevalence exceeding 50% to 70%, increasing above 90% after midlife, with advanced disease concentrated in rural, older, and less educated populations.<sup>60,61</sup>

The global CKM burden is expected to grow, especially in low- and middle-income countries, where limited resources restrict preventive and therapeutic care. In these regions, CKM syndrome is influenced by infections, genetics, environmental factors, traditional medicines, and poor prenatal care.<sup>62</sup> The result is increased health costs, lost productivity, and deepening inequities, perpetuating poverty and poor health.

Participants emphasized that successful implementation of CKM care will depend not only on scientific advances, but also on policies supporting equitable access to effective therapies. Generic medications, reimbursement frameworks, and insurance coverage will strongly influence scalability worldwide. Early identification and treatment of high-risk individuals may also generate substantial long-term economic benefits by slowing CKD progression, reducing cardiovascular events, and delaying kidney failure.

Advanced CKM syndrome closely tracks with adverse social determinants of health. Poverty, limited education, food insecurity, unemployment, and poor health care access act as a major upstream driver of risk and progression (Figure 4). Unfavorable social determinants of health strongly correlate with advanced CKM, highlighting the cumulative effects of structural inequities. Surveillance systems remain poorly equipped to capture CKM's interconnected

nature, especially in low- and middle-income countries and rural settings. Undermeasurement of albuminuria, limited data linkage, siloed disease management, and weak registration systematically underestimate burden and delay intervention, disproportionately affecting disadvantaged populations and accelerating disease progression.<sup>63</sup>

Participants emphasized that advances in CKM therapeutics will only translate into meaningful population benefit if accompanied by equitable implementation strategies, affordable access pathways, and models of care adaptable to diverse health care systems and vulnerable populations. A life-course perspective underscores that CKM risk begins early. Maternal metabolic health, low birth weight, early-life illness, and nutritional adversity increase susceptibility to CKM syndrome and influence interventions across multiple stages of life. In addition, sex (biological differences [chromosomal, hormonal, reproductive]) and gender (socially constructed roles, behaviors, activities, and expectations associated with femininity and masculinity) shape CKM risk, progression, and treatment response. Women also experience excess mortality across multisystem CKM dysfunction due to biological factors and gender-related social determinants. For cardiovascular risk, a diagnosis of diabetes confers larger increased risk in women than men, yet women<sup>64</sup> remain underrepresented in CKM research—perpetuating “one-size-fits-all” care.<sup>65</sup> Emerging evidence identifies sex-specific genetic associations, immune responses, and pharmacokinetic and pharmacodynamic differences that may influence therapeutic efficacy and adverse event risk.<sup>66</sup> Observational data suggest optimal dosing for some CKM therapies may differ between women and men. Reassuringly, trials of key interventions for CKM (e.g., statins, SGLT2 inhibitors, and semaglutide) report clear benefit by sex in subgroup analyses, despite numeric underrepresentation of women in these trials.<sup>66</sup> Consistent with Kidney Disease: Improving Global

