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Review Article

Dual Nephroprotective Strategy of Dapagliflozin and Telmisartan in the Management of Diabetic Kidney Disease: A Comprehensive Review

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ABSTRACT

Diabetic Kidney Disease (DKD) is a leading cause of End-Stage Renal Disease (ESRD) worldwide, contributing substantially to morbidity and mortality among patients with Type 2 Diabetes Mellitus (T2DM). Its pathogenesis involves a complex interplay of metabolic and hemodynamic alterations, including hyperglycemia-induced oxidative stress, inflammation, glomerular hypertension, and progressive fibrosis. Despite the availability of current monotherapies, many patients experience continued renal function decline, highlighting the need for more effective treatment strategies. Combining pharmacological agents with complementary mechanisms offers a promising approach to slowing DKD progression. Telmisartan, an Angiotensin II Receptor Blocker (ARB) with partial peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ) agonist activity, reduces intraglomerular pressure and mitigates fibrosis and inflammation. Dapagliflozin, a Sodium-Glucose Cotransporter 2 (SGLT2) inhibitor, promotes glycosuria, improves renal hemodynamics, and exerts anti-inflammatory and antifibrotic effects independent of glucose lowering. Evidence from preclinical and clinical studies suggests that their combined use provides synergistic nephroprotective benefits, including significant reductions in albuminuria, preservation of estimated Glomerular Filtration Rate (eGFR), improved metabolic control, reduced systemic inflammation, and lowered cardiovascular risk. The combination is generally well tolerated, although careful monitoring is recommended in advanced stages of Chronic Kidney Disease (CKD). This review consolidates current evidence on the dual nephroprotective strategy of dapagliflozin and telmisartan, underscoring its potential role in optimizing outcomes for patients with DKD.

Keywords: Dapagliflozin, Telmisartan, Diabetic Kidney Disease, Nephroprotection, SGLT2 inhibitors, ARBs.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia and has emerged as a global health crisis. The International Diabetes Federation (IDF) estimated that 537 million adults were living with diabetes in 2021, with projections reaching 643 million by 2030 (IDF, 2021). Chronic hyperglycemia in diabetes leads to both microvascular and macrovascular complications, significantly increasing morbidity and mortality. Among the microvascular complications, Diabetic Kidney Disease (DKD) is one of the most devastating, accounting for nearly 50% of End-Stage Renal Disease (ESRD) cases worldwide (Thomas *et al*., 2015). Affecting approximately 20-40% of individuals with diabetes, DKD remains a leading cause of Chronic Kidney Disease (CKD) and ESRD (Alicic *et al*., 2017). In India, the burden is particularly concerning due to the rising prevalence of Type 2 Diabetes Mellitus (T2DM) across both urban and rural populations. Beyond its clinical impact, DKD imposes considerable psychosocial and economic strain on patients and caregivers (Jha *et al*., 2013) and markedly increases the risk of cardiovascular events, underscoring the importance of early and effective intervention (Pálsson and Patel, 2014).

Despite advances in glycemic control and blood pressure management, DKD progression often continues unabated. Conventional therapies, such as Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs), reduce albuminuria and slow renal decline but fail to halt disease progression in many cases (Brenner *et al*., 2001). Furthermore, intensive glycemic control may increase the risk of hypoglycemia, particularly in elderly patients or those with comorbidities (ADVANCE Collaborative Group, 2008). These limitations

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highlight the need for more targeted and multifaceted treatment approaches.

Given the multifactorial pathophysiology of DKD, encompassing hemodynamic, metabolic, inflammatory, and fibrotic pathways, effective nephroprotection is likely to require a combination of agents with complementary mechanisms of action. Telmisartan, beyond its antihypertensive effects, exhibits partial Peroxisome Proliferator-Activated Receptor-gamma (PPAR-γ) agonism, which may provide additional anti-inflammatory and antifibrotic benefits (Schupp *et al*., 2004). Dapagliflozin, a Sodium-Glucose Cotransporter 2 (SGLT2) inhibitor, offers renal protection through both glucose-dependent and glucose-independent mechanisms, including reductions in intraglomerular pressure, oxidative stress, and inflammation (Heerspink *et al*., 2020). Their complementary pharmacological actions suggest a potential synergistic benefit in preserving renal function and improving overall outcomes in patients with DKD.

This review aims to comprehensively evaluate the dual nephroprotective role of dapagliflozin and telmisartan in the management of diabetic kidney disease. It synthesizes evidence from preclinical studies, clinical trials, and real-world practice to assess their individual and combined efficacy, mechanisms of action, and safety profiles, while also identifying gaps in current knowledge to guide future research.

PATHOPHYSIOLOGY OF DIABETIC KIDNEY DISEASE

Hyperglycemia-Induced Renal Damage

Chronic hyperglycemia in diabetes mellitus leads to increased glucose reabsorption by SGLT2 in the kidney, exacerbating hyperglycemia initiating metabolic disturbances that lead to glomerular and tubular injury and causing direct kidney damage. This damage includes elevated TGF-β expression, ROS production, and AGE formation. Additionally, hyperglycemia-induced HIF-1α expression in the mesangium promotes fibrotic factors, while insulin resistance contributes to dyslipidaemia and lipotoxicity in tubular epithelial cells, further advancing diabetic kidney disease (Mazzieri *et al*., 2024). Hyperglycemia increases the production of Advanced Glycation End products (AGEs), which promote mesangial expansion, basement membrane thickening, and podocyte dysfunction (Brownlee, 2005). Additionally, glucose overload in renal tubular cells leads to glucotoxicity, which impairs mitochondrial function and induces apoptosis (Vallon and Thomson, 2017).

Hemodynamic and Non-Hemodynamic Factors

In the incipient phase of Diabetic Kidney Disease (DKD), glomerular hyperfiltration is primarily attributed to an increased Single-Nephron Glomerular Filtration Rate (SNGFR) coupled with elevated intraglomerular hypertension, culminating in hypertrophic remodelling of the renal parenchyma and proximal tubular segments. The Renin-Angiotensin-Aldosterone System (RAAS), notably via angiotensin II and aldosterone, exerts a critical pathogenic influence by mediating vasoconstriction, stimulating Reactive Oxygen Species (ROS) generation, and activating downstream profibrotic signalling cascades. Concurrently, upregulated Sodium-Glucose Cotransporter 2 (SGLT2) expression in the proximal tubule diminishes sodium chloride delivery to the macula densa, abrogating Tubuloglomerular Feedback (TGF), thereby inducing afferent arteriolar vasodilation and exacerbating intraglomerular pressure. These synergistic hemodynamic perturbations and molecular mechanisms initiate and perpetuate glomerulosclerosis and interstitial fibrosis, driving the progression of DKD (Yang and Xu, 2022).

It is an early hemodynamic abnormality in DKD, resulting from afferent arteriole dilation and efferent arteriole constriction. This hemodynamic stress causes mechanical injury to podocytes and glomerular capillaries (Hostetter, 2003). Non-hemodynamic factors-such as metabolic imbalances, lipotoxicity, and hormonal dysregulation-amplify this damage, contributing to renal fibrosis and functional decline (Cooper, 2001).

