European Journal of Internal Medicine 143 (2026) 106557

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Invited Review Article

Contemporary management of advanced chronic kidney disease: An evidence-based review

Lyle W. Baker [a], Cene Ovincy [a], Levon Souvalian [a,b], LaTonya J. Hickson [a], Fouad T. Chebib [a,b,*]

[a] Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Jacksonville, FL, USA
[b] Mayo Clinic Florida PKD Center of Excellence, Jacksonville, FL, USA

ARTICLE INFO

Keywords:
Chronic kidney disease
CKD
Autosomal dominant polycystic kidney disease
ADPKD
Vaptans
Sodium-glucose cotransporter-2 inhibitors
SGLT2i
Nonsteroidal mineralocorticoid receptor antagonists
nsMRAs
Disease modifying treatment
End stage kidney disease
ESKD
Xenotransplant
Mesenchymal stem cell
MSC

ABSTRACT

Chronic kidney disease (CKD) is a major contributor to global morbidity and mortality, traditionally managed through renin-angiotensin system (RAS) inhibition and supportive care. Recent therapeutic advances have transformed this landscape, offering targeted interventions that modify disease progression and improve cardiovascular and renal outcomes. This review summarizes emerging treatments across key domains of CKD management. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated robust cardiorenal benefits, particularly in patients with type 2 diabetes mellitus (T2DM). SGLT2 inhibitors are now widely used in CKD and heart failure, including among non-diabetic populations. GLP-1 receptor agonists are approved for T2DM and cardiovascular risk reduction, with recent expansion to CKD in T2DM. Nonsteroidal mineralocorticoid receptor antagonists (nsMRAs), particularly finerenone, provide additional cardiorenal protection with a lower risk of hyperkalemia than traditional steroidal agents. In autosomal dominant polycystic kidney disease (ADPKD), tolvaptan remains the only approved disease-modifying therapy, with clinical trials and real-world data supporting its efficacy across a range of disease stages. Emerging regenerative strategies, including mesenchymal stem cell (MSC) therapy and xenotransplantation using genetically modified pig kidneys, have shown early promise in preclinical models and limited human studies. While further research is needed to optimize patient selection and long-term outcomes, these approaches represent important future directions in nephrology. Together, these developments mark a shift toward mechanism-based, precision therapies in CKD care. Internal medicine clinicians are pivotal in identifying appropriate candidates for these treatments and integrating evolving evidence into practice to improve patient outcomes.

1. Introduction

Chronic kidney disease (CKD) is a growing global health burden, affecting over 850 million people worldwide and contributing substantially to cardiovascular morbidity, premature mortality, and escalating health care resource utilization [1,2]. For decades, the cornerstone of CKD management has been inhibition of the renin–angiotensin system (RAS), primarily through angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [3]. While these therapies reduce proteinuria and slow disease progression, they provide only partial protection and do not fully address the complex pathophysiology of CKD [4].

Over the past decade, however, there has been a paradigm shift in the therapeutic landscape. Patients with CKD are more likely to experience cardiovascular mortality than to reach kidney failure, shifting treatment priorities to comprehensive cardiorenal protection [1]. A new generation of disease-modifying therapies has emerged, targeting mechanisms beyond RAS inhibition and offering broader cardiorenal benefits. This evidence-based review highlights recent key advances in the management of advanced CKD, including sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists (nsMRAs) – all of which have demonstrated efficacy in reducing kidney disease progression and cardiovascular events across diverse populations.

We also review novel therapies for specific CKD subtypes, such as tolvaptan in autosomal dominant polycystic kidney disease (ADPKD),

* Corresponding author at: Mayo Clinic, 4500 San Pablo Rd S , Jacksonville, FL 32224, USA.
E-mail address: Chebib.fouad@mayo.edu (F.T. Chebib).

https://doi.org/10.1016/j.ejim.2025.106557
Received 2 July 2025; Received in revised form 5 October 2025; Accepted 14 October 2025
Available online 23 October 2025

which slows cyst growth and preserves renal function. In addition, we explore emerging frontiers in kidney replacement strategies, including xenotransplantation using genetically modified porcine kidneys and the potential of mesenchymal stem cell (MSC) therapy in regenerative nephrology. Together, these innovations reflect a shift from supportive care to targeted, mechanism-based interventions aimed at altering disease trajectory and improving outcomes worldwide.

2. Recent advances in CKD Management

2.1. Sodium-glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 is expressed in the proximal tubule of the nephron, where it reabsorbs approximately 90 % of filtered glucose [5]. Inhibition of this transporter leads to glucosuria and osmotic diuresis [6], resulting in modest reduction in plasma glucose, body weight, and blood pressure, alongside a decrease in intraglomerular pressure [5,6]. Over time, the benefits of SGLT2 inhibitors have proven to extend far beyond glycemic control, offering significant cardiovascular and renal protection. As a result, these agents have become foundational therapies in the management of type 2 diabetes mellitus (T2DM), heart failure, and CKD.

SGLT2 inhibitors are now widely approved in Europe and North America for use in patients with T2DM, heart failure (both reduced and preserved ejection fraction), and CKD [1]. Dapagliflozin was first approved for T2DM by the European Medicines Agency (EMA) in 2012 and the U.S. Food and Drug Administration (FDA) in 2014; it subsequently gained approval for CKD in both regions in 2021. Canagliflozin was the first SGLT2 inhibitor to receive a kidney-specific indication, approved by the FDA in 2019 and by the EMA in 2020 [1,7,8]. Their broad utility is supported by robust evidence from large, multicenter, randomized, controlled trials (Table 1 **and** Fig. 1).

Initial cardiovascular outcome trials in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) demonstrated significant reductions in major adverse cardiovascular events (MACE). In the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke by 14 %, and reduced nephropathy risk by 39 % [9,10]. The CANVAS program showed that canagliflozin reduced MACE events from 31.5 to 26.9 per 1,000 patient-years [11]. The DECLARE-TIMI 58 trial, which included patients without established ASCVD, showed a 17 % reduction in heart failure hospitalization with dapagliflozin [12]. Similarly, the VERTIS-CV trial found that ertugliflozin reduced heart failure hospitalization by 30 % [13].

The heart failure benefits of SGLT2 inhibitors were further confirmed in dedicated trials across diabetic and non-diabetic populations. The DAPA-HF trial showed that dapagliflozin reduced the composite of cardiovascular death or worsening heart failure from 21 % to 16 % [14]. EMPEROR-Reduced reported a 25 % relative risk reduction in the same outcome with empagliflozin [14,15]. DEFINE-HF demonstrated improvements in heart failure-related health status and NT-proBNP levels with dapagliflozin [16]. In the SOLOIST-WHF trial, sotagliflozin reduced total cardiovascular deaths, heart failure hospitalizations, or urgent visits by 33 % in patients recently hospitalized for worsening heart failure [17,18]. The SCORED trial, using sotagliflozin in patients with T2DM and moderate CKD (eGFR 25-60 mL/min/1.73 m^2), showed a 23 % reduction in these same outcomes [19]. In heart failure with preserved ejection fraction (HFpEF), the EMPEROR-Preserved and DELIVER trials showed consistent benefit, with 21 % and 18 % relative risk reductions, respectively, in the composite of cardiovascular death or heart failure hospitalization [20,21].

Beyond their cardiovascular outcomes, SGLT2 inhibitors are firmly established as disease-modifying agents in CKD. In the CREDENCE trial, canagliflozin reduced the risk of kidney failure, doubling of serum creatinine, or renal/cardiovascular death by 30 % in patients with T2DM and albuminuric CKD receiving background RAS blockade [22]. The DAPA-CKD trial extended these findings to a broader population, including non-diabetic patients, showing that dapagliflozin reduced the composite renal outcome – including sustained ≥50 % decline in eGFR, ESKD, or renal/cardiovascular death – from 14.5 % to 9.2 % [23,24]. Most recently, the EMPA-KIDNEY trial showed a 28 % reduction in kidney disease progression or cardiovascular death with empagliflozin, with over half the participants being non-diabetic, reinforcing the generalizability in CKD [25].

In response to this expanding evidence base, major international guidelines now recommend SGLT2 inhibitors for CKD management, regardless of diabetes status. Both the European Renal Association (ERA) and Kidney Disease: Improving Global Outcomes (KDIGO) 2022 and 2024 guidelines endorse initiating SGLT2 inhibitors in patients with CKD and eGFR ≥20 mL/min/1.73 m^2 to reduce cardiovascular risk and slow kidney function decline, independent of glycemic control [4,26].

2.2. Glucagon-like peptide-1 (GLP-1) receptor agonists

Like SGLT2 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated cardiovascular and renal protective benefits, particularly in patients with T2DM [27]. GLP-1 receptor agonists enhance glucose-dependent insulin secretion, suppress appetite, and promote weight loss [28].

The FLOW trial was the first large-scale study to evaluate the kidney-specific effects of a GLP-1 receptor agonist in CKD. The trial enrolled patients with T2DM and CKD stages 3-4, defined by an eGFR of 25-75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 200-5000 mg/g [29]. Participants were randomized to receive semaglutide 1.0 mg weekly or placebo, in addition to standard care, which included RAS and SGLT2 inhibitor therapy when indicated. Semaglutide reduced the risk of major renal events by 24 %, slowed the eGFR decline rate by 1.16 mL/min/1.73 m^2/year, and was associated with an 18 % reduction in MACE and a 20 % reduction in all-cause mortality [30]. These findings reinforce the renal and cardiovascular benefits previously observed with other GLP-1 receptor agonists, such as dulaglutide in the AWARD-7 trial and efpeglenatide in AMPLITUDE-O [31,32].

