# Revolutionising CKD Care: Novel Treatment Paradigms and Cutting-edge Strategies

**Dinesh Khullar[1*], Narinder Pal Singh[1], Anish Kumar Gupta[1]**

[1]Department of Nephrology and Renal Transplant Medicine, Max Super Speciality Hospital, Saket, New Delhi

**Correspondence:**

**Dinesh Khullar**

Max Super Speciality Hospital, Saket, New Delhi

E-mail: drdineshkhullar@gmail.com

**Abstract:** Chronic Kidney Disease (CKD) represents a public health crisis globally. New therapeutic horizons in CKD management encompass a diverse array of options for a more holistic and personalised approach. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors exhibit promising results in preserving kidney function and mitigating cardiovascular risks in patients with or without diabetes. Non-steroidal selective Mineralocorticoid Receptor Antagonists (MRA) present targeted strategies for CKD management. Glucagon-like peptide-1 (GLP-1) receptor agonists offer innovative approaches for glycaemic control and complication reduction. Endothelin Receptor Antagonists contribute to CKD care by modulating endothelial function and reducing kidney damage. Aldosterone synthase inhibitors offer a unique angle, targeting aldosterone production to manage CKD-related complications. Additionally, hypoxia-inducible factor (HIF) inhibitors represent a cutting-edge therapeutic class, addressing the hypoxic conditions associated with kidney damage. This diverse range of advancements underscores a transformative shift towards more personalised and effective CKD treatments, providing newfound optimism for improved patient outcomes. Beyond providing evidence-based insights into recent therapeutic advancements in CKD, this review also delineates contemporary treatment guidelines for CKD. It underscores the imperative for holistic strategies to enhance outcomes for individuals grappling with this complex condition.

**Key words:** Chronic kidney disease, Sodium-glucose cotransporter-2 inhibitors, Hypoxia-inducible factor inhibitors, Glucagon-like peptide-1 receptor agonists, Mineralocorticoid receptor antagonists

## Introduction

Chronic Kidney Disease (CKD) is a significant global public health concern, impacting around 10% of the worldwide population and posing substantial challenges in terms of health and mortality.[1] Individuals with CKD face heightened risks of kidney failure, cardiovascular diseases, acute kidney injury, heart failure and re-hospitalisation. Despite its considerable impact, CKD often goes unrecognised by both patients and healthcare providers. It commonly coexists with hypertension and diabetes. The causes of CKD are diverse, involving genetic factors, drug-related adverse effects, and autoimmune processes.[2] In specific regions, such as Central America, Sri Lanka, Egypt and Central India, clusters of CKD cases with unknown causes have been identified.[3] CKD is a progressive, long-term condition marked by a gradual decline in kidney function. Diagnosis relies on more than serum creatinine levels, as they lack sensitivity in assessing glomerular filtration rate (GFR). An accurate CKD diagnosis involves evaluating factors like estimated GFR, urinalysis and albuminuria quantification. CKD is indicated by an eGFR below

60 mL/min/1.73 $m^2$, even without apparent kidney damage and confirmation of kidney damage is necessary for those with an eGFR ≥60 mL/min/1.73 $m^2$. The condition requires persistence for over three months for an accurate diagnosis.[4]

The demand for innovative CKD therapies arises from the limitations of current treatments, the progressive nature of the disease and the desire for more effective, targeted drug delivery and patient-centred interventions. Innovations in medical science, offer promising avenues for developing therapies that can minimise side effects, improve cost-effectiveness and provide tailored solutions to individual patients. While angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are recognised as standard treatments in CKD management, their efficacy can be limited. These medications primarily target the Renin-angiotensin-aldosterone system (RAAS), reducing proteinuria and managing blood pressure. However, they may not provide comprehensive renoprotection, as CKD involves diverse pathophysiological pathways. Responses to ACEIs and ARBs vary and some patients experience a continued decline in kidney function despite treatment. Adverse effects, tolerability issues and controversies surrounding dual blockade further contribute to their limitations. This review describes novel treatment paradigms along with contemporary treatment guidelines for CKD.

