Chronic Kidney Disease 3

Chronic kidney disease, complex conditions, and advancing therapeutics: new hope and challenges

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Chronic kidney disease (CKD) is increasingly recognised as a complex, multisystem condition that rarely occurs in isolation. This Series paper outlines major advances in therapeutics that target shared inflammatory, metabolic, and fibrotic pathways across CKD, cardiovascular disease, diabetes, obesity, and infection. Novel therapeutics, including SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists, and GLP receptor agonists, show substantial benefits for slowing CKD progression and improving cardiovascular outcomes, with combination strategies showing additive potential. This Series paper discusses complexities for therapeutic decision-making in CKD, highlighting multimorbidity, frailty, and polypharmacy care as major challenges for implementation in general or primary care settings. We identify under-recognised, groups of patients at high risk with infection and cancer-related CKD, in whom early detection and integrated care could markedly improve outcomes. Finally, we call for more inclusive and representative evidence generation, improved CKD screening within other disease pathways, and coordinated implementation of emerging therapies to reduce the global burden of CKD.

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Introduction

Since its first description in 2002, chronic kidney disease (CKD) has been transformed from an enigma of modern medicine to a treatable condition. Major advances in our understanding of the pathophysiology of CKD, particularly concerning the roles of immunity,

Search strategy and selection criteria

We searched PubMed and Cochrane Library for articles published in English from database inception to Feb 13, 2026, with the following terms and related keywords: "chronic kidney disease" OR "CKD" OR "kidney disease" OR "renal disease" in combination with "treatment" OR "therapy" OR "therapeutic" OR "drug" OR "multimorbidity" OR "frailty" OR "polypharmacy" OR "infection" OR "infectious disease" OR "human immunodeficiency virus" OR "HIV" OR "flu" OR "influenza" OR "COVID-19" OR "coronavirus" OR "SARS-CoV-2" OR "vector-borne" OR "cancer" OR "oncology" OR "systemic anticancer therapy" OR "SACT" OR "VEGF" OR "vascular endothelial growth factor" OR "ICI" OR "immune checkpoint inhibitor" OR "kidney failure" OR "cardiovascular disease" OR "outcomes" OR "acute kidney injury" OR "AKI". Priority was given to systematic reviews, meta-analyses, and consensus statements published within the past 5 years, supplemented with seminal articles, and original research published within the same 5-year window. The search was done by JSL with input from all authors. We reviewed articles resulting from these searches and their references and selected those relevant to therapeutic advances in CKD. We also reviewed the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease to frame the content of this Series paper. The selection of articles was proposed by lead authors and reviewed by all co-authors, with disagreements resolved through consensus via email discussion.

Key messages

- Novel chronic kidney disease (CKD) therapeutics (including SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists, and GLP-1 receptor agonists) and emerging agents can now preserve kidney function, reduce albuminuria, slow progression, and improve cardiovascular outcomes across diverse CKD populations. Multiple new drug classes are in late-phase development.
- Evidence suggests additive benefits when combining novel CKD therapeutics, although randomised evidence is awaited. Fixed-dose polypills might simplify prescribing but remain untested in CKD and underused in cardiovascular disease due to regulatory and dosing challenges.
- Multimorbidity, polypharmacy, frailty, and sarcopenia complicate prescribing, increase adverse events, and reduce confidence in applying trial evidence. Guidance for managing CKD in these complex populations is inconsistent, and safety data for high-risk groups remain scarce, making individualised treatment challenging, particularly in primary care.
- CKD risk and progression are amplified by cancer and its therapies, infections, autoimmune disease, and cardiometabolic conditions. Integrating CKD screening and treatment into disease-specific management may improve CKD outcomes but is rarely implemented.
- CKD trials under-represent advanced CKD and kidney failure, older adults (>75 years), females, individuals with multimorbidity, patients with frailty, children, and populations in low-income and middle-income countries. The absence of these populations from CKD trials limits generalisability and delays access to effective treatments. More inclusive trial design and individual-level data sharing are urgently needed.

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inflammation, and fibrosis, discussed in the first Series paper,[1] have led to novel drug therapeutics to reduce CKD progression, kidney failure, and cardiovascular disease associated with CKD (figure 1). The advances in understanding biological sex differences and their relevance for novel diagnostics and therapeutics is discussed in the second Series paper.[2]

Despite these therapeutic improvements, the management of CKD continues to increase in complexity. CKD only rarely occurs as an isolated health condition and is frequently seen alongside health conditions where there are shared causal pathways, including cardiovascular diseases, metabolic conditions, infections, and cancer. In many countries, most patients with CKD are found in the community, under general or non-nephrology specialty care, where health-care providers might be less aware of the evolving burden of CKD and the tremendous opportunities for improvements through prompt CKD detection and management. This growing burden requires new approaches to care and changing roles for health-care practitioners.

We discuss the clinical complexity of CKD and identify how promising new drug therapeutics for the prevention and treatment of CKD could be better integrated with the management of other long-term conditions. We concentrate on the use of novel drug therapeutics for CKD complications, where care is not primarily directed by a nephrologist. We acknowledge that there have been many exciting developments in disease-modifying therapeutics for genetic kidney diseases, glomerular diseases, and multisystem diseases with kidney involvement, and to improve outcomes for people receiving kidney failure replacement therapy (dialysis or kidney transplantation).[3] However, these advances are less relevant to individuals working outside nephrology and have been covered in detail elsewhere, so we discuss these advances only where required for context.

We acknowledge that much of the evidence for novel drug therapeutics has been generated in high-income countries (HICs), and evidence might not always be generalisable to all geographical regions and health-care settings. Similarly, it is beyond the scope of this Series paper to detail the barriers to global implementation of equitable, sustainable, high-quality CKD care; these issues have been well discussed by others.[4,5] Suffice to say that implementation challenges remain varied and substantial, particularly in low-income and middle-income countries (LMICs) as well as vulnerable and marginalised communities in HICs,[4] despite the inclusion of empagliflozin and semaglutide (and their therapeutic equivalents) on the WHO List of Essential Medicines.

In the third paper of this Series, we do not seek to reiterate clinical guidance[5] or suggest solutions to the major implementation challenges that remain.[4] Instead, we hope to raise awareness of the complexity of managing CKD in clinical practice and encourage health-care providers to consider how integrated CKD care might best be implemented within the boundaries of their own practice and health-care circumstances.