Inflammation, Oxidative Stress, and Fibrosis in DKD

The pathogenesis of Diabetic Kidney Disease (DKD) is largely driven by immune-mediated inflammatory processes initiated through the activation of Nuclear Factor-kappa B (NF-κB), which upregulates the expression of endothelial adhesion molecules such as Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) within the renal microvasculature. These adhesion molecules facilitate the extravasation and accumulation of leukocytes and macrophages into renal tissues, leading to the secretion of pro-inflammatory cytokines and chemokines that contribute to injury of glomerular and tubular compartments. Both resident and infiltrating immune cells, including T lymphocytes and macrophages, coordinate complex innate and adaptive immune responses that intensify local inflammation and promote fibrogenesis. Moreover, a skewed immune profile characterized by predominance of pro-inflammatory Th1 and Th17 subsets alongside diminished regulatory T cell function exacerbates renal damage and accelerates progression of DKD (Navarro-González and Mora-Fernández, 2008). The pathophysiology also involves a complex interaction between oxidative stress and the accumulation of Advanced Glycation End Products (AGEs) resulting from chronic hyperglycemia. Elevated generation of Reactive Oxygen Species (ROS), predominantly mediated by NADPH oxidase activity, induces oxidative damage to cellular macromolecules including lipids, proteins and DNA. In parallel, the buildup of AGEs and their engagement with the receptor for Advanced Glycation End products (RAGE) potentiate oxidative stress and inflammatory signalling cascades. This vicious cycle of enhanced oxidative and inflammatory mediators drives progressive renal cell injury,

extracellular matrix deposition, and architectural remodelling characteristic of DKD progression (Mazzieri *et al.*, 2024).

The imbalance between ROS production and antioxidant defences accelerates renal fibrosis via activation of TGF-β and extracellular matrix accumulation (Ha and Lee, 2000). Tubulointerstitial fibrosis in diabetic kidney disease results from sustained hyperglycemia triggering the release of profibrotic factors like TGF-β, ET-1, fibronectin, collagen-1, and CTGF. TGF-β plays a central role by promoting epithelial-mesenchymal transition and stimulating extracellular matrix deposition, while ET-1 induces vasoconstriction and enhances inflammatory and fibrotic signalling. Accumulation of fibronectin and collagen-1 further disrupts tissue architecture, and elevated CTGF exacerbates glomerulosclerosis and fibrosis. Together, these mechanisms drive tubular atrophy, interstitial matrix expansion, and progressive kidney dysfunction (Xu *et al.*, 2023).

Role of Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS plays a pivotal role in the pathogenesis of DKD. Hyperglycemia and mechanical stress stimulate intrarenal RAAS activation, particularly angiotensin II, which promotes vasoconstriction, sodium retention, and aldosterone secretion (Remuzzi *et al.*, 2002). Angiotensin II also stimulates inflammatory and profibrotic pathways, including TGF-β and Connective Tissue Growth Factor (CTGF), leading to glomerulosclerosis and tubulointerstitial fibrosis (Anderson *et al.*, 1993).

Glomerular and Tubular Injury Mechanisms

Patients exhibiting albuminuria primarily demonstrate structural modifications of the glomerular filtration barrier, characterized by podocyte loss and increased thickness of the glomerular basement membrane. These pathological changes lead to increased permeability, permitting the passage of albumin into the urinary space. The presence of filtered albumin in the tubular lumen subsequently activates tubular epithelial cells, triggering inflammatory responses and the secretion of profibrotic mediators, including Transforming Growth Factor-beta (TGF-β). These processes facilitate tubulointerstitial fibrosis, characterized by excessive extracellular matrix deposition, tubular atrophy, and scarring, ultimately resulting in progressive renal functional decline (Naaman and Bakris, 2023; Pagtalunan *et al.*, 1997). Podocytes are particularly susceptible to injury from AGEs, oxidative stress, and angiotensin II. Tubular injury occurs due to increased glucose and protein load, which triggers epithelial-to-mesenchymal transition (EMT), tubular atrophy, and interstitial fibrosis (Gilbert, 2004). This progressive tubular damage contributes significantly to the decline in estimated Glomerular Filtration Rate (eGFR) and advancement toward ESRD.

NEPHROPROTECTIVE ROLE OF TELMISARTAN

Telmisartan is a long-acting, selective angiotensin II type 1 receptor (AT1) blocker with a unique pharmacological profile among Angiotensin Receptor Blockers (ARBs). It has high lipophilicity and a prolonged terminal half-life of approximately 24 hr, allowing for once-daily dosing (Stangier *et al.*, 2000). Telmisartan exhibits high binding affinity and slow dissociation from AT1 receptors, contributing to sustained Blood Pressure (BP) reduction and receptor blockade (Michel *et al.*, 2013).

Role as an Angiotensin II Receptor Blocker (ARB)

As an ARB, telmisartan inhibits the vasoconstrictive and sodium-retentive effects of angiotensin II by selectively blocking AT1 receptors. This leads to vasodilation, reduced aldosterone secretion, and decreased sodium and water retention, which together lower systemic and intraglomerular pressure (Burnier, 2001). The blockade of RAAS by telmisartan also attenuates the downstream inflammatory and fibrotic responses involved in DKD progression (Remuzzi *et al.*, 2002).

PPAR-γ Agonistic Effect

Unlike other ARBs, telmisartan acts as a partial agonist of peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ), a nuclear receptor that regulates glucose and lipid metabolism, inflammation, and oxidative stress (Schupp *et al.*, 2004). This dual action enhances insulin sensitivity, reduces pro-inflammatory cytokine production, and inhibits mesangial cell proliferation-factors implicated in the pathogenesis of DKD (Benson *et al.*, 2004). Thus, telmisartan exerts metabolic benefits beyond RAAS blockade, positioning it as a pleiotropic agent in diabetes care.

Clinical Evidence of Nephroprotection

On-target and Transcend trials found that telmisartan exhibited comparable efficacy to ramipril in influencing key renal endpoints, including the doubling of serum creatinine levels and progression to end-stage renal disease. The TRANSCEND trial's subgroup analyses indicated that telmisartan may confer renal protective effects in patients presenting with microalbuminuria or macroalbuminuria alongside decreased estimated Glomerular Filtration Rate (eGFR); however, no significant renal advantages were observed in participants with maintained renal function (Tobe *et al.*, 2011).

The AMADEO study rigorously compared telmisartan and losartan in hypertensive type 2 diabetic patients with overt nephropathy using a randomized, double-blind design over one year. Results demonstrated that telmisartan achieved a significantly greater reduction in proteinuria than losartan, independent of blood pressure differences. The superior renoprotective effect of telmisartan may be attributed to its

extended pharmacokinetic properties and distinct molecular actions (Boehringer Ingelheim., 2023).

Randomized controlled trials involving patients with advanced Chronic Kidney Disease (CKD), the addition of telmisartan to standard antihypertensive regimens resulted in a marked decrease in the progression to renal replacement therapy, with a reported relative risk reduction of 45%. Furthermore, telmisartan significantly lowered proteinuria levels. These therapeutic effects were observed without a corresponding rise in serious adverse events, demonstrating the safety and efficacy of telmisartan in this patient population with advanced renal impairment (Tokunaga *et al*., 2010).

Observational clinical trials and meta-analyses have consistently shown that telmisartan administration effectively reduces proteinuria levels and may retard the decline of renal function in both diabetic and non-diabetic patients with chronic kidney disease. These renoprotective benefits are particularly apparent in patients who have significant proteinuria at baseline (Agrawal *et al*., 2016).

Impact on Proteinuria, BP, and Renal Function

Telmisartan significantly reduces proteinuria, an important marker and mediator of DKD. Studies show up to a 50% reduction in albuminuria with telmisartan therapy, especially when used at higher doses (Yuyun *et al*., 2004). Its potent antihypertensive action contributes to lowering glomerular hypertension, a key pathogenic factor in DKD progression. Moreover, telmisartan stabilizes or slows the decline of estimated Glomerular Filtration Rate (eGFR), indicating renal preservation (Bakris *et al*., 2008).

Safety and Tolerability

Telmisartan is generally well tolerated, with a safety profile comparable to or better than other ARBs. Adverse effects are infrequent and include mild hypotension, hyperkalemia, and dizziness (Michel *et al*., 2013). Unlike ACE inhibitors, telmisartan does not cause cough or angioedema, making it suitable for long-term use. Importantly, it is safe in patients with mild to moderate renal impairment, though serum potassium and creatinine should be monitored regularly in advanced Chronic Kidney Disease (CKD) stages (Bakris *et al*., 2008).

NEPHROPROTECTIVE ROLE OF DAPAGLIFLOZIN

SGLT2 Inhibition and Glucose Reabsorption

Dapagliflozin is a selective Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitor that reduces glucose reabsorption in the proximal renal tubules, leading to increased urinary glucose excretion and improved glycemic control (DeFronzo *et al*., 2013). By lowering blood glucose levels independently of insulin secretion, it avoids the risk of hypoglycemia associated with traditional antidiabetic medications (Bailey *et al*., 2010). Moreover, its glucuronic effect contributes to mild weight loss and blood pressure reduction, indirectly benefiting renal health.

Hemodynamic Modulation and Tubuloglomerular Feedback

Dapagliflozin improves renal hemodynamic through restoration of Tubuloglomerular Feedback (TGF). In diabetes, increased proximal glucose and sodium reabsorption reduces sodium delivery to the macula densa, blunting TGF and causing afferent arteriolar vasodilation and glomerular hyperfiltration (Cherney and Perkins, 2014). By inhibiting SGLT2, dapagliflozin increases sodium delivery to the distal nephron, restoring TGF, causing afferent vasoconstriction, and reducing glomerular pressure-a key pathogenic mechanism in diabetic kidney disease (Heerspink *et al*., 2021).

Reduction of Intraglomerular Pressure and Albuminuria

One of dapagliflozin's hallmark renal benefits is its ability to reduce intraglomerular pressure and albuminuria, independent of its glycemic effects. Clinical studies have demonstrated significant reductions in Urinary Albumin-To-Creatinine Ratio (UACR) and preservation of estimated Glomerular Filtration Rate (eGFR) in diabetic and non-diabetic populations (Wanner *et al*., 2016). These effects are attributed to improvements in glomerular hemodynamics, reduced inflammation, and better oxygenation of renal tissues (Vallon and Thomson, 2017).

Anti-Inflammatory and Anti-Fibrotic Properties

Beyond hemodynamic changes, dapagliflozin exerts anti-inflammatory and anti-fibrotic actions. It reduces renal inflammation by downregulating pro-inflammatory cytokines like IL-6, TNF-α, and MCP-1, and inhibits NLRP3 inflammasome activation (Birnbaum *et al*., 2021). Dapagliflozin also decreases fibrotic markers such as TGF-β1 and collagen IV, thereby slowing tubulointerstitial fibrosis and chronic kidney damage (Kang *et al*., 2020). These pleiotropic effects contribute to long-term nephroprotection.

Cardiovascular and Renal Outcomes from Major Trials (e.g., DAPA-CKD)

Dapagliflozin significantly reduces the progression of chronic kidney disease and lowers the risk of kidney failure and cardiovascular death. This benefit was observed in patients both with and without type 2 diabetes. Patients receiving dapagliflozin showed slower decline in kidney function and fewer hospitalizations for heart failure compared to placebo. The drug was well tolerated, with a safety profile similar to placebo. These results highlight dapagliflozin as a key treatment option for improving renal and cardiovascular outcomes in CKD.

The DAPA-CKD trial provided robust evidence of dapagliflozin's renoprotective and cardioprotective benefits. In patients with CKD-with or without type 2 diabetes-dapagliflozin significantly reduced the risk of sustained eGFR decline, ESRD, and renal or cardiovascular death by 39% compared to placebo. The drug was well tolerated, with a safety profile similar to placebo. These results highlight dapagliflozin as a key treatment option for improving renal and cardiovascular outcomes in CKD (Heerspink *et al*., 2020). Similarly, the DECLARE-TIMI 58 trial showed that dapagliflozin reduced the risk of heart failure hospitalization and preserved renal function in high-risk diabetic patients (Wiviott *et al*., 2019). These landmark trials underscore dapagliflozin's therapeutic role in cardiorenal protection.

Safety Profile

Dapagliflozin is generally well tolerated, with a low risk of hypoglycemia and a favorable safety profile. Common adverse effects include genital mycotic infections and mild volume depletion, especially in older adults or those on diuretics (Zinman *et al*., 2015). Rare complications such as euglycemic Diabetic Ketoacidosis (DKA) and urinary tract infections have been reported but are manageable with proper patient selection and monitoring. Importantly, dapagliflozin has been shown to be safe and effective even in patients with moderate to advanced CKD (eGFR >25 mL/min/1.73 m^2), expanding its utility in renal care (Heerspink *et al*., 2021).

RATIONALE FOR THE DUAL THERAPY APPROACH

Complementary Mechanisms of Action

The combination of dapagliflozin (SGLT2 inhibitor) and telmisartan (ARB and partial PPAR-γ agonist) offers a multifaceted therapeutic approach for managing Diabetic Kidney Disease (DKD). While telmisartan acts primarily on the renin-angiotensin-aldosterone system (RAAS) to reduce glomerular pressure and fibrotic signalling, dapagliflozin enhances Tubuloglomerular Feedback (TGF) and modulates glucose and sodium reabsorption (DeFronzo *et al*., 2013; Schupp *et al*., 2004). Their complementary mechanisms address distinct yet converging pathways in the pathophysiology of DKD-hemodynamic, metabolic, and inflammatory.

Synergistic Effects on Glomerular Hemodynamic

Telmisartan reduces efferent arteriolar resistance, while dapagliflozin lowers afferent arteriolar pressure via restoration of TGF (Heerspink *et al*., 2021; Vallon and Thomson, 2017). This dual modulation optimally reduces intraglomerular hypertension, a major contributor to glomerular injury and proteinuria in DKD (Anderson *et al*., 1993). By targeting both vascular poles of the glomerulus, the combination can normalize glomerular hemodynamic more effectively than monotherapy.

Combined Reduction in Proteinuria, Blood Pressure, and Metabolic Stress

Both agents independently reduce albuminuria and blood pressure, but their combination yields additive or even synergistic effects. Telmisartan reduces proteinuria by attenuating RAAS-mediated glomerular injury, while dapagliflozin lowers albuminuria through pressure-independent mechanisms, including reduced tubular workload and metabolic stress (Barnett *et al*., 2007; Wiviott *et al*., 2019). Furthermore, dapagliflozin improves glycemic control, body weight, and insulin sensitivity, and telmisartan enhances PPAR-γ-mediated metabolic regulation, offering broad systemic benefits (Benson *et al*., 2004).

Anti-Inflammatory and Antifibrotic Synergy

Chronic inflammation and fibrosis are key drivers of progressive DKD. Telmisartan suppresses pro-inflammatory cytokines like TNF-α and IL-6 via RAAS inhibition and PPAR-γ activation (Schupp *et al*., 2004). Dapagliflozin complements this action by reducing NLRP3 inflammasome activity, oxidative stress, and macrophage infiltration in renal tissues (Birnbaum *et al*., 2021). Their co-administration may exert synergistic antifibrotic effects by downregulating TGF-β1 and inhibiting mesangial matrix expansion, slowing DKD progression (Kang *et al*., 2020).

Evidence from Preclinical and Clinical Studies

Preclinical models of diabetic nephropathy have shown enhanced renal protection when combining SGLT2 inhibitors with RAAS blockers. For instance, mice treated with telmisartan and dapagliflozin had reduced glomerulosclerosis, albuminuria, and renal inflammation compared to monotherapy groups (Umino *et al*., 2018). Clinically, subgroup analyses from the DAPA-CKD trial indicated consistent renal and cardiovascular benefits of dapagliflozin in patients already receiving ARBs, including telmisartan (Heerspink *et al*., 2020). While direct head-to-head trials are limited, real-world data support the safety and enhanced efficacy of this dual approach in high-risk diabetic populations (Alicic *et al*., 2017).

CLINICAL EVIDENCE OF COMBINED USE IN DKD

Overview of Available Clinical Trials and Studies

The prospective observational study investigated the efficacy of combination therapy with dapagliflozin and telmisartan in patients with diabetic nephropathy over 12 weeks. Compared to telmisartan monotherapy, the combination significantly reduced albuminuria as measured by Urinary Albumin-To-Creatinine Ratio (UACR), along with improvements in glycaemic control (fasting blood glucose and HbA1c), lipid profile, and waist-to-hip ratio. Notably, inflammatory markers such as CCL21 mRNA and MCP-1 were also substantially decreased in the combination therapy group, indicating reduced systemic inflammation. These findings suggest that dapagliflozin plus telmisartan not

only confers superior renal protection by lowering albuminuria but also attenuates inflammation, thereby enhancing overall renal function recovery in diabetic nephropathy patients. The combination therapy was well tolerated and demonstrated notable clinical benefits over monotherapy, highlighting its potential as an effective treatment strategy for diabetic kidney disease (Chauhan *et al*., 2025).

Although direct Randomized Controlled Trials (RCTs) specifically evaluating the combination of dapagliflozin and telmisartan in DKD are limited, evidence from individual studies and subgroup analyses strongly supports their concurrent use. Most major trials, such as DAPA-CKD, permitted background RAAS blockade (including telmisartan), providing indirect but robust support for the dual therapy strategy (Heerspink *et al*., 2020). Additionally, real-world observational data and small-scale cohort studies have explored the additive effects of this combination in slowing kidney function decline in patients with Type 2 Diabetes Mellitus (T2DM) and early-stage DKD (Bakris *et al*., 2021).

Comparative Studies vs Monotherapy

In comparative analyses, the combination therapy consistently outperforms monotherapies in improving renal outcomes. A study by Umino *et al*., (2018) using a mouse model of diabetic nephropathy found that dapagliflozin + telmisartan significantly reduced mesangial expansion, glomerular hypertrophy, and albuminuria compared to either drug alone. Clinical data from the DAPA-CKD trial showed that dapagliflozin added to existing RAAS blockade led to a further 39% risk reduction in the composite renal endpoint compared to placebo (Heerspink *et al*., 2020). This suggests a synergistic benefit when both drugs are used together.

Outcome Measures: eGFR Decline, Albuminuria, ESRD Progression

Key renal outcome measures-estimated Glomerular Filtration Rate (eGFR) decline, albuminuria, and progression to End-Stage Renal Disease (ESRD)-are favorably affected by the dual therapy. Dapagliflozin slows eGFR decline through hemodynamic and anti-inflammatory mechanisms, while telmisartan's RAAS inhibition reduces glomerular pressure and proteinuria (Barnett *et al*., 2007). In the DAPA-CKD trial, patients receiving dapagliflozin on top of an ARB (telmisartan in many cases) experienced a significant delay in ESRD progression, and more patients achieved ≥50% reduction in UACR compared to monotherapy (Heerspink *et al*., 2020; Wanner *et al*., 2016).

Cardiovascular Benefits

Cardiorenal protection is a major advantage of this combination. Telmisartan reduces cardiovascular events through RAAS modulation and potential lipid/lipoprotein effects (Benson *et al*., 2004), while dapagliflozin improves heart failure outcomes and reduces Major Adverse Cardiovascular Events (MACE), as shown in the DECLARE-TIMI 58 trial (Wiviott *et al*., 2019). In high-risk patients, the combination therapy enhances systolic blood pressure control, reduces left ventricular hypertrophy, and improves vascular function, resulting in better cardiovascular outcomes (Cherney and Zinman, 2016).

Meta-Analysis Findings

Although there is no dedicated meta-analysis solely focused on dapagliflozin + telmisartan, a few meta-analyses have evaluated SGLT2 inhibitors plus RAAS blockers in general. A meta-analysis by Neuen *et al*., (2019) concluded that SGLT2 inhibitors added to background RAAS blockade significantly reduce risks of renal failure, albuminuria, and cardiovascular death across patient populations with CKD and diabetes. These results strongly support the additive nephroprotective and cardioprotective roles of dual therapy.

Comparative meta-analyses reveal no significant differences between dapagliflozin and empagliflozin regarding reductions in major cardiovascular events such as myocardial infarction, heart failure, stroke, or cardiovascular mortality, highlighting a consistent class effect (Tanawan *et al*., 2023). Dapagliflozin's impact on eGFR in CKD closely aligns with the effects seen with other SGLT2 inhibitors, characterized by an early dip followed by slower progression of kidney function decline and strong renal protection (Heerspink *et al*., 2020). Notably, dapagliflozin's lower selectivity ratio for SGLT2 versus SGLT1 receptors may provide additional cardioprotective benefits by modulating myocardial SGLT1 pathways that are less influenced by other agents. Furthermore, dapagliflozin does not elevate levels of plasma noradrenaline or aldosterone, which could contribute to its favourable cardiovascular profile. These pharmacodynamic characteristics, combined with well-substantiated clinical safety and efficacy data, support dapagliflozin's role as an optimal adjunct to telmisartan in managing diabetic kidney disease to enhance cardiorenal protection. Overall, the comprehensive evidence underscores dapagliflozin as a reliable and effective option within the SGLT2 inhibitor class.

SAFETY CONSIDERATIONS AND CONTRAINDICATIONS

Risk of Hyperkalemia, Hypotension, and AKI

The dual use of dapagliflozin and telmisartan is generally well tolerated but requires attention to specific adverse effects. Telmisartan, an ARB, can cause hyperkalemia, particularly in patients with advanced Chronic Kidney Disease (CKD) or those taking potassium-sparing diuretics (Weir, 2011). Concurrent use of dapagliflozin, which causes natriuresis and osmotic diuresis, may potentiate volume depletion and lead to hypotension, especially in elderly or volume-depleted individuals (Zinman *et al*., 2015).

Although SGLT2 inhibitors were initially associated with concerns over Acute Kidney Injury (AKI), large-scale trials have shown that dapagliflozin reduces AKI incidence in the long term by stabilizing intraglomerular hemodynamic and mitigating inflammatory damage (Heerspink *et al.*, 2020; Neuen *et al.*, 2019). Nonetheless, transient eGFR reduction may occur early in treatment due to hemodynamic changes and should not be mistaken for renal injury.

Drug Interactions

Both drugs have low potential for serious pharmacokinetic interactions, but certain combinations require caution. Telmisartan, being a substrate of CYP2C9 and inhibitor of P-glycoprotein, may affect drugs with similar metabolic pathways (Benson *et al.*, 2004). Co-administration with NSAIDs, potassium supplements, or aldosterone antagonists can increase the risk of renal dysfunction and hyperkalaemia (Bakris *et al.*, 2000).

Dapagliflozin is primarily excreted via glucuronidation and poses minimal cytochrome-related interactions. However, its combination with loop diuretics may augment diuresis and increase dehydration risk (Vallon and Thomson, 2017).

Monitoring Guidelines

Regular monitoring of renal function (eGFR, serum creatinine), electrolytes (especially potassium), and blood pressure is essential, especially during initiation and dose escalation. A baseline and periodic assessment of urinary albumin-to-creatinine ratio (UACR) is recommended to track nephroprotective effects (KDIGO, 2020).

In cases of acute illness, surgery, or volume depletion (e.g., vomiting, diarrhoea), temporary discontinuation of dapagliflozin is advisable to avoid euglycemic Diabetic Ketoacidosis (DKA) and further kidney stress (ADA, 2023). Similarly, telmisartan may be withheld if hyperkalaemia or rising creatinine is observed.

Special Populations: Elderly, CKD Stages, and Heart Failure Patients

Elderly patients are more prone to adverse effects such as hypotension and volume depletion, necessitating careful dose titration and monitoring (Cherney and Zinman, 2016). Both drugs are effective in patients with CKD stages 2-4, but caution is needed when eGFR falls below 25 mL/min/1.73 m^2, where SGLT2 inhibitor efficacy may diminish (Heerspink *et al.*, 2020).

In patients with heart failure, especially those with reduced ejection fraction (HFrEF), dapagliflozin has shown significant mortality and hospitalization benefits, making it a preferred agent (McMurray *et al.*, 2019). Telmisartan is also safe and beneficial in heart failure patient's intolerant to ACE inhibitors, but careful potassium and renal function monitoring remains essential (Yusuf *et al.*, 2003).

FUTURE DIRECTIONS AND ONGOING TRIALS

Emerging Research on Combination Therapies in DKD

As evidence continues to accumulate on the efficacy of dapagliflozin and telmisartan individually, there is growing interest in combination therapies targeting multiple pathogenic pathways in Diabetic Kidney Disease (DKD). Preclinical studies have shown additive renal benefits when SGLT2 inhibitors are combined with agents like RAAS blockers, endothelin receptor antagonists, and Mineralocorticoid Receptor Antagonists (MRAs) (Umino *et al.*, 2018). Ongoing clinical trials, such as EMPA-KIDNEY and FLOW, are expanding the scope by including broader CKD populations and evaluating dual or triple therapy strategies (Herrington *et al.*, 2023).

A promising area of research involves direct comparison and combination of SGLT2 inhibitors (e.g., dapagliflozin) with PPAR-γ active ARBs like telmisartan, focusing on long-term renal and cardiovascular endpoints. These trials are expected to define optimized treatment protocols and evaluate whether early dual therapy initiation provides superior renal preservation.

Potential Biomarkers for Predicting Therapeutic Response

Identifying predictive biomarkers remains a key area of future research to optimize patient selection and enhance treatment efficacy. Biomarkers such as urinary NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule-1), TGF-β, and IL-18 are being studied to assess early kidney injury and therapeutic response in DKD (Parikh *et al.*, 2011). Moreover, plasma copeptin and SUPAR (soluble urokinase-type plasminogen activator receptor) are emerging as potential markers for glomerular stress and inflammation (Hayek *et al.*, 2015).

Omics-based approaches such as proteomics and metabolomics are expected to help identify signatures that differentiate responders from non-responders to dual therapy (Gadegbeku *et al.*, 2020). Integration of such biomarkers into clinical practice could facilitate personalized nephroprotection strategies.

Personalized Nephroprotection Strategies

The paradigm is gradually shifting from generalized treatment to personalized nephroprotection, which considers individual genetic, metabolic, and environmental factors in therapy design. Advances in pharmacogenomics may enable clinicians to predict patient-specific efficacy and adverse reactions to telmisartan or dapagliflozin (Patel *et al.*, 2016). Machine learning models are also being developed to stratify DKD patients based on progression risk, response prediction, and optimal drug selection (Nadkarni *et al.*, 2022).

In this context, dual therapy with dapagliflozin and telmisartan may be particularly beneficial in patients with high baseline albuminuria, insulin resistance, and metabolic syndrome, but prospective validation in stratified cohorts is essential.

Integration with Lifestyle and Dietary Interventions

Pharmacotherapy alone cannot fully address the complexity of DKD. Emerging research underscores the value of integrating dietary modifications (e.g., reduced sodium/protein intake, DASH and Mediterranean diets) and lifestyle interventions such as regular physical activity, smoking cessation, and weight loss with pharmacologic regimens (Ikizler *et al.*, 2020). These non-pharmacologic strategies enhance the effectiveness of telmisartan and dapagliflozin by mitigating inflammation, oxidative stress, and hemodynamic load.

Future studies are expected to focus on holistic DKD management models that blend precision medicine, dual-agent pharmacotherapy, and behavior change interventions to delay renal decline and improve quality of life.

LIMITATIONS OF EXISTING STUDIES

Short Follow-up Durations

Many of the available studies investigating the individual or combined effects of dapagliflozin and telmisartan have relatively short follow-up periods-often ranging from 12 to 36 months-which may not fully capture the long-term progression of Diabetic Kidney Disease (DKD) or sustained renal function decline (Barnett *et al.*, 2007). Given that DKD is a slowly progressive condition, extended follow-up is essential to evaluate the durability of nephroprotection, particularly the ability of dual therapy to delay End-Stage Renal Disease (ESRD) or reduce long-term cardiovascular mortality (Neuen *et al.*, 2019).

Small Sample Sizes

Several trials and preclinical studies exploring the synergistic effects of dapagliflozin and telmisartan are limited by small sample sizes. For example, the study by Umino *et al.*, (2018), although promising, was conducted in a murine model and lacked human data. Even in clinical settings, subgroup analyses of patients on combination therapy often include limited participants, reducing the statistical power and generalizability of findings. Small sample sizes hinder the detection of rare adverse effects and limit stratification by age, sex, and comorbid conditions (Alicic *et al.*, 2017).

Lack of Head-to-Head Trials Comparing Dual vs Monotherapy

A critical limitation in the current literature is the absence of randomized head-to-head trials comparing dual therapy (dapagliflozin + telmisartan) against either monotherapy alone in patients with DKD. Most available data are derived from studies allowing background RAAS blockade while evaluating SGLT2 inhibitors, or vice versa, rather than directly evaluating comparative efficacy and safety (Heerspink *et al.*, 2020). Without such trials, it remains challenging to quantify the incremental benefit or potential risks of the combination over established monotherapies.

Need for Real-World Data

Randomized controlled trials often involve carefully selected participants under controlled conditions, which may not reflect the complexity of real-world populations. There is a pressing need for large-scale real-world observational studies or registry data that assess the long-term safety, adherence, cost-effectiveness, and efficacy of dual therapy across diverse patient demographics, including those with multiple comorbidities, polypharmacy, or socioeconomic challenges (Jha *et al.*, 2013). Real-world evidence would help determine the practical applicability of dual nephroprotective strategies in routine clinical care.

CONCLUSION

Diabetic Kidney Disease (DKD) remains a major global health challenge, with limited success from monotherapy in halting disease progression. The combination of dapagliflozin, a Sodium-Glucose Cotransporter 2 (SGLT2) inhibitor, and telmisartan, an angiotensin II receptor blocker with partial PPAR-γ agonist activity, offers a complementary and synergistic approach to nephroprotection. Telmisartan lowers intraglomerular pressure and reduces inflammation and fibrosis, while dapagliflozin improves renal hemodynamics, lowers albuminuria, and provides anti-inflammatory and antifibrotic effects independent of glycemic control. Together, these agents can slow the decline in estimated Glomerular Filtration Rate (eGFR), reduce cardiovascular risk, and improve renal outcomes, particularly in patients with persistent albuminuria and declining kidney function despite standard therapy. Their cardioprotective properties further support their use in patients with coexisting cardiovascular disease, and their oral administration and good tolerability make integration into clinical practice feasible with appropriate monitoring of renal function, electrolytes, and blood pressure.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACEIs: Angiotensin-Converting Enzyme Inhibitors; **AGEs:** Advanced Glycation End Products; **ARB:** Angiotensin II Receptor Blocker; **CKD:** Chronic Kidney Disease; **CTGF:** Connective Tissue Growth Factor; **DM:** Diabetes Mellitus; **DKD:** Diabetic Kidney Disease; **eGFR:** Estimated Glomerular Filtration Rate; **ESRD:** End-Stage Renal Disease; **ET-1:** Endothelin-1; **HIF-1α:** Hypoxia-Inducible Factor-1 alpha; **ICAM-1:** Intercellular Adhesion Molecule-1; **IDF:** International Diabetes Federation; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of Activated B cells; **PPAR-γ:** Peroxisome Proliferator-Activated Receptor-gamma; **RAAS:** Renin-Angiotensin-Aldosterone System; **RAGE:** Receptor for Advanced Glycation End Products; **ROS:** Reactive Oxygen Species; **SGLT2:** Sodium-Glucose Cotransporter 2; **SNGFR:** Single-Nephron Glomerular Filtration Rate; **T2DM:** Type 2 Diabetes Mellitus; **TGF-β:** Transforming Growth Factor-beta; **TGF:** Tubuloglomerular Feedback; **VCAM-1:** Vascular Cell Adhesion Molecule-1.

REFERENCES

ADVANCE Collaborative Group, Patel, A., MacMahon, S., Chalmers, J., Neal, B., Billot, L., Woodward, M., Marre, M., Cooper, M., Glasziou, P., Grobbee, D., Hamet, P., Harrap, S., Heller, S., Liu, L., Mancia, G., Mogensen, C. E., Pan, C., Poulter, N., Travert, F. (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The New England Journal of Medicine, 358(24), 2560–2572. https://doi.org/10.1056/NEJMoa0802987

Agrawal, A., Kamila, S., Reddy, S., Lilly, J., & Mariyala, M. S. (2016). Effect of telmisartan on kidney function in patients with chronic kidney disease: An observational study. Journal of Drug Assessment, 5(1), 24–28. https://doi.org/10.1080/21556660.2016.1252380

Alicic, R. Z., Rooney, M. T., & Tuttle, K. R. (2017). Diabetic kidney disease: Challenges, progress, and possibilities. Clinical Journal of the American Society of Nephrology: CJASN, 12(12), 2032–2045. https://doi.org/10.2215/CJN.11491116

Anderson, S., Rennke, H. G., & Brenner, B. M. Therapeutic advantage of converting-enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. The Journal of Clinical Investigation, 76 (1993), 612–619.

Bailey, C. J., Gross, J. L., Pieters, A., Bastien, A., & List, J. F. (2010). Effect of dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin. The Lancet, 375(9733), 2223–2233. https://doi.org/10.1016/S0140-6736(10)60407-2

Bakris, G. L., Agarwal, R., Anker, S. D. *et al.* (2021). Effect of dapagliflozin on kidney function in patients with CKD. New England Journal of Medicine, 384, 694–703.

Bakris, G. L., Williams, M., Dworkin, L., Elliott, W. J., Epstein, M., Toto, R., Tuttle, K., Douglas, J., Hsueh, W., & Sowers, J. (2000). Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. American Journal of Kidney Diseases, 36(3), 646–661. https://doi.org/10.1053/ajkd.2000.16225

Barnett, A. H., Bain, S. C., Bouter, P. *et al.* (2007). Angiotensin-receptor blockade versus ACE inhibition in type 2 diabetes and nephropathy. New England Journal of Medicine, 351, 1952–1961.

Benson, S. C., Pershadsingh, H. A., Ho, C. I., Chittiboyina, A., Desai, P., Pravenec, M., Qi, N., Wang, J., Avery, M. A., & Kurtz, T. W. (2004). Telmisartan as a unique angiotensin II receptor antagonist with selective PPAR-γ modulation. Hypertension, 43(5), 993–1002. https://doi.org/10.1161/01.HYP.0000123072.34629.57

Birnbaum, Y., Bajaj, M., Qian, J., & Ye, Y. (2021). Dapagliflozin inhibits the NLRP3 inflammasome in kidney, heart, and liver in diabetes. Cardiovascular Drugs and Therapy, 35, 1017–1030.

Brownlee, M. (2005). The pathobiology of diabetic complications: A unifying mechanism. Diabetes, 54(6), 1615–1625. https://doi.org/10.2337/diabetes.54.6.1615

Burnier, M. (2001). Angiotensin II type 1 receptor blockers. Circulation, 103(6), 904–912. https://doi.org/10.1161/01.cir.103.6.904

Cahn, A., Wiviott, S. D., Raz, I. *et al.* (2021). Cardiovascular and renal outcomes with SGLT2 inhibition. Diabetes Care, 44, 273–279.

Campbell, K. L., Carrero, J. J., & Ekart, R. (2019). Dietary patterns and CKD progression. Nature Reviews. Nephrology, 15, 529–545.

Chauhan, S., Bhandari, U., & Habib, A. (2025). Efficacy of dapagliflozin and telmisartan combination therapy in reducing albuminuria and inflammatory markers in diabetic nephropathy: A prospective observational study. Current Vascular Pharmacology. https://doi.org/10.2174/0115701611361265250211062540

Cherney, D. Z., & Perkins, B. A. (2014). SGLT2 inhibition in type 1 diabetes: Simultaneous glucose lowering and nephroprotection? Diabetes, 63, 3992–3994.

Cherney, D. Z., & Zinman, B. (2016). Cardiorenal risk reduction with SGLT2 inhibition. Journal of the American College of Cardiology, 69, 684–698.

Chicharro-Luna, E., Ortega-Avila, A. B., Requena-Martínez, A., & Gijon Nogueron, G. (2021). Concordance between sudomotor disorder and the clinical diagnosis of diabetic peripheral neuropathy, according to various clinical guidelines. Primary Care Diabetes, 15(5), 853–858. https://doi.org/10.1016/j.pcd.2021.05.012

Cooper, M. E. (1998). Pathogenesis, prevention, and treatment of diabetic nephropathy. The Lancet, 352(9123), 213–219. https://doi.org/10.1016/S0140-6736(98)01346-4

Cowie, M. R., Fisher, M., & Lowe, R. (2020). Heart failure and diabetes: A paradigm shift. Diabetes, Obesity and Metabolism, 22, 1650–1658.

DeFronzo, R. A., Norton, L., & Abdul-Ghani, M. (2017). Renal, metabolic, and cardiovascular considerations of SGLT2 inhibition. Nature Reviews. Nephrology, 13(1), 11–26. https://doi.org/10.1038/nrneph.2016.170

Derosa, G., Ragonesi, P. D., Mugellini, A. *et al.* (2004). Telmisartan versus losartan on blood pressure and insulin resistance in metabolic syndrome. Hypertension Research, 27, 449–456.

Dwyer, J. P., Parvin-Nejad, F. P., & Warram, J. (2022). Early DKD biomarkers: From bench to bedside. Kidney International, 101, 1027–1040.

Elmarakby, A. (2012). SGLT2 inhibition and oxidative stress in diabetic models. American Journal of Physiology. Renal Physiology, 303, F885–F894.

Fernandes, G., Costa, J., Alarcón, R. *et al.* (2020). Combination therapy in DKD: A systematic review. Diabetic Medicine, 37, 1353–1366.

Ferreira, J. P., Butler, J., Pitt, B. *et al.* (2021). SGLT2 inhibitors in heart failure and CKD. Circulation, 143, 298–300.

Gadegbeku, C. A., Gipson, D. S., Holzman, L. B. *et al.* (2020). Design of the Neptune study: Nephrotic syndrome network. Kidney International, 77, 737–744.

Gæde, P., Vedel, P., Larsen, N., Jensen, G. V. H., Parving, H.-H., & Pedersen, O. (2003). Multifactorial intervention in type 2 diabetes. New England Journal of Medicine, 348(5), 383–393. https://doi.org/10.1056/NEJMoa021778

Gallagher, H., Jardine, M., Perkovic, V. *et al.* (2019). SGLT2 inhibition for renal outcomes: Lessons from CREDENCE. Kidney International, 96, 37–49.

Gilbert, R. E. (2004). Proximal tubulopathy: Prime mover in diabetic kidney disease. Diabetes, 53, 2544–2553.

Ha, H., & Lee, H. B. (2000). Reactive oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. Kidney International, 58, S19–S25. https://doi.org/10.1046/j.1523-1755.2000.07704.x

Hamada, Y., & Fujita, T. (2021). SGLT2 inhibitors and kidney oxygenation. Kidney International Reports, 6, 675–685.

Hayek, S. S., Sever, S., Ko, Y.-A., Trachtman, H., Awad, M., Wadhwani, S., Altintas, M. M., Wei, C., Hotton, A. L., French, A. L., Sperling, L. S., Lerakis, S., Quyyumi, A. A., & Reiser, J. (2015). Soluble urokinase receptor and chronic kidney disease. The New England Journal of Medicine, 373(20), 1916–1925. https://doi.org/10.1056/NEJMoa1506362

Heerspink, H. J. L., Oshima, M., & Jardine, M. J. (2021). SGLT2 inhibition and kidney protection. Clinical Journal of the American Society of Nephrology: CJASN, 16, 631–633.

Heerspink, H. J. L., Stefánsson, B. V., Correa-Rotter, R., Chertow, G. M., Greene, T., Hou, F.-F., Mann, J. F. E., McMurray, J. J. V., Lindberg, M., Rossing, P., Sjöström, C. D., Toto, R. D., Langkilde, A.-M., Wheeler, D. C., & DAPA-CKD Trial Committees, and Investigators. (2020). Dapagliflozin in patients with chronic kidney disease. The New England Journal of Medicine, 383(15), 1436–1446. https://doi.org/10.1056/NEJMoa2024816

Herrington, W. G., Preiss, D., Haynes, R. *et al.* (2023). The EMPA-KIDNEY trial: Clinical design and rationale. Clinical Journal of the American Society of Nephrology: CJASN, 18, 123–133.

Hirst, J. A., Farmer, A. J., Dyar, A. *et al.* (2012). SGLT2 inhibition to improve glycemic control: Meta-analysis. Diabetes, Obesity and Metabolism, 14, 850–861.

Hostetter, T. H. (2003). Hyperfiltration and glomerulosclerosis. Seminars in Nephrology, 23(2), 194–199. https://doi.org/10.1053/anep.2003.50017

IDF. (2021). IDF diabetes atlas (10th ed.). International Diabetes Federation.

Ikizler, T. A., Burrowes, J. D., Byham-Gray, L. D., Campbell, K. L., Carrero, J.-J., Chan, W., Fouque, D., Friedman, A. N., Ghaddar, S., Goldstein-Fuchs, D. J., Kaysen, G. A., Kopple, J. D., Teta, D., Yee-Moon Wang, A., & Cuppari, L. (2020). KDOQI guideline for nutrition in CKD: 2020 update. American Journal of Kidney Diseases, 76(3) (Suppl. 1), S1–S107. https://doi.org/10.1053/j.ajkd.2020.05.006

Jha, V., Garcia-Garcia, G., Iseki, K., Li, Z., Naicker, S., Plattner, B., Saran, R., Wang, A. Y.-M., & Yang, C.-W. (2013). Chronic kidney disease: Global dimension and perspectives. The Lancet, 382(9888), 260–272. https://doi.org/10.1016/S0140-6736(13)60687-X

Kang, M. J., Lee, J. H., Oh, S. H. *et al.* (2020). Anti-fibrotic effect of dapagliflozin in diabetic kidney disease. American Journal of Nephrology, 51, 1–12.

Kawanami, D., Matoba, K., & Utsunomiya, K. (2020). RAAS blockade and SGLT2 inhibition: Integrated renoprotective strategy. Cells, 9, 2573–2585.

KDIGO. (2020). KDIGO clinical practice guideline for diabetes management in CKD. Kidney disease: Improving global outcomes.

Kennedy, C., & Fowler, C. (2022). PPAR-γ agonists in kidney disease. Kidney International Reports, 7, 1–12.

Kim, S. R., Lee, Y. H., Kim, M. G. *et al.* (2022). Renoprotective mechanisms of dapagliflozin: Beyond glucose lowering. Frontiers in Endocrinology, 13, 1–10.

Kitada, K., Nakano, D., Hitomi, H. *et al.* (2018). Sodium reabsorption and tubuloglomerular feedback in diabetes. Journal of Physiology, 596, 567–583.

Ko, B., & Tuttle, K. (2022). Antifibrotic therapies in DKD. American Journal of Physiology. Renal Physiology, 322, F585–F596.

Kohan, D. E. (2013). Endothelin antagonism in chronic kidney disease. Kidney International, 84, 25–37.

Kongmalai, T., Hadnorntun, P., Leelahavarong, P., Kongmalai, P., Srinonprasert, V., Chirakarnjanakorn, S., Chaikledkaew, U., McKay, G., Attia, J., & Thakkinstian, A. (2023). Comparative cardiovascular benefits of individual SGLT2 inhibitors in type 2 diabetes and heart failure: A systematic review and network meta-analysis of randomized controlled trials. Frontiers in Endocrinology, 14, Article 1216160. https://doi.org/10.3389/fendo.2023.1216160

Ku, E., Lee, B. J., Wei, J., & Weir, M. R. (2019). Hypertension in CKD: Core curriculum 2019. American Journal of Kidney Diseases, 74(1), 120–131. https://doi.org/10.1053/j.ajkd.2018.12.044

Lachin, J. M., Wanner, C., Hantel, S. *et al.* (2020). Empagliflozin slows kidney disease progression. Diabetes Care, 43, 1655–1663.

LDLT Study Group. (2004). Losartan versus telmisartan in diabetic nephropathy. Nephrology Dialysis Transplantation, 19, 1947–1953.

Lewis, E. J., Hunsicker, L. G., Clarke, W. R. *et al.* (2001). Renoprotective effect of losartan in diabetic nephropathy. New England Journal of Medicine, 345, 861–869.

Lewis, E. J., Hunsicker, L. G., Clarke, W. R. *et al.* (1993). Captopril in diabetic nephropathy. New England Journal of Medicine, 329, 1456–1462.

Li, J., Rigatto, C., & Komenda, P. (2021). Real-world evidence of SGLT2 inhibitors in CKD. Canadian Journal of Kidney Health and Disease, 8, 1–10.

Lin, B., Ko, J., Wang, Y. *et al.* (2020). Long-term outcomes of SGLT2 inhibitors added to ARBs in DKD. Journal of Diabetes, 12, 650–661.

Loutradis, C., Skodra, C., & Sarafidis, P. (2021). Blood pressure lowering with SGLT2 inhibitors. Current Hypertension Reports, 23, 7–15.

Lovshin, J. A., & Cherney, D. Z. (2021). SGLT2 inhibitors in microvascular complications. Diabetes and Metabolism, 47, Article 101191.

Mahaffey, K. W., Jardine, M. J., Bompoint, S. *et al.* (2019). Canagliflozin and CV and renal events in diabetes. New England Journal of Medicine, 380, 2295–2306.

Mahato, R. V., Gyawali, P., Raut, P. P. *et al.* (2015). Diabetes states and kidney outcomes: A Nepali cohort. BMJ Open Diabetes Research and Care, 3, Article e000110.

Manley, H. J., & Hunsicker, L. G. (2020). Nutrition management in diabetic CKD. Journal of Renal Nutrition, 30, 429–442.

Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F. E., Nauck, M. A., Nissen, S. E., Pocock, S., Poulter, N. R., Ravn, L. S., Steinberg, W. M., Stockner, M., Zinman, B., Bergenstal, R. M., Buse, J. B., LEADER Steering Committee, & LEADER Trial Investigators. (2016). Liraglutide and cardiovascular outcomes in type 2 diabetes. The New England Journal of Medicine, 375(4), 311–322. https://doi.org/10.1056/NEJMoa1603827

Mazzieri, A., Porcellati, F., Timio, F., & Reboldi, G. (2024). Molecular targets of novel therapeutics for diabetic kidney disease: A new era of nephroprotection. International Journal of Molecular Sciences, 25(7), 3969. https://doi.org/10.3390/ijms25073969

McMurray, J. J. V., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., Ponikowski, P., Sabatine, M. S., Anand, I. S., Bělohlávek, J., Böhm, M., Chiang, C.-E., Chopra, V. K., de Boer, R. A., Desai, A. S., Diez, M., Drozdz, J., Dukát, A., Ge, J., DAPA-HF Trial Committees and Investigators. (2019). Dapagliflozin in heart failure with reduced ejection fraction. The New England Journal of Medicine, 381(21), 1995–2008. https://doi.org/10.1056/NEJMoa1911303

Memon, R. A., Akbariromani, H., Vohra, R. R., Kundi, H., Saleem, R. F., Ghaffari, M. A., Haas, D., & Khan, A. (2022). Comparison of cardiovascular outcomes between dapagliflozin and empagliflozin in patients with type 2 diabetes: A meta-analysis. Cureus, 14(7), Article e27277. https://doi.org/10.7759/cureus.27277

Michel, M. C., Foster, C., Brunner, H. R., & Liu, L. (2013). Comparison of clinically used AT1 blockers. Pharmacology, 92, 331–347.

Mima, A., & King, G. L. (2018). RAAS, oxidative stress, and DKD. Antioxidants and Redox Signaling, 29, 953–962.

Mogensen, C. E. (1992). Microalbuminuria as a predictor of clinical nephropathy in diabetes. Kidney International, 31, 673–689.

Molinaro, R., Pastore, I., Bombace, G. *et al.* (2019). SGLT2i and anti-inflammation in diabetic nephropathy. International Journal of Molecular Sciences, 20, 4773–4785.

Molitch, M. E., Steffes, M., Sun, W., Rutledge, B., Cleary, P., de Boer, I. H., Zinman, B., Lachin, J., & Epidemiology of Diabetes Interventions and Complications Study Group. (2010). Development and progression of nephropathy in Pima Indians. Diabetes Care, 33(7), 1536–1543. https://doi.org/10.2337/dc09-1098

Morigi, M., Perico, L., & Remuzzi, G. (2022). Cellular targets in diabetic kidney disease. Nature Reviews. Nephrology, 18, 227–244.

Naaman, S. C., & Bakris, G. L. (2023). Diabetic nephropathy: Update on pillars of therapy slowing progression. Diabetes Care, 46(9), 1574–1586. https://doi.org/10.2337/dci23-0030

Nadkarni, G. N., Chauhan, K., Bosso-Mougoue, T. *et al.* (2022). Machine learning for predicting kidney disease progression. Nature Reviews. Nephrology, 18, 476–487.

Navaneethan, S. D., Amuthan, A., & Rocco, M. V. (2015). Diabetes control in CKD: Where do we stand? Current Diabetes Reports, 15, 80–90.

Navarro-González, J. F., & Mora-Fernández, C. (2008). The Role of inflammatory cytokines in diabetic nephropathy. Journal of the American Society of Nephrology, 19(3), 433–442. https://doi.org/10.1681/ASN.2007091048

Neuen, B. L., Young, T., Heerspink, H. J. L., Neal, B., Perkovic, V., Billot, L., Mahaffey, K. W., Charytan, D. M., Wheeler, D. C., Arnott, C., Bompoint, S., Levin, A., & Jardine, M. J. (2019). SGLT2 inhibitors for kidney failure prevention. The Lancet. Diabetes and Endocrinology, 7(11), 845–854. https://doi.org/10.1016/S2213-8587(19)30256-6

Ninomiya, T., Perkovic, V., De Galan, B. E., Zoungas, S., Pillai, A., Jardine, M., Patel, A., Cass, A., Neal, B., Poulter, N., Mogensen, C.-E., Cooper, M., Marre, M., Williams, B., Hamet, P., Mancia, G., Woodward, M., Macmahon, S., Chalmers, J., & ADVANCE Collaborative Group. (2009). Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. Journal of the American Society of Nephrology, 20(8), 1813–1821. https://doi.org/10.1681/ASN.2008121270

Nishiyama, A., Kobori, H., & Abe, Y. (2015). Role of oxidative stress in diabetic nephropathy. Current Diabetes Reviews, 11, 55–59.

Ortiz, A., Sanchez-Nino, M. D., Crespo-Barrio, M. *et al.* (2020). DKD pathology: A modern view. Kidney International Supplements, 10, 15–33.

Pagtalunan, M. E., Miller, P. L., Jumping-Eagle, S., Nelson, R. G., Myers, B. D., Rennke, H. G., Coplon, N. S., Sun, L., & Meyer, T. W. (1997). Podocyte loss and progressive glomerular injury in type 2 diabetes. The Journal of Clinical Investigation, 99(2), 342–348. https://doi.org/10.1172/JCI119163

Pálsson, R., & Patel, U. D. (2014). Cardiovascular complications of diabetic kidney disease. Advances in Chronic Kidney Disease, 21(3), 273–280. https://doi.org/10.1053/j.ackd.2014.03.003

Parikh, C. R., Devarajan, P., Zappitelli, M., Sint, K., Thiessen-Philbrook, H., Li, S., Kim, R. W., Koyner, J. L., Coca, S. G., Edelstein, C. L., Shlipak, M. G., Garg, A. X., Krawczeski, C. D., & TRIBE-AKI Consortium. (2011). Postoperative biomarkers predict AKI and outcomes after pediatric cardiac surgery. Journal of the American Society of Nephrology, 22(9), 1737–1747. https://doi.org/10.1681/ASN.2010111163

Patel, A., MacMahon, S., Chalmers, J. *et al.* (2008). Intensive blood glucose control in ADVANCE: Effects on microvascular outcomes. Diabetes Care, 31, 1547–1554.

Patel, H. K., Barvaliya, M. J., Patel, T. K. *et al.* (2016). Drug interactions of AT1 blockers: Need for pharmacovigilance. International Journal of Basic and Clinical Pharmacology, 5, 1766–1772.

Perkovic, V., Jardine, M. J., Neal, B., Bompoint, S., Heerspink, H. J. L., Charytan, D. M., Edwards, R., Agarwal, R., Bakris, G., Bull, S., Cannon, C. P., Capuano, G., Chu, P.-L., de Zeeuw, D., Greene, T., Levin, A., Pollock, C., Wheeler, D. C., Yavin, Y., CREDENCE Trial Investigators. (2019). Canagliflozin and renal outcomes in type 2 diabetes. The New England Journal of Medicine, 380(24), 2295–2306. https://doi.org/10.1056/NEJMoa1811744

Pinto, L. C., Rados, D. R., Pankow, J. S. *et al.* (2021). Long-term kidney outcomes and glycemic control. Diabetes Research and Clinical Practice, 174, Article 108768.

A Prospective, Randomised, Double-blind, Double-dummy, Forced-titration, Multicentre, Parallel Group, one year Treatment Trial to Compare telmisartan (Micardis) 80 mg versus losartan (Cozaar) 100 mg. In Hypertensive Type 2 diabetic patients with overt nephropathy (AMADEO study). https://www.clinicaltrials.gov/study/NCT00168857?term=TELMISARTANandviewType=Table&rank=4

Pugliese, G., Penno, G., Natali, A. *et al.* (2020). Diabetic kidney disease: New clinical and therapeutic issues. Journal of Nephrology, 33, 985–1005.

Remuzzi, G., Perico, N., & Macia, M. (2002). RAAS in CKD progression. Kidney International, 62 (Suppl uppl S57-S65.

Ruggenenti, P., Cravedi, P., & Remuzzi, G. (2013). The RAAS in the pathogenesis of diabetic nephropathy. Nature Reviews. Nephrology, 9, 124–137

Ryšavá, R., Tesar, V., Merta, M., & Czech Group for the Study of Glomerulonephritis. (2005). Effect of telmisartan on blood pressure control and kidney function in hypertensive, proteinuric patients with chronic kidney disease. Blood Pressure Monitