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Management of non-dialysis dependent chronic kidney disease: A practical approach for clinicians

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Abstract

Chronic kidney disease (CKD) affects approximately 10% of the global population and represents a major health challenge with significant cardiovascular morbidity and mortality. This review provides an update on evidence-based management strategies for non-dialysis-dependent CKD. Key advances include the widespread adoption of sodium-glucose cotransporter-2 (SGLT2) inhibitors across the CKD spectrum, introduction of non-steroidal mineralocorticoid receptor antagonists such as finerenone, and refined approaches to CKD-associated complications, including anaemia and mineral bone disorders. Contemporary management emphasises early detection through systematic screening, aggressive cardiovascular risk modification, combination nephroprotective therapies, and timely preparation for kidney replacement therapy. The integration of novel therapeutic agents with established treatments offers unprecedented opportunities to slow disease progression and improve patient outcomes through multidisciplinary, team-based care approaches.

Key words: chronic kidney disease, SGLT2 inhibitors, nephroprotection, cardiovascular risk, kidney replacement therapy

Introduction

Chronic kidney disease (CKD) represents one of the most significant global health challenges, affecting approximately 850 million people worldwide with a prevalence ranging from 8-16% globally.[1,2] This burden translates to a 2-4-fold increased mortality risk, primarily attributed to cardiovascular complications and progressive kidney disease. The situation is particularly concerning in regions like Sri Lanka, which faces both traditional CKD and chronic kidney disease of unknown aetiology (CKDu), with CKDu prevalence in the North Central Province reaching 15.1% to 22.9%.[1]

The evolving landscape of CKD management emphasises early identification of high-risk patients, implementation of evidence-based management strategies, establishment of clear referral patterns, and ultimately reducing progression to end-stage kidney disease (ESKD) while minimising mortality.[3] This comprehensive approach requires a thorough understanding of current diagnostic criteria, risk stratification methods, therapeutic interventions, and optimal timing for specialist referral.

Diagnostic framework and risk stratification

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define CKD as abnormalities of kidney structure or function present for a minimum of three months with health implications.[4,5] The diagnostic framework employs a comprehensive CGA classification system based on Cause, Glomerular filtration rate (GFR) category (G1-G5), and Albuminuria category (A1-A3). This systematic approach enables clinicians to accurately categorise patients and implement appropriate management strategies based on individual risk profiles (Figure 1).

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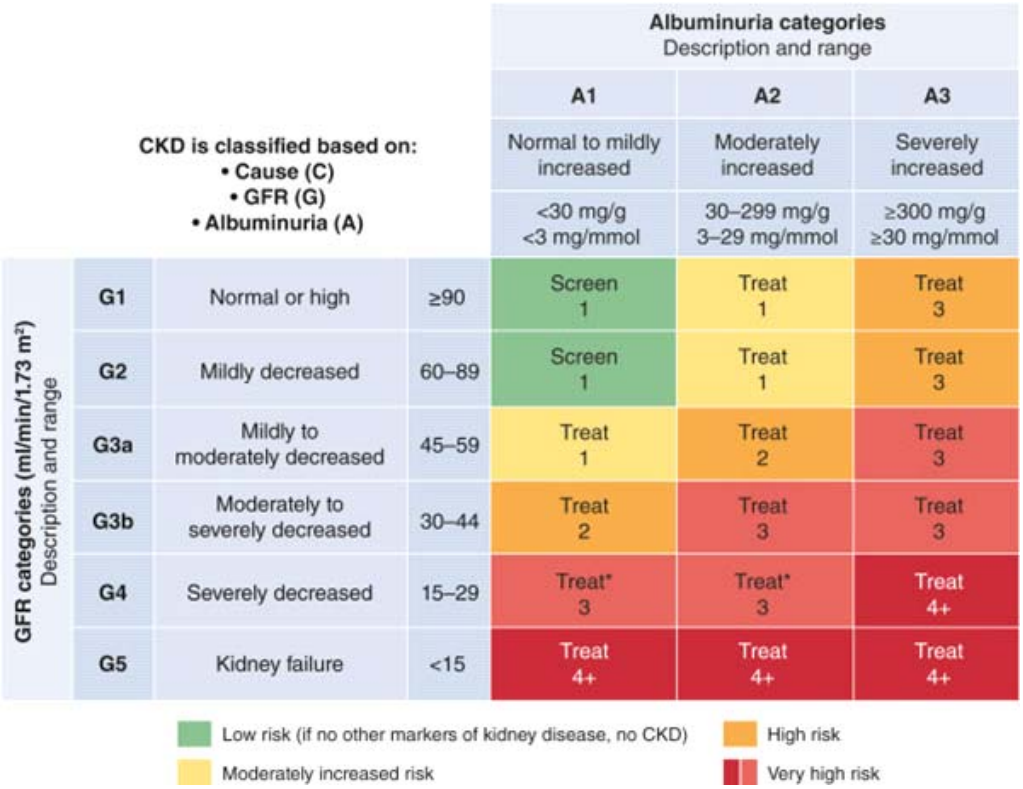