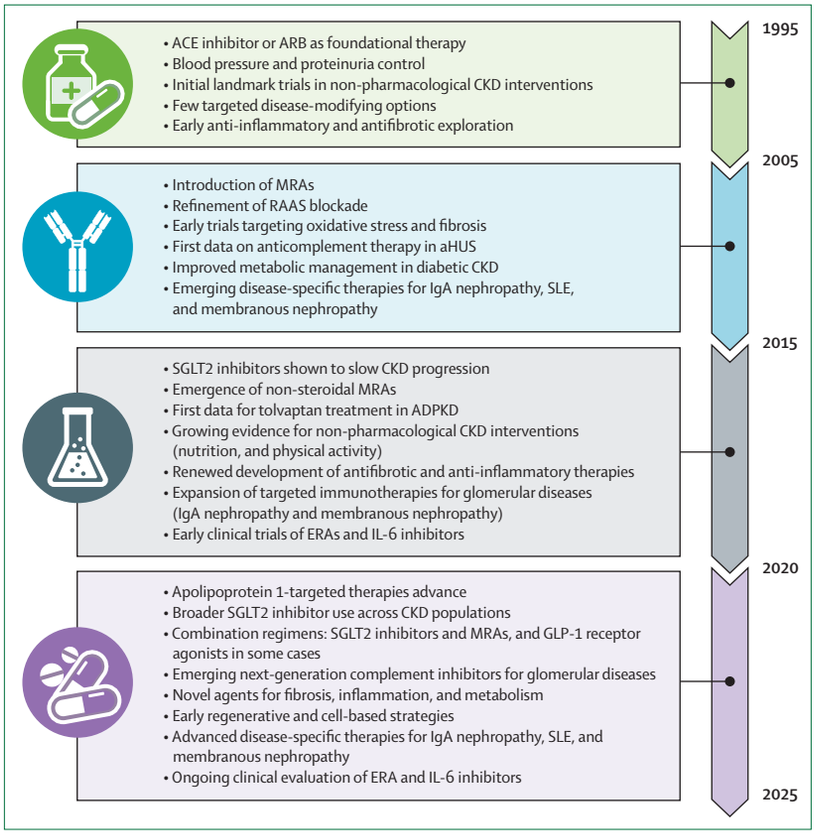

Figure 1: **Advances in CKD therapeutic discovery**
ACE=angiotensin-converting enzyme. ADPKD=autosomal dominant polycystic kidney disease. ARB=angiotensin II receptor blocker. CKD=chronic kidney disease. ERA=endothelin receptor antagonist. MRA=mineralocorticoid receptor antagonist. RAAS=renin–angiotensin–aldosterone system. HUS=haemolytic uraemic syndrome. SLE=systemic lupus erythematosus.

Novel therapeutics for CKD: a decade of progress

In the past decade, the expectations for CKD management have shifted dramatically. Although care goals were historically limited to slowing an inevitable decline in kidney function, advances in drug therapeutics can now support preservation or even normalisation of glomerular filtration rate (GFR) and albuminuria.[6] In individuals with a range of cardiovascular, kidney, and metabolic conditions (including heart failure, CKD, diabetes, and obesity), targeting common pathophysiology has led to a plethora of available therapeutic options to improve CKD outcomes (including reducing CKD progression and kidney failure), cardiovascular (including heart failure) disease, and to reduce hospitalisations and mortality.

The evolution in drug development, available evidence, and indications for novel drug therapeutics now available for individuals with or at high risk of CKD have been described in detail.[6–8] The current state of knowledge and data supporting these newer agents, and the major gaps that still remain, is summarised in the table.

	Selected mechanisms	Populations	Outcomes	Considerations
Existing evidence and implemented in clinical practice				
RAS inhibitors (ACE inhibitors and ARBs)	Reduce glomerular hydraulic pressure and the ultrafiltration of plasma proteins; reduce cell growth, inflammation, and fibrosis; and reduce cardiac remodelling	There is evidence for use of RAS inhibitors in people with CKD and albuminuria, CKD and hypertension, and heart failure with reduced and preserved ejection fraction (with or without CKD)	Reduce blood pressure and proteinuria; slow decline in kidney function; and reduce risks of kidney failure and cardiovascular disease in CKD populations[9]	STOP-ACEi trial: no benefit to stopping RAS inhibitors in advanced CKD to increase or preserve eGFR;[10] target trial emulation suggests that RAS inhibitor discontinuation in CKD is associated with higher rate of major cardiovascular events and death;[11,12] continuing RAS inhibitors in advancing CKD might be preferable to discontinuation in the absence of a strong indication to stop (such as severe hyperkalaemia)
SGLT2 inhibitors	Promote natriuresis, change in tissue sodium handling and glycosuria, with a range of downstream effects beyond plasma glucose control, including enhanced tubuloglomerular feedback, reduced intraglomerular pressure, reduction in plasma volume and systemic blood pressure, improved vascular function, and reduced uric acid, inflammation, and oxidative stress[13]	There is evidence for use of SGLT2 inhibitors in people with CKD with and without diabetes, including a range of glomerular diseases; people with type 2 diabetes; and people with heart failure with reduced and preserved ejection fraction; more evidence is required to support SGLT2 inhibitor use in children with CKD (NCT07107945), people with advanced CKD[14] and kidney failure (dialysis and kidney transplantation)[14]	Reduce AKI, CKD progression (by over 1 mL/min per 1·73m^2 per year on average, corresponding to approximately 57% improvement in eGFR decline compared with untreated individuals,[15] albuminuria, heart failure diagnoses, hospitalisation for heart failure, cardiovascular death, and all-cause mortality[16–24]	Early (within 2–4 weeks) drop in eGFR is commonly observed but is considered a protective mechanism due to reduced intraglomerular pressure[19,20]
Non-steroidal MRAs	Reduces oxidative activity, fibroblast proliferation, pro-fibrotic mediators, and immune and inflammatory mediators, leading to reduced tubular and podocyte injury, reduced fibrosis and glomerulosclerosis, reduced inflammation and vascular injury, and net vasodilation[25]	There is evidence for use of non-steroidal MRAs in people with CKD with type 2 diabetes and albuminuria and people with heart failure with reduced and preserved ejection fraction; evidence is required to support use in children with CKD (trial in progress),[26] people with CKD without type 2 diabetes (trials in progress),[27,28] and people with kidney failure (dialysis and kidney transplantation; no trials in progress)	Reduce proteinuria, prevention of the AKI to CKD transition, slows CKD progression, reduces cardiovascular events, particularly heart failure[27,29,30]	Not currently recommended in patients who have uncontrolled serum potassium, advanced CKD, or kidney failure because of safety concerns, primarily relating to risk of hyperkalaemia
Incretin analogues (GLP-1 receptor agonists; dual GLP-1 receptor agonists and GIPs; dual GLP-1 receptor agonists and glucagon agonists; and triple GLP-1 receptor agonists, GIPs, and glucagon agonists)	Reduces glycaemia, improves insulin sensitivity, decreases glucagon and free fatty acid concentrations, suppresses appetite (through increased satiety and slowed gastric emptying), decreases bodyweight, and downregulates proteomic profiles associated with cardiovascular disease risk[31,32]	There is evidence for use of incretin analogues in people with type 2 diabetes and people with CKD with type 2 diabetes; evidence is required for use in children with CKD (no trials in progress); CKD without overweight or obesity or type 2 diabetes (no trials in progress); and CKD with overweight or obesity, with or without type 2 diabetes (trials in progress)[33,34]	Reduces major adverse kidney and cardiovascular events; slows rate of eGFR decline by over 1 mL/min/1·73m^2 per year[35]	Significant (12·7%) GLP-1 receptor agonist treatment discontinuation due to adverse (mainly gastrointestinal) events in the trials;[36] treatment discontinuation might be higher in clinical practice (over 50% at 1 year) than in trials, and more common in patients who do not have type 2 diabetes or who lack access to an appropriate source of funding for treatment[37]