## Sodium-glucose cotransporter-2 (SGLT-2) inhibitors

Over the last decade, a significant breakthrough in managing CKD has emerged with the discovery of the robust protective effects of SGLT-2 inhibitors on both the heart and kidneys, irrespective of diabetes status. Recent trials, including CREDENCE, DAPA-CKD and EMPA-KIDNEY, revealed an approximately 30% reduction in the risk of various kidney outcomes, even in patients with baseline estimated GFR as low as 20 mL/min/1.73 m2.[5-8] Notably, these trials were concluded ahead of schedule due to meeting pre-defined efficacy criteria, demonstrating the compelling benefits of SGLT-2 inhibitors (Table 1).

| Parameters | CREDENCE[5] | DAPA-CKD[6,7] | EMPA-KIDNEY[8] |
|---|---|---|---|
| **N** | 4464 | 4304 | 6609 |
| **eGFR related Inclusion criteria** | eGFR 30 to <90 ml/min and ACR>300 to 5000 mg/g | eGFR 25 to 75 ml/min and ACR 200 to 5000 mg/g | eGFR >20 to <45 ml/min OR eGFR >45 to <90 ml/min and ACR >200 mg/g |
| **Investigational agent** | Canagliflozin 100 mg OD | Dapagliflozin 100 mg OD | Empagliflozin 10 mg OD |
| **Median follow-up duration (in years)** | 2.6 | 2.4 | 2.0 |
| **Diabetes (in %)** | 100 | 68 | 46 |
| **CKD cause** | 100% diabetes | diabetes (58%); hypertension (16%), IgA nephropathy (6%), FSGS (3%), Pyelonephritis (2%), interstitial nephritis (1%), unknown (5%), other (9%) | Diabetes: 31%, Hyperetnsion: 22% Glomerural: 25% other: 12%, unknown: 10% |
| **Mean eGFR at baseline** | 56 ml/min | 43 ml/min | 37 ml/min |
| **Median ACR** | 927 mg/g | 949 mg/g | 329 mg/g |
| **Primary outcome** | Composite of doubling of SCr, ESKD, or death from CV/renal cause: 0.70 (0.59-0.82) | A composite outcome involving a significant and reduction in eGFR >50%, ESKD, or CV/renal related death 0.61 (0.51-0.72) | A composite of a decline in eGFR to <10 mL/min or a reduction of at least 40% from the initial level, along with the outcomes of ESKD or CV/ kidney related death 0.72 (0.64 – 0.82) |
| **CKD progression** | 0.66 (0.53 - 0.81) | 0.56 (0.45 - 0.68) | 0.71 (0.62 - 0.81) |
| **ESKD** | 0.68 (0.54 - 0.86) | 0.64 (0.50 - 0.82) | 0.73 (0.59 - 0.89) |

**Table 1.** Landmark randomised clinical trials on SGLT2 in CKD

### Criteria for CKD progression:

**CANVAS:** 40% decline in eGFR, dialysis or transplantation requirement, or kidney-related death

**CREDENCE:** doubling of serum creatinine, ESKD, or kidney-related death

**DAPA-CKD:** ≥50% reduction in eGFR, ESKD, or kidney-related death

**EMPA-KIDNEY:** reduction in eGFR to <10 mL/min/1.73 $m^2$ or by ≥40% from baseline, ESKD, or kidney-related death

Crucially, the majority of participants in these trials were already on ACE inhibitors or ARBs before randomisation, underscoring the additive benefits of SGLT-2 inhibitors in slowing CKD progression alongside RAAS inhibitors. A simulation study estimated that a non-diabetic adult with albuminuric CKD could potentially gain an additional seven years free from adverse outcomes by combining SGLT-2 inhibitors and RAAS inhibitors.[9]

Analyses of subgroups in the DAPA-CKD and EMPA-KIDNEY trials have revealed that both dapagliflozin and empagliflozin exhibited effectiveness across diverse subpopulations. These include variations in age, gender, race, diabetes status, blood pressure levels and baseline kidney function. In particular, the protective effects were consistent regardless of diabetes status or baseline GFR, with exploratory analyses suggesting benefits even in patients with ACR between 30 and 300 mg/g.

The DAPA-CKD trial extended the evidence by showing kidney protective effects in patients with IgA nephropathy, with dapagliflozin associated with a substantial reduction in the risk of adverse outcomes. However, the evidence in patients with focal segmental glomerulosclerosis (FSGS) was limited due to low power, with only exploratory analyses indicating a potential benefit in slowing chronic decline in estimated GFR.