Figure 1. CKD classification and risk stratification (CGA System).

Modern CKD screening should target high-risk populations, including patients with diabetes mellitus, hypertension, cardiovascular disease, family history of kidney disease, individuals over 60 years, high-prevalence ethnic groups, and those with a history of acute kidney injury.[4] The screening protocol encompasses serum creatinine with estimated GFR (eGFR) calculation, urine albumin-to-creatinine ratio measurement, comprehensive urinalysis, and blood pressure assessment. For patients with diabetes or hypertension, annual screening is recommended to facilitate early detection and intervention.[5]

Risk stratification extends beyond simple GFR categorisation to include progression risk assessment. Rapid progression is defined by eGFR decline exceeding 5 mL/min/1.73m^2 per year, persistent albuminuria greater than 300 mg/g despite ACE inhibitor or ARB therapy, poorly controlled diabetes or hypertension, cardiovascular comorbidities, and recurrent acute kidney injury episodes.[4] For patients with CKD stages G3-G5, utilising validated risk equations such as the Kidney Failure Risk Equation (KFRE) provides valuable prognostic information, though individualised assessment remains the gold standard.[6]

Blood pressure management and Renin-Angiotensin system inhibition

Blood pressure control remains the cornerstone of CKD management, with current KDIGO recommendations targeting a blood pressure below 130/80 mmHg, with consideration of a systolic target below 120 mmHg if tolerated.[7,8] ACE inhibitors or ARBs represent first-line treatment due to proven renoprotective effects beyond blood pressure reduction. These agents reduce intraglomerular pressure, decrease proteinuria, and slow disease progression through mechanisms independent of their antihypertensive effects.[7] (Table 1).

When initiating ACE inhibitor or ARB therapy, clinicians must carefully monitor serum creatinine and potassium levels, with up to 30% increases in creatinine considered acceptable if clinically stable.[7] Follow-up investigations should be performed 2-4 weeks after initiation to ensure therapeutic safety. The goal is to achieve maximum tolerated doses to optimise renoprotective benefits while maintaining patient safety.

Table 1. Contemporary nephroprotective therapies in CKD

Agent Class	Examples	Mechanism	eGFR Threshold	Key Benefits	Monitoring
ACE Inhibitors/ ARBs	Lisinopril, Losartan	RAS blockade	Any eGFR	BP reduction, proteinuria reduction	Serum creatinine, Serum K^+ at 2-4 weeks
SGLT2 Inhibitors	Empagliflozin, Dapagliflozin	Glucose/ sodium transport	≥20 mL/min/ 1.73m^2	Renal/CV protection	eGFR, volume status
MRA (Non-steroidal)	Finerenone	Selective MR antagonism	≥25 mL/min/ 1.73m^2	Anti-inflammatory/ fibrotic	Serum K^+ at 2-4 weeks
GLP-1 RAs	Semaglutide, Liraglutide	Incretin pathway	Any eGFR	Weight reduction,CV protection, glycaemic control	Hypoglycemia, GI effects

Revolutionary impact of SGLT2 inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have fundamentally transformed CKD management, particularly in diabetic kidney disease.[9] These agents exert renoprotective effects through multiple mechanisms, including reduced intraglomerular pressure, decreased hyperfiltration and albuminuria, anti-inflammatory and anti-fibrotic effects, and beneficial metabolic effects. SGLT2 inhibitors can be initiated when eGFR is ≥20 mL/min/1.73 m^2 and should be continued even if eGFR falls below 20 mL/min/1.73 m^2 after initiation, demonstrating sustained benefit across the CKD spectrum.[9]