(Table continues on next page)

	Selected mechanisms	Populations	Outcomes	Considerations
(Continued from previous page)				
In development (awaiting further evidence or not implemented in clinical practice)				
Endothelin receptor antagonists	Endothelin receptor A antagonists promote vasoconstriction, cell proliferation, and matrix accumulation; endothelin receptor B antagonists lead to vasodilation and antiproliferative and antifibrotic effects[38]	People with CKD and type 2 diabetes;[39,40] people with CKD with albuminuria;[41] two endothelin receptor antagonists (atrasentan and sparsentan)[42,43] are already licensed for use in IgA nephropathy	Atrasentan reduced albuminuria and kidney function decline, but at the expense of increased risks of fluid retention and heart failure, particularly in women;[39,40] zibotentan with dapagliflozin enhanced albuminuria reduction and mitigated fluid retention in patients with CKD[41]	Zibotentan in combination with dapagliflozin being tested in CKD with albuminuria for CKD outcomes in phase 3 trial (NCT06087835)
Aldosterone synthase inhibitors	Blocks the adverse effects of aldosterone for kidney and cardiovascular health (see non-steroidal MRAs), but additionally target direct effects of aldosterone that are not mediated by altered gene expression (such as deleterious cardiac remodelling)	People with CKD and albuminuria[44] and people with CKD and uncontrolled hypertension[45]	Vicadrostat in combination with empagliflozin dose-dependently reduced albuminuria in patients with albuminuric CKD;[44] baxdrostat reduced systolic blood pressure[45]	Vicadrostat in combination with empagliflozin being testing for kidney and cardiovascular protection in patients with CKD and albuminuria (NCT06531824);[46] baxdrostat in combination with dapagliflozin is being tested to slow CKD progression, and reduce albuminuria, kidney, and cardiovascular events among participants with CKD and hypertension (NCT06268873)
Anti-IL-6 ligand monoclonal antibodies	Inhibits IL-6: a key component in the inflammatory cascade leading to development of thrombosis and atherosclerosis	People with moderate to severe CKD[47]	Ziltivekimab reduced biomarkers of inflammation and thrombosis that are implicated in the development of atherosclerosis[47]	Therapeutic efficacy of ziltivekimab for reducing cardiovascular outcomes in patients with CKD and systemic inflammation is being tested in ongoing phase 3 trial (NCT05021835)
Small soluble guanylate cyclase molecule activator	Enhances nitric oxide production and nitric oxide signalling, improving endothelial function	People with CKD with diabetes and without diabetes	Avenciguat lowered albuminuria[48]	NA
Complement inhibitors	Inhibit the main soluble component of the innate immune system; complement activation and over-activity plays a role in the pathogenesis of a range of glomerular diseases, including IgA nephropathy, membranous nephropathy, lupus nephritis, C3 glomerulopathy, dense deposit disease, diabetic nephropathy, and hypertensive nephrosclerosis	Under investigation in phase 1, 2, and 3 trials across a range of diseases[49]	NA	NA
Apolipoprotein-1 blockers (small molecule inhibitors and gene therapy)	Apolipoprotein-1 is an innate immunity gene; gene variants protect against African trypanosomiasis but can cause rapidly progressive proteinuric CKD for those carrying one or two apolipoprotein-1 risk variants; blocking expression or activity of gene might reduce CKD progression	People with apolipoprotein-1 associated CKD	Small molecule inhibitors of the apolipoprotein-1 channel reduce proteinuria[50]	Beyond proof of efficacy in phase 3 trials, successful implementation will require broader genetic testing to identify individuals at risk

ACE=angiotensin-converting enzyme. AKI=acute kidney injury. ARB=angiotensin receptor blockers. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. GIP=glucose-dependent insulinotropic polypeptide. MRA=mineralocorticoid receptor antagonists. NA=not applicable. RAS=renin-angiotensin system.

Table: **Novel and emerging drug therapeutics in the prevention and treatment of CKD**

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In brief, renin–angiotensin system (RAS) inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), have myriad benefits in reducing blood pressure and proteinuria, slowing decline in kidney function, and reducing risks of kidney failure and cardiovascular disease in CKD populations.[9] Among people with CKD, RAS inhibitors have long formed the backbone of a risk reduction strategy for CKD progression and, along with statin therapy,[5,16] for cardiovascular disease. Stable and optimised treatment with RAS inhibitors was mandated in all landmark trials supporting the use of SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists (MRAs), and GLP-1 receptor agonists in CKD.

SGLT2 inhibitors have been the most widely tested therapy, showing similar benefits in CKD with and without diabetes, including a range of glomerular diseases (as well as type 2 diabetes and heart failure with reduced and preserved ejection fraction), on reducing acute kidney injury (AKI), CKD progression, albuminuria, heart failure diagnoses, hospitalisation for heart failure, cardiovascular death, and all-cause mortality.[17–24] Efforts to expand the evidence for use of SGLT2 inhibitors in children (NCT07107945) and patients with advanced CKD, including those on kidney replacement therapy, are underway (NCT05374291).[14]

In CKD, evidence for third-generation, non-steroidal MRAs and GLP-1 receptor agonists is currently limited to patients with type 2 diabetes. In CKD with type 2 diabetes, the four pillars of diabetic kidney disease management now comprise RAS inhibitors, SGLT2 inhibitors, non-steroidal MRAs, and GLP-1 receptor agonists.

In phase 3 trials, non-steroidal MRAs have been studied in patients with albuminuric CKD with type 2 diabetes[29,51] (as well as patients with heart failure with both reduced and preserved ejection fraction) and found to reduce albuminuria, CKD progression, and cardiovascular disease, particularly heart failure.[27,29,30] Trials of non-steroidal MRAs in children[26] with CKD and patients with CKD without type 2 diabetes[28] are underway. With both oral and injectable forms available, GLP-1 receptor agonists have recently found roles in the treatment of a range of cardiometabolic diseases[36] and have been popularised by celebrities and on social media for cosmetic weight loss.[52] In the treatment of type 2 diabetes and obesity, dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonists, dual GLP-1 and glucagon agonists, and triple GLP-1, GIP, and glucagon agonists show similar or improved glycaemic control, weight loss, and cardiovascular protection compared with single GLP-1 receptor agonists, with consistent results in patients with pre-existing CKD.[53] There are currently no trials planned of incretin analogues in children with CKD nor in people with CKD without either type 2 diabetes or overweight or obesity; however, subgroup analysis from the FLOW trial indicated that the benefits of semaglutide for CKD and cardiovascular outcomes were present across the spectrum of BMI.[54] Trials of dual or triple incretin analogues for CKD with overweight or obesity (with or without type 2 diabetes) are in progress.[33,34,53] In the meantime, studies in routine care suggest that dual incretin agonists might confer additional kidney protection (including for AKI and kidney failure) compared with GLP-1 receptor agonists alone,[55] although whether dual or triple incretin analogues increase the likelihood of adverse events compared with single GLP-1 receptor agonist therapy is yet to be confirmed.[56–58]