In January 2025, the U.S. FDA expanded the indication of semaglutide (Ozempic) to include treatment of CKD in patients with T2DM, based on the positive outcomes from FLOW [33]. According to the 2024 KDIGO Clinical Practice Guidelines for CKD, GLP-1 receptor agonists with proven cardiovascular and kidney benefits are recommended for patients with T2DM and CKD – particularly for those unable to tolerate SGLT2 inhibitors. KDIGO further recommends combining GLP-1 receptor agonists with metformin and/or SGLT2 inhibitors to improve glycemic control and reduce cardiorenal risk [1].

Although FLOW established GLP-1 receptor agonists as kidney-protective agents in patients with T2DM, recent data extend this concept to non-diabetic CKD. The SMART trial showed that semaglutide reduced albuminuria by 52 % in overweight or obese patients with non-diabetic CKD [34]. Similarly, the SELECT trial, conducted in overweight or obese patients with cardiovascular disease but without diabetes, demonstrated that semaglutide not only reduced major cardiovascular events but also lowered the risk of a composite kidney outcome – including new onset macroalbuminuria, sustained >50 % decline in eGFR, kidney failure, or death from kidney disease – by 22 % [35,36].

2.3. Nonsteroidal mineralocorticoid receptor antagonists (nsMRAs)

Overactivation of the mineralocorticoid receptor (MR) contributes to inflammation and fibrosis in the kidneys, heart, and vasculature – key pathophysiologic drivers of CKD progression and cardiovascular morbidity [37]. While traditional steroidal MRAs such as spironolactone and eplerenone have demonstrated both reno- and cardioprotective effects [38], their use is often limited by dose-dependent adverse effects, including hyperkalemia and hormonal side effects such as gynecomastia [39].

Nonsteroidal MRAs (nsMRAs) – including finerenone, esaxerenone,

Table 1
Summary of Landmark and Ongoing SGLT2 Inhibitor Trials in CKD, HF, and T2DM.

Study, year, citation	Population	Drug	Primary Endpoint	Key Findings
EMPA-REG OUTCOME (2015) Zinman et al. [9]	T2DM + high CV risk (eGFR >30)	Empagliflozin	MACE	Reduced MACE by 14 % (HR 0.86; 95 % CI 0.74-0.99). Reduced incidents of worsening nephropathy by 39 % (HR 0.61; 95 % CI 0.53-0.70). Slope analysis showed slower eGFR decline by 1.48 mL/year (95 % CI 1.23-1.72).
CANVAS Program (2017) Neal et al. [11]	T2DM + high CV risk (eGFR >30)	Canagliflozin	MACE	Reduced MACE by 14 % (HR 0.86; 95 % CI 0.75-0.97). Slowed eGFR decline by 1.2 mL/year (95 % CI 1.0-1.4). Reduced UACR by 18 % (95 % CI 16-20).
DECLARE-TIMI 58 (2019) Wiviott et al. [12]	T2DM + CV risk or ASCVD (CrCl >60)	Dapagliflozin	MACE and composite of CV death or hospitalization for HF	Non-significant reduction in MACE (HR 0.93; 95 % CI 0.84- 1.03). Reduced composite of CV death or HF hospitalization by 17 % (HR 0.83; 95 % CI 0.73-0.95).
DAPA-HF (2019) McMurray et al. [14]	HFrEF ± T2DM (eGFR >30)	Dapagliflozin	Worsening HF or CV death	Reduced worsening HF or CV death by 26 % (HR 0.74; 95 CI 0.65-0.85).
CREDENCE (2019) Jardine et al. [22]	T2DM + CKD (eGFR 30-90; UACR >300–5000 mg/g)	Canagliflozin	Composite of ESKD (dialysis, transplantation, or sustained eGFR <15), doubling of serum creatinine, or death from renal or CV causes	Stopped early due to positive efficacy results. Reduced renal composite outcome by 30 % (HR 0.70; 95 % CI 0.59-0.82). Slowed eGFR decline by 2.74 ml/year (95 % CI 2.37-3.11).
DEFINE-HF (2019) Nassif et al. [16]	HFrEF ± T2DM (eGFR >30)	Dapagliflozin	NT-proBNP and KCCQ	No significant change in NT-proBNP, but improved HF-related health status per KCCQ.
DAPA-CKD (2020) Heerspink et al. [24]	CKD ± T2DM (eGFR 25-75; UACR 200-5000 mg/g)	Dapagliflozin	Sustained decline in the eGFR of at least 50 %, ESKD, or death from renal or CV causes	Reduced renal/CV composite outcome by 39 % (HR 0.61; 95 % CI 0.51-0.72). Slowed eGFR decline by 1.92 ml/year (95 % CI 1.62-2.24). Reduced UACR by 29 %.
VERTIS CV (2020) Cannon et al. [13]	T2DM + ASCVD (eGFR >30)	Ertugliflozin	MACE	Non-inferior to placebo for MACE (HR 0.97; 95 % CI 0.85-1.11). Reduced HF hospitalization by 30 % (HR 0.70; 95 % CI 0.54-0.90). Slowed eGFR decline by 1.19 ml/year (95 % CI 0.95-1.42).
EMPEROR-Reduced (2020) Anker et al. [15]	HFrEF (eGFR >20)	Empagliflozin	CV death or HF hospitalization	Reduced CV death or HF hospitalization by 25 % (HR 0.75; 95 % CI 0.65-0.86). Slowed eGFR decline by 1.73 ml/year (95 % CI 1.10-2.37).
EMPEROR-Preserved (2021) Anker et al. [20]	HFpEF (eGFR >20)	Empagliflozin	CV death or HF hospitalization	Reduced CV death or HF hospitalization by 21 % (HR 0.79; 95 % CI 0.69-0.90). Slowed eGFR decline by 1.36 ml/year (95 % CI 1.06-1.66).
SCORED (2021) Aggarwal et al. [19]	T2DM + CV risk + CKD (eGFR 25-60)	Sotagliflozin (SGLT1/2i)	Composite of CV death, HF hospitalization, or urgent HF visit	Reduced composite CV endpoint by 26 % (HR 0.74; 95 % CI 0.63-0.88). Slowed eGFR decline by 1.22 ml/year (95 % CI 0.90-1.54).
SOLOIST-WHF (2021) Bhatt et al. [17]	T2DM + recent worsening HF (eGFR >30)	Sotagliflozin (SGLT1/2i)	Composite of CV death, HF hospitalization, or urgent HF visit	Reduced composite CV endpoint by 33 % (HR 0.67; 95 % CI 0.52-0.85).
DELIVER (2022) Solomon et al. [21]	HFmrEF +HFpEF (eGFR >25)	Dapagliflozin	CV death or HF hospitalization	Reduced CV death or HF hospitalization by 18 % (HR 0.82; 95 % CI, 0.73-0.92). Slowed eGFR decline by 1.4 ml/year (95 % CI 1.0-1.8).
EMPA-KIDNEY (2022) Herrington et al. [25]	CKD ± T2DM (eGFR 20-90; UACR ≥200 if eGFR ≥45)	Empagliflozin	Composite of CKD progression (defined as ESKD, sustained decrease in eGFR to <10, sustained decrease in eGFR ≥40 % from baseline, or death from renal causes) or CV death	Reduced primary endpoint by 28 % (HR 0.72; 95 % CI 0.64-0.82). Slowed eGFR decline by 1.37 ml/year (95 % CI 1.16-1.59). Reduced UACR by 19 %.
DAPA-MI (2023) James et al. [97]	Post-MI patients (eGFR >30)	Dapagliflozin	Hierarchical composite (win ratio): death, HF hospitalization, MI, AF/flutter, T2DM, NYHA class, ≥5 % weight loss	Did not significantly reduce primary composite endpoint (HR 0.93; 95 % CI 0.81-1.07; p=0.30). More wins for dapagliflozin than placebo by win ratio of 1.34 (95 % CI 1.20-1.50).
EMPACT-MI (2024) Butler et al. [98]	Post-MI patients (eGFR >20)	Empagliflozin	Time to first HF hospitalization or all-cause death	Did not significantly reduce primary outcome (HR 0.90; 95 % CI 0.76-1.06; p=0.21).

Abbreviations: ASCVD (atherosclerotic cardiovascular disease), CKD (chronic kidney disease), CV (cardiovascular), ESKD (end-stage kidney disease), HF (heart failure), HFrEF (heart failure with mid-range ejection fraction), HFpEF (heart failure with preserved ejection fraction), HFrEF (heart failure with reduced ejection fraction), HTN (hypertension), KCCQ (Kansas City Cardiomyopathy Questionnaire), MACE (major adverse cardiovascular events), MI (myocardial infarction), NT-proBNP (N-terminal pro b-type natriuretic peptide), NYHA (New York Heart Association), T2DM (type 2 diabetes mellitus), UACR (urine albumin-to-creatinine ratio).

