

Cardiorenal Medicine

Cardiorenal Med , DOI: 10.1159/000550423

Received: October 30, 2025

Accepted: January 7, 2026

Published online: January 13, 2026

Therapeutic Advances in Diabetic Kidney Disease: Thirty Years of Evidence and the Rise of the ‘Fantastic Four’ in Nephrology

Husain-Syed F, Yucel G, Daschner C, Jochims J, Yazdani B

ISSN: 1664-3828 (Print), eISSN: 1664-5502 (Online)

<https://www.karger.com/CRM>

Cardiorenal Medicine

Disclaimer:

Accepted, unedited article not yet assigned to an issue. The statements, opinions and data contained in this publication are solely those of the individual authors and contributors and not of the publisher and the editor(s). The publisher and the editor(s) disclaim responsibility for any injury to persons or property resulting from any ideas, methods, instructions or products referred to the content.

Copyright:

This article is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC) (<https://karger.com/Services/OpenAccessLicense>). Usage and distribution for commercial purposes requires written permission.

© 2026 The Author(s). Published by S. Karger AG, Basel

Review Article

Therapeutic Advances in Diabetic Kidney Disease: Thirty Years of Evidence and the Rise of the ‘Fantastic Four’ in Nephrology

Faeq Husain-Syed^{a*}, Goekhan Yucel^{b*}, Clara Daschner^c, Jan Jochims^d, Babak Yazdani^d

^a Department of Medicine II, University Hospital Giessen and Marburg, Justus-Liebig-University Giessen, Giessen, Germany

^b First Department of Medicine, University Medical Center Mannheim, Faculty of Medicine of the University of Heidelberg, Mannheim, Germany.

^c Nephrologisches MVZ Mannheim, ze:ro Praxen, Mannheim, Germany.

^d Fifth Department of Medicine (Nephrology, Hypertensiology, Rheumatology, Endocrinology, Pneumology), University Medical Center Mannheim, Faculty of Medicine of the University of Heidelberg, Mannheim, Germany.

*Shared first authorship

Short Title: Advances in Diabetic Kidney Disease

Word count of the abstract: 223

Word count of the text: 4279

Number of references: 51

Number of figures: 1

Number of tables: 5

Corresponding Author:

PD Dr. Babak Yazdani, Fifth Department of Medicine, University Medical Center Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. babak.yazdani@umm.de

Keywords: Chronic Kidney Disease, Proteinuria, Renin-Angiotensin System, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Antagonists, Sodium-Glucose Transporter 2 Inhibitors, Mineralocorticoid Receptor Antagonists, Glucagon-Like Peptide 1 Receptor Agonists

Abstract

Background: Diabetic kidney disease (DKD) remains the leading cause of chronic kidney disease (CKD) and kidney failure worldwide. Over the past three decades, management has evolved from strict glycemic and blood pressure control to targeted therapies that modify disease progression.

Summary: The *DCCT/EDIC (1993)* confirmed the impact of intensive glycemic and multifactorial risk factor management. But the early 1990s established the foundation of nephroprotective therapy with the *Captopril trial (1993)* in type 1 diabetes and subsequent *IRMA-1 (2001)*, *IDNT (2001)*, and the *RENAAL (2001)* studies established renin–angiotensin-system (RAAS) blockade as the first disease-specific therapy. More than a decade later, sodium-glucose cotransporter-2 (SGLT2) inhibitors transformed care, with *EMPA-REG OUTCOME (2015)* and *CANVAS (2017)* studies first demonstrating kidney benefits as secondary outcomes, which were confirmed in subsequent dedicated kidney trials: *CREDESCENCE (2019)*, *DAPA-CKD (2020)*, and *EMPA-KIDNEY (2022)* studies, demonstrating consistent reductions in kidney failure and cardiovascular mortality. Finerenone further advanced outcomes in *FIDELIO-DKD (2020)* and *FIGARO-DKD (2021)*, and combination therapy with SGLT2 inhibition showed additive benefit in the *CONFIDENCE (2025)* study. Most recently, the *FLOW (2024)* trial confirmed glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as promising fourth pillar of nephroprotective therapies.

Key Messages: Together, these advances, termed the “Fantastic Four”, have redefined standards of care in DKD. This review synthesizes pivotal clinical trials and highlights evolving strategies to guide individualized treatment and future research.

Introduction

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) and kidney failure worldwide, affecting approximately 30–40% of patients with diabetes [1-3]. Moreover, the global incidence of CKD attributable to type 2 diabetes mellitus increased by 74% in 2017 compared with 1990 [3]. DKD is characterized by persistent albuminuria, a progressive decline in glomerular filtration rate (GFR), and increased risk of cardiovascular (CV) morbidity and mortality [4]. Beyond glomerular lesions, tubulointerstitial fibrosis and vascular rarefaction are critical determinants of DKD progression [5]. Notably, up to one-third of patients may develop reduced GFR without overt albuminuria, underscoring the heterogeneity of DKD and the limitations of albuminuria as a sole marker [6, 7]. The pathophysiology involves metabolic and hemodynamic disturbances driven by chronic hyperglycemia, including glomerular hyperfiltration, podocyte injury, oxidative stress, advanced glycation end-products, activation of the renin-angiotensin-aldosterone system, and maladaptive inflammatory and fibrotic responses. These processes link DKD with systemic vascular dysfunction, explaining the close overlap between renal and CV risk. Clinically, DKD progression is staged from microalbuminuria to macroalbuminuria, followed by declining GFR and eventual kidney failure, with current KDIGO guidelines recommending risk stratification based on both albuminuria and estimated GFR (eGFR) categories [8].

For decades, therapeutic strategies in diabetes focused primarily on glycemic control. Landmark trials such as the Diabetes Control and Complications Trial (DCCT) in patients with insulin dependent diabetes mellitus [9] and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes [10], demonstrated that intensive glucose control significantly reduced the risk of microvascular complications.

A major breakthrough was achieved in the early 1990s with the demonstration that renin-angiotensin-aldosterone system (RAAS) blockade confers kidney-specific protection. The Captopril Trial (1993) demonstrated that angiotensin-converting enzyme (ACE) inhibition reduced the risk of serum creatinine doubling and progression to kidney failure in patients with DKD, independent of blood pressure control [11]. Subsequent trials, including IRMA-1, IDNT, and RENAAL (2001), firmly established angiotensin receptor blockers (ARBs) as nephroprotective agents in type 2 diabetes [12-14] (Fig. 1). These findings shaped international guidelines, which for more than a decade recommended ACE inhibitors or ARBs as the cornerstone of DKD management.

However, from 2001 to 2015, progress stagnated (Fig. 1). Trials of novel agents such as bardoxolone (BEACON trial), an Nrf2 activator with anti-inflammatory and antioxidant effects failed to improve hard renal outcomes and raised safety concerns [15]. The therapeutic landscape changed dramatically with the advent of sodium-glucose cotransporter-2 (SGLT2) inhibitors. Empagliflozin, as demonstrated in the EMPA-REG OUTCOME trial (2015) [16], subsequently canagliflozin in CANVAS (2017) [17] and dapagliflozin in DECLARE-TIMI 58 (2019) [18], reduced the risk of major CV events in patients with type 2 diabetes. However, the beneficial effects on kidney outcomes were specifically demonstrated in the landmark trials CREDENCE (2019) with canagliflozin [19], DAPA-CKD (2020) with dapagliflozin [20], and EMPA-KIDNEY (2023) with empagliflozin [21], which consistently established robust benefits in reducing albuminuria and slowing CKD progression.