Although detailed discussion is beyond the scope of this Series paper, there are several classes of drug therapeutics that are showing promise in the prevention or treatment of CKD or its complications. Phase 3 trials of endothelin receptor antagonists,[39,41] aldosterone synthase inhibitors,[44–46] and anti-IL-6 ligand monoclonal antibodies[47] in CKD are in progress (table). Therapeutics showing promise in earlier phases of development include soluble guanylate cyclase small molecule activators,[48,59] and complement inhibitors,[49] with potential for benefits across a range of CKD indications. The identification of genetic variants in the apolipoprotein-1 gene has led to early phase trials of small molecule inhibitors of the apolipoprotein-1 channel,[50] and disease-modifying therapies that target apolipoprotein-1 gene expression,[60] with important potential improvements for CKD outcomes for relevant individuals of African ancestry. There are emerging roles for vaccine products in the prevention and treatment of several non-communicable diseases where inflammation and immunity are implicated in pathophysiology, including diabetes,[61] hypertension,[62,63] atherosclerosis,[64] and cancer,[65] with plausible downstream effects on reducing incident and progressive CKD.

Combination therapies and therapeutic hierarchy

There have been no head-to-head comparisons of novel drug therapeutic for improving CKD outcomes; however, a network meta-analysis of 27 trials (50 237 participants) in type 2 diabetes or CKD populations indicated that SGLT2 inhibitors provided greater kidney and cardiovascular protection in trial populations than non-steroidal MRAs and GLP-1 receptor agonists.[66] These findings are supported by real-world data from Hong Kong, suggesting that SGLT2 inhibitors are superior to GLP-1 receptor agonists in reducing adverse kidney events.[67] However, data from the UK indicate that the optimal choice of medication in type 2 diabetes to lower glycaemia can be individualised using key patient characteristics, with enhanced effects on reducing CKD progression and cardiovascular disease when the optimal treatment is selected.[68]

Combination therapies might be more effective than single-agent strategies. In a meta-analysis of GLP-1

receptor agonist trials, additional beneficial effects of GLP-1 receptor agonists were present in patients who were receiving SGLT2 inhibitors.[36] In a meta-analysis of SGLT2 inhibitor trials, patients receiving GLP-1 receptor agonists experienced additional benefits for CKD progression and cardiovascular disease.[15] In the phase 2 CONFIDENCE trial, finerenone plus empagliflozin treatment yielded greater improvements on albuminuria than either treatment alone.[51] Modelling of the expected benefits on CKD and cardiovascular disease in patients with type 2 diabetes and albuminuria—assuming independent and at least partially additive effects of SGLT2 inhibitors, GLP-1 receptor agonists, and non-steroidal MRAs—suggests that combination treatments using all three classes would provide substantial gains in CKD and cardiovascular event-free survival compared with single or dual therapy.[69] Randomised evidence for using treatment combinations to improve adverse outcomes is being collected in phase 3 trials of aldosterone synthase inhibitors (CKD with albuminuria: NCT06531824; CKD with hypertension: NCT06268873), endothelin receptor antagonists (CKD with albuminuria: NCT06087835), and in an international, multicentre, phase 3, adaptive platform trial (NCT06058585).[70]

Given myriad indications, and complementary benefits, for improving CKD and cardiovascular outcomes across CKD, diabetes, heart failure, and obesity, fixed-dose treatment combinations (polypills) might simplify implementation of novel therapeutics across high-risk, vulnerable, or marginalised populations, particularly in LMICs. The benefits and acceptability of polypills have been widely accepted in managing chronic infectious conditions such as HIV and hepatitis C. In cardiovascular disease prevention, including in subgroups with pre-existing CKD, outcomes were better in some studies when treating with a polypill compared with individual drug components,[71,72] although early results from a systematic review and meta-analysis of 13 trials indicated minimal benefit across a range of cardiovascular diseases at the expense of higher adverse events.[73] In type 2 diabetes, combination treatments of fixed-dose formulations have been associated with improved disease outcomes, with around half of this association mediated through better treatment adherence.[74] However, polypills remain underused because of complexity in the manufacturing process, poor availability, challenges in obtaining regulatory approvals, and prescribing concerns; particularly, the risks of overmedicalisation and the inability to individualise the doses of component drugs.[75] Polypills are yet to be specifically tested to improve CKD progression or kidney failure, but this is worth dedicated study given the potential to improve treatment adherence and to distribute widely in a cost-effective manner.[76]

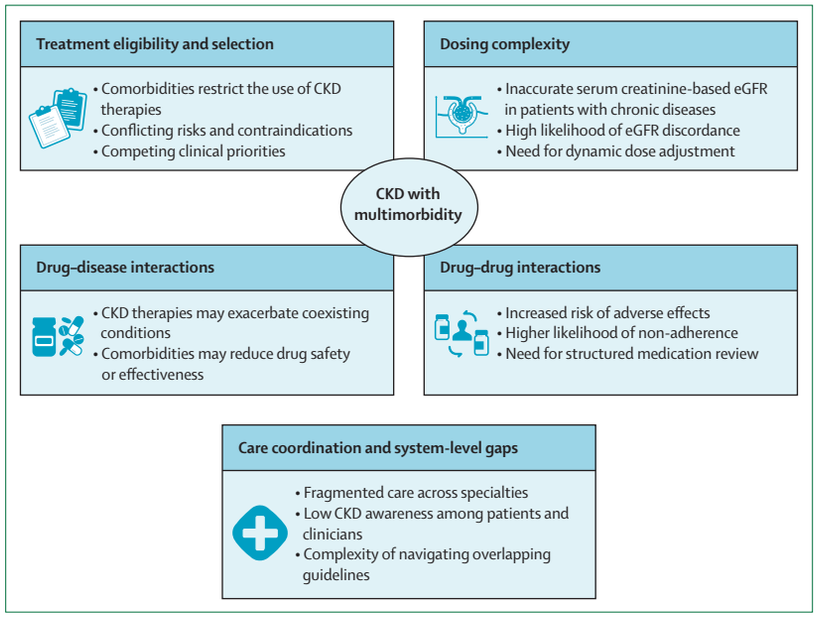

Figure 2: **How multimorbidity complicates CKD management**
CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate.

Challenges for therapeutic decision making in CKD

Despite increasing evidence for a range of novel therapeutics, clinical decision-making in CKD is becoming increasingly complex (figure 2); CKD rarely occurs as an isolated health condition. In a European multicentre observational study of older adults (over 75 years), CKD was present without any other apparent disease in fewer than 1% (20/2252) of individuals.[77] A multicentre observational cohort study of patients across all stages of CKD in the UK identified that 96% (936/978) of participants had two or more long-term conditions including CKD (multimorbidity) and 57% (560/978) had four or more long-term conditions (complex multimorbidity).[78] Although more common in older individuals, multimorbidity is also on the rise in younger individuals (eg, <60 years), particularly among those at higher socioeconomic disadvantage.[79] The literature on multimorbidity is not well developed in paediatric populations, but children with advanced CKD often have coexisting health conditions, including growth and developmental problems, cardiovascular risk factors and disease, and depression.[80–82]

Multimorbidity also contributes to a high prevalence of polypharmacy and frailty among people with CKD. Polypharmacy affects over 80% of all individuals with CKD, and is associated with adverse health outcomes, including CKD progression, kidney failure, and premature death.[83] Frailty is present in 14% to 40% of individuals with non-dialysis CKD, and is associated with a range of adverse health outcomes, including increased health-care use, dialysis, and premature death.[84]

Although management might be streamlined in patients with concordant conditions, such as diabetes,

heart failure, and obesity (cardiovascular-kidney-metabolic [CKM] syndrome), patients with CKD often have discordant health conditions, including musculoskeletal disorders, chronic pain, and mental health conditions.[77,85] Competing or conflicting health-care priorities, a requirement for therapeutic monitoring and lack of incentivisation (particularly in reaching vulnerable or marginalised groups) often render it infeasible for primary health-care providers to deliver some of the proposed medication regimens. Polypharmacy introduces a propensity for drug–drug and disease–drug interactions, lowers adherence with medication regimens, increases complexity in following sick day rules, and increases the likelihood of experiencing treatment-related side-effects.[83,86,87] In a prospective observational study of medical admissions in the UK, 16·5% of admissions resulted from adverse drug reactions, with a substantially higher rate of adverse drug reactions among patients with advanced CKD, multimorbidity, and polypharmacy.[88]

The risk to benefit ratio of new drug therapeutics in CKD among patients with multimorbidity, frailty, and polypharmacy has been underexplored. Dedicated analysis of recent trials of treatments used in CKD, such as SGLT2 inhibitors and GLP-1 receptor agonists, suggest that older patients, or those with multimorbidity and polypharmacy, can expect to derive similar relative benefits and greater absolute benefits from guideline-directed treatments than younger, healthier individuals,[89,90] and benefits seems to outweigh risks, at least for SGLT2 inhibitors.[89] However, there are very sparse trial data in individuals at the highest levels of multimorbidity,[91] as well as concerns over the reliability of frailty assessments in trial settings.[92] The absence of robust safety and efficacy data limits the confidence with which these treatments can be used in frail and multimorbid populations.[92]

Compounding these problems are the risks seen with sarcopenia: a progressive loss of muscle mass, quality, and strength that is observed with increasing age,[93] CKD severity,[94] and multimorbidity (in both HICs and LMICs),[95,96] and associated with adverse cardiovascular outcomes[97] and mortality.[98] Incretin analogues are thought to increase the risk of sarcopenia, particularly in individuals who are already at higher risk,[99] and the risk to benefit balance of potentially exacerbating sarcopenia in favour of improving CKD and cardiovascular outcomes is not known. Sarcopenia might also contribute to adverse drug reactions through uncertainty in the accuracy of kidney function estimates: increasing discordance in kidney function estimates based on creatinine and cystatin C (discussed in the first Series paper)[1,100] increases the risk of spurious overestimation of creatinine-based eGFR, which has been shown in studies of critically ill patients and those with cancer to lead to uncertainty over treatment eligibility, errors in dosing, and increased harms.[101,102]

Due to a paucity of evidence, advice about the prescribing or deprescribing of novel therapeutics for CKD in multimorbidity, frailty, or polypharmacy is both non-specific and contradictory. International guidelines for the evaluation and management of CKD encourage individualised therapeutic decisions for older adults,[5] with potential for very wide variability in practice between prescribers. In 2025, the British Geriatric Society launched clinical guidance on *Pragmatic prescribing to reduce harm for older people with moderate to severe frailty*, encouraging more lenient treatment targets, limiting prescribing, and even deprescribing medications for hypertension, type 2 diabetes, hypercholesterolaemia, and heart failure, although with no specific guidance provided for CKD.[103] In a powerful response from the British Society of Heart Failure, routine limitation to fewer medications was discouraged, recommending instead that "clinicians should consider each patient individually, attempting quadruple therapy where possible and appropriate, individualising dose escalation, and closely monitoring for adverse events while keeping the patient's goals central".[104]

Acknowledging the projected increases in CKD prevalence and the rising burden of multimorbidity in older and younger age groups, the lack of consensus for best use of novel therapeutics and appropriate treatment targets in these complex populations needs to be urgently addressed.

Increasing awareness and recognition of CKD: integrating diagnostic and therapeutic approaches

Although the coexistence of CKD often exists as a modifier of risk and predictor of worse outcomes, the diagnosis of CKD can also be missed due to focus on other conditions.[77] In this section, we outline how infections, autoimmune diseases, multisystem diseases, cancer, cardiovascular diseases, and metabolic diseases contribute to the burden of CKD and its adverse outcomes and how integrated management pathways could improve outcomes for people with CKD.

Infections

The rising incidence of infectious disease—both endemic and pandemic—is a key contributor to the increasing burden of CKD and its complications. Moreover, patients with CKD are uniquely affected by a global increase in infections, as progressive loss of kidney function is an independent risk factor for incident infections, morbidity, and mortality from infectious disease.[105–107] Detailed discussion of the causes and consequences of infection-associated CKD (including hepatitis C[108] and hepatitis B[109]) is beyond the scope of this Series paper but these relationships have been summarised previously.[108,110–113] Here, we highlight some key exemplars of how where and how CKD risk reduction strategies could be better integrated with management of infection.

Viruses

Viral infections such as HIV, SARS-CoV-2, and influenza are associated with adverse outcomes, amplified in those with CKD, and associated with additional risks of AKI and cardiovascular disease through the activation of inflammatory and profibrotic pathways. Data to support the value of vaccination against and treatment of these conditions for prevention of adverse CKD outcomes are accumulating. It is beyond the scope of this Series paper to detail each of these conditions, but we highlight some key findings to facilitate understanding of the value of both preventive and treatment strategies for viral infections.

HIV is the leading global cause of morbidity and mortality from infectious disease, with the greatest prevalence of CKD among people with HIV in west Africa (around 14%).[114] With improvements in efficacy of and access to antiretroviral therapies, HIV has evolved an increasingly chronic course, including a transition away from classic HIV-associated nephropathy towards more heterogeneous forms of CKD, including treatable non-communicable diseases such as diabetic kidney disease.[113,115] Antiretroviral therapies compound pre-existing cardiovascular, kidney, and metabolic diseases by causing substantial weight gain, particularly among Black females.[116] By 2030, it is forecast that 30% of individuals treated with antiretroviral therapy in the USA will have CKD.[117]

People with HIV were excluded from practice-changing trials of SGLT2 inhibitors; however, the randomised evidence suggests that all patients across the CKD spectrum will benefit.[118] Real-world data support the benefits of SGLT2 inhibitors and GLP-1 receptor agonists in reducing hospitalisations and mortality in people with HIV and heart failure, particularly when also living with obesity.[119] GLP-1 receptor agonists are showing promise in the treatment of HIV-associated lipodystrophy,[120] with potential to reduce cardiometabolic comorbidity, including CKD.[121] Yet guidance to treat people with HIV for CKD and cardiovascular outcomes, as in the general population[122] is inadequately implemented: only 8·8% of eligible individuals living in the USA with HIV and type 2 diabetes are prescribed a SGLT2 inhibitor.[123]

Immediate clinical actions include the integration of CKD detection, monitoring, and treatment—aligning with international guidance on detection and management of CKD—within local HIV management protocols.[5,122] Further research is required to establish whether and what means can be used to prevent the development of CKD and other cardiovascular and metabolic conditions among patients treated with antiretroviral therapies.

The COVID-19 pandemic provides a striking example of the implications of respiratory viruses for CKD. Individuals infected with SARS-CoV-2 had more rapid kidney function decline.[124] CKD was among the most common comorbidities in hospitalised patients with SARS-CoV-2, and pre-existing CKD was associated with higher risks of severe AKI, a requirement for kidney replacement therapy and death.[125,126] Influenza, one of the commonest infections globally, is associated with more severe illness and higher rate of complications among people with CKD.[127,128] Prolonged, pro-inflammatory, pro-atherogenic states are observed to persist long after resolution of acute infection and are thought to drive the higher incidence of adverse kidney and cardiovascular events among infected individuals.[129,130]

Prevention of infection through vaccination against SARS-CoV-2 and influenza is a means of improving CKD outcomes. Although immune alteration and persistent low-grade inflammation resulted in diminished vaccine responses against SARS-CoV-2 in patients receiving kidney failure replacement therapy,[131–133] vaccination against SARS-CoV-2 still appeared to reduce dramatically the risks of kidney failure and death among patients with CKD, with greater improvements observed among those who received at least three doses of the vaccine.[134,135] Vaccination against influenza reduces the incidence of infection-related hospitalisation,[128] is associated with a lower rate of incident CKD and kidney failure,[136] and protects against major vascular events, including ischaemic heart disease, stroke, and peripheral vascular disease.[137,138] Annual influenza vaccination is recommended among people with CKD, although uptake is suboptimal,[106] and the potential for benefits beyond direct infection-related consequences is little appreciated.[139]

Immediate clinical actions include encouraging eligible individuals to take up vaccination against relevant infections, maintaining awareness that there are higher risks of developing CKD and its complications after infection, and using infection as an additional trigger to screen for CKD. Further research is required to establish the optimal vaccine dose and delivery schedules, and optimal detection and monitoring strategies for CKD after infections.

Vector-borne infections

Environmental disruption and climate change promote the increased spread of vector-borne diseases and other infections, both in endemic areas and in regions outside their typical ranges.[140,141] Relevant examples are malaria, leptospirosis, schistosomiasis, and tick-borne diseases. Flaviviruses, a group of RNA viruses typically transmitted by arthropod vectors, cause over 400 million infections annually, primarily in densely populated areas in LMIC.[142] Dengue is the most widespread and rapidly growing vector-borne disease, infecting more than 100 million people in tropical and subtropical regions each year. AKI is a common complication in severe disease, with underlying mechanisms that include cytokine storm, endothelial damage, atypical haemolytic uremic syndrome, haemodynamic instability, rhabdomyolysis, and direct kidney injury. Dengue virus reinfection can

lead to more severe outcomes due to viral-specific immunity, potentially increasing the burden of CKD, especially in individuals with previous AKI or pre-existing CKD.[143–145] Although the optimal strategy is prevention of infection (through public health initiatives, infection surveillance, vector control, and vaccine development), prompt treatment of the infection, early detection, and management of AKI might reduce the likelihood or severity of subsequent CKD.[110]

Immediate clinical actions include vigilance for AKI potential after infection, initiating prompt treatment for AKI and establishing local protocols to ensure monitoring and treating for CKD after AKI. Further research is required to establish the optimal processes to detect AKI proactively in the setting of infection (for example, deploying point-of-care blood biomarker tests and urine dipstick to detect glomerular injury) and the optimal treatment strategies to reduce renal injury in the setting of infection.

Autoimmune and multisystem glomerular diseases

Autoimmune and multisystem glomerular diseases are responsible for around 20–25% of cases of CKD leading to kidney failure globally.[146] Major advances in understanding the pathophysiology and evolution in management of glomerular diseases such as IgA nephropathy,[147] antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis[148] and lupus nephritis[149] have been covered in detail elsewhere. A therapeutic strategy common to all is a move away from the administration of systemic immunosuppression with high-dose glucocorticoids in favour of systemic steroid minimisation and a preference for disease-modifying therapies.[147–150]

The TESTING trial in IgA nephropathy showed that systemic administration of high-dose glucocorticoids compared with placebo resulted in a higher rate of serious adverse events, which were primarily infections.[151] In ANCA-associated vasculitis, the PEXIVAS trial showed that reduced-dose versus standard-dose tapering of glucocorticoid therapies was non-inferior for reducing death or kidney failure but resulted in fewer serious infections.[152] Modern regimens for ANCA-associated vasculitis, which avoid high-dose glucocorticoids, are more effective in inducing remission of disease, more likely to prevent recurrent disease, increase recovery of kidney function, and are safer, particularly with a lower rate of infection.[148] There are no large-scale trials yet comparing high-dose versus low-dose steroid regimens for lupus nephritis, but pooled analyses of published trials suggest similar renal response and better safety profiles (particularly fewer infection-related events) in those receiving low-dose glucocorticoids.[153]

Given what we understand about the pathophysiology of AKI, CKD, and cardiovascular disease in the setting of infection, and the potential additional role of steroids in the development of cardiovascular disease,[154] steroid minimisation represents a major advance in the management of glomerular disease and in the prevention of adverse CKD outcomes. Health-care practitioners are encouraged to be vigilant in offering cardiovascular risk-reduction therapies alongside treatment of glomerular diseases, particularly with systemic corticosteroids, in line with current guidance.[146]

Cancer

With the rising population of patients diagnosed with cancer, and improved survival since the introduction of targeted systemic anticancer therapies, there is a growing population of cancer survivors at risk of long-term health problems.[155,156] CKD, cardiovascular disease, diabetes, and obesity commonly coexist in patients with cancer and are mutually exacerbated by cancer, both by shared risk factors and pathophysiology of disease,[157,158] and the off-target effects of cancer treatments.[159–161] From around 5 years after cancer diagnosis, cardiovascular disease may overtake cancer as the leading cause of death: a pattern that varies by cancer type but becomes more prominent with older age.[162] The complex inter-relationship between CKD and cancer and the consequences of cancer treatments has been discussed in detail previously.[163–165] Here, we briefly outline the consequences for CKD of two widely used classes of targeted systemic anticancer therapies—vascular endothelial growth factor system pathway inhibitors and immune-checkpoint inhibitors—and the potential for better recognition and novel therapeutics to improve adverse CKD outcomes.

Vascular endothelial growth factor system pathway inhibitors

Vascular endothelial growth factor system pathway inhibitors are used widely in the treatment of solid organ cancers; however, their use is known to cause proteinuria (20–63%),[160,161] CKD progression,[166] hypertension (up to 80%),[160,161] and heart failure (3–18%).[160,161] Monitoring of proteinuria and blood pressure are recommended during therapy, but primarily to guide ongoing treatment decisions and not as a prompt to consider CKD and cardiovascular risk-reduction strategies.

Immune checkpoint inhibitors

Immune checkpoint inhibitors have markedly improved survival for a range of cancer types; however, their use is associated with immune checkpoint inhibitor-associated AKI (typically a delayed presentation of acute tubulointerstitial nephritis) in around 1–5% of individuals according to the immune checkpoint inhibitor regimen, and occasionally with glomerular disease.[167] Although most individuals reach partial or complete recovery of kidney function with interruption of treatment, corticosteroid therapy, or (rarely) steroid-sparing immunosuppression, observational data indicate that immune checkpoint inhibitor-treated individuals commonly develop CKD: around 13% within 1 year of

treatment and around 20% within 5 years.[167] Corticosteroid treatment might compound cardiovascular and metabolic risk factors and risk of adverse CKD and cardiovascular outcomes.

Use of novel therapeutics for CKD in patients with cancer

Although randomised and robust safety data are scarce, observational evidence suggests similar benefits for CKD and cardiovascular outcomes in patients with cancer as in general populations.[168–172] Subgroup analysis of the FIDELIO-DKD and FIGARO-DKD trials suggest that finerenone is effective in reducing albuminuria in patients with a history of cancer, with similar rates of adverse events observed between subgroups with and without previous cancer at baseline.[173]

Immediate clinical actions include vigilance for the development of CKD alongside cancer treatment, acknowledging the limitations of creatinine-based eGFR for detecting eGFR decline in the context of progressive sarcopenia (discussed in the first Series paper).[1] Novel therapeutics for CKD should be introduced when clinically appropriate in the treatment course to prevent the rising burden of adverse outcomes in cancer survivors. Among patients with cancer, and especially those treated with targeted systemic anticancer therapies, further research is required to determine the role of novel therapeutics for CKD in the prevention of AKI, CKD, or cardiometabolic risk factors in people without established disease; the optimal timing of introducing novel therapeutics for CKD in patients with established disease; and to deliver robust safety data in this setting.

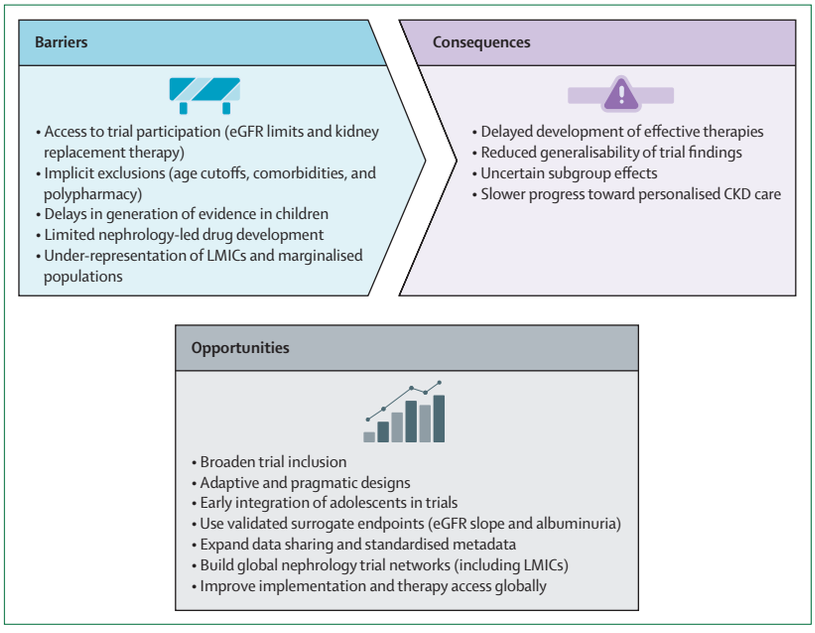

Figure 3: **Effect of CKD on evidence generation and opportunities for improvement**
CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. LMICs=low-income and-middle income countries.

CKM syndrome

There have been efforts already to streamline therapeutic approaches across cardiovascular diseases, metabolic diseases (obesity and type 2 diabetes), and CKD through the 2023 American Heart Association CKM syndrome framework.[174] The central hypothesis is that CKM syndrome originates primarily from excess or dysfunctional adipose tissue, or both, leading to inflammation, oxidative stress, insulin resistance, and vascular dysfunction, and causing a rise in metabolic risk factors, CKD progression, and cardiovascular disease.[175] Lifestyle interventions remain foundational in maintaining kidney health and preventing CKD, but have inadequately addressed the rising problem of CKM diseases. Novel therapeutics have a range of indications across the CKM spectrum to improve these outcomes.

Although the CKM approach introduces concerns about diluting diagnostic specificity, and its criteria are challenging to apply even in well phenotyped research cohorts,[176] the CKM framework has the potential to advance care in patients with CKD. Particularly in the early stages of disease, the CKM framework might improve recognition of CKD as an important and treatable chronic disease, and simplifying guidance on screening and early detection (eg, annual albuminuria testing across all CKM diseases), risk stratification (eg, using risk scores that incorporate eGFR and albuminuria),[1] and treatment.[174,175,177] Numerous groups in the USA, Europe, and internationally are developing shared guidelines, with publications expected in 2026–2028, which aim to help minimise the challenges of navigating complex clinical guidance across diseases with similar therapeutic approaches and proven benefit.

Considerations and recommendations for future evidence generation

Although ongoing developments in CKD therapeutics are welcome, if we fail to acknowledge the clinical complexity of CKD populations in the developing evidence, there will continue to be downstream consequences for clinical guidance and implementation strategies (figure 3). Pivotal trials of novel therapeutics for CKD do not adequately represent the communities they seek to treat (panel 1). The generalisability of trial evidence to many patients with CKD, including older individuals, females, and those living with high levels of multimorbidity and frailty, is therefore uncertain. Although there are broader efforts to improve efficiency and diversity of future clinical trials, substantial additional knowledge can be gained by aggregating and re-evaluating existing data. Improved access to individual-participant level trial data offers flexibility and power to assess subgroup-specific effects across broad populations.[40,90,183–185] By developing and mandating the publication of minimum trial metadata, detection of subgroup effects for both efficacy and safety could be

substantially and efficiently improved, advancing the personalisation of CKD care.

There remains the critical omission of under-represented populations from clinical trial spaces. This omission is particularly stark for continental African populations and other LMICs, where the absence of local data to inform policy and to advocate for access to therapies, the frank unaffordability of many drugs, and the ethical concerns of minimal post-trial access, substantially hinder downstream benefits. In continental African populations, where novel therapeutics mostly remain out of reach, there is little direct experience with these drugs, compromising clinical training and causing considerable uncertainty about efficacy and safety in local populations. There is an unresolved tension between the challenges of delivering trials in LMIC settings, where potential sites might not fulfil the usual requirements for trials and have not been capacitated to participate, and excluded populations facing the highest risk. Currently, major clinical trial networks and pharmaceutical research and development organisations are based in HICs, where scientific and economic strategies might not reflect the interests of LMICs. There should be a balance of guaranteeing that novel therapeutics are appropriately prioritised, tested, and made available at fair market value for LMICs and ensuring that pharmaceutical development remains financially viable. Where responsibility lies to resolve this tension remains uncertain.

There is a recognised delay or absence of evidence reaching children and adolescents in all settings,[186] with distinct ethical, moral, legal, and biological considerations. The exclusion of children in clinical trials evaluating the use of SGLT2 inhibitors in CKD means that high-quality trial data for children are expected to be published 13 years after the adult data.[186,187] Many inherited or congenital paediatric kidney diseases are ultra-rare, adding to logistical challenges and costs of recruitment to clinical trials. Despite these barriers, the recent ground-breaking discovery of nephron autoantibodies in podocytopathies showed the benefits of including children, with a far greater frequency of antibody positivity seen in children.[188] Considering children early in trial design, with the use of integrated protocols that allow better inclusion, especially for post-pubertal teenagers who can consent and might biologically be sufficiently similar to the adult population, could speed up the evidence generation for this group.

Conclusion

There is a large and growing burden of CKD worldwide, with major implications for human health and the global economy. In the past decade, major advances in understanding the pathophysiology of disease and individualised diagnosis, through improvements in biomarkers, kidney biopsy, genetic testing, and multiomics approaches,[1] have led to an expanding evidence base for mechanism-targeted treatments to improve CKD outcomes;[2] however, much work is still to

Panel 1: Outstanding questions and key research priorities

Representativeness of chronic kidney disease (CKD) populations in CKD trials

- Key trials of CKD therapeutics do not adequately represent the populations they seek to treat
- Trials commonly recruit from specialist settings in high-income countries (HICs), rather than primary or general care and low-income and middle-income countries (LMICs), where most patients with CKD exist
- Trial participants are typically younger, less often female, and have lower levels of multimorbidity than in community settings
- Exclusions might be explicit, implicit, or subjective
- Serious adverse event rates are typically lower in trials than in community settings

Representation of patients with CKD in trials of other conditions

- Low representation of patients with advanced CKD, and those with kidney failure with or without replacement therapy are almost absent, across trials for other chronic medical conditions, including heart failure, cancer, and infections

Opportunities for improvement

- Ongoing efforts to improve trial efficiency, pragmatic, decentralised delivery, and representativeness
- Improved confidence in surrogate markers of CKD progression and kidney failure (eGFR slope,[178] change in albuminuria,[179] or a composite of both measures[180]) offer opportunities to identify off-target therapeutic benefits and harms for CKD progression
- Collaborative consortia[181] and data-sharing platforms[182] have improved access to individual-participant level data and offer flexibility and power to assess subgroup-specific effects across broad populations

Key research priorities

- Key therapeutic gaps and target populations are highlighted in the table
- Improve representation in LMICs and in under-studied, marginalised, and vulnerable populations in HICs
- Evidence for novel CKD therapeutics in children
- Evidence to improve cardiovascular disease outcomes in patients with advanced CKD and kidney failure
- Integrate surrogate markers of CKD progression in non-CKD trials
- Approaches to CKD prevention in populations at high risk such as those with cancer and infections
- Design standard set of mandatory trial metadata (eg, age, sex, comorbidity count, and baseline eGFR subgroups and their interactions) to facilitate secondary meta-analysis for subgroup effects

Panel 2: **Series recommendations**

Clinical

- Integrate CKD detection, screening, monitoring, and treatment for populations at high-risk (eg, pregnancy, cancer, infections, autoimmune, multisystem, and cardiometabolic disease) in local or regional care pathways
- Recognise albuminuria as a strong, independent, and modifiable risk factor for adverse CKD and cardiovascular outcomes even when eGFR appears normal
- Prioritise early, combination treatment of CKD where appropriate to prevent adverse CKD and cardiovascular outcomes: individualised decisions and application of clinical judgement remain necessary for complex patients

Research

- Acknowledge heterogeneity of CKD populations in research, considering demographic and clinical characteristics, pathophysiology of CKD, and geographical distribution
- Integrate consideration of sex differences to the design, reporting, and review of research as default
- Report subgroup metadata to facilitate meta-analysis and maximise use of existing research

be done and we have made six key recommendations in panel 2.

CKD remains underdiagnosed, particularly in LMICs, where inadequate health system capacity limits access to basic kidney testing and advanced diagnostics.[1] With the advances in novel CKD therapeutics, population-wide CKD screening with eGFR and albuminuria is cost-effective and can reduce the lifetime risk of kidney replacement therapy and cardiovascular disease, but needs to be implemented and actioned more effectively, particularly in populations at high risk.

The complexity of CKD has been under-appreciated in clinical practice and in research. Key physiological differences between females and males, that serve to optimise reproduction, create meaningful differences in the risk factors, presentation, progression, and response to treatment in CKD.[2] Females remain under-represented in preclinical and clinical research, limiting understanding of sex-specific mechanisms, and clinical guidelines largely ignore sex-specific differences with implications for treatment harms. Systematic integration of sex differences into CKD education programmes, individual attention to the design, reporting, and review of research, and organisation-level responsibility for integrating sex considerations into clinical guidance and health-care policy, will help to advance models of CKD care.

CKD commonly complicates the management of other physiological states and diseases (including pregnancy, cancer, infection, autoimmune and multisystem diseases, and cardiometabolic conditions). However, this complexity offers yet untapped opportunities to integrate CKD prevention, screening, diagnosis, and treatment, actions that could be implemented immediately within relevant local and regional care pathways. There is both biological plausibility and adequate evidence to support the use of novel CKD therapeutics across a much broader range of conditions than guidelines currently specify, with substantial potential to streamline CKD care and improve population health.

Finally, current evidence and clinical guidance inadequately account for high levels of multimorbidity, polypharmacy, and frailty in CKD: treatment recommendations in these populations are non-specific or contradictory, and complex treatment and monitoring regimens create real implementation challenges in non-specialist settings.

Formalising a shared and more inclusive research agenda that acknowledges the heterogeneity of patients with CKD across pathophysiology, demographic, and clinical characteristics (including sex, gender, age, and medical history), and geographical region would be expected to improve the understanding of CKD epidemiology, targeted therapeutic development, specificity of clinical guidance, and the personalisation of CKD care.

Contributors

JSL and AL conceptualised the Series theme and invited the authors. JSL and AL conceptualised this Series paper, which was then discussed with all authors and agreed upon. JSL wrote the first draft of the manuscript. All authors contributed to writing—review and editing via improvements to subsections of the manuscript. Figures were conceptualised by JSL, AL, AŠ, and LZ and created by LZ with the support of graphical artists. The table was collated by JSL. Each iteration of the paper was reviewed and discussed by all authors who all helped in drafting the response to the reviewers, revision, and approval of the final manuscript.

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