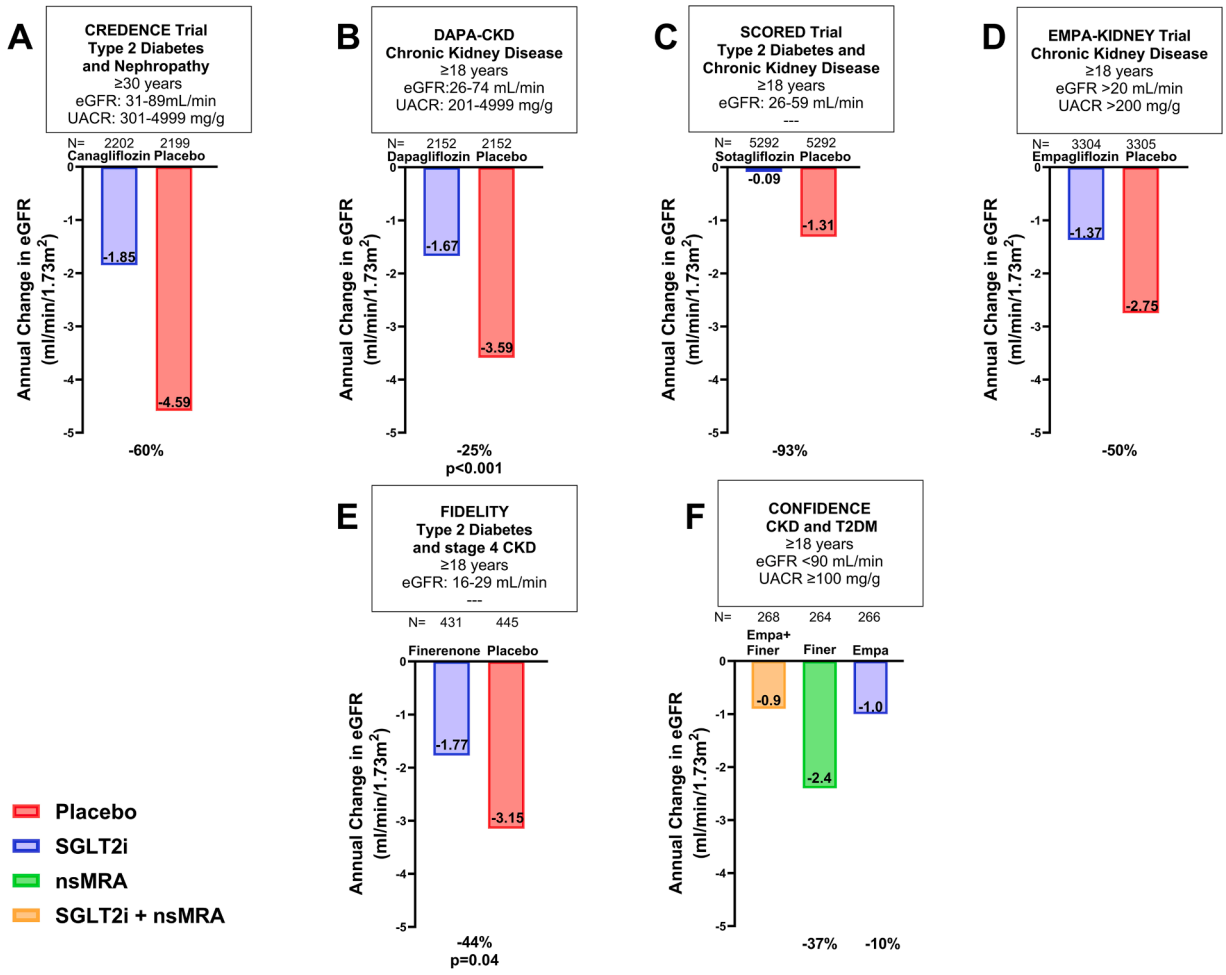

Fig. 1. Annual Change in eGFR in Landmark Trials of SGLT2 inhibitors and Nonsteroidal MRAs in Type 2 Diabetes and Chronic Kidney Disease. A) In CREDENCE, canagliflozin reduced the annual eGFR decline compared to placebo (−1.85 vs −4.59 mL/min/1.73 m^2; 60 % relative reduction). B) In DAPA-CKD, dapagliflozin slowed annual eGFR decline compared to placebo (−1.67 vs −3.59; 25 % relative reduction). C) In SCORED, a post hoc analysis showed that sotagliflozin reduced the annual eGFR decline compared to placebo (−0.09 vs −1.31; 93 % relative reduction). D) In EMPA-KIDNEY, empagliflozin reduced the annual eGFR decline compared to placebo (−1.37 vs −2.75; 50 % reduction). E) In the FIDELITY pooled analysis, finerenone reduced the annual eGFR decline compared to placebo (−1.77 vs −3.15; 44 % relative reduction). F) In CONFIDENCE, the combination of finerenone and empagliflozin reduced the annual eGFR decline compared to either agent alone (−0.9 vs −1.0 vs −2.4 for combination, empagliflozin, and finerenone, respectively).

and investigational agents like apararenone and balcinrenone – represent a newer class of MR antagonists developed to overcome some of these limitations. They demonstrate greater MR selectivity, reduced off-target receptor activation, and more balanced distribution between kidney and heart. These properties translate into fewer hormonal side effects and more predictable pharmacokinetics, with shorter half-lives and no accumulation of active metabolites. However, hyperkalemia remains a class effect [40,41].

Finerenone is currently the only nsMRA approved for the treatment of CKD associated with T2DM in both Europe and the United States. It received FDA approval in 2021 and EMA approval in 2022 [42]. Its efficacy is supported by two large, multicenter, randomized controlled trials: FIDELIO-DKD and FIGARO-DKD [43,44]. Both trials enrolled patients with T2DM and albuminuric CKD receiving maximally tolerated RAS blockade and with baseline serum potassium ≤4.8 mmol/L [45,46]. The FIDELIO-DKD trial focused on patients with more advanced CKD (eGFR 25-75 mL/min/1.73 m^2; UACR 30-5,000 mg/g). Finerenone significantly reduced the risk of the composite renal outcome – kidney failure, sustained ≥40 % decline in eGFR, or renal death – compared to placebo (17.8 % vs. 21.1 %; HR 0.82; 95 % CI 0.73-0.93; p=0.0014) [43]. In contrast, the FIGARO-DKD trial included patients with earlier stage CKD and moderately increased albuminuria (eGFR ≥25 mL/min/1.73 m^2; UACR of 30-300 mg/g) but higher cardiovascular risk. Finerenone reduced the composite cardiovascular outcome – CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure – by 13 % (HR 0.87; 95 % CI 0.76-0.98; p=0.03) [44]. Although the secondary renal endpoint did not reach statistical significance, the trend favored finerenone (HR 0.87; 95 % CI 0.76-1.01) [44]. To provide a comprehensive assessment, the FIDELITY prespecified pooled analysis combined data from over 13,000 patients across both trials. Finerenone significantly reduced kidney outcomes (HR 0.77) and cardiovascular events (HR 0.86), establishing it as a dual cardiorenal protective therapy in T2DM and CKD [45].

The benefits of finerenone have also been evaluated in heart failure. In the FINEARTS-HF trial, which enrolled over 6,000 patients with HFpEF or HFmrEF regardless of diabetes status, finerenone reduced the composite outcome of cardiovascular death and total heart failure events by 16 % (RR 0.84; 95 % CI 0.74-0.95), primarily through reductions in heart failure hospitalizations. Subgroup analysis showed a reduction in albuminuria, suggesting renoprotective potential even in non-diabetic patients [46].

Ongoing phase 3 trials aim to broaden the role of nsMRAs. The FIND-CKD trial is evaluating finerenone in non-diabetic CKD, using change in eGFR slope over 32 months as the primary endpoint [37]. The

CONFIDENCE trial examined whether combining finerenone with empagliflozin would provide greater albuminuria reduction than either agent alone in patients with T2DM and CKD. After 180 days, the combination reduced UACR by 29 % more than finerenone alone and by 32 % more than empagliflozin alone [47]. The MIRACLE trial is assessing the combination of balcinrenone and dapagliflozin in patients with coexisting CKD and heart failure [40].

Among currently available nsMRAs, finerenone remains the only agent approved in Europe and the U.S. for CKD in T2DM [48]. Esaxerenone is approved in Japan for hypertension and has shown reductions in albuminuria but is not yet available in Western markets [4]. Apararenone and balcinrenone remain investigational [48].

Collectively, these developments (Table 2) represent a significant advance in targeted mineralocorticoid receptor blockade, offering a more refined and potentially safer approach to slowing CKD progression and reducing cardiovascular risk in high-risk populations.

Beyond mineralocorticoid receptor blockade, aldosterone synthase inhibitors (ASi) offer a novel strategy by directly reducing aldosterone production through selective inhibition of CYP11B2 [49]. By targeting aldosterone synthesis itself, these agents may more effectively blunt the downstream profibrotic and proinflammatory effects of excess aldosterone. The recent phase 3 trial of baxdrostat in patients with uncontrolled and resistant hypertension provides the first large-scale clinical data for this class. Baxdrostat lowered systolic blood pressure by ~11-13 mmHg at 12 weeks, compared to a 5-6 mmHg reduction with placebo, yielding a between-group difference of about 6-7 mmHg. This was accompanied by only modest increase in serum potassium and no major renal safety concerns. Although these results were not obtained in CKD cohorts, they highlight the potential of ASi as an emerging therapeutic option. Further studies will be needed to determine whether aldosterone synthase inhibition can serve as an alternative to mineralocorticoid receptor antagonists in reducing aldosterone-mediated kidney injury and improving cardiorenal outcomes [50].

2.4. *Vaptans in autosomal dominant polycystic kidney disease (ADPKD)*

ADPKD is the most common inherited kidney disorder and the fourth leading cause of kidney failure worldwide [51,52]. It is characterized by progressive cyst development and bilateral kidney enlargement, driven by pathogenic variants in *PKD1* or *PKD2* [53,54]. Dysregulated polycystin signaling leads to increased cyclic adenosine monophosphate (cAMP) levels, which promote cyst epithelial proliferation and fluid secretion [54,55]. These insights led to the development of vasopressin V2 receptor antagonists to inhibit cAMP generation in collecting duct

Table 2
Summary of landmark and ongoing nsMRA Trials in CKD, HF, and T2DM.