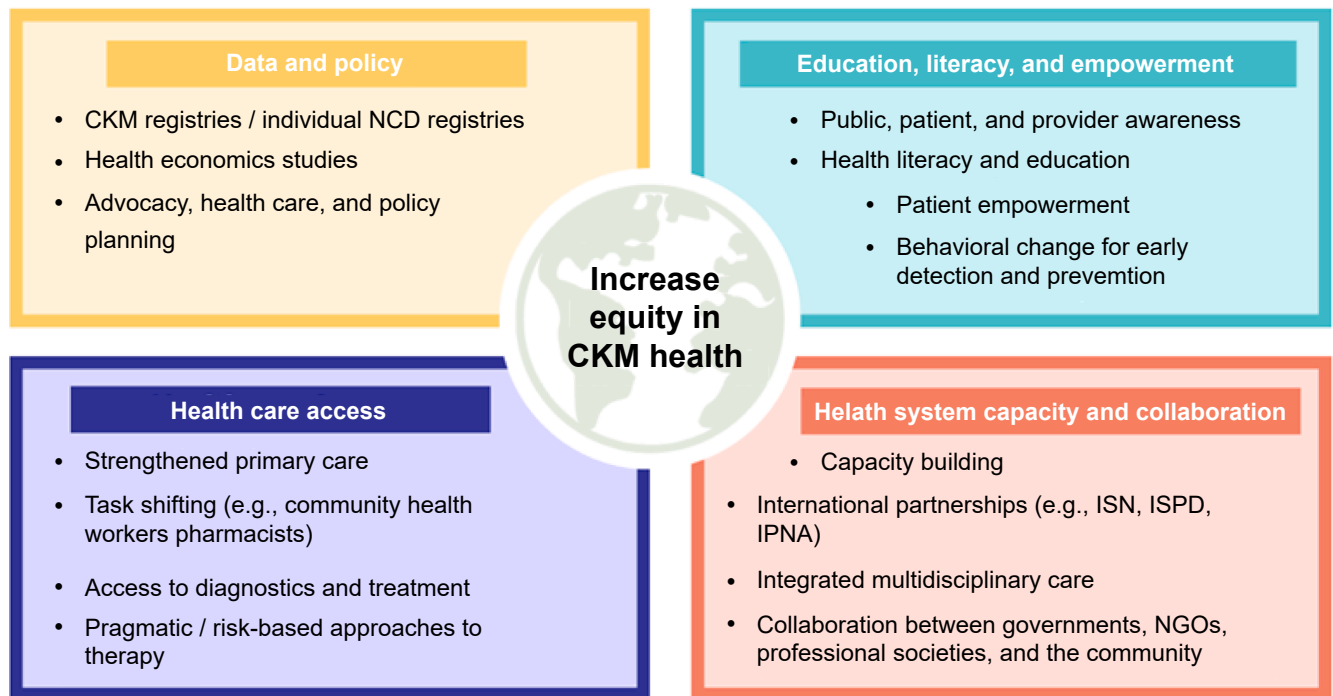


**Figure 4 | Integrated framework to improve equity in cardiovascular-kidney-metabolic (CKM) health in low and middle-income countries.** This schematic illustrates key interdependent domains for advancing equity in CKM health in low- and middle-income countries. The framework emphasizes 4 core areas—data and policy; education, literacy, and empowerment; care access; and health system capacity and collaboration—linked in a continuous system centered on the goal of improving CKM health equity. Each domain includes specific strategies spanning data generation, health literacy, primary care strengthening, and international collaboration to support prevention, early detection, and equitable care delivery. IPNA, International Pediatric Nephrology Association; ISN, International Society of Nephrology; ISPD, International Society of Peritoneal Dialysis; NCD, noncommunicable disease; NGO, nongovernmental organization.

Outcomes and American Heart Association guidance, embedding sex and gender into CKM research, risk stratification, and clinical decision support is essential to advancing precision and equity.<sup>3,4</sup>

Reducing CKM disparities requires coordinated global action integrating data generation, policy, education and health literacy, equitable care access, and stronger health systems. An integrated framework centered on prevention, early detection, and scalable implementation was proposed as a pathway to improve outcomes and reduce inequities across diverse populations and settings (Supplementary Figure S1).

#### Models of care for integrated CKM management

Models of care emerged as a central theme for advancing integrated CKM management. Participants emphasized the need to move away from traditional structures fragmented across specialties toward integrated care models that preserve specialty-specific expertise while improving coordination across disciplines that can result in unintended medication discrepancies, therapeutic inertia, duplicated or conflicting prescriptions, inconsistent monitoring, and suboptimal implementation of GDMT. They also agreed on the need to develop diverse models that share common principles (multidisciplinary collaboration, coordinated pathways, proactive use of GDMT, and continuous evaluation) while

differing in scope and scalability. Participants emphasized that integrated CKM programs should include nephrology expertise, particularly because patients with diabetes or CVD may have complex or alternative kidney disease etiologies, progressive CKD despite standard therapies, or CKD-specific complications requiring specialized management. Nephrologists therefore contribute not only to kidney risk stratification, but also to diagnostic evaluation, complication management, kidney failure risk assessment, and preparation for kidney replacement therapy when appropriate. Table 4 summarizes 3 illustrative models from the high-income countries of the United Kingdom, Spain, and the United States presented in the Forum, highlighting how integrated CKM care can be operationalized at clinic, hospital, and health-system levels. Participants also emphasized that successful implementation of integrated CKM programs requires foundational system-level components, including multidisciplinary collaboration between PCPs and specialists, shared care pathways, access to laboratory infrastructure capable of supporting longitudinal monitoring of kidney and cardiovascular risk markets, implementation of risk stratification tools, medication optimization frameworks, and coordinated referral and follow-up processes. These elements are essential to support scalable, patient-centered, and equitable CKM care across diverse health care settings. Although definitive evidence for CKM models on hard