Ongoing investigations are exploring the use of SGLT-2 inhibitors in other patient populations, such as those with polycystic kidney disease and kidney transplant recipients.

SGLT2 inhibitors exhibit a favourable safety profile in patients with CKD. A combined analysis of individuals with diabetes and CKD stages G3-4 indicated comparable rates of serious adverse events between empagliflozin and a placebo. However, the use of SGLT2 inhibitors is linked to a heightened occurrence of mild genital infections.[10]

## Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RA), initially studied for cardiac outcomes in type 2 diabetes, have demonstrated notable effectiveness in improving kidney outcomes. A comprehensive meta-analysis involving approximately 44,000 participants across 6 trials showed a 21% reduced risk of composite kidney outcomes, such as new-onset albuminuria, doubling of serum creatinine, significant decline in estimated GFR, kidney replacement therapy, or kidney-related death. The risk reduction for albuminuria and other kidney-related issues ranged from 15% to 36%[11] Landmark randomised clinical trials on GLP-1 receptor agonists in CKD have been described in Table 2.

| Parameters | EXSCEL[12] | REWIND[13] | AMPLITUDE-O[14] | FLOW[15] |
|---|---|---|---|---|
| **N** | 14752 | 9901 | 4076 | 3534 |
| **Inclusion criteria related to kidney (eGFR)** | eGFR ≥30 | eGFR ≥15 mL/ min | Individuals at least 18 years old with a medical history of CVD or<br>age ≥50( for men) or ≥55 (for women) years with eGFR between 25 to 60 ml/min | eGFR ≥50 to ≤75 ml/ min/1.73 m2 and UACR >300 to <5000 mg/g or eGFR ≥25 to <50 ml/min and UAR >100 to <5000 mg/g |
| **Drug** | Exenatide 2 mg weekly | Dulaglutide 1.5 mg weekly | Efpeglenatide 4 mg or 6 mg weekly | Semaglutide 1.0 mg |
| **Median follow-up** | 3.2 | 5.4 | 1.8 | On-going trial |
| **Baseline eGFR** | Median eGFR 76 ml/min | Mean eGFR 78 ml/ min | Mean eGFR 72 ml/min | Mean eGFR 47 ml/min |
| **Baseline median ACR** | - | 1.94 mg/mmol | 28 mg/g | ACR 568 mg/g |
| **Kidney outcome** | ACR level >300 mg/g, ≥40% reduction in eGFR, initiation of KRT, or kidney-related death | ACR: >300 mg/g, eGFR: ≥30% decline from baseline, or maintenance KRT | ACR: >300 mg/g ACR: ≥30% increase from baseline, eGFR: ≥40% decline from baseline | Composite primary endpoint: time to first kidney failure (initiation of KRT or persistent eGFR <15 ml/min), eGFR: persistently ≥50% reduction from baseline or death from CV or kidney causes |
| **Hazard ratio (HR)** | 0.85 (0.74 to 0.98) | 0.85 (0.77 to 0.93) | 0.68 (0.57 to 0.79) | Ongoing trial |

**Table 2.** Landmark randomized clinical trials on GLP-1 receptor agonists in CKD

The precise mechanism by which GLP-1 RA contributes to the slowdown of eGFR decline and/or the reduction of albuminuria is not fully understood. Proposed mechanisms involve enhancements in glycaemic control, weight loss, heightened natriuresis and a decrease in inflammation and oxidative stress. Common adverse effects linked to GLP-1 RA include diarrhoea, vomiting and nausea.[12-14]

The recent FLOW trial is set to evaluate the impact of semaglutide on kidney outcomes in individuals with both CKD and T2D, addressing a critical research gap.[15] FLOW aims to determine whether once-weekly subcutaneous semaglutide can effectively delay CKD progression, mitigate the risk of kidney failure and reduce rates of kidney and cardiovascular disease mortality compared to a placebo. Enrolled participants, identified as high or very high risk for CKD progression based on established guidelines, will provide valuable data to inform clinical decision-making and potentially broaden treatment options for patients dealing with both T2D and CKD. The trial's anticipated completion in late 2024 underscores its significance in providing timely insights into the potential benefits of semaglutide on kidney outcomes in this high-risk population.