Study, year, citation	Population	Drug	Primary Endpoint	Key Findings
ARTS-HF (Phase 2) (2016) Filippatos et al. [99]	HFrEF + T2DM or CKD	Finerenone	NT-proBNP reduction	Finerenone showed a trend toward mortality benefit over eplerenone; NT-proBNP reduction was not significant. Possible renal protective trend.
ESAX-HTN (2019) Ito et al. [100]	Japanese + Essential HTN	Esaxerenone	BP reduction	Esaxerenone demonstrated significant, dose-dependent reductions in systolic and diastolic BP.
ESAX-DN (2020) Ito et al. [101]	Japanese + T2DM + early DN (eGFR ≥30; UACR 45-300 mg/g)	Esaxerenone	UACR reduction	Esaxerenone significantly reduced albuminuria by 58 %.
FIDELIO-DKD (2020) Bakris et al. [43]	T2DM + CKD (eGFR 25-75; UACR 30-5000 mg/g)	Finerenone	Time to first: kidney failure, eGFR decline ≥40 %, death from renal causes	Finerenone reduced CKD progression and CV events (HR 0.82; 95 % CI 0.73-0.93). Hyperkalemia was more frequent (18 % vs. 9 %) but rarely led to discontinuation
FIGARO-DKD (2021) Pitt et al. [44]	T2DM + CKD (eGFR ≥25; UACR 30-300 mg/g)	Finerenone	Time to first: CV death, HF hospitalization, nonfatal MI, or stroke	Finerenone reduced CV events (HR 0.87, 95 % CI 0.76-0.98). Secondary renal benefits included reduced albuminuria and slower eGFR decline in early CKD.
Apararenone (Phase 2) (2021) Jiang et al. [48]	Stage 2 DN (eGFR ≥30; UACR 50-300 mg/g)	Apararenone	UACR reduction	Phase 2 study showed that Apararenone reduced albuminuria by 40-60 %. No phase 3 trial has been published to date.
FIDELITY (2022) Agarwal et al. [45]	T2DM + CKD (pooled FIDELIO + FIGARO)	Finerenone	Composite of renal and CV outcomes	Finerenone reduced both renal outcomes (HR 0.77) and CV outcomes (HR 0.86), reinforcing its role in delaying CKD progression.
CONFIDENCE (2025) Agarwal et al. [47]	T2DM + CKD	Finerenone + Empagliflozin	UACR reduction	UACR reduction 29 % greater than finerenone alone (CI 0.61 to 0.82; P<0.001) and 32 % greater than empagliflozin alone (CI 0.59 to 0.79; P<0.001)
FINEARTS-HF (2024) Yang et al. [46]	HFpEF or HFmrEF	Finerenone	Composite of CV death and total HF events	Finerenone reduced the composite of CV death and total HF events (RR 0.84, 95 % CI 0.74-0.95) with benefit driven by fewer HF events. Subgroup analysis showed an albuminuria reduction.
FIND-CKD (ongoing) Epstein et al. [37]	Non-diabetic CKD	Finerenone	Change in eGFR slope over 32 months	Ongoing Phase 3 trial evaluating finerenone's effect on eGFR decline in non-diabetic CKD.
MIRACLE (ongoing) Pandey et al. [40]	HF + CKD	Balcinrenone + Dapagliflozin	UACR reduction	Phase 3 trial evaluating whether balcinrenone with dapagliflozin provides additive benefit on albuminuria reduction.

Abbreviations: CKD (chronic kidney disease), CV (cardiovascular), DN (diabetic nephropathy), HF (heart failure), HFrEF (heart failure with reduced ejection fraction), HTN (hypertension), SBP (systolic blood pressure), T2DM (type 2 diabetes mellitus), UACR (urine albumin-to-creatinine ratio).

cells. Preclinical studies in PKD models showed that suppressing vasopressin or blocking its receptor reduced kidney volume growth and preserved renal function [55]. Pharmacologic inhibition of the V2 receptor with tolvaptan—a selective vasopressin V2 receptor antagonist—significantly slowed cystogenesis, reduced interstitial fibrosis, and improved survival in animal models, supporting clinical translation [55,56].

The TEMPO 3:4 trial first demonstrated clinical efficacy in humans. This randomized, placebo-controlled study enrolled 1,445 adults with preserved renal function (creatinine clearance ≥60 mL/min) and large kidneys (total kidney volume ≥750 mL). Over three years, tolvaptan reduced the annual increase in total kidney volume (2.8 % vs. 5.5 %) and slowed eGFR decline by 1.2 mL/min/1.73 m^2 per year [57]. Tolvaptan also reduced key secondary endpoints, including kidney pain, hypertension, and albuminuria [57].

The open-label TEMPO 4:4 extension study enrolled 871 participants from TEMPO 3:4 and demonstrated sustained benefits on eGFR over time [58]. The REPRISE trial extended efficacy data to patients with more advanced CKD (eGFR 25–65 mL/min/1.73 m^2 for ages 18-55; 25–44 mL/min/1.73 m^2 for ages 56-65), showing that tolvaptan slowed eGFR decline by 1.27 mL/min/1.73 m^2 per year compared to placebo over 12 months [59]. In the REPRISE open-label extension (OLE), patients initially assigned to placebo who later initiated tolvaptan experienced an improvement in annualized eGFR decline, from −5.2 to −3.4 mL/min/1.73 m^2 – supporting benefit even when started at later disease stages [60,61]. Observational data from Mayo Clinic further corroborate these findings, showing sustained preservation of kidney function over five or more years, with eGFR slopes comparable to clinical trial results [62]. Importantly, long-term safety data remains favorable, with a low incidence of significant hepatic enzyme elevations under routine monitoring.

Based on this robust evidence, tolvaptan is now recommended by both the EMA and the 2025 KDIGO guidelines as a disease-modifying treatment for adults with ADPKD who are at risk for rapid progression and have an eGFR ≥25 mL/min/1.73 m^2 [63,64]. Progression risk may be determined using imaging-based criteria (e.g., Mayo Imaging Classification 1C–1E), a documented eGFR decline of ≥3 mL/min/1.73 m^2 per year (in the absence of other causes), or a PROPKD score >6. For patients aged 18-55 years, imaging-based classification is preferred; for those aged 56-65 years, historical eGFR decline is emphasized [62]. While initiation is not recommended for eGFR <25 mL/min/1.73 m^2, emerging data from REPRISE-OLE and real-world experience support continuing therapy in patients who started earlier and continue to benefit, even into later disease stages [64].

Tolvaptan is typically initiated at 45 mg orally followed by 15 mg after 8 hours and titrated to the highest tolerated dose (ideally 90/30 mg per day) [64]. Common side effects include aquaretic symptoms (polyuria, nocturia, thirst), which may limit adherence. Hepatic safety monitoring is mandatory – monthly for the first 18 months, then quarterly. Clinical use requires careful patient counseling, multidisciplinary support, and enrollment in a Risk Evaluation and Mitigation Strategy (REMS) program in the U.S. When implemented appropriately, tolvaptan therapy (Table 3 **and** Fig. 2) provides a valuable opportunity to delay disease progression, defer kidney failure, and improve long-term outcomes in selected patients with ADPKD.

Beyond vasopressin antagonism, molecular therapies targeting dysregulated signaling pathways in ADPKD are in development. First, anti–microRNA-17 oligonucleotides derepress PKD1/PKD2 transcripts to raise polycystin dosage and slow cystogenesis (e.g., farabursen/RGLS8429) [65,66]. Second, neutralization of pregnancy-associated plasma protein-A (PAPP-A) lowers pericystic IGF-1 bioavailability and attenuates epithelial proliferation; a clinical-stage monoclonal antibody (ABBV-CLS-628) is now being evaluated after robust preclinical efficacy [67,68]. Third, small-molecule “correctors” aim to stabilize select misfolded PC1 variants and restore trafficking/function—an approach analogous to CFTR correction—with VX-407 entering first-in-human

Table 3
Summary of landmark trials and post hoc analysis using tolvaptan in ADPKD.

Study	Population	Drug	Primary Endpoint	Key Findings
TEMPO 3:4 (2012) Torres et al. [57]	ADPKD, age 18-50, TKV ≥750 mL, CrCl ≥60 ml/min	Tolvaptan	Percentage change in TKV and eGFR	Tolvaptan reduced TKV growth (2.8 % vs 5.5 % per year; P<0.001) and slowed kidney function decline (–2.61 vs. –3.81 [1/Scr]/year; P<0.001). Fewer composite events (44 vs. 50 per 100 person-years; P=0.01), worsening kidney function (2 vs. 5 per 100 person-years; P<0.001), and kidney pain (5 vs. 7 per 100 person-years; P=0.007).
TEMPO 4:4 OLE (2018) Torres et al. [58]	ADPKD (same as TEMPO 3:4)	Tolvaptan	Percentage change in TKV, eGFR and safety profile	TKV growth over full follow-up was 29.9 % in the early treatment group vs. 31.6 % in the delayed treatment group. No difference in eGFR slope. Safety profile remained consistent.
REPRISE (2017) Torres et al. [59]	ADPKD, age 18-55 (eGFR 25-65) or 56-65 (eGFR 25-44)	Tolvaptan	Change in eGFR (1 year)	eGFR decline was slower with tolvaptan (−2.34 vs −3.61; difference 1.27; 95 % CI, 0.86-1.68; P<0.001).
REPRISE OLE (2020) Torres et al. [61]	ADPKD (same as REPRISE)	Tolvaptan	Annualized eGFR slope	eGFR decline improved after switching to tolvaptan from placebo (−3.4 vs. −5.2; difference 1.8; P<0.001).
Post Hoc Analysis of Tolvaptan versus Standard of Care (SOC) Chebib et al. [62]	ADPKD, age 56-65	Tolvaptan	Annual change in eGFR	eGFR decline was slower with tolvaptan (−2.33 vs. −3.99; difference 1.66; 95 % CI 0.43-2.90; P=0.009).
Post Hoc Analysis of Tolvaptan versus Standard of Care (SOC) Chebib et al. [102]	ADPKD, age 18-35	Tolvaptan	Annual change in eGFR	eGFR decline was slower with tolvaptan (−2.58 vs. −4.28; difference 1.69; 95 % CI 0.87-2.52; P<0.001).

Abbreviations: ADPKD (autosomal polycystic kidney disease), TKV (total kidney volume), eGFR (estimate glomerular filtration rate), CrCl (creatinine clearance), SOC (standard of care), OLE (open-label extension).

testing [69].

2.5. Mesenchymal Stem/Stromal Cell (MSC) Therapy in CKD

Regenerative medicine is a rapidly advancing field, and among the most extensively studied cell-based therapies are mesenchymal stem/stromal cells (MSCs). These adult stem cells have garnered attention for their anti-inflammatory, immunomodulatory, and pro-repair properties across a wide range of conditions [70]. In December 2024, the U.S. FDA approved the first MSC therapy, Ryoncil, for pediatric steroid-refractory acute graft-versus-host disease – a milestone that has energized interest in expanding MSC applications to kidney disease [71]. MSC therapies have already received approval in other countries and continue to gain regulatory momentum.

In both acute and chronic kidney injury, MSCs have shown the ability to modulate inflammation, attenuate fibrosis, promote angiogenesis, and support tubular epithelial repair – thereby acting on several key pathogenic pathways [72,73]. These therapeutic effects are thought to be mediated not by engraftment and differentiation, but by paracrine signaling through the release of cytokines, chemokines, growth factors, and extracellular vesicles [73–75].

A seminal preclinical study using a cisplatin-induced AKI mouse model demonstrated that human bone marrow-derived MSCs significantly reduced tubular cell apoptosis and leukocyte infiltration, resulting in improved kidney function and survival [76]. In a separate rat model of CKD induced by 5/6 nephrectomy, repeated MSC infusions over 8 weeks led to reductions in renal fibrosis, downregulation of type I collagen and TGF-β, and a shift toward an anti-inflammatory cytokine profile—supporting the potential of MSC therapy in progressive CKD [77].

Early human studies, while limited, have provided encouraging signals of feasibility and safety. In a 2010 pilot trial of patients with treatment-refractory systemic lupus erythematosus (SLE), MSC infusion was associated with reduced disease activity and proteinuria [78]. Another prospective study evaluating autologous MSC administration in seven patients with CKD reported stable eGFR over 18 months and no adverse events, suggesting possible disease stabilization [79]. In a Mayo Clinic study on renovascular disease, intra-arterial kidney delivery of adipose-derived MSCs improved kidney function, reduced renal hypoxia, and lowered blood pressure [80,81]. More recently, an intra-arterial autologous MSC trial in diabetic kidney disease demonstrated feasibility and safety, with early signals of stabilization in kidney function and reductions in albuminuria – representing one of the first applications of MSCs directly in diabetic CKD patients [82].

However, not all trials have demonstrated benefit. A multicenter trial assessing MSCs in acute kidney injury after cardiac surgery found no

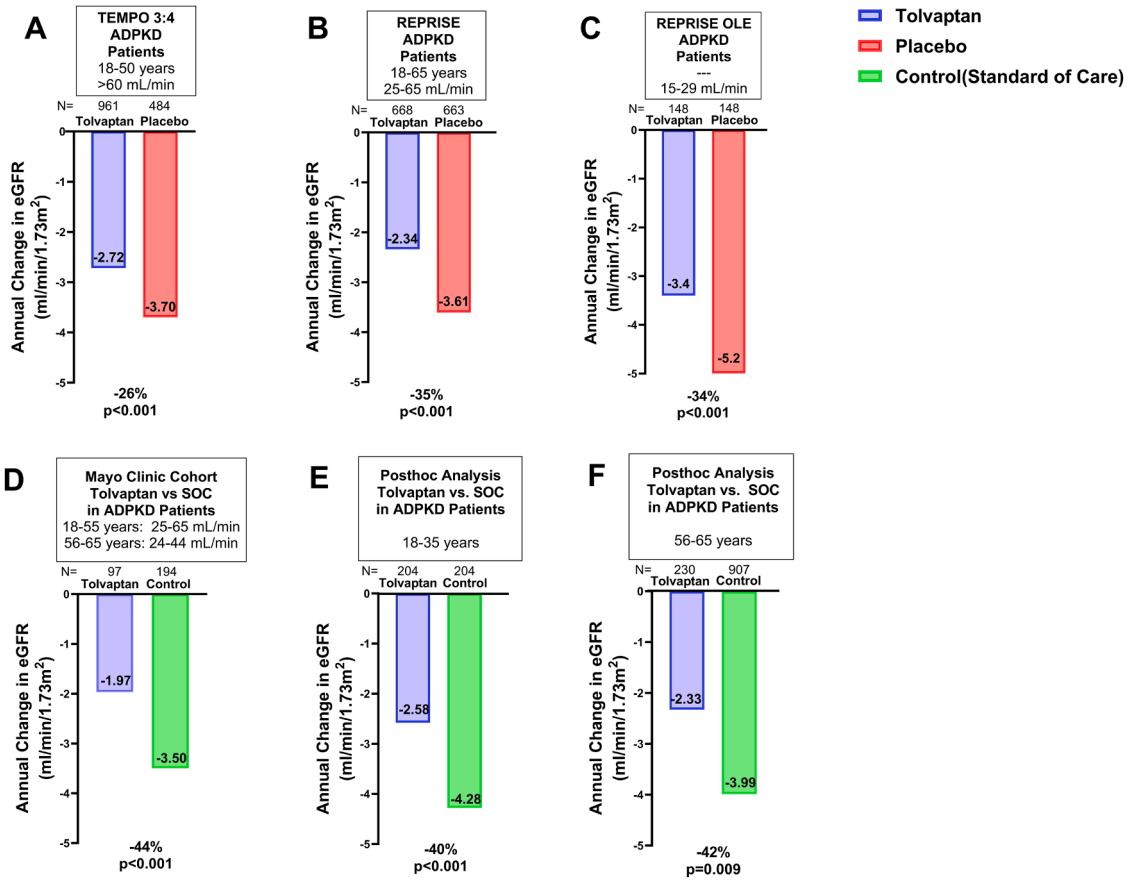

Fig. 2. Effect of Tolvaptan on eGFR Decline in Autosomal Dominant Polycystic Kidney Disease. A) In TEMPO 3:4, tolvaptan reduced the annual eGFR decline in patients with ADPKD (age 18–50 years, eGFR >60 ml/min/1.73 m^2) compared to placebo (−2.72 vs −3.70; 26 % reduction). B) In REPRISE, tolvaptan slowed eGFR loss in patients with more advanced CKD (eGFR 25–65), tolvaptan reduced the annual decline in eGFR compared to placebo (−2.34 vs −3.61; 35 % reduction). C) In the REPRISE open-label extension (OLE), tolvaptan continued to slow eGFR decline in patients with advanced CKD (eGFR 15–29) (−3.4 vs −5.2; 34 % reduction). D) In a long-term observational cohort from Mayo Clinic, patients receiving tolvaptan had a slower eGFR decline compared to match controls on standard of care (−1.97 vs −3.50; 44 % reduction). E) Post hoc analysis of patients aged 18–35 showed a 40 % slower eGFR decline with tolvaptan (−2.58 vs −4.28; 40 % reduction). F) In patients aged 56–65, tolvaptan also slowed eGFR decline in those who have CKD stage 3 or 4 and had a historical eGFR rate of decline of > 3 ml/min/year (−2.33 vs −3.99; 42 % reduction).

significant improvement in renal recovery with MSC therapy compared to placebo [83]. Meanwhile, studies in diabetic nephropathy have shown promising early signals, with MSC-treated patients exhibiting slower disease progression than controls [84,85].

While most studies report favorable safety outcomes, the variability in efficacy highlights the need to refine key parameters such as MSC source, dosing, route of administration, and timing [86]. Fig. 3 illustrates a representative process of delivering autologous MSC therapy directly to the kidney. Currently, several trials are actively investigating or have published MSC therapy across a spectrum of kidney disorders, with intravenous delivery being the most common approach (NCT04869761, NCT05362786) [70,86,87]. Importantly, not all patients are eligible or willing to participate in clinical trials but still seek access to stem cell-based therapies for CKD. In response, the Mayo Clinic in Florida Regenerative Nephrology Program received FDA authorization in 2024 to provide investigational MSC therapy under an Expanded Access (Compassionate Use) Investigational New Drug (IND) protocol (NCT06752577). This initiative allows patients with CKD to access MSC therapy outside of a formal clinical trial while adhering to regulatory oversight.

Other regenerative strategies are also emerging. Rilparencel, a renal progenitor-derived cell therapy, has shown potential to enhance tubular repair and reduce fibrosis in early studies. The Renal Autologous Cell Therapy (REACT) program, which combines autologous kidney progenitor cells with a hydrogel matrix, has advanced into phase 3 trials, with early data suggesting stabilization of kidney function [88–90]. Together with Ryoncil and other MSC-based approaches, these therapies represent a promising frontier in regenerative nephrology. Recent perspectives have emphasized the value of multitarget strategies that integrate regenerative and senotherapeutic approaches, underscoring how these emerging therapies may fit into a broader framework for improving outcomes in progressive or treatment-resistant CKD [90].

2.6. *Xenotransplant for kidney replacement therapy*

Xenotransplantation using genetically modified pig organs has emerged as a potential solution to the critical shortage of donor kidneys for patients with end-stage kidney disease (Fig. 4). Advances in gene-editing technologies have enabled the development of porcine kidneys with significantly reduced immunologic incompatibility, thereby minimizing the risk of hyperacute rejection and improving graft survival [91]. For example, pigs engineered to lack the *alpha-1,3-galactosyltransferase (GGTA1)* gene – responsible for expressing a major xenoantigen – exhibit markedly improved compatibility with human immune systems [92]. Additional modifications, including the insertion of human transgenes and co-transplantation of porcine thymic tissue, have further advanced efforts to induce immune tolerance [93,94].

In a landmark U.S.-based proof-of-concept study, two genetically modified pig kidneys were transplanted into brain-dead human recipients. Both donor pigs also received subcapsular implantation of autologous porcine thymic tissue to facilitate immune adaptation. Post-transplantation, both recipients immediately produced urine and demonstrated significant improvements in renal function [95]. One recipient's eGFR rose from 23 to 62 mL/min/1.73 m^2 and serum creatinine declined from 1.97 to 0.82 mg/dL. The other showed an eGFR increase from 55 to 109 mL/min/1.73 m^2, with a corresponding drop in creatinine from 1.10 to 0.57 mg/dL [95]. Biopsies over the 54-hour observation period showed no signs of hyperacute or antibody-mediated rejection, supporting the immunologic feasibility of xenotransplantation in humans [95].

Building on these encouraging findings, Massachusetts General Hospital (MGH) in Boston, MA, performed the first genetically modified pig kidney transplant in a living human in March 2024. The recipient, who had no suitable living donor options, demonstrated early graft function before passing away two months later from an unrelated cardiac event. Importantly, autopsy confirmed no evidence of graft rejection or dysfunction [96]. In January 2025, MGH conducted a second pig-to-human kidney transplant in another living recipient. While early graft function appeared favorable, detailed long-term outcomes have not yet been published.

Despite these remarkable milestones, significant challenges must be addressed before xenotransplantation can be integrated into routine clinical care. Key concerns include the risk for zoonotic virus transmission (e.g., porcine endogenous retroviruses), the complexity of chronic immunologic monitoring, ethical considerations, and the absence of long-term safety and efficacy data. Nevertheless, these early

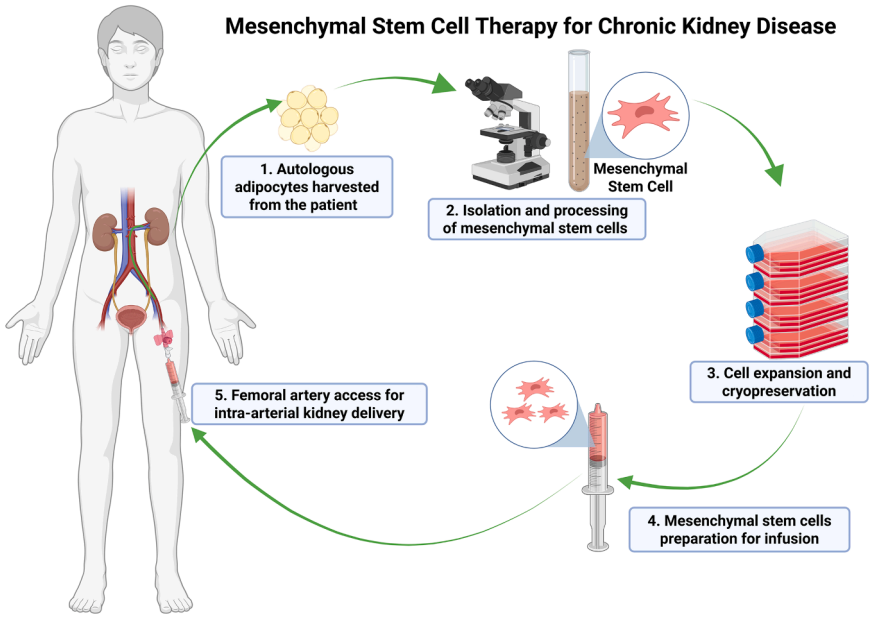

Fig. 3. Mesenchymal Stem Cell (MSC) Therapy for Chronic Kidney Disease: An Autologous, Intra-Arterial Kidney Delivery Approach. MSCs can be isolated from various tissue sources, including bone marrow, adipose tissue, and umbilical cord, and may be derived from either autologous (self) or allogeneic (non-self) donors. Once isolated, MSCs are culture-expanded and cryopreserved. Delivery routes include intravenous, intra-arterial, or direct intrarenal injection. This schematic illustrates a therapeutic approach using autologous, adipose-derived MSCs administered via intra-arterial infusion to the kidney.

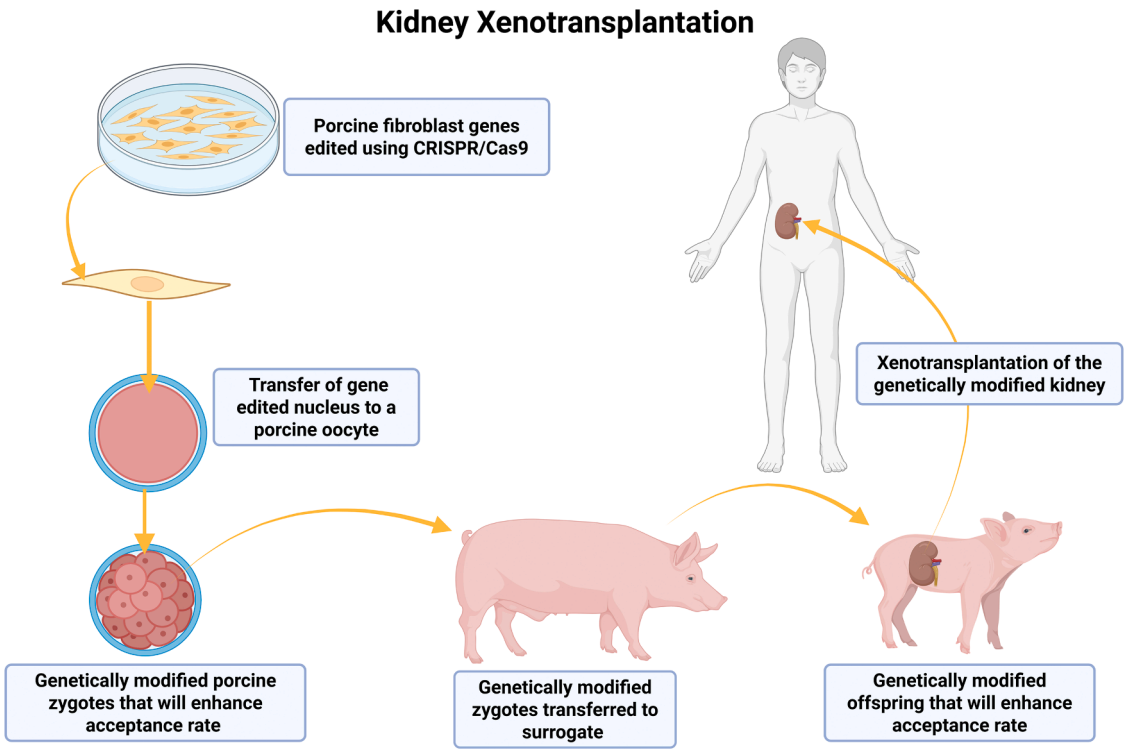

Fig. 4. Schematic of Genetically Modified Pig Kidney Xenotransplantation. This illustration outlines the multistep process of xenotransplantation. Porcine fibroblasts undergo CRISPR-based gene editing to eliminate immunogenic epitopes. The edited nuclei are transferred into enucleated oocytes to generate embryos, which are implanted into surrogate sows. The resulting genetically modified piglets serve as organ donors, with kidneys harvested for transplantation into human recipients.

clinical experiences lay a critical foundation for future research and represent a pivotal step toward realizing xenotransplantation as a viable therapeutic option for patients with advanced kidney failure who lack access to traditional transplantation.

3. Conclusion

The management of CKD has evolved dramatically, shifting from a singular focus on RAS inhibition to a broader, mechanism-based therapeutic framework. Robust evidence now supports the use of SGLT2 inhibitors in patients with and without diabetes, and GLP-1 receptor agonists in those with T2DM, for reducing cardiovascular events and slowing CKD progression. nsMRAs, such as finerenone, provide complementary cardiorenal protection with a more favorable safety profile than traditional steroidal agents, particularly in relation to hyperkalemia.

Tolvaptan represents a major advance in disease-modifying therapy for ADPKD, demonstrating consistent benefits in attenuating kidney volume growth and preserving renal function across various disease stages and age groups. Its inclusion in international guidelines underscores the growing emphasis on early risk stratification and targeted intervention in ADPKD. Meanwhile, emerging strategies such as xenotransplantation and MSC therapy signal a promising future for regenerative and replacement therapies in advanced CKD, though they remain investigational.

Collectively, these innovations represent a paradigm shift in CKD care – one that emphasizes precision medicine, proactive intervention, and systemic risk reduction. Continued research, widespread implementation of evidence-based guidelines, and interdisciplinary collaboration will be essential to fully realize the potential of these therapies and to improved long-term outcomes for patients with CKD worldwide.

Declaration of competing interest

The authors declare no relevant conflicts of interest related to the content of this manuscript.

Dr. Fouad T. Chebib has received research funding from Otsuka Pharmaceuticals, Natera, Mezzion, Vertex, AbbVie, and Regulus Therapeutics. He serves on the Board of Directors for the PKD Foundation. He also serves on the Advisory Board for Vertex, Otsuka, Hikma and AstraZeneca. Dr. Fouad T. Chebib received research funding from the National Institutes of Health (NIDDK).

Dr. LaTonya J. Hickson has received research funding from the National Institutes of Health (NIDDK and NIA) and from Regenerative Medicine Minnesota. She has served as a consultant for ETTA Biotechnology and Resolution Therapeutics.