The evidence base for SGLT2 inhibitors is robust and compelling. The CREDENCE trial demonstrated a 30% relative risk reduction in renal outcomes,[10] while the DAPA-CKD study showed a 39% reduction in the primary endpoint of sustained eGFR decline, end-stage kidney disease, or death from renal or cardiovascular causes.[11] The EMPA-KIDNEY trial further substantiated these findings with a 28% reduction in kidney disease progression,[12] establishing SGLT2 inhibitors as essential therapeutic agents across the CKD spectrum, regardless of diabetes status.

Nonsteroidal mineralocorticoid receptor antagonists

Finerenone represents a significant advancement in CKD therapeutics as a selective, nonsteroidal mineralocorticoid receptor antagonist.[13] This agent provides anti-inflammatory and anti-fibrotic effects with lower hyperkalaemia risk compared to traditional steroidal mineralocorticoid receptor antagonists. Finerenone can be initiated at 10mg daily when eGFR is ≥25 mL/min/1.73m^2 and serum potassium is ≤4.8 mmol/L, with potassium monitoring required after 2-4 weeks.[13]

The clinical evidence supporting finerenone is substantial. The FIDELIO-DKD trial demonstrated an 18% reduction in kidney outcomes,[13] while the FIGARO-DKD study showed a 13% reduction in cardiovascular outcomes.[14] Finerenone provides additive benefits to ACE inhibitor/ARB therapy and can be safely combined with SGLT2 inhibitors, offering clinicians powerful combination therapy approaches for high-risk patients.

Comprehensive metabolic management

Glycaemic control remains crucial in diabetic kidney disease, with individualised HbA1c targets around 7.0% for most patients.[9] The integration of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as semaglutide provides additional cardiorenal protection beyond glycaemic control.[15] These agents offer weight management benefits, cardiovascular risk reduction, and potential renoprotective effects, making them valuable therapeutic additions.

Lifestyle modifications play equally essential roles in CKD management. Sodium restriction to less than 2g daily (equivalent to less than 5g salt daily) helps control blood pressure and reduce cardiovascular risk.[7] Moderate protein restriction to 0.8g/kg/day may slow progression in advanced CKD while avoiding malnutrition.[4] Weight management and regular physical activity contribute to overall cardiovascular health and may slow CKD progression through multiple mechanisms.[4]

Management of CKD-associated complications

Anaemia

CKD-associated anaemia typically develops when eGFR falls below 30 mL/min/1.73m^2 and requires systematic evaluation, including iron studies (ferritin and transferrin saturation), exclusion of other causes of anaemia, and consideration of erythropoietin deficiency.[16] The treatment approach prioritises iron repletion with target ferritin levels above 100 ng/mL and transferrin saturation above 20%. Intravenous iron is preferred in advanced CKD due to superior efficacy compared to oral preparations[16] (Table 2).

Erythropoiesis-stimulating agent (ESA) therapy should be considered when haemoglobin level falls below 10 g/dL after adequate iron repletion, with target haemoglobin levels maintained between 10-11.5 g/dL to avoid potential cardiovascular complications associated with higher targets.[16] Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) such as roxadustat represent newer therapeutic options that stimulate endogenous erythropoietin production, enhance iron utilisation, and may offer cardiovascular benefits compared to traditional ESAs.[16]

Chronic kidney disease-mineral and bone disorder

CKD-mineral and bone disorder (CKD-MBD) requires regular monitoring with calcium and phosphate levels assessed every 3-6 months, parathyroid hormone (PTH) levels every 6-12 months, and 25-hydroxyvitamin D levels assessed annually.[17] Management involves dietary phosphate restriction to 800-1000 mg daily, correction of vitamin D deficiency, and targeted therapy for elevated PTH levels using calcitriol or vitamin D analogues in hypocalcaemic patients.[17]

When phosphate levels become elevated, phosphate binders are indicated, with clinicians choosing between calcium-based and non-calcium-based options based on individual patient factors.[17] The decision requires careful balance between fracture risk reduction and prevention of vascular calcification, with non-calcium-based binders often preferred in patients with concurrent hypercalcemia or evidence of vascular calcification.