## Mineralocorticoid receptor antagonists (MRA)

Several MRAs are beneficial supplements to RAAS inhibitors, particularly in individuals experiencing albuminuria and/or diabetes. Steroidal non-selective MRAs, including both spironolactone and eplerenone, have demonstrated efficacy in decreasing albuminuria. Findings from a meta-analysis encompassing seven trials having 372 participants indicated that the combination of a non-selective MRA with an ACEI and/or ARB led to a notable decrease in proteinuria.[16] The study population commonly experienced Hyperkalemia.

The recent approval of finerenone, a non-steroidal selective MRA, provides a promising alternative.

When compared to non-selective steroidal MRAs, finerenone exhibits increased specificity for the mineralocorticoid receptor, a shorter duration of action, milder blood pressure reduction effects and a more favourable profile of side effects. It may also offer greater anti-inflammatory and antifibrotic effects.[17]

The FIGARO-DKD and FIDELIO-DKD clinical trials were conducted to assess cardio-renal advantages of finerenone in individuals with type 2 diabetes exhibiting albuminuria (ACR≥30 mg/g), demonstrating its effectiveness[18,19] (table 3). A comprehensive analysis of the data indicated that finerenone significantly reduces the risk of composite kidney-related outcomes by 15-23%, along with a 32% decrease in the average change in ACR levels from the start to 4 months. Although hyperkalemia was prevalent in the finerenone group, pre-specified analyses revealed that use of SGLT2 inhibitors/GLP1-RA at baseline did not alter the positive impact of finerenone on kidney outcomes. This suggests the potential for dual therapy in patients with type 2 diabetes and CKD.

| Parameters | FIDELIO-DKD[19] | FIGARO-DKD[18] |
|---|---|---|
| **Inclusion criteria (renal related)** | UACR of ≥30 mg/g but <300 mg/g along with an eGFR of ≥25 but <60 mL/min, and a history of diabetic retinopathy OR<br>UACR of ≥ 300 mg/g and eGFR ≥ 25 but < 75 mL/min | UACR of ≥30 mg/g but <300 mg/g along with an eGFR of ≥25 but <90 mL/min<br>UACR of ≥ 300 mg/g and eGFR ≥60 mL/min |
| **Median follow-up** | 2.6 years | 3.4 years |
| **Mean eGFR at baseline** | 44 ml/min | 68 ml/min |
| **Median ACR at baseline** | 852 mg/g | 308 mg/g |
| **Hazard ratio: finerenone vs placebo** | | |
| **Primary composite outcome: renal failure, a decrease in eGFR by at least 40% from the baseline eGFR, or death resulting from kidney-related reasons** | 0.82 (0.73 to 0.93) | 0.87 (0.76 to 1.01) |
| **Secondary composite outcome: kidney failure, a decrease in eGFR by at least 57% from the baseline eGFR, or death resulted from kidney related causes** | 0.76 (0.65 to 0.90) | 0.77 (0.60 to 0.99) |
| **ESKD: initiation of kidney replacement therapy** | 0.86 (0.67 to 1.10) | 0.64 (0.41 to 0.995) |
| **ACR change (baseline to month 4)** | 0.69 (0.66 to 0.71) | 0.68 (0.65 to 0.70) |

**Table 3.** Landmark randomized clinical trials on finerenone in CKD

A significant ongoing clinical trial, identified as FIND-CKD is currently investigating the impact of finerenone in nondiabetic kidney disease (ClinicalTrials.gov: NCT05047263). The trial aims to assess the effects of finerenone in conjunction with guideline-directed therapy on the progression of CKD. Another ongoing clinical trial, identified as CONFIDENCE "combination effect of FInerenone and EmpagliflOziN in participants with CKD and type 2 diabetes using a UACR endpoint" is a multicentric, phase 2, double-blind, parallel-group, randomised study enrolling 807 diabetic patients with CKD (stage 2-3) and UACR of 300-5000 mg/g. The primary outcome of the study is to investigate change in UACR from baseline to 9 months.[20]

## Hypoxia-inducible factor prolyl hydroxylase inhibitors

Recently, a novel class of medications known as HIF-PHIs has emerged as a promising addition to the armamentarium against anemia in CKD (Table 4). These medications work by stabilising HIF, a key player in EPO regulation. HIF-PHIs have demonstrated non-inferiority to traditional ESAs in terms of their ability to increase and sustain hemoglobin (Hb) concentrations in CKD patients, both those not on dialysis and those receiving dialysis therapy. Moreover, HIF-PHIs have shown a favourable impact on reducing transfusion requirements when compared to a placebo. However, an essential consideration in the evaluation of HIF-PHIs is their cardiovascular safety profile. In this regard, the data suggest that HIF-PHIs may be inferior to conventional ESAs or, at best, demonstrate similar cardiovascular outcomes. This aspect raises important questions and prompts further research into the long-term safety and efficacy of these agents, particularly in the context of CKD patients who often have a heightened cardiovascular risk.

| Study | N | Treatment | Study duration (in weeks) | Primary efficacy outcomes |
|---|---|---|---|---|
| **CKD-Non dialysis** | | | | |
| **DREAM-ND [21] (Desidustat)** | 588 | Desidustat 100 mg TIW vs. Darbepoetin | 24 | ΔHb, at wk 16–24,<br>Desidustat: 1.95 g/dl vs Darbepoetin: 1.83 g/dl |
| **ASCEND-ND[22] (Daprodustat)** | 3872 | Daprodustat 2 mg and 4 mg QD (ESA naïve) and 1-4 mg QD (ESA-users) vs. Darbepoetin | 148 | ΔHb, at wk 28–52,<br>Daprodustat: 0.74 g/dl vs Darbepoetin: 0.66 g/dl |
| **OLYMPUS[23] (Roxadustat)** | 2781 | Roxadustat 70 mg TIW vs. Placebo | 164 | FDA endpoint, wk 28–52:<br>Roxadustat: 1.75 g/dl vs PBO: 0.4 g/dl |
| **PRO2TECT[24] (Vadadustat)** | 1751 | Vadadustat 300 mg QD, then adjusted to 150, 450, or 600 mg QD vs. Darbepoetin | 168 | ΔHb, at wk 24–36<br>Vadadustat: 0.41 g/dl DPO: 0.42 g/dl,<br>ΔHb, at wk 40–52,<br>Vadadustat: 0.43 g/dl DPO: 0.44 g/dl |
| **CKD-Dialysis** | | | | |
| **DREAM-D[25] (Desidustat)** | ESA naïve (n=50), ESA treated (n=392) | Desidustat 100 mg TIW (ESA naïve); 100, 125, or 150 mg TIW (ESA-treated) vs. epoetin alfa | 24 | ΔHb, at wk 16–24,<br>Desidustat: 0.95 g/dl Epoetin alfa: 0.80 g/dl |
| **ASCEND-D[26]** | 2964 | Daprodustat 4–12 mg QD vs. epoetin alfa (for HD)/ darbepoetin (for PD) | 52 | ΔHb, at wk 28–52<br>Daprodustat: 0.28 g/dl ESA: 0.10 g/dl |
| **ROCKIES[27]** | 2133 | Roxadustat 70–200 mg TIW (in ESA-treated) and 70 or 100 mg TIW (in ESA-naïve) vs. epoetin alfa | 52–164 | ΔHb, at wk 28–52<br>Roxadustat: 0.77 g/dl Epoetin alfa: 0.68 g/dl |
| **INNO2VATE[28]** | 369 | Vadadustat 300 mg QD, (adjusted to 150, 450, or 600 mg) vs. Darbepoetin | 116 | ΔHb, wk 24–36:<br>Vadadustat: 0.19 g/dl vs Darbepoetin: 0.36 g/dl<br>ΔHb, wk 40–52:<br>Vadadustat: 0.23 g/dl vs Darbepoetin: 0.41 g/dl |

**Table 4.** Landmark randomized clinical trials on HIF-PHI in CKD

Δ, difference in mean Hb

## Emerging treatments

### Aldosterone synthase inhibitors

The acceleration of chronic kidney disease progression is linked to an excess of aldosterone. An appealing strategy to mitigate various pathologies associated with aldosterone involves inhibiting aldosterone synthase. A recently conducted randomised, controlled Phase 2 clinical trial evaluated the efficacy, safety and optimal dosage of BI 690517, an aldosterone synthase inhibitor (ASI).[29] The findings demonstrated that BI 690517 exhibited a dose-dependent reduction in albuminuria when combined with RAAS inhibition and empagliflozin. This suggests an additional therapeutic benefit for CKD treatment without any unexpected safety concerns. The investigation into aldosterone synthase inhibition is still ongoing.

Baxdrostat, an innovative ASI, demonstrates encouraging outcomes concerning safety and tolerability in reducing systolic BP among individuals with treatment-resistant hypertension.[30] Nevertheless, additional RCTs are required to explore their long-term effectiveness and to evaluate their potential role in CKD, uncontrolled hypertension and primary aldosteronism.

### Endothelin receptor antagonists

Elevated levels of endothelin (ET) in kidney disease, triggered by factors like diabetes, hypertension, proinflammatory cytokines and acidosis, lead to the activation of endothelin receptor type A (ETA). This activation results in persistent vasoconstriction of afferent arterioles, causing hyperfiltration, proteinuria, podocyte damage and a decline in eGFR. To reduce proteinuria and slow the progression of kidney disease, the use of endothelin receptor antagonists (ERAs) has been suggested.

Recent findings indicate that ERAs can reduce kidney fibrosis, inflammatory cytokines and proteinuria. Nevertheless, the effectiveness of many ERAs in treating kidney disease is still under investigation. The limited utilisation of ERAs in clinical practice is attributed to setbacks in phase III trials and side effects like edema. To overcome these challenges, ongoing research explores combination therapies involving ERAs with SGLT2 inhibitors and dual angiotensin-II type 1/ET receptor blockers.[31]

Promising research, exemplified by ongoing trials like ZENITH-CKD, which assesses the effectiveness of zibotentan and dapagliflozin in treating CKD, holds potential in determining the future role of ERAs in the treatment of CKD.[32]

## Recent guidelines

The KDIGO[33] and NICE guidelines[34] recommend ACE inhibitors or ARBs as the primary antihypertensive treatment for individuals with albuminuria (defined as urine ACR >70 mg/mmol by NICE and KDIGO A3), without diabetes and for those with diabetes and CKD stage G1-G4, with albuminuria A2-A3. RAAS inhibitors may be continued even if eGFR is <30 mL/min/1.73 $m^2$.

Both KDIGO and ADA guidelines[35] advocate for the use of SGLT-2 inhibitors as first-line pharmacotherapy in patients with diabetes, CKD and in those with eGFR ≥20 mL/min/1.73 $m^2$. NICE guidelines also recommend SGLT2 inhibitors when ACR is >30 mg/mmol and possibly when ACR is 3-30 mg/mmol in diabetes patients with CKD on RAAS inhibitors and meeting eGFR thresholds. Dapagliflozin is recommended in patients with eGFR 25-75 mL/min/1.73 $m^2$ and ACR ≥22.6 mg/mmol, irrespective of diabetes status. According to KDIGO, SGLT2 inhibitors are recommended for those with ACR ≥200 mg/g and eGFR ≥20 mL/min/1.73 $m^2$ as well as for those with CKD and heart failure. Once initiated, SGLT2 inhibitors may be continued even if eGFR drops below 20 mL/min/1.73 $m^2$, given well tolerability and absence of kidney replacement therapy (KRT). KDIGO and ADA guidelines support GLP-1 receptor agonists in type 2 diabetes patients with CKD who cannot tolerate metformin or an SGLT-2 inhibitor. KDIGO and ADA guidelines recommend the use of Finerenone as add-on therapy in patients with diabetes and CKD, maximally tolerated with ACEI/ARBs if ACR is ≥30 mg/g and potassium level is within normal limits. The recommended starting dose varies based on estimated GFR, with emphasis on regular potassium monitoring. It is also noted that finerenone need not be discontinued if eGFR falls below 25 mL/min/1.73 $m^2$, as long as the patient maintains normokalemia.

## Conclusion

Emerging management strategies for CKD involve the utilisation of various pharmacological agents. Among these, SGLT2 inhibitors, GLP-1 receptor agonists and MRAs have shown promise in improving renal outcomes. Additionally, HIF-PHIs have emerged as a potential therapeutic avenue. Recent developments also include the exploration of Endothelin receptor antagonists and aldosterone synthase inhibitors in CKD management, offering novel approaches to address renal complications.

The updated guidelines from KDIGO and ADA provide comprehensive insights into the contemporary management of CKD. These guidelines emphasise the integration of newer therapies, particularly highlighting the role of SGLT2 inhibitors and GLP-1 receptor agonists in patients with diabetes and CKD. These advancements mark a significant stride in the pursuit of more effective and targeted approaches to address the complexities of CKD.

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