All other authors declare no conflicts of interest.

Acknowledgments

Dr. Chebib is supported by the Mayo Clinic Florida RACER Award, CURE2030 Award, CATALYST Award, Department of Medicine Team Science Award, the Mayo Clinic Pirnie Polycystic Kidney Disease (PKD) Center, the Zell Family Foundation, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) U54 DK144863 and R01 DK142878.

References

[1] KDIGO. 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2024;105:S117–s314.
[2] Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global burden of disease study 2017. Lancet 2020;395:709–33.
[3] Cortinovis M, Perico N, Remuzzi G. Innovative therapeutics for renoprotection: where we are. Pharmacol Rev 2025;77:100060.
[4] de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the

American diabetes association (ADA) and Kidney disease: improving global outcomes (KDIGO). Kidney Int 2022;102:974–89.
[5] Fonseca-Correa JI, Correa-Rotter R. Sodium-glucose cotransporter 2 inhibitors mechanisms of action: a review. Front Med 2021;8:777861.
[6] Yanai H, Hakoshima M, Adachi H, Katsuyama H. Multi-organ protective effects of sodium glucose cotransporter 2 inhibitors. Int J Mol Sci 2021;22.
[7] Chronic kidney disease and risk management: standards of care in diabetes-2025. Diabetes Care 2025;48. S239-s51.
[8] Solomon J, Festa MC, Chatzizisis YS, Samanta R, Suri RS, Mavrakanas TA. Sodium-glucose co-transporter 2 inhibitors in patients with chronic kidney disease. Pharmacol Ther 2023;242:108330.
[9] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[10] Levin A, Perkovic V, Wheeler DC, Hantel S, George JT, von Eynatten M, et al. Empagliflozin and cardiovascular and kidney outcomes across KDIGO risk categories: post hoc analysis of a randomized, double-blind, placebo-controlled, multinational trial. Clin J Am Soc Nephrol 2020;15:1433–44.
[11] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[12] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.
[13] Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425–35.
[14] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
[15] Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of Empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-reduced trial. Circulation 2021;143:337–49.
[16] Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation 2019;140:1463–76.
[17] Bhatt AS, Bhatt DL, Steg PG, Szarek M, Cannon CP, Leiter LA, et al. Effects of Sotagliflozin on health status in patients with worsening heart failure: results from SOLOIST-WHF. J Am Coll Cardiol 2024;84:1078–88.
[18] Pitt B, Bhatt DL, Szarek M, Cannon CP, Leiter LA, McGuire DK, et al. Effect of Sotagliflozin on early mortality and heart failure-related events: A post hoc analysis of SOLOIST-WHF. JACC Heart Fail 2023;11:879–89.
[19] Aggarwal R, Bhatt DL, Szarek M, Cannon CP, Leiter LA, Inzucchi SE, et al. Effect of sotagliflozin on major adverse cardiovascular events: a prespecified secondary analysis of the SCORED randomised trial. Lancet Diabetes Endocrinol 2025;13:321–32.
[20] Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–61.
[21] Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail 2021;23:1217–25.
[22] Jardine MJ, Zhou Z, Mahaffey KW, Oshima M, Agarwal R, Bakris G, et al. Renal, cardiovascular, and safety outcomes of Canagliflozin by baseline kidney function: A secondary analysis of the CREDENCE randomized trial. J Am Soc Nephrol 2020;31:1128–39.
[23] Wheeler DC, Stefánsson BV, Jongs N, Chertow GM, Greene T, Hou FF, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol 2021;9:22–31.
[24] Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–46.
[25] Herrington WG, Staplin N, Agrawal N, Wanner C, Green JB, Hauske SJ, et al. Long-term effects of Empagliflozin in patients with chronic Kidney disease. N Engl J Med 2025;392:777–87.
[26] Czupryniak L, Mosenzon O, Rychlík I, Clodi M, Ebrahimi F, Janez A, et al. Barriers to early diagnosis of chronic kidney disease and use of sodium-glucose cotransporter-2 inhibitors for renal protection: A comprehensive review and call to action. Diabetes Obes Metab 2024;26:4165–77.
[27] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. A consensus report by the american diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 2018;41:2669–701. 2018.
[28] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. A consensus report by the american diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 2022;45:2753–86. 2022.
[29] Rossing P, Baeres FMM, Bakris G, Bosch-Traberg H, Gislum M, Gough SCL, et al. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. Nephrol Dial Transpl 2023;38:2041–51.
[30] Mann JFE, Rossing P, Bakris G, Belmar N, Bosch-Traberg H, Busch R, et al. Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial. Nat Med 2024;30:2849–56.
[31] Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol 2018;6:605–17.
[32] Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med 2021;385:896–907.
[33] Administration USFaD. FDA Approves New Indication For Ozempic To Treat Chronic Kidney Disease In Adults With Type 2 Diabetes. U.S. Food and Drug Administration; 2025.
[34] Apperloo EM, Gorriz JL, Soler MJ, Cigarran Guldris S, Cruzado JM, Puchades MJ, et al. Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized double-blind placebo-controlled clinical trial. Nat Med 2025;31:278–85.
[35] Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389:2221–32.
[36] Yan H, Karthikeyan H, Fan W, Yang Q, Wong NDUS. Eligibility and preventable cardiovascular, Diabetes, and kidney outcomes from Semaglutide in the SELECT trial. JACC Adv 2025;4:101773.
[37] Epstein M, Kovesdy CP, Clase CM, Sood MM, Aldosterone Pecoits-Filho R. Mineralocorticoid receptor activation, and CKD: A review of evolving treatment paradigms. Am J Kidney Dis 2022;80:658–66.
[38] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. J Am Coll Cardiol 2022;79:e263–421.
[39] Lainscak M, Pelliccia F, Rosano G, Vitale C, Schiariti M, Greco C, et al. Safety profile of mineralocorticoid receptor antagonists: spironolactone and eplerenone. Int J Cardiol 2015;200:25–9.
[40] Pandey AK, Bhatt DL, Cosentino F, Marx N, Rotstein O, Pitt B, et al. Non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease. Eur Heart J 2022;43:2931–45.
[41] Barrera-Chimal J, Kolkhof P, Lima-Posada I, Joachim A, Rossignol P, Jaisser F. Differentiation between emerging non-steroidal and established steroidal mineralocorticoid receptor antagonists: head-to-head comparisons of pharmacological and clinical characteristics. Expert Opin Investig Drugs 2021;30:1141–57.
[42] Frampton JE. Finerenone: first approval. Drugs 2021;81:1787–94.
[43] Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219–29.
[44] Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021;385:2252–63.
[45] Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022;43:474–84.
[46] Yang M, Henderson AD, Talebi A, Atherton JJ, Chiang CE, Chopra V, et al. Effect of finerenone on the KCCQ in patients with HFmrEF/HFpEF: A prespecified analysis of FINEARTS-HF. J Am Coll Cardiol 2025;85:120–36.
[47] Agarwal R, Green JB, Heerspink HJL, Mann JFE, McGill JB, Mottl AK, et al. Finerenone with Empagliflozin in chronic kidney disease and type 2 diabetes. N Engl J Med 2025;393:533–43.
[48] Jiang X, Zhang Z, Li C, Zhang S, Su Q, Yang S, et al. Efficacy and safety of non-steroidal mineralocorticoid receptor antagonists in patients with chronic kidney disease and type 2 diabetes: A systematic review incorporating an indirect comparisons meta-analysis. Front Pharmacol 2022;13:896947.
[49] Azizi M, Amar L, Menard J. Aldosterone synthase inhibition in humans. Nephrol Dial Transpl 2013;28:36–43.
[50] Flack JM, Azizi M, Brown JM, Dwyer JP, Fronczek J, Jones ESW, et al. Efficacy and safety of Baxdrostat in uncontrolled and resistant hypertension. N Engl J Med 2025.
[51] Chebib FT, Hanna C, Harris PC, Torres VE, Dahl NK. Autosomal dominant polycystic Kidney disease: a review. JAMA 2025;333:1708–19.
[52] Torres VE, Ahn C, Barten TRM, Brosnahan G, Cadnapaphornchai MA, Chapman AB, et al. KDIGO 2025 clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD): executive summary. Kidney Int 2025;107:234–54.
[53] Borghol AH, Bou Antoun MT, Hanna C, Salih M, Rahbari-Oskoui FF, Chebib FT. Autosomal dominant polycystic kidney disease: an overview of recent genetic and clinical advances. Ren Fail 2025;47:2492374.
[54] Chebib FT, Sussman CR, Wang X, Harris PC, Torres VE. Vasopressin and disruption of calcium signalling in polycystic kidney disease. Nat Rev Nephrol 2015;11:451–64.
[55] 2nd Wang X, Gattone V, Harris PC, Torres VE. Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. J Am Soc Nephrol 2005;16:846–51.
[56] Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. Nat Med 2004;10:363–4.

[57] Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367:2407–18.
[58] Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Dandurand A, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. Nephrol Dial Transpl 2018;33:477–89.
[59] Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017;377:1930–42.
[60] Edwards ME, Chebib FT, Irazabal MV, Ofstie TG, Bungum LA, Metzger AJ, et al. Long-term administration of Tolvaptan in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 2018;13:1153–61.
[61] Torres VE, Gansevoort RT, Perrone RD, Chapman AB, Ouyang J, Lee J, et al. Tolvaptan in ADPKD patients with very low kidney function. Kidney Int Rep 2021;6:2171–8.
[62] Chebib FT, Zhou X, Garbinsky D, Davenport E, Nunna S, Oberdhan D, et al. Tolvaptan and kidney function decline in older individuals with autosomal dominant polycystic kidney disease: A pooled analysis of randomized clinical trials and observational studies. Kidney Med 2023;5:100639.
[63] Blair HA, Keating GM. Tolvaptan: A review in autosomal dominant polycystic kidney disease. Drugs 2015;75:1797–806.
[64] Chebib FT, Perrone RD, Chapman AB, Dahl NK, Harris PC, Mrug M, et al. A practical guide for treatment of rapidly progressive ADPKD with Tolvaptan. J Am Soc Nephrol 2018;29:2458–70.
[65] Lakhia R, Ramalingam H, Chang CM, Cobo-Stark P, Biggers L, Flaten A, et al. PKD1 and PKD2 mRNA cis-inhibition drives polycystic kidney disease progression. Nat Commun 2022;13:4765.
[66] Lee EC, Valencia T, Allerson C, Schairer A, Flaten A, Yheskel M, et al. Discovery and preclinical evaluation of anti-miR-17 oligonucleotide RGLS4326 for the treatment of polycystic kidney disease. Nat Commun 2019;10:4148.
[67] Kashyap S, Hein KZ, Chini CC, Lika J, Warner GM, Bale LK, et al. Metalloproteinase PAPP-A regulation of IGF-1 contributes to polycystic kidney disease pathogenesis. JCI Insight 2020;5.
[68] ClinicalTrials.gov. A Study to Assess Adverse Events and Effectiveness of IntraVenous Infusions of ABBV-CLS-628 in Adult Participants With Autosomal Dominant Polycystic Kidney Disease (ADPKD). AbbVie Phase 2, ClinicalTrials.gov NCT06902558; 2025.
[69] Kurbegovic A, Pacis RC, Trudel M. Modeling Pkd1 gene-targeted strategies for correction of polycystic kidney disease. Mol Ther Methods Clin Dev 2023;29:366–80.
[70] Hickson LJ, Abedalqader T, Ben-Bernard G, Mondy JM, Bian X, Conley SM, et al. A systematic review and meta-analysis of cell-based interventions in experimental diabetic kidney disease. Stem Cells Transl Med 2021;10:1304–19.
[71] Blanc KL, Dazzi F, English K, Farge D, Galipeau J, Horwitz EM, et al. ISCT MSC committee statement on the US FDA approval of allogenic bone-marrow mesenchymal stromal cells. Cytotherapy 2025;27:413–6.
[72] Hickson LJ, Herrmann SM, McNicholas BA, Griffin MD. Progress toward the clinical application of mesenchymal stromal cells and other disease-modulating regenerative therapies: examples from the field of nephrology. Kidney360 2021;2:542–57.
[73] Perico N, Casiraghi F, Remuzzi G. Clinical translation of mesenchymal stromal cell therapies in nephrology. J Am Soc Nephrol 2018;29:362–75.
[74] Hickson LJ, Eirin A, Conley SM, Taner T, Bian X, Saad A, et al. Diabetic kidney disease alters the transcriptome and function of Human adipose-derived mesenchymal stromal cells but maintains immunomodulatory and paracrine activities important for renal repair. Diabetes 2021;70:1561–74.
[75] Hickson LJ, Eirin A, Lerman LO. Challenges and opportunities for stem cell therapy in patients with chronic kidney disease. Kidney Int 2016;89:767–78.
[76] Morigi M, Introna M, Imberti B, Corna D, Abbate M, Rota C, et al. Human bone marrow mesenchymal stem cells accelerate recovery of acute renal injury and prolong survival in mice. Stem Cells 2008;26:2075–82.
[77] Lee SR, Lee SH, Moon JY, Park JY, Lee D, Lim SJ, et al. Repeated administration of bone marrow-derived mesenchymal stem cells improved the protective effects on a remnant kidney model. Ren Fail 2010;32:840–8.
[78] Liang J, Zhang H, Hua B, Wang H, Lu L, Shi S, et al. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. Ann Rheum Dis 2010;69:1423–9.
[79] Makhlough A, Shekarchian S, Moghadasali R, Einollahi B, Dastgheib M, Janbabaee G, et al. Bone marrow-mesenchymal stromal cell infusion in patients with chronic kidney disease: A safety study with 18 months of follow-up. Cytotherapy 2018;20:660–9.
[80] Saad A, Dietz AB, Herrmann SMS, Hickson LJ, Glockner JF, McKusick MA, et al. Autologous mesenchymal stem cells increase cortical perfusion in renovascular disease. J Am Soc Nephrol 2017;28:2777–85.
[81] Abumoawad A, Saad A, Ferguson CM, Eirin A, Herrmann SM, Hickson LJ, et al. In a phase 1a escalating clinical trial, autologous mesenchymal stem cell infusion for renovascular disease increases blood flow and the glomerular filtration rate while reducing inflammatory biomarkers and blood pressure. Kidney Int 2020;97:793–804.
[82] Alatta LS, Elhusseiny KM, Dietz AB, Herrmann SM, Lorenz EC, Lawson DK, et al. Intraarterial autologous mesenchymal stem cell therapy for diabetic kidney disease. Kidney Int Rep 2025.
[83] Swaminathan M, Stafford-Smith M, Chertow GM, Warnock DG, Paragamian V, Brenner RM, et al. Allogeneic mesenchymal stem cells for treatment of AKI after cardiac surgery. J Am Soc Nephrol 2018;29:260–7.
[84] Perico N, Remuzzi G, Griffin MD, Cockwell P, Maxwell AP, Casiraghi F, et al. Safety and preliminary efficacy of mesenchymal stromal cell (ORBCEL-M) therapy in diabetic kidney disease: A randomized clinical trial (NEPHSTROM). J Am Soc Nephrol 2023;34:1733–51.
[85] Packham DK, Fraser IR, Kerr PG, Segal KR. Allogeneic mesenchymal precursor cells (MPC) in diabetic nephropathy: A randomized, placebo-controlled, dose escalation study. EBioMedicine 2016;12:263–9.
[86] Wang Y, Luo P, Wuren T. Narrative review of mesenchymal stem cell therapy in renal diseases: mechanisms, clinical applications, and future directions. Stem Cells Int 2024;2024:8658246.
[87] Bian X, Conley SM, Eirin A, Zimmerman Zuckerman EA, Smith AL, Gowan CC, et al. Diabetic kidney disease induces transcriptome alterations associated with angiogenesis activity in human mesenchymal stromal cells. Stem Cell Res Ther 2023;14:49.
[88] Stavas J, Silva AL, Wooldridge TD, Aqeel A, Saad T, Prakash R, et al. Rilparencel (Renal Autologous Cell Therapy-REACT(R)) for chronic kidney disease and type 1 and type 2 diabetes: phase 2 trial design evaluating bilateral kidney dosing and redosing triggers. Am J Nephrol 2024;55:389–98.
[89] ProKidney I. ProKidney reports statistically and clinically significant topline results for the phase 2 REGEN-007 trial evaluating Rilparencel in patients with chronic kidney disease and diabetes. 2025.
[90] Patel HA, Wang J, Zinn CJ, Learmonth M, Lerman LO, Wolfram J, et al. Fortifying the diabetic kidney disease treatment armamentarium: multitarget senotherapeutic and regenerative strategies. J Am Soc Nephrol 2025;36:1655–8.
[91] 3rd Meier RPH, Pierson RN, Fishman JA, Buhler LH, Bottino R, Ladowski JM, et al. International Xenotransplantation Association (IXA) position paper on Kidney Xenotransplantation. Transplantation 2025.
[92] Cooper DK, Ezzelarab MB, Hara H, Iwase H, Lee W, Wijkstrom M, et al. The pathobiology of pig-to-primate xenotransplantation: a historical review. Xenotransplantation 2016;23:83–105.
[93] Peterson L, Yacoub MH, Ayares D, Yamada K, Eisenson D, Griffith BP, et al. Physiological basis for xenotransplantation from genetically modified pigs to humans. Physiol Rev 2024;104:1409–59.
[94] Elisseeff J, Badylak SF, Boeke JD. Immune and genome engineering as the future of transplantable tissue. N Engl J Med 2021;385:2451–62.
[95] Montgomery RA, Stern JM, Lonze BE, Tatapudi VS, Mangiola M, Wu M, et al. Results of two cases of pig-to-Human kidney xenotransplantation. N Engl J Med 2022;386:1889–98.
[96] Kawai T, Williams WW, Elias N, Fishman JA, Crisalli K, Longchamp A, et al. Xenotransplantation of a porcine kidney for end-stage kidney disease. N Engl J Med 2025;392:1933–40.
[97] James S, Erlinge D, Storey RF, McGuire DK, de Belder M, Eriksson N, et al. Dapagliflozin in myocardial infarction without diabetes or heart failure. NEJM Evid 2024;3. EVIDoa2300286.
[98] Butler J, Jones WS, Udell JA, Anker SD, Petrie MC, Harrington J, et al. Empagliflozin after acute myocardial infarction. N Engl J Med 2024;390:1455–66.
[99] Filippatos G, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 2016;37:2105–14.
[100] Ito S, Itoh H, Rakugi H, Okuda Y, Yoshimura M, Yamakawa S. Double-blind randomized phase 3 study comparing Esaxerenone (CS-3150) and Eplerenone in patients with essential hypertension (ESAX-HTN Study). Hypertension 2020;75:51–8.
[101] Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, Okuda Y, et al. Esaxerenone (CS-3150) in patients with type 2 diabetes and microalbuminuria (ESAX-DN): phase 3 randomized controlled clinical trial. Clin J Am Soc Nephrol 2020;15:1715–27.
[102] Chebib FT, Dahl N, Zhou X, Garbinsky D, Wang J, Nunna S, et al. Tolvaptan and autosomal dominant polycystic kidney disease progression in individuals aged 18-35 years: a pooled database analysis. Kidney Med 2025;7:100935.