Table 2. Management of CKD Complications

Complication	*Screening/Monitoring*	*Treatment targets*	*Therapeutic options*
Anaemia	Haemoglobin, serum ferritin, TSAT when eGFR <30	Hb 10-11.5 g/dL, Ferritin >100 ng/mL	Iron supplementation, ESAs, HIF-PHIs
CKD-MBD	Ca/PO^4 q3-6mo, PTH q6-12mo, 25(OH)D annually	PO4 <4.5 mg/dL, PTH 2-9×ULN	Phosphate binders, vitamin D analogues
Metabolic acidosis	Serum bicarbonate	Bicarbonate ≥ 22 mmol/L	Sodium bicarbonate, Veverimer
Cardiovascular risk	BP, lipids, diabetes control	BP<130/80 mmHg, individualized targets	Statins, antihypertensives, diabetes management

Metabolic Acidosis

Metabolic acidosis correction offers multiple benefits, including slowing eGFR decline, improving nutritional status, reducing bone demineralisation, and decreasing hyperkalaemia risk.[18] The therapeutic target is serum bicarbonate levels ≥22 mmol/L, typically achieved through sodium bicarbonate supplementation at doses of 600 mg administered as 1-2 tablets twice to three times daily. Alternative options include sodium citrate solution, though clinicians must monitor for volume overload and worsening hypertension. Newer agents like veverimer offer sodium-free alkali therapy advantages when available.[18]

Advanced CKD management and preparation for kidney replacement therapy

As CKD progresses to stages G4-G5, management becomes increasingly complex, requiring attention to multiple complications while preparing patients for potential kidney replacement therapy (KRT).[4] Conservative management strategies become crucial, including careful medication dose adjustments based on kidney function, avoidance of nephrotoxic agents, and minimisation of contrast exposure to prevent further kidney injury.

Prevention of acute kidney injury is paramount through the implementation of "sick day" protocols (in which metformin, SGLT2 inhibitors, and diuretics are temporarily discontinued when patients develop vomiting, diarrhoea, and/or loss of appetite), volume optimisation during hospitalisations, and avoidance of prolonged fasting periods. Symptom management addressing pruritus, sleep disturbances, and muscle cramps improves quality of life and patient comfort.[19] Vaccination strategies should include influenza, pneumococcal, hepatitis B, and COVID-19 vaccines to prevent infections that could precipitate acute deterioration.[4]

Planning for kidney failure requires comprehensive patient education regarding treatment options, including in-center haemodialysis, home dialysis modalities (peritoneal dialysis and home haemodialysis), transplantation with emphasis on pre-emptive transplantation when possible, and conservative kidney management for appropriate patients.[4] Conservative management represents a valid option for frail elderly patients, focusing on symptom management, prognosis discussions, and palliative care involvement when appropriate.

Preparation steps for KRT include vascular access planning when eGFR falls below 30 mL/min/1.73 m^2, transplant evaluation for eligible candidates, advanced care planning discussions, and conversations about goals of care to ensure that patient preferences are respected throughout the disease trajectory.[4]

Optimal referral patterns and multidisciplinary care

Timely nephrology referral significantly impacts patient outcomes,[20] with clear indications including eGFR below 30mL/min/1.73m^2 (stages G4-G5), rapid GFR decline exceeding 5 mL/min/1.73m^2 per year, significant albuminuria despite ACE inhibitor/ARB therapy, persistent haematuria after urological evaluation, resistant hypertension, recurrent or severe acute kidney injury, complex electrolyte disorders, and suspected glomerular or genetic kidney diseases[4] (Table 3).

Early referral provides numerous benefits, including improved preparation for kidney replacement therapy (KRT), a higher likelihood of pre-emptive transplantation, reduced hospitalisation rates and mortality, more effective management of complications, and enhanced shared decision-making.[20] The optimal care model involves shared responsibility between primary care physicians managing cardiovascular risk factors and screening, and nephrologists providing specialised care and KRT preparation, with regular communication and clear delineation of responsibilities.[3]

Clinical case applications

Contemporary CKD management can be illustrated through representative clinical scenarios. 1) A 68-year-old woman with asymptomatic CKD G3a (eGFR 58 mL/min/1.73m^2) and A2 albuminuria (150 mg/g) in the setting of diabetes and hypertension represents a high-risk patient requiring aggressive blood pressure management with ACE inhibitor/ARB therapy, glycaemic optimisation potentially including SGLT2 inhibitor therapy, and lifestyle modifications including sodium and protein restriction.

2) A 58-year-old man with rapidly progressive diabetic kidney disease (eGFR decline from 55 to 44 mL/min/1.73m^2 over 18 months with persistent albuminuria of 850 mg/g) exemplifies the very high-risk category requiring combination therapy with maximised ACE inhibitor/ARB therapy, SGLT2 inhibitor initiation, consideration of finerenone therapy, and prompt nephrology referral for specialised management.

3) Advanced CKD management is demonstrated by a 72-year-old man with stage G4 CKD experiencing fatigue, poor appetite, and muscle cramps, requiring comprehensive management of anaemia, mineral bone disorder, metabolic acidosis, and preparation for kidney replacement therapy while addressing multiple comorbidities and symptom management needs.

Table 3. Indications for nephrology referral

Indication	*Criteria*	*Rationale*
Advanced CKD (G4-G5)	eGFR <30 mL/min/1.73m^2	KRT preparation, complication management
Rapid progression	eGFR decline >5 mL/min/1.73m^2 per year	Specialised intervention, cause evaluation
Significant proteinuria	ACR >300 mg/g despite ACEi/ARB	Advanced nephroprotective strategies
Persistent haematuria	After urological evaluation	Glomerular disease evaluation
Resistant hypertension	Uncontrolled despite 3+ agents	Specialised BP management
Recurrent AKI	Multiple episodes or severe AKI	Prevention strategies, cause evaluation
Complex electrolytes	Difficult to manage disorders	Specialised expertise required
Suspected GN/Genetic diseases	Clinical suspicion	Diagnosis and specific treatment

Future directions and emerging therapies

The landscape of CKD management continues to evolve with emerging therapeutic options and a refined understanding of disease mechanisms. Novel agents targeting inflammatory pathways, preventing fibrosis, and addressing metabolic dysfunction show promise in clinical trials. The concept of precision medicine in CKD management, incorporating genetic factors, biomarkers, and individual risk profiles, may allow for more personalised therapeutic approaches in the future.[5]

Artificial intelligence and machine learning applications in CKD risk prediction, progression modelling, and treatment optimisation represent exciting frontiers that may enhance clinical decision-making and improve patient outcomes. Telemedicine and remote monitoring technologies offer opportunities to improve access to specialised care and enhance patient engagement in disease management.

Conclusion

The management of non-dialysis-dependent chronic kidney disease has been revolutionised by advances in understanding disease mechanisms, refined risk stratification methods, and the introduction of highly effective therapeutic agents.[4] Early detection through systematic screening of high-risk populations enables timely intervention that can dramatically alter the disease trajectory. The evidence-based treatment approach centred on ACE inhibitor/ARB therapy[7] has been enhanced by the introduction of SGLT2 inhibitors[10,11,12] and nonsteroidal mineralocorticoid receptor antagonists,[13,14] providing clinicians with powerful combination therapies that offer additive renoprotective benefits.

The comprehensive management approach addressing cardiovascular risk factors, metabolic complications, and CKD-associated disorders requires a multidisciplinary team-based approach with clear communication between primary care physicians and nephrologists.[3] Early referral and preparation for kidney replacement therapy, when appropriate, significantly improve patient outcomes and quality of life.[20]

Understanding of these contemporary approaches to CKD management is an essential clinical competency given the high prevalence of kidney disease and its significant impact on patient morbidity and mortality. The integration of novel therapeutic agents with established treatments, combined with patient education and shared decision-making, offers unprecedented opportunities to slow disease progression and improve outcomes for patients with chronic kidney disease.

Author declaration

Conflict of interests

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SDS is responsible for conception and design, data collection, analysis and interpretation and manuscript preparation.

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