More recently, non-steroidal mineralocorticoid receptor antagonism with finerenone in FIDELIO-DKD and FIGARO-DKD further improved kidney and CV outcomes [22, 23]. The CONFIDENCE trial (2024) provided proof-of-concept for dual therapy with finerenone and empagliflozin, showing additive reductions in albuminuria [24, 25]. Parallel to these developments, glucagon-like peptide-1 receptor agonists (GLP-1 RA) have gained worldwide attention. The FLOW trial (2024) demonstrated that semaglutide reduced the risk of adverse kidney outcomes in type 2 diabetes with CKD, marking another emerging therapeutic class [24].

Taken together, therapeutic advances over the past 30 years have transformed the care of DKD, evolving from glycemic control, monotherapy with RAS blockade to multidrug strategies incorporating SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonist, and GLP-1 RAs representing the “*Fantastic Four in Nephrology*”. Furthermore, the significantly positive results regarding CV outcomes have led to the widespread use of many of these medications for heart

failure, irrespective of the presence of DKD, reflected within the “Fantastic Four in Cardiology” [26-28]. This review summarizes the evidence from pivotal RCTs, highlights clinical implications, and outlines future directions for individualized management of DKD.

Methods

This review was conducted as a narrative, structured synthesis of pivotal randomized controlled trials (RCTs) in DKD published over the past three decades. Our primary objective was to identify and summarize clinical evidence that has shaped current therapeutic practice in the management of diabetic kidney disease.

Search strategy and study identification:

We searched PubMed/MEDLINE and major bibliographic databases from 1990 to 2025 using the following keywords: “diabetic nephropathy”, “diabetic kidney disease”, “randomized controlled trial”, “albuminuria”, “end-stage kidney disease”, “SGLT2 inhibitors”, “finerenone”, “GLP-1 receptor agonists”. In addition, reference lists of relevant reviews, meta-analyses, and international guideline documents were manually screened.

Inclusion criteria:

- Randomized controlled trials (phase III or IV) enrolling ≥ 500 patients with diabetes and kidney involvement (microalbuminuria, proteinuria, or reduced estimated GFR).
- Published in journals with an Impact Factor (IF) >10 (Journal Citation Reports 2023).
- Trials demonstrating clinically meaningful kidney outcomes, defined as progression of albuminuria, doubling of serum creatinine, kidney failure, or validated composite kidney endpoints.
- Pivotal studies that changed clinical practice, irrespective of whether results were positive or neutral.

Exclusion criteria:

- Phase II studies, pilot trials, or mechanistic studies without hard renal endpoints.
- Abstract-only publications, conference proceedings, or unpublished data.
- Trials focusing exclusively on CV outcomes without renal endpoints or pre-specified renal subanalyses.

Study selection:

Based on these criteria, we identified 15 pivotal RCTs conducted between 1993 and 2024. These include landmark studies of RAAS inhibition (Captopril, IRMA-1, IDNT, RENAAL), glycemic control (DCCT/EDIC, UKPDS), sodium–glucose cotransporter-2 (SGLT2) inhibitors (EMPA-REG OUTCOME, CANVAS, CREDENCE, DAPA-CKD, EMPA-KIDNEY), non-steroidal mineralocorticoid receptor antagonists (FIDELIO-DKD, FIGARO-DKD, CONFIDENCE), and glucagon-like peptide-1 receptor agonists (FLOW).

Data extraction and synthesis:

For each trial, we extracted study design, patient population, sample size, intervention and comparator, primary renal outcomes, and key results. Trials were categorized as *practice-changing* if their findings directly influenced international guidelines and standards of care. Results are presented along a historical timeline (1990–2025) to illustrate the evolution of therapeutic strategies in DKD.

Results

1. Glycemic and multifactorial control

The Diabetes Control and Complications Trial (DCCT, 1993) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated that intensive glycemic control in type 1 diabetes substantially reduced the incidence of both microalbuminuria and overt DKD [9]. Similarly, the UK Prospective Diabetes Study (UKPDS, 1998) in type 2 diabetes showed that strict blood glucose and blood pressure management lowered the risk of microvascular complications, including early stages of kidney disease [10]. These trials established hyperglycemia

and hypertension as modifiable drivers of diabetic nephropathy and formed the cornerstone of multifactorial management.

2. Renin–angiotensin system (RAS) blockade

The Captopril trial (1993) was the first to demonstrate beneficial effects of angiotensin-converting enzyme (ACE) inhibition in diabetic nephropathy [11]. It enrolled 409 patients with type 1 diabetes and overt nephropathy, defined as proteinuria ≥ 500 mg per 24 hours, and baseline serum creatinine ≤ 2.5 mg/dl. At baseline, the mean serum creatinine was approximately 1.3 mg/dl and average proteinuria was around 2.5 g/24 h. Over a median follow-up of three years, captopril significantly reduced the risk of the primary composite endpoint of doubling of serum creatinine or progression to kidney failure by 48% compared with placebo ($P=0.007$). This effect was most pronounced in patients with higher baseline serum creatinine, reaching up to a 76% relative risk reduction in those with levels above 2.0 mg/dl. The annual decline in creatinine clearance was -11% in the captopril group versus -17% in the placebo group. Importantly, the treatment also halved the risk of the composite outcome of death, dialysis, or transplantation, independent of blood pressure reduction.

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-1) trial randomized 590 patients with type 2 diabetes and persistent microalbuminuria, defined as urinary albumin excretion of 20–200 $\mu\text{g}/\text{min}$, while baseline renal function was preserved (creatinine in men < 1.5 mg/dl, in women < 1.1 mg/dl). Participants were assigned to receive either placebo, irbesartan 150 mg, or irbesartan 300 mg daily. Over a median follow-up of two years, progression to overt nephropathy occurred in 5.2% of patients in the 300 mg irbesartan group compared with 9.7% in the 150 mg irbesartan and 14.9% in the placebo group, corresponding to a hazard ratio (HR) of 0.30 [95% CI, 0.14 to 0.61; $P<0.001$] and 0.61 [95% CI, 0.34 to 1.08; $P=0.08$] for the two irbesartan groups, respectively. Treatment with irbesartan also reduced urinary albumin excretion in a dose-dependent manner, with decreases of 24% in the 150 mg group and 38% in the 300 mg group. Importantly, these renal benefits were observed without significant differences in systemic blood pressure compared with placebo, supporting the concept of a direct renoprotective effect [12].

The Irbesartan Diabetic Nephropathy Trial (IDNT, 2001) investigated the effects of angiotensin receptor blockade in 1,715 patients with type 2 diabetes, hypertension, and proteinuric CKD. At baseline, the mean serum creatinine was approximately 1.7 mg/dl, and albuminuria 1.9 g/day. Patients were randomized to receive irbesartan, amlodipine, or placebo, and were followed for a median of 2.6 years. Irbesartan significantly reduced the risk of the composite primary endpoint of doubling of serum creatinine, kidney failure, or death from any cause by 20% vs placebo ($P=0.02$) and by 23% vs amlodipine ($P=0.006$). By contrast, amlodipine did not confer renal protection despite similar blood pressure lowering, underscoring the independent benefit of RAAS blockade in DKD [13].