**Table 4 | Scope, core components, and scalability of international models of integrated CKM care**

| Model/region                                                                | Scope of care                                                       | Primary setting                                           | Core components                                                                                                                                                     | Key strengths                                                                                 | Scalability                                                            |
|-----------------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| United Kingdom: multidisciplinary CKM Clinic (St George's Hospital, London) | Comprehensive CKM care (HF, CKD, diabetes, obesity)                 | Tertiary center with extension into primary care networks | Joint cardiology-nephrology assessment; standardized pathways; proactive GDMT optimization across CKD stages; linkage with community care                           | Deep specialty integration; improved GDMT use despite CKD; continuity across care transitions | Moderate—resource intensive but adaptable within large centers         |
| Spain: integrated cardiorenal units                                         | Advanced HF and CKD with high comorbidity burden                    | Hospital-based multidisciplinary units                    | Structured cardiology-nephrology collaboration; protocolized GDMT optimization; systematic management of CKD-specific complications (hyperkalemia, anemia, CKD-MBD) | Reduced HF hospitalizations; pragmatic real-world implementation; focus on high-risk patients | Moderate—well suited for hospital systems managing complex populations |
| United States: American Heart Association CKM Health Initiative             | System-level CKM framework spanning CVD, CKD, diabetes, and obesity | Multisite health systems and community settings           | Implementation science approach; standardized CKM metrics and tools; education for clinicians and patients; outcome measurement and learning health system          | Designed for dissemination; adaptable to heterogeneous systems; emphasis on equity and scale  | High—national rollout targeting diverse regions and health systems     |

CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; HF, heart failure.

clinical outcomes remains limited, emerging data support their potential value: coordinated CKM programs have been associated with improved patient experience, fewer health-related problems, better attendance, lower cost, and increased uptake of evidence-based cardio- and kidney-protective therapies.<sup>67</sup>

### Synthesis, controversies, and future directions

Participants outlined major controversies, evidence gaps, and priorities influencing future CKM research and care. The Expert Forum noted progress in defining CKM risk and broadening medical therapies, while acknowledging unresolved issues about practical implementation worldwide.

A major unresolved controversy is how to implement integrated CKM risk stratification in global clinical practice. Current screening methods often focus on short-term or disease-specific outcomes, failing to fully assess long-term kidney health or long-term chronic conditions. Participants highlighted the need for risk tools that combine kidney and cardiovascular risk in clinically useful, patient-centered ways and can be tailored to different practice settings.

Therapeutic implementation represents another area of active debate. Although evidence supports early combination therapies, uncertainty remains regarding optimal timing, patient selection, and safety in diverse populations. Addressing these questions will require targeted strategy trials and particularly real-world evidence and implementation science, complementing traditional outcome studies. From a global perspective, access and affordability of therapies represent a central challenge. Future CKM care should increasingly incorporate precision medicine approaches that account for biologic heterogeneity and individualized disease trajectories.

Participants emphasized that advances in CKM science will be limited without redesigning care delivery. Fragmented systems, global inequalities, and workforce shortages hinder progress. Ensuring equitable access to new therapies is crucial for improving CKM outcomes worldwide. Future CKM frameworks should integrate both population-level implementation strategies through primary care and mechanisms to preserve specialized evaluation of complex phenotypes and CKD-specific complications. Participants also highlighted the need for structural enablers of integrated care, including the development of CKM-specific International Classification of Diseases coding frameworks and alignment of multidisciplinary affordability for scalable implementation across health systems.

Since the convening of this Expert Forum, the 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome has further established CKM as a clinical framework. The guideline reinforces key priorities identified by the forum, including integrated risk assessment, implementation of evidence-based kidney- and cardiovascular-protective therapies, and coordinated multidisciplinary care models, while highlighting the need for continued efforts toward global adaptation and equitable implementation.<sup>68</sup>

Future directions include the following: (i) refining integrated CKM risk tools that incorporate longer-term kidney-specific outcomes; (ii) generating implementation-focused evidence and action plans to GDMT; and (iii) scaling multidisciplinary models of care adapted to regional contexts. *Aligned with ISN's mission, this forum represents a foundational step toward connecting disciplines, bridging evidence-to-practice gaps, and building global capacity to improve CKM outcomes equitably.*

## APPENDIX

## Meeting participants

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## DISCLOSURE

RP-F is an employee of Arbor Research Collaborative for Health, which receives global support for the ongoing Dialysis Outcomes and Practice Patterns Study Programs (without restriction on publications) by Vantive, GlaxoSmithKline, and Bayer; he reports investigator-initiated research grants from Vantive, Fresenius Medical Care, AstraZeneca, Bayer, Otsuka, Ardelix, GSK, and Akebia; consulting fees from AstraZeneca, Novo Nordisk, CSL Vifor, Vantive, Boehringer Ingelheim, Bayer, Otsuka, Vera, Emerald Clinical, Global Patient Alliance for Kidney Health, Biogen, and Duke Clinical Research Institute; payment/honoraria from AstraZeneca, Novo Nordisk, CSL Vifor, Vantive, Boehringer Ingelheim, Bayer, Lilly, Vantive, and Fresenius Medical Care; meeting travel support from AstraZeneca, Novo Nordisk, CSL Vifor, Vantive, Boehringer Ingelheim, Bayer, Lilly, Vantive, and Fresenius Medical Care; participation on Data Safety Monitoring/Advisory Boards of Albert Einstein CRO, Emerald Clinical, and University of Hong Kong; and leadership roles with the International Society of Nephrology (ISN), Kidney Disease: Improving Global Outcomes (KDIGO), Patient Alliance for Kidney Health, and Biogen, outside the submitted work. DB reports grant from AstraZeneca, paid to St. George's University Hospitals NHS Foundation Trust, outside the submitted work. MJJ is supported by an Australian government National Health and Medical Research Council Investigator Grant; is responsible for research projects that have received unrestricted funding from Amgen, Baxter, CSL, Dimerix, Eli Lilly, Gambro, Kensana, MSD, and MRFF-Nex Gen Clinical Researchers Program-CDF; reports consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, CSL, Janssen, Merck Sharp & Dohme, Vifor, Chinook Therapeutics, Novartis, and Avance; reports payment/honoraria from Cestas Medical, AstraZeneca, Janssen, Medcon International Physician's Academy for Cardiovascular Education, Medscape, Roche, Vifor, Merck Sharp & Dohme, Amgen, IMC Group, and Peer-Voice; reports meeting travel support from Amgen, Boehringer Ingelheim, Janssen, Novo Nordisk, Roche, and Vifor, with consultancy, honoraria, or travel support directed to her institution; reports participation on advisory boards sponsored by Akebia, AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Merck Sharp & Dohme, Occurx, Vifor, and Avance; reports Steering Committees for trials sponsored by Chinook, CSL and Janssen; and reports leadership roles with Australian Clinical Trials Alliance (ACTA), Rural, Regional and Remote

Trial Enabling Program, Kidney Health Initiative, KDIGO, ISN, and ISN-Advancing Clinical Trials (ISN-ACT) Group, outside the submitted work. BN reports consulting fees from AstraZeneca, Alexion, Bayer, Boehringer Ingelheim, CSL-Seqirus, Novo Nordisk, Travere, Otsuka, and Vera Therapeutics; payment/honoraria from AstraZeneca, Boehringer Ingelheim, Bayer, MJH Life Sciences, and Cornerstone Medical Education; meeting travel support from AstraZeneca, CSL Behring, and Novo Nordisk; and an unpaid leadership role with the ISN as Deputy Chair-Clinical Science of the 2026 World Congress of Nephrology Scientific Program Working Group, outside the submitted work. MSJ reports grants/contracts from Boehringer Ingelheim, Instituto Carlos III, and Marato TV3; honoraria from Novo Nordisk, Boehringer Ingelheim, AstraZeneca, Ingelheim Lilly, CSL, ICU Medical, Travere Therapeutics, Bayer, Medice, and Novartis; payment/honoraria from Otsuka; meeting travel support from Travere; Advisory Board participation with Novo Nordisk, Boehringer Ingelheim, AstraZeneca, Ingelheim Lilly, CSL, ICU Medical, Bayer, GE Healthcare, Travere Therapeutics, Medice, Otsuka, Dimerix, and Novartis; unpaid leadership roles as Sociedad Española de Cardiología group member, Sociedad Española de Nefrología board member, former European Renal Association board member, and ISN Western Europe Regional Board member and Council member; and leadership role as former editor-in-chief of *Clinical Kidney Journal* (paid to institution), outside the submitted work. SBA reports grants from Canadian Institutes of Health Research and Heart and Stroke Foundation of Canada, outside the submitted work. S. Bavanandan reports honoraria from AstraZeneca, Boehringer Ingelheim, Bayer, Novo Nordisk, Fresenius Medical Care, and Vantive; Advisory Board participation on Malaysia ADPKD (Tolvaptan), Finerenone, Malaysia, and Malaysia CKD with primary care (Boehringer Ingelheim); leadership roles as past Chair of ISN's Oceania and South East Asia (OSEA) Regional Board; past Executive Committee member of KDIGO; member of National Kidney Foundation (NKF) of Malaysia's Board of Directors; and fiduciary role as Honorary Secretary of Asian Pacific Society of Nephrology, outside the submitted work. S. Bansal reports grants or contracts from Bayer, ProKidney, Boehringer Ingelheim, and AstraZeneca, all with S. Bansal's institution; royalties/licenses from UpToDate; consulting fees from Novartis, Boehringer Ingelheim, Travere, Calliditas, and Vera; and payment/honoraria from Home Dialysis University, all outside the submitted work. JOB reports personal fees from AstraZeneca, CSL Vifor, Boehringer Ingelheim, and Novo Nordisk, outside the submitted work; he is also the Clinical Vice-President of the UK Kidney Association and is a National Institute for Health and Care Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. JJC reports grants/contracts from AstraZeneca, Otsuka, MSD, CSL Vifor, and Novo Nordisk to his institution; and payment/honoraria from Fresenius Kabi, outside the submitted work. TIC reports personal fees from Novo Nordisk, Pro-Kidney, Alexion, Eli Lilly, AstraZeneca, and Humacyte; and other (fees paid to her employer to support salary) from CSL Behring, outside the submitted work. M-CM reports personal fees from Boehringer Ingelheim, Bayer, Novo Nordisk, Lilly, AstraZeneca, Rovi, and Vifor, outside the submitted work. ACM reports other (travel grants and payments for lectures) from Boehringer Ingelheim Mexico, outside the submitted work. IHD reports personal fees from Alnylam, AstraZeneca, Boehringer Ingelheim, GSK, Lilly, Mitre, and Breakthrough T1D; grants and personal fees from Novo Nordisk and DexCom; and nonfinancial support from Abbott (contract with institution), outside the submitted work. SAG reports payment/honoraria for education lecture from Chiesi; meeting travel support from Davita Healthcare; and has stock in Kidney Beam Ltd, outside the submitted work. WGH reports grants/contracts from Boehringer

Ingelheim, Eli Lilly, and UK Medical Research Council, outside the submitted work. HJLH reports research grants from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, and Novo Nordisk; consulting fees from AstraZeneca, Alexion, Alnylam, Amgen, Bayer, Boehringer Ingelheim, Biocity Biopharmaceuticals, Dimerix, Eli Lilly, Novo Nordisk, Novartis, Roche, Otsuka, and Travere Therapeutics; payment/honoraria from AstraZeneca and Novo Nordisk; and meeting travel support from AstraZeneca and Eli Lilly, outside the submitted work. VJ reports consulting fees/honoraria from Bayer, Boehringer Ingelheim, Vantive, Vera, Otsuka, Novartis, Astra Zeneca, Timberlyne, and Biogen under the policy of all payments going to the George Institute. SSK reports consulting fees from Dimerix Pharmaceuticals, Chinook Pharmaceuticals, Novartis Pharmaceuticals, AstraZeneca, Novo Nordisk, Boehringer Ingelheim, and Amgen. Bayer and Novo Nordisk have supplied the trial medication for his trial, outside the submitted work. The George Institute for Global Health and its affiliated entities work with numerous health and pharmaceutical companies in the design, implementation, and analyses of clinical research and clinical trials; it is possible that some of these companies have products relevant to the clinical space covered in this analysis, but SSK is not aware of any possible conflicts arising from this work. CPK reports royalties from UpToDate and Springer; consulting fees from Abbott, Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Cara Therapeutics, CSL Behring, GSK, Pharmacosmos, Tricida, CSL Vifor, ProKidney, and Renibus; payment from Takeda for expert testimony; meeting travel support from AstraZeneca, Bayer, and Boehringer Ingelheim; participation on DIALIZE-O trial executive committee, GRAZE trial scientific committee, CardioRenal council, and FOUNTAIN Program Executive Advisory Committee; is President Elect of International Society of Renal Nutrition and Metabolism; and stock in Beamlink, outside the submitted work. RK reports honoraria from Bayer Australia and Eli Lilly; grants from Baxter Australia; honoraria and consultancy fees from Astra Zeneca; consultancy fees and travel support from Novo Nordisk; Steering Committee and consultancy fees from CSL Behring; and other (Steering Committee for Educational Meeting) from Amgen Australia and Boehringer Ingelheim, outside the submitted work. AL reports grants/contracts from Bayer, Boehringer Ingelheim, and Novo Nordisk; consulting fees from Bayer, Boehringer Ingelheim, Novo Nordisk, and Novartis; payment or honoraria from Bayer, Boehringer Ingelheim, and Novo Nordisk; and participation on Data Safety Monitoring Board/Advisory Board for Bayer, Boehringer Ingelheim, Novo Nordisk, Novartis, and AstraZeneca, with all payments to her institution/organization; AL is Chair of ISN Advancing Clinical Trials Committee, Canadian Society of Nephrology Advocacy Group, Steering Committee Chair for Australian Kidney Clinical Trials and National Institutes of Health (NIH) (unpaid), all outside submitted work. MMA reports grant/contract with Fundacion Rio Arrente, consulting fees from AstraZeneca, Boehringer Ingelheim, and CSL Behring; payment/honoraria from AstraZeneca and Boehringer Ingelheim; leadership roles as Associate Editor of *Journal of the American Society of Nephrology*; council member of International Society for Peritoneal Dialysis (ISPD); and Deputy Chair of the ISN's i3C Consortium, outside the submitted work. CM reports personal fees (employee) from the ISN outside the submitted work. EDM reports consulting fees from Bayer, Boehringer Ingelheim, Arrowhead, Ionis, Eli Lilly, Edwards Lifescience, Merck, Novo Nordisk, New Amsterdam, Novartis, and Pfizer; and participation on Data Safety Monitoring/Advisory Board for Eli Lilly, outside the submitted work. MMoorthy reports personal fees (consultant) from the ISN outside the submitted work. SDN reports personal fees from Alnylam, Intercept, ProKidney, Vertex, AstraZeneca, Bayer, Boehringer-Ingelheim, and Novartis, outside the submitted work. VP reports personal fees from AstraZeneca, Bayer, Biogen, Boehringer

Ingelheim, Cajal Consulting, Emerald Clinical, GSK, Guard Therapeutics, Incyte, Janssen, Mineralys, Novo Nordisk, Novartis, Otsuka, Purespring, Sidera, Sitala, Shanxi Micot, Travere, Tricida, and Vifor; other from St Vincents Health Australia, Kidney Health Australia, and Mindgardens Neuroscience Network; and other (stock) from Emerald Clinical, outside the submitted work. PR reports grants to his institution from AstraZeneca, Bayer, and Novo Nordisk; other (honoraria for education and consultancy) to his institution from AstraZeneca Bayer, Boehringer Ingelheim, Amgen, Abbott, Novo Nordisk, Gilead, and Lexicon; and other (study drugs to investigator-initiated trials) from AstraZeneca, Bayer, Novo Nordisk, and Lexicon, outside the submitted work. JEBR reports consulting fees from Medtronics paid to her institution; unpaid participation on Data Safety Monitoring/Advisory Board of OSMB NIH CODA study; and paid leadership role as Executive Editor of *Hypertension*, outside of submitted work. BMR reports personal fees from Novo Nordisk, outside the submitted work. MJS reports personal fees from Akebia and Boehringer Ingelheim, outside the submitted work; and spouse is employed by Eli Lilly. LS reports personal fees from Novo Nordisk, Merck, Corcept, BI Lilly, Lilly, Madrigal, Xeris, and Amgen, outside the submitted work. PS reports grants/contracts from AstraZeneca and Bayer; consulting fees from CSL, Fresenius Medical Care, Vantive, Vera, Alexion, Novo Nordisk, GSK, and Invizius; payment/honoraria from AstraZeneca, Fresenius Medical Care, Boehringer Ingelheim, Pfizer, Novo Nordisk, Amgen, and Vantive; and payment for expert testimony from CSL. MWT reports personal fees from Boehringer Ingelheim and Bayer; other (meeting travel support) from Bayer; and leadership position with the ISN, outside the submitted work. NT reports grants/contracts from Bayer, AstraZeneca, Boehringer Ingelheim, and Otsuka Pharmaceutical Co Ltd; consulting fees from Bayer, AstraZeneca, Boehringer Ingelheim, Otsuka Pharmaceutical Co Ltd, ProKidney, Roche, Vera, and ASN; patent issued for a microfluidic device for point-of-care detection of urine albumin and patent pending on the use of laboratory data to predict chronic kidney disease (CKD) progression; participation on Data Safety Monitoring/Advisory Board of the NKF; and stock in ProKidney, Klinrisk, Quanta, Mesentech, and pulsedata, outside the submitted work. KRT reports grants/contracts from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Heart, Lung, and Blood Institute (NHLBI), National Center for Advancing Translational Sciences, NIH Director's Office, Centers for Disease Control and Prevention (CDC), Travere, Bayer, and Otsuka, all paid to her institution; consulting fees from Lilly, Boehringer Ingelheim, Bayer, Novo Nordisk, ProKidney, Alnylam, AstraZeneca, GSK, Roche, and Otsuka; payment/honoraria from Bayer, Novo Nordisk, and Travere; participation on Data Safety Monitoring/Advisory Boards for AstraZeneca (paid) and NIDDK and George Clinical Institute (unpaid); and unpaid leadership roles with the American Society of Nephrology as Chair of Diabetic Kidney Disease Collaboration and Chair of Kidney Week 2025 Program Committee, outside the submitted work. AY-MW reports grants from National Medical and Research Council and Duke-National University of Singapore Khoo Bridge Funding; consulting fees from Consun Pharma; payment or honoraria from AstraZeneca, Bayer Corporation, Fresenius Kabi, and VitaFlo; meeting travel support from Bayer Corporation, AstraZeneca, Fresenius Kabi, and Consun Pharma; participation on Data Safety Monitoring Board/Advisory Board for ASPIRED and BEAT-CALCI Trials; and leadership roles as Past President of International Society of Renal Nutrition and Metabolism, and Scientific Advisor of Consun Pharma, outside the submitted work. DCW reports consulting fees from AstraZeneca, Bayer, Alnylam/Roche, CSL Vifor, Inversago/Novo Nordisk, Tricida, Emerald Clinical, HighTide, and Purespring; payment/honoraria from AstraZeneca and Boehringer Ingelheim; meeting travel support from AstraZeneca and Boehringer

Ingelheim; participation on Data Safety Monitoring Board/Advisory Board for Aion, Dimerix, Eledon, Galderma, Janssen, Pathaly, Pro-Kidney, Sana, Senya, Syntherine, and Vertex; and leadership role in KDIGO, outside the submitted work. MMYW reports grants/contracts from Canadian Institutes of Health Research, Michael Smith Health Research BC, and Kidney Foundation of Canada; consulting fees from Emerald Clinical Trials; and payment/honoraria from Bayer and Novo Nordisk, outside the submitted work. CAH reports personal fees from AstraZeneca, Bayer, Merck, Novo Nordisk, UpToDate, University of British Columbia, and University of Oxford; other (stock ownership) from Boston Scientific, Johnson & Johnson, Merck, and Pfizer; and other (travel grant) from ISN, outside the submitted work. All the other authors declared no competing interests.

## DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used AI tools to support the design of [Figures 1–4](#) and [Supplementary Figure S1](#) from text written without the aid of AI. After using the AI tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

## ACKNOWLEDGMENTS

This article is an output of the International Society of Nephrology's International Expert Forum: Exploring the Nexus of Cardiovascular-Kidney-Metabolic Health, a multisupported initiative by AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and CSL Vifor.

## FUNDING STATEMENT

This article was supported by the International Society of Nephrology.

Supplementary material is available online at [www.kidney-international.org](http://www.kidney-international.org).

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