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL, 2001) trial evaluated the effects of losartan in 1,513 patients with type 2 diabetes, hypertension, and overt nephropathy. At study entry, the mean baseline serum creatinine was 1.9 mg/dl, and median urinary albumin-to-creatinine ratio (UACR) 1.2g/g Creatinine. Patients were randomized to losartan or placebo on top of conventional antihypertensive therapy, and were followed for mean 3.4 years. Losartan reduced the risk of the composite primary endpoint (doubling of serum creatinine, kidney failure, or death) by 16% compared with placebo ($p=0.02$). The risk of doubling of serum creatinine was reduced by 25% ($P=0.006$), and the risk of progression to kidney failure was reduced by 28% ($P=0.002$). Losartan also reduced proteinuria by 35% compared to placebo and decreased hospitalization for heart failure by 32%, highlighting both renal and cardiac benefits [14] (Table 1).

3. Sodium–glucose cotransporter-2 (SGLT2) inhibitors

The EMPA-REG OUTCOME trial enrolled 7,020 patients with type 2 diabetes and established CV disease, all with baseline eGFR above 30 ml/min/1.73 m² (mean eGFR 74 ml/min/1.73 m²). Albuminuria status at entry varied, with 60% normoalbuminuria, 29% microalbuminuria, and 11% macroalbuminuria. Participants received empagliflozin 10 or 25 mg daily or placebo, with a median follow-up of 3.1 years. Empagliflozin reduced progression to macroalbuminuria by 38%, doubling of serum creatinine by 44%, and initiation of renal replacement therapy by 55%. The composite

nephropathy outcome was reduced with a hazard ratio (HR) of 0.61 (95% CI 0.53–0.70). In addition, major CV benefits were demonstrated, including a reduction in major adverse CV events (MACE) (HR 0.86; 95% CI 0.74–0.99), a 38% reduction in CV death, a 35% reduction in hospitalization for heart failure, and a 32% reduction in all-cause mortality [29].

The CANVAS Program combined data from two sister trials and randomized 10,142 patients with type 2 diabetes and high CV risk. The mean baseline eGFR was 76 ml/min/1.73 m², and median UACR was 12.3 mg/g, with 70% normoalbuminuria, 23% microalbuminuria, and 8% macroalbuminuria. Over a mean follow-up of 3.6 years, canagliflozin reduced progression of albuminuria by 31% and increased regression of albuminuria by 57%. The composite renal endpoint of sustained $\geq 40\%$ decline in eGFR, need for renal replacement therapy, or renal death was reduced by 39%. CV outcomes demonstrated a significant reduction in MACE (HR 0.86; 95% CI 0.75–0.97) [17].

The CREDENCE trial enrolled 4,401 patients with type 2 diabetes and albuminuric CKD, with a mean eGFR of 56 ml/min/1.73 m² and UACR 300–5000 mg/g. About half had established CV disease. Patients were randomized to canagliflozin 100 mg or placebo and followed for a median of 2.62 years. The primary composite endpoint—kidney failure (dialysis, transplantation, or sustained eGFR < 15 ml/min/1.73 m²), doubling of serum creatinine, or death from renal or CV causes—was reduced by 30% with canagliflozin. Secondary endpoints included reductions in MACE (HR 0.80; 95% CI 0.67–0.95) and hospitalization for heart failure (HR 0.61; 95% CI 0.47–0.80) [19].

The DAPA-CKD trial investigated dapagliflozin in 4,304 patients with CKD, with or without diabetes. Baseline mean eGFR was 43.1 ml/min/1.73 m² and median UACR was 949 mg/g; 67.5% of participants had type 2 diabetes. Patients received dapagliflozin 10 mg daily or placebo, with a median follow-up of 2.4 years. The primary composite endpoint—a sustained $\geq 50\%$ decline in eGFR, kidney failure, or death from renal or CV causes—was reduced by 37% with dapagliflozin. CV outcomes also improved, with a hazard ratio of 0.71 (95% CI 0.55–0.92) for the composite of CV death or hospitalization for heart failure [20].

The EMPA-KIDNEY trial randomized 6,609 patients with CKD, defined as eGFR 20–45 ml/min/1.73 m² or eGFR 45–90 with albuminuria. The mean baseline eGFR was 37.3 ml/min/1.73 m² and median UACR was 329 mg/g; 46% had diabetes. Patients received empagliflozin 10 mg daily or placebo, with a median follow-up of 2.0 years. The primary composite outcome—progression of CKD (kidney failure, sustained decrease in eGFR to < 10 ml/min/1.73 m², decline of $\geq 40\%$ in eGFR, or renal death) or CV death—was reduced by 23%. Secondary outcomes showed no significant effect on the composite of hospitalization for heart failure or CV death, although overall renal protection was consistent across subgroups [21]. Complementing these RCTs, the multinational DISCOVER-CKD study provided prospective real-world evidence. Despite guideline recommendations, a substantial proportion of patients with CKD, of whom nearly half had type 2 diabetes, were not treated with RAS blockade or SGLT2 inhibitors; yet, those who received guideline-directed medical therapy experienced significantly fewer adverse renal outcomes, highlighting the ongoing treatment gap in clinical practice [30] (Table 2).

4. Non-steroidal mineralocorticoid receptor antagonists (MRAs)

The FIDELIO-DKD trial enrolled 5,674 patients with type 2 diabetes and CKD already receiving ACE inhibitor or ARB therapy. The mean baseline eGFR was 44 ml/min/1.73 m², and median UACR was 852 mg/g, reflecting patients with advanced DKD. Patients were randomized to finerenone or placebo and followed for a median of 2.6 years. Finerenone significantly reduced the risk of the primary composite outcome—kidney failure, sustained $\geq 40\%$ decline in eGFR, or renal death—with a HR of 0.82 (95% CI 0.73–0.93), corresponding to a relative risk reduction of 15.7%. Secondary outcomes showed a 12.2% relative risk reduction in the composite of CV death, myocardial infarction, stroke, or hospitalization for heart failure (HR 0.86; 95% CI 0.75–0.99) [22].

The FIGARO-DKD trial included 7,352 patients with type 2 diabetes and earlier stages of CKD. At baseline, mean eGFR was 68 ml/min/1.73 m², and median UACR was 308 mg/g. Participants were randomized to finerenone or placebo and followed for a median of 3.4 years. Finerenone reduced the risk of the composite renal outcome (kidney failure, sustained $\geq 40\%$ eGFR decline, or death from renal causes), though the effect did not reach conventional statistical significance (HR 0.87; 95% CI

0.76–1.01; RRR 11.9%). For CV outcomes, finerenone significantly reduced the composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (HR 0.87; 95% CI 0.76–0.98), a benefit driven primarily by a 29% reduction in heart failure hospitalization (HR 0.71; 95% CI 0.56–0.90) [23]. More recently, the large FINE-HEART pooled analysis, including nearly 19,000 patients with CKD and type 2 diabetes, confirmed and extended these findings [31]. Finerenone consistently reduced CV events, kidney outcomes, and mortality across a wide spectrum of eGFR and albuminuria categories, thereby broadening the evidence base for its use in routine practice.

The CONFIDENCE trial tested dual therapy with finerenone and the SGLT2 inhibitor empagliflozin in 800 patients with type 2 diabetes and CKD. Baseline mean eGFR was 54.2 ml/min/1.73 m², and median UACR was 579 mg/g. Patients were randomized to combination therapy versus either drug as monotherapy and followed for 180 days. Combination therapy achieved an additional 29% reduction in UACR compared with finerenone alone, and a 32% greater reduction compared with empagliflozin alone [24] (Table 3).

5. GLP-1 receptor agonists

The FLOW trial (2024) evaluated semaglutide 1 mg weekly vs placebo in 3533 patients with type 2 diabetes and CKD, with a mean eGFR of 47 ml/min/1.73m² and a median UACR of 567.6 mg/g. Semaglutide significantly reduced the risk of the primary composite endpoint of major adverse kidney events (kidney failure, ≥50% eGFR decline, or renal/CV death) with a HR of 0.76 (95% CI 0.66–0.88). CV death was also reduced with a HR of 0.71 (95% CI, 0.56 to 0.89) (Table 4).

Discussion

Over the past three decades, the therapeutic landscape of DKD has shifted from monotherapy approaches to multidrug strategies that target both renal and CV risk. The evidence summarized in this review underscores how glycemic and blood pressure control, RAAS blockade, SGLT2 inhibitors, non-steroidal MRAs, and GLP-1 receptor agonists have progressively redefined the standard of care. Together, these interventions represent a paradigm shift toward comprehensive cardiorenal-metabolic protection.

This evolving paradigm aligns with the recent American Heart Association Presidential Advisory on cardiovascular-kidney-metabolic (CKM) health, which calls for a unified approach to prevent and manage the intertwined risks of diabetes, CKD, and CV disease. Framing DKD within the broader CKM construct underscores the need for integrated, multidrug strategies that simultaneously address metabolic, renal, and CV pathways [32].

RAAS and SGLT2 inhibitors derive their kidney-protective effect primarily from the reduction of intraglomerular pressure and glomerular hyperfiltration. RAAS inhibitors act by blocking angiotensin II-mediated efferent arteriolar vasoconstriction, thereby lowering glomerular capillary pressure. In addition, RAAS inhibition attenuates maladaptive cellular signaling pathways involved in inflammation and fibrosis, contributing further to structural protection of the nephron [33]. SGLT2i, on the other hand, reduce glucose and sodium reabsorption in the proximal tubule, which increases sodium delivery to the macula densa and restores tubuloglomerular feedback. This results in afferent arteriolar vasoconstriction and a reduction in intraglomerular pressure. In parallel, SGLT2 inhibitors have been shown to stimulate erythropoietin production, leading to increases in hematocrit and potentially enhanced systemic oxygen delivery [34]. Beyond their hemodynamic actions, SGLT2 inhibitors may confer additional kidney and CV protective effects by reducing systemic uremic toxin levels [35] and improving renal tissue oxygenation, thereby attenuating hypoxia-related kidney inflammation, fibrosis, and progressive nephron loss [34, 36, 37]. Finerenone as a selective, non-steroidal mineralocorticoid receptor antagonist confers kidney protection predominantly through anti-inflammatory and anti-fibrotic pathways [22]. Spironolacton as a steroidal mineralocorticoid receptor antagonist also reduces albuminuria, supporting mineralocorticoid receptor blockade as a promising nephroprotective strategy [38]. However, it is more likely associated with hyperkalemia, especially in advanced CKD stages [39].

Despite these advances, residual risk remains substantial [40]. Even in contemporary landmark trials such as CREDENCE, DAPA-CKD, FIDELITY, and FLOW, many patients progressed to kidney failure or experienced major CV events. This highlights the need for earlier detection and intervention as well as the development of additional therapeutic classes. Moreover, real-world data suggest that implementation of evidence-based therapy remains suboptimal. In the United States, fewer than 15% of eligible patients with type 2 diabetes and ASCVD receive an SGLT2 inhibitor or GLP-1 RA, with prescription rates of only 7.2% and 7.9%, respectively [41]. In the UK, finerenone has only recently been recommended by NICE [42], underscoring how slowly novel therapies are adopted into practice. Even ACEi/ARB uptake in the US for DKD historically lagged at 25–40% before more recent improvements to ~70% [43]. Compounding this, less than half of patients with diabetes undergo annual albuminuria testing [44], limiting opportunities for early initiation of the

“Fantastic Four”. Uptake is also low worldwide, particularly in low- and middle-income regions where access is even more restricted. Closing these gaps and inequities is critical if the benefits demonstrated in clinical trials are to be translated into population health.

Another challenge is the heterogeneity of DKD. Traditional staging based on albuminuria and eGFR fails to fully capture disease variability. Up to one-third of patients may experience GFR decline without significant albuminuria [45], and these non-albuminuric phenotypes are underrepresented in current trials. Certain patient groups also remain understudied in contemporary trials; i.e. elderly patients, who represent a large proportion of the CKD population, are frequently underrepresented despite their high risk of adverse outcomes and polypharmacy. Similarly, individuals with advanced CKD (eGFR <20 ml/min/1.73 m²) are typically excluded from pivotal trials, leaving uncertainty about efficacy and safety in this vulnerable group.

Also, most modern RCTs enrolled patients with type 2 diabetes, leaving a knowledge gap in type 1 diabetes and in more advanced CKD stages. Although the concept of the “Fantastic Four” represents a major paradigm shift in the management of DKD, it is important to emphasize that the supporting evidence is predominantly derived from large randomized controlled trials in patients with type 2 diabetes. Robust outcome data exist for the combined use of RAAS inhibition, SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists, and GLP-1 receptor agonists in this population, allowing for an approach analogous to guideline-directed medical therapy (GDMT) as established in heart failure. In contrast, the applicability of this comprehensive therapeutic framework to DKD in type 1 diabetes remains limited by a substantial lack of dedicated clinical trial data.

To date, the CAPTOPRIL trial remains the only landmark randomized study demonstrating kidney protective effects in patients with type 1 diabetes and overt diabetic nephropathy. In contrast to type 2 diabetes, individuals with type 1 diabetes have been largely excluded from contemporary DKD outcome trials evaluating SGLT2 inhibitors, mineralocorticoid receptor antagonists, and GLP-1 receptor agonists, resulting in a significant evidence gap. Consequently, the extrapolation of combination strategies or “quadruple therapy” to type 1 diabetes cannot currently be supported by high-quality outcome data and should be approached with caution.

Nevertheless, renewed interest in advancing therapeutic strategies for DKD in type 1 diabetes is emerging. In this context, acetazolamide has recently gained attention as a potential kidney protective agent, supported by early experimental and clinical evidence suggesting favorable effects on tubular workload, glomerular hemodynamics, relieving glomerular hyperfiltration and intraglomerular pressure [46]. While these findings remain preliminary and require confirmation in adequately powered outcome trials, they highlight a growing effort to develop disease-modifying therapies tailored specifically to DKD in type 1 diabetes.

Taken together, these observations underscore that, while GDMT-like approaches are now well supported for DKD in type 2 diabetes, substantial unmet needs persist in type 1 diabetes. Future clinical trials specifically designed for this population are urgently required to establish evidence-based therapeutic strategies and to close the longstanding translational gap in DKD care.

There is an urgent need for biomarkers that reflect active injury, inflammation, and fibrosis to guide risk stratification and therapy selection beyond albuminuria [47–49]. Recent work has highlighted urinary Dickkopf-3 as a promising tubular stress biomarker that predicts short-term eGFR decline and

fibrosis even in the absence of albuminuria [50]. Notably, the association of RAAS inhibition with lower Dickkopf-3 levels suggests that this biomarker may reflect treatment-responsive tubular stress, thereby offering potential value not only for early risk stratification but also for monitoring the effectiveness of nephroprotective therapy in routine clinical practice [51].

The question of optimal sequencing and combination of therapies also remains unanswered. While SGLT2 inhibitors are widely recommended as foundational therapy; however, the potentially distorting effect of the high level of recommendation for SGLT2 inhibitors for all types of chronic heart failure must also be taken into account. On the other hand, the integration of finerenone and GLP-1 receptor agonists into clinical practice raises issues of drug sequencing, additive benefit, and long-term safety. The CONFIDENCE trial provided proof-of-concept for combination therapy, but larger, longer trials are required. Recently, a modeling study by Neuen et al. projected that combined use of an SGLT2 inhibitor, GLP-1 receptor agonist, and non-steroidal MRA in patients with type 2 diabetes and albuminuria could substantially extend lifetime survival free of kidney failure and CV events compared with conventional care [52]. Mechanistically, this “pillared” approach is attractive because each class targets complementary pathways: SGLT2 inhibitors reduce intraglomerular pressure and improve hemodynamics, non-steroidal MRAs attenuate inflammation and fibrosis, and GLP-1 receptor agonists address the metabolic derangements characteristic of type 2 diabetes. This strategy closely parallels the multidrug regimen commonly used in heart failure, where the ability of SGLT2 inhibitors to address different pathophysiological signaling pathways than the other drugs of “Fantastic Four of Cardiology” is well known [26, 27, 53, 54].

However, looking forward, the field is entering a phase of precision nephrology. Advances in imaging, digital health, and molecular profiling may soon allow more personalized therapeutic decisions, identifying patients most likely to benefit from specific agents or combinations. Meanwhile, novel therapies under investigation, including endothelin receptor antagonists [55], anti-inflammatory agents such as JAK/STAT inhibitors [56], and cell-based [57, 58] or extracellular vesicle therapies [59], offer new opportunities to further reduce residual risk.

Across regions, ACE inhibitors and ARBs remain relatively inexpensive and are broadly reimbursed, whereas SGLT2 inhibitors and non-steroidal MRAs carry substantially higher costs, particularly in the United States. European health systems benefit from negotiated prices, resulting in lower annual expenditures, while Gulf Cooperation Council countries generally exhibit intermediate pricing. Reimbursement policies vary by drug class and region, with coverage often contingent on indication approval and, in some cases, prior authorization (Table 5).

In conclusion, therapeutic progress in DKD has been remarkable, yet incomplete. The challenge now lies not only in discovering new drugs, but also in implementing, individualizing, and equitably delivering the therapies we already have. Multidrug regimens that combine hemodynamic, metabolic, and anti-inflammatory strategies are likely to define the future standard of care, while precision approaches promise to further refine outcomes in this high-risk population.

Conflict of Interest Statement

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Sources

The authors declare that no financial support was received for the research and/or publication of this article.

Author Contributions

FH-S and GY contributed equally to this work and wrote the first draft of the manuscript. They conducted the literature search and identified relevant studies. Both authors were also substantially involved in the discussion and interpretation of the current literature. CD and JJ critically reviewed the manuscript and provided intellectual input. BY curated, extracted, and validated the data, played

a leading role in data interpretation and discussion. He prepared the visualizations and was responsible for the overall supervision, and final editing of the manuscript as the senior author.

Accepted Manuscript

Figure Legend

Figure 1. Landmark Studies Shaping the Therapy and Management of Diabetic Kidney Disease (1990–2025)

Each study is labeled with its acronym and publication year to avoid overlap.

- **Blue:** Glycemic control
- **Orange:** ACE inhibitors / Angiotensin II receptor antagonists
- **Green:** SGLT2 inhibitors
- **Red:** Mineralocorticoid receptor antagonists
- **Purple:** GLP-1 agonists

Accepted Manuscript

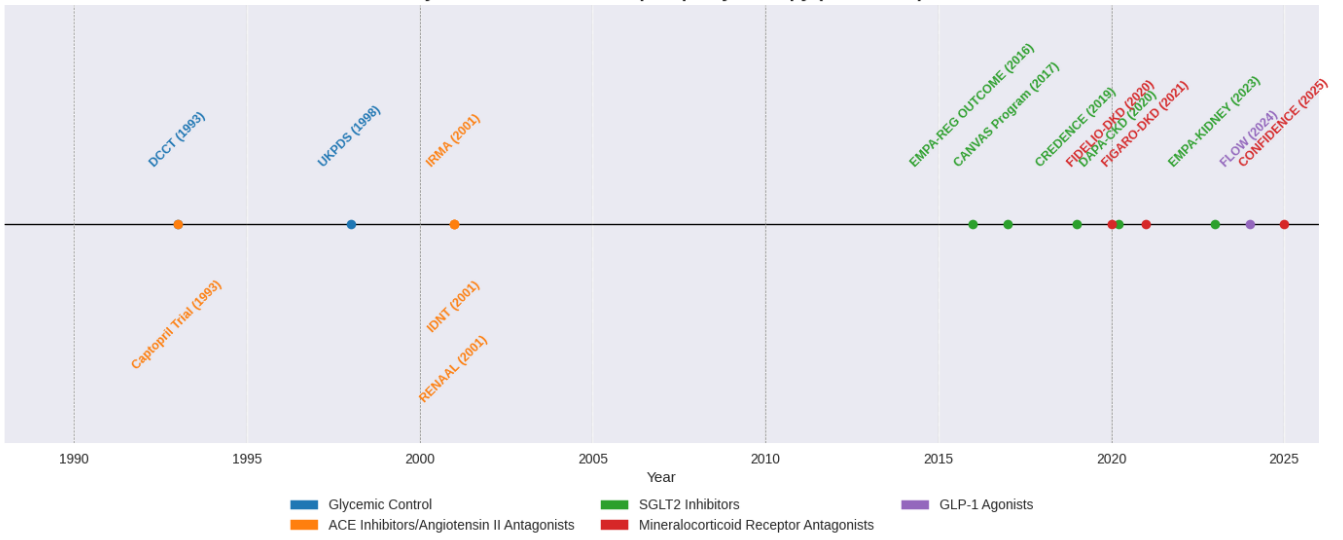
References

1. Tomino Y, Gohda T. The Prevalence and Management of Diabetic Nephropathy in Asia. *Kidney Dis (Basel)*. 2015;1(1):52-60.
2. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. *Clin J Am Soc Nephrol*. 2017;12(12):2032-45.
3. Li H, Lu W, Wang A, Jiang H, Lyu J. Changing epidemiology of chronic kidney disease as a result of type 2 diabetes mellitus from 1990 to 2017: Estimates from Global Burden of Disease 2017. *Journal of Diabetes Investigation*. 2021;12(3):346-56.
4. Ma X, Liu R, Xi X, Zhuo H, Gu Y. Global burden of chronic kidney disease due to diabetes mellitus, 1990-2021, and projections to 2050. *Frontiers in Endocrinology*. 2025;Volume 16 - 2025.
5. Schnaper HW. The Tubulointerstitial Pathophysiology of Progressive Kidney Disease. *Adv Chronic Kidney Dis*. 2017;24(2):107-16.
6. Porrini E, Ruggenti P, Mogensen CE, Barlovic DP, Praga M, Cruzado JM, et al. Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes. *Lancet Diabetes Endocrinol*. 2015;3(5):382-91.
7. Kramer H, Boucher RE, Leehey D, Fried L, Wei G, Greene T, et al. Increasing Mortality in Adults With Diabetes and Low Estimated Glomerular Filtration Rate in the Absence of Albuminuria. *Diabetes Care*. 2018;41(4):775-81.
8. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2022;102(5s):S1-s127.
9. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-86.
10. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-53.
11. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*. 1993;329(20):1456-62.
12. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345(12):870-8.
13. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-60.
14. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-9.
15. Levin J. Reata Company Statement: Termination of the BEACON Trial 2012 [Available from: https://www.fiercebiotech.com/biotech/reata-company-statement-termination-of-beacon-trial?utm_source=chatgpt.com].
16. 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(22):2117-28.
17. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-57.
18. 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(4):347-57.
19. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-306.
20. 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(15):1436-46.
21. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388(2):117-27.
22. 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(23):2219-29.
23. 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(24):2252-63.

24. 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(6):533-43.
25. Mårup FH, Thomsen MB, Birn H. Additive effects of dapagliflozin and finerenone on albuminuria in non-diabetic CKD: an open-label randomized clinical trial. *Clin Kidney J*. 2024;17(1):sfad249.
26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-726.
27. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-39.
28. Bauersachs J. Heart failure drug treatment: the fantastic four. *Eur Heart J*. 2021;42(6):681-3.
29. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):323-34.
30. Pecoits-Filho R, Kanda E, Kashihara N, Ofori-Asenso R, Chen H, Pentakota S, et al. Characteristics and cardio-renal outcomes in CKD patients receiving guideline-directed therapy: insights from DISCOVER CKD. *Nephrol Dial Transplant*. 2025.
31. Ostrominski JW, Filippatos G, Claggett BL, Miao ZM, Desai AS, Jhund PS, et al. Effect of Finerenone on Morbidity and Mortality in CKD. *J Am Soc Nephrol*. 2025.
32. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. *Circulation*. 2023;148(20):1606-35.
33. Chawla T, Sharma D, Singh A. Role of the renin angiotensin system in diabetic nephropathy. *World J Diabetes*. 2010;1(5):141-5.
34. Tian Q, Guo K, Deng J, Zhong Y, Yang L. Effects of SGLT2 inhibitors on haematocrit and haemoglobin levels and the associated cardiorenal benefits in T2DM patients: A meta-analysis. *J Cell Mol Med*. 2022;26(2):540-7.
35. Billing AM, Kim YC, Gullaksen S, Schrage B, Raabe J, Hutzfeldt A, et al. Metabolic Communication by SGLT2 Inhibition. *Circulation*. 2024;149(11):860-84.
36. Upadhyay A. SGLT2 Inhibitors and Kidney Protection: Mechanisms Beyond Tubuloglomerular Feedback. *Kidney360*. 2024;5(5):771-82.
37. Ribatti D. Angiogenic effects of erythropoietin. *Int Rev Cell Mol Biol*. 2012;299:199-234.
38. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol*. 2009;20(12):2641-50.
39. Currie G, Taylor AH, Fujita T, Ohtsu H, Lindhardt M, Rossing P, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol*. 2016;17(1):127.
40. Chaudhuri A, Ghanim H, Arora P. Improving the residual risk of renal and cardiovascular outcomes in diabetic kidney disease: A review of pathophysiology, mechanisms, and evidence from recent trials. *Diabetes Obes Metab*. 2022;24(3):365-76.
41. Nelson AJ, Ardissino M, Haynes K, Shambhu S, Eapen ZJ, McGuire DK, et al. Gaps in Evidence-Based Therapy Use in Insured Patients in the United States With Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease. *J Am Heart Assoc*. 2021;10(2):e016835.
42. Excellence. NIfHaC. Finerenone for treating chronic kidney disease in type 2 diabetes. Technical appraisal guidance [TA877]. 23 March 2023 [Available from: <https://www.nice.org.uk/guidance/ta877>].
43. Nicholas SB, Daratha KB, Alicic RZ, Jones CR, Kornowske LM, Neumiller JJ, et al. Prescription of guideline-directed medical therapies in patients with diabetes and chronic kidney disease from the CURE-CKD Registry, 2019-2020. *Diabetes Obes Metab*. 2023;25(10):2970-9.
44. Tuttle KR, Wong L, St Peter W, Roberts G, Rangaswami J, Mottl A, et al. Moving from Evidence to Implementation of Breakthrough Therapies for Diabetic Kidney Disease. *Clin J Am Soc Nephrol*. 2022;17(7):1092-103.
45. D'Marco L, Guerra-Torres X, Viejo I, Lopez-Romero L, Yugueros A, Bermúdez V. Non-albuminuric Diabetic Kidney Disease Phenotype: Beyond Albuminuria. *touchREV Endocrinol*. 2022;18(2):102-5.
46. Ginsberg C, Seegmiller JC, Vallon V, SeungMi Jin S, Thomas RL, Boeder SC, et al. Acetazolamide Therapy and Kidney Function in Persons with Nonalbuminuric Diabetes Mellitus Type 1. *J Am Soc Nephrol*. 2025;36(3):463-70.

47. Gutiérrez OM, Shlipak MG, Katz R, Waikar SS, Greenberg JH, Schrauben SJ, et al. Associations of Plasma Biomarkers of Inflammation, Fibrosis, and Kidney Tubular Injury With Progression of Diabetic Kidney Disease: A Cohort Study. *Am J Kidney Dis.* 2022;79(6):849-57.e1.
48. Phanish MK, Chapman AN, Yates S, Price R, Hendry BM, Roderick PJ, Dockrell MEC. Evaluation of Urinary Biomarkers of Proximal Tubular Injury, Inflammation, and Fibrosis in Patients With Albuminuric and Nonalbuminuric Diabetic Kidney Disease. *Kidney Int Rep.* 2021;6(5):1355-67.
49. Joumaa JP, Raffoul A, Sarkis C, Chatrieh E, Zaidan S, Attieh P, et al. Mechanisms, Biomarkers, and Treatment Approaches for Diabetic Kidney Disease: Current Insights and Future Perspectives. *J Clin Med.* 2025;14(3).
50. Zewinger S, Rauen T, Rudnicki M, Federico G, Wagner M, Triem S, et al. Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss. *J Am Soc Nephrol.* 2018;29(11):2722-33.
51. Speer T, Schunk SJ, Sarakpi T, Schmit D, Wagner M, Arnold L, et al. Urinary DKK3 as a biomarker for short-term kidney function decline in children with chronic kidney disease: an observational cohort study. *Lancet Child Adolesc Health.* 2023;7(6):405-14.
52. Neuen BL, Heerspink HJL, Vart P, Claggett BL, Fletcher RA, Arnott C, et al. Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria. *Circulation.* 2024;149(6):450-62.
53. Packer M. Foetal recapitulation of nutrient surplus signalling by O-GlcNAcylation and the failing heart. *Eur J Heart Fail.* 2023;25(8):1199-212.
54. Palmiero G, Cesaro A, Vetrano E, Pafundi PC, Galiero R, Caturano A, et al. Impact of SGLT2 Inhibitors on Heart Failure: From Pathophysiology to Clinical Effects. *Int J Mol Sci.* 2021;22(11).
55. Smeijer JD, Gomez MF, Rossing P, Heerspink HJL. The effect of the endothelin receptor antagonist atrasentan on insulin resistance in phenotypic clusters of patients with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab.* 2025;27(2):511-8.
56. Tuttle KR, Brosius FC, 3rd, Adler SG, Kretzler M, Mehta RL, Tumlin JA, et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a Phase 2 randomized controlled clinical trial. *Nephrol Dial Transplant.* 2018;33(11):1950-9.
57. Wang J, Liu H, Yue G, Deng Y, Cai W, Xu J. Human placenta-derived mesenchymal stem cells ameliorate diabetic kidney disease by modulating the T helper 17 cell/ regulatory T-cell balance through the programmed death 1 / programmed death-ligand 1 pathway. *Diabetes Obes Metab.* 2024;26(1):32-45.
58. Han X, Wang J, Li R, Huang M, Yue G, Guan L, et al. Placental Mesenchymal Stem Cells Alleviate Podocyte Injury in Diabetic Kidney Disease by Modulating Mitophagy via the SIRT1-PGC-1alpha-TFAM Pathway. *Int J Mol Sci.* 2023;24(5).
59. Malin SK, Erdbrügger U. Extracellular Vesicles in Metabolic and Vascular Insulin Resistance. *J Vasc Res.* 2024;61(3):129-41.

Key Studies in Diabetic Nephropathy Therapy (1990–2025)



Accepted Manuscript

Table 1. ACE inhibitors and angiotensin receptor blockers

Group	Study (Year)	Population (N)	Baseline kidney status	Intervention vs comparator	Primary renal endpoint	Key secondary results
ACEi	Captopril Trial (1993) [11]	409 (T1D, overt DKD)	Mean serum creatinine 1.3 mg/dL; mean proteinuria 2500 mg/24h	Captopril vs placebo Median Follow-up 3 years	- Baseline creatinine 2.0 mg/dL: RRR: 76% - Baseline creatinine 1.5 mg/dL: RRR: 55% - Baseline creatinine 1.0 mg/dL: RRR: 17%	Rate of decline in creatinine clearance: <ul style="list-style-type: none"> Captopril: 11 ± 21% per year Placebo: 17 ± 20% per year (P = 0.03) Among patients with baseline creatinine ≥ 1.5 mg/dL: Captopril 23 ± 25%/year vs placebo 37 ± 25%/year (P = 0.01) Composite endpoint (death, dialysis, transplantation): 50% risk reduction, independent of small differences in blood pressure
ARB	IRMA (2001) [12]	590 (T2D, microalbuminuria, hypertensive)	Microalbuminuria: mean albumin excretion rate 55.5 µg/min; creatinine in men < 1.5 mg/dl, in women < 1.1 mg/dl	Irbesartan 300 mg (or 150 mg) vs placebo Median Follow-up 2 years	Progression to overt DKD (persistent albuminuria >200 µg/min + ≥30% above baseline) Irbesartan 300 mg: RRR of 67% vs placebo Irbesartan 150 mg: RRR of 35% vs placebo	Albuminuria reduction by Irbesartan 300 mg: -38%, Irbesartan 150 mg: -24%
ARB	IDNT (2001) [13]	1715 (T2D, hypertension, proteinuric CKD)	Overt DKD. Mean UACR 1.9g/24h. Mean serum creatinine 1.67 mg/dL	Irbesartan vs amlodipine vs placebo (blood pressure targets similar, <135/85 mmHg) Mean Follow-up 2.6 years	Composite of doubling baseline creatinine, kidney failure, or death from any cause: Irbesartan: -20% risk vs placebo (P=0.02), -23% vs amlodipine (P=0.006)	Irbesartan: risk of doubling of serum creatinine -33% vs placebo (P=0.003), -37% vs amlodipine (P<0.001). RRR for kidney failure: 23% vs placebo/other groups (P=0.07) Blood pressure-adjusted: Effect independent of achieved blood pressure
ARB	RENAAL (2001) [14]	1513 (T2D, DKD)	Overt DKD; hypertensive. Median UACR 1.2 g/g Creatinine. Serum creatinine 1.9 mg/dl	Losartan vs placebo (on background blood pressure therapy) Mean Follow-up 3.4 years	Composite endpoint: -16% RR vs placebo (P=0.02) Doubling of serum creatinine: -25% RR (P=0.006) Kidney failure: -28% RR (P=0.002) Effect independent of BP lowering	Proteinuria -35% Losartan vs. Placebo (P<0.001) Hospitalization for HF: - 32% by Losartan vs placebo (P<0.001)

T1D: type 1 diabetes mellitus
T2D: type 2 diabetes mellitus
ACEi: Angiotensin-Converting Enzyme Inhibitor
ARB: Angiotensin II Receptor Blocker
UACR : urinary albumin-to-creatinine ratio

RRR: relative risk reduction
RR: risk reduction
RRT: renal replacement therapy
HF: heart failure

Accepted Manuscript

Table 2. SGLT2 inhibitors

Group	Study (Year)	Population (N)	Baseline kidney status	Intervention vs comparator	Primary renal endpoint	Key cardiovascular results
Empagliflozin	EMPA-REG OUTCOME (2016) – renal microvascular analysis [29]	7020 (T2D, CV disease, eGFR>30ml/min/1.73 m ²)	Mean eGFR ~74 ml/min/1.73m ² ; albuminuria spectrum: <30 mg/g: 60,0 %	Empagliflozin 10mg vs 25mg vs placebo.	Progression to macroalbuminuria: RRR of 38% Doubling of the serum creatinine: RRR of 44%	Major adverse CV events (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke): HR 0.86 (95% CI 0.74–0.99); CV death: RRR of 38%; Hospitalization for HF: RRR of 35%; All-cause mortality: RRR of 32%
			30–300 mg/g: 28,9 % >300 mg/g: 11,1 %	Median Follow-up 3.1 years	Initiation RRT: RRR of 55% HR 0.61 (95% CI 0.53–0.70) for nephropathy composite.	
Canagliflozin	CANVAS Program (2017) [17]	10,142 (T2D, high CV risk)	Mean eGFR 76 ml/min/1.73m ² Median UACR 12.3 mg/gCreatinine,	Canagliflozin vs placebo	Progression of albuminuria: RRR of 30.6% Regression of albuminuria: Relative Increase of 56.5%	Major CV events (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke): HR 0.86 (95% CI 0.75–0.97).
			albuminuria spectrum: UACR <30 mg/g: 69.8 %	Mean Follow-up 3.6 years	Composite (sustained ≥40% eGFR reduction, RRT, or renal death): RRR of 38.9%	
			UACR 30–300 mg/g: 22.6 % UACR >300 mg/g: 7.6 %			
Canagliflozin	CREDENCE (2019) [19]	4401 (T2D, albuminuric CKD)	Mean eGFR 56 ml/min/1.73m ² ; UACR: 300 - 5000 mg/g (all patients); 50.4% had CV disease	Canagliflozin 100 mg vs placebo Median follow-up of 2.62 years	Composite of kidney failure (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m ²), a doubling of the serum creatinine, or death from renal or CV causes: RRR of 30%	Composite MACE (CV death, nonfatal MI, nonfatal stroke): HR 0.80 (0.67–0.95); HF hospitalization: HR 0.61 (0.47–0.80)
Dapagliflozin	DAPA-CKD (2020) [20]	4304 (CKD with/without T2D, albuminuric)	Mean eGFR 43.1 ml/min/1.73m ² ; median UACR 949 mg/g; 67.5% T2D	Dapagliflozin 10mg vs placebo Median follow-up of 2.4 years	Composite of a sustained decline in the eGFR of at least 50%, kidney failure, or death from renal or CV causes: RRR of 36.9%	CV death or HF hosp.: HR 0.71 (0.55–0.92); Consistent benefit with/without Diabetes
Empagliflozin	EMPA-KIDNEY (2023) [21]	6609 (CKD, eGFR 20-45 or 45-90 w/albuminuria; with/without T2D)	Mean eGFR 37.3 ml/min/1.73m ² ; median UACR 329 mg/g; 46% T2D	Empagliflozin 10 mg vs placebo Median follow-up of 2.0 years of	Composite of progression of CKD (defined as kidney failure, decrease in eGFR to <10 ml/min 1.73 m ² , decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from CV causes: RRR of 22.6%	No significant differences regarding the composite outcome of hospitalization for HF or death from CV causes

T1D: type 1 diabetes mellitus
T2D: type 2 diabetes mellitus
ACEi: Angiotensin-Converting Enzyme Inhibitor
ARB: Angiotensin II Receptor Blocker
UACR : urinary albumin-to-creatinine ratio
RRR: relative risk reduction
RR: risk reduction
RRT: renal replacement therapy
HF: heart failure

Accepted Manuscript

Table 3. Nonsteroidal mineralocorticoid receptor antagonist

Group	Study (Year)	Population (N)	Baseline kidney status	Intervention vs comparator	Primary renal endpoint	Key cardiovascular results
Finerenone	FIDELIO-DKD (2020) [22]	5674 (T2D, CKD on ACEi/ARB)	Mean eGFR 44 ml/min/1.73m ² ; median UACR 852 mg/g	Finerenone vs placebo Median follow-up of 2.6 years	Composite of kidney failure, sustained decrease in eGFR \geq 40%, or renal death: HR 0.82 (95% CI 0.73–0.93); RRR 15.7 %	Composite of CV death, MI, stroke, HF hospitalizations: HR 0.86 (95% CI 0.75–0.99); RRR 12.2 %
Finerenone	FIGARO-DKD (2021) [23]	7352 (T2D, earlier CKD)	Mean eGFR 68 ml/min/1.73m ² ; median UACR 308 mg/g	Finerenone vs placebo Median follow-up of 3.4 years	Composite: Kidney failure or sustained \geq 40% decrease in eGFR or death from renal causes: HR 0.87 (95% CI 0.76-1.01); RRR of 11.9%	Composite: CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF: HR 0.87 (95% CI 0.76–0.98); RRR of 12.3%; driven by lower HF hospitalizations HR 0.71 (95% CI, 0.56 - 0.90)
Finerenone + Empagliflozin	CONFIDENCE (2025) [24]	800 (T2D, CKD)	Mean eGFR 54.2 ml/min/1.73m ² ; median UACR 579 mg/g	Finerenone + SGLT2i vs respective monotherapy Follow-up 180 days	UACR reduction: – 29% greater vs. finerenone alone – 32% greater vs. empagliflozin alone	NA

T1D: type 1 diabetes mellitus
T2D: type 2 diabetes mellitus
ACEi: Angiotensin-Converting Enzyme Inhibitor
ARB: Angiotensin II Receptor Blocker
UACR : urinary albumin-to-creatinine ratio
RRR: relative risk reduction
RR: risk reduction
RRT: renal replacement therapy
HF: heart failure

Table 4. GLP-1 receptor agonist

Group	Study (Year)	Population (N)	Baseline kidney status	Intervention vs comparator	Primary renal endpoint	Key cardiovascular results
Semaglutide	FLOW (2024) [51]	3533 (T2D, CKD)	Mean eGFR 47 ml/min/1.73m ² ; median UACR 567.6 mg/g	Semaglutide 1.0 mg weekly vs placebo (standard care) median follow-up was 3.4 years	Composite of major kidney events (kidney failure, $\geq 50\%$ eGFR decline, or renal/CV death) HR 0.76 (95% CI 0.66–0.88); RRR 19.3%	CV death (HR, 0.71; 95% CI, 0.56 to 0.89)

T1D: type 1 diabetes mellitus

T2D: type 2 diabetes mellitus

ACEi: Angiotensin-Converting Enzyme Inhibitor

ARB: Angiotensin II Receptor Blocker

UACR : urinary albumin-to-creatinine ratio

RRR: relative risk reduction

RR: risk reduction

RRT: renal replacement therapy

HF: heart failure

Accepted Manuscript

Table 5. Comparison of medication costs in the USA, Germany/Europe and the Middle East

Drug Class / Example	Annual Costs (USA)	Annual Costs (Europe)	Annual Costs (Gulf Cooperation Council)	Reimbursement Notes
ACE inhibitors / ARBs (e.g., Irbesartan 300 mg/d)	~USD 1,060	~EUR 100	~USD 280	Broadly covered in all regions; usually fully reimbursed or subject to minimal copayment in public and private insurance systems.
SGLT2 inhibitors (e.g., Empagliflozin 10 mg/d, Dapagliflozin 10 mg/d)	~USD 6,000 (list prices); out-of-pocket often USD 0–50/month via insurance/assistance	EUR 750–950 (negotiated net price)	~USD 570	Increasingly reimbursed for approved indications (T2D, CKD, HF); may require formulary inclusion or prior authorization.
Mineralocorticoid receptor antagonists				
• Non-steroidal MRA (Finerenone 20 mg/d)	~USD 9,900	~EUR 800	~USD 1,460	Coverage depends on national decisions and insurer policies; usually reimbursed for DKD with restrictions.
• Steroidal MRA (Spironolactone 25 mg/d)	~USD 240	~EUR 80	~USD 65	Widely available and fully reimbursed or associated with negligible copayment.
GLP-1 receptor agonists (e.g., Semaglutide 1 mg/week)	~USD 4,100	EUR 3,500	~USD 1,600	Coverage is heterogeneous; often restricted to approved indications with prior authorization. Patient copayments can be substantial, particularly outside public insurance schemes.

Pricing data were obtained from Amazon Pharmacy (USA), Kulud Pharmacy (Qatar/Gulf Cooperation Council), and the “Arznei aktuell” application (Germany/Europe); all sources accessed on 11 December 2025.

ACE: Angiotensin-Converting Enzyme

ARB: Angiotensin II Receptor Blocker

SGLT2: Sodium–Glucose Cotransporter 2

MRA: Mineralocorticoid receptor antagonists.

GLP-1: Glucagon-like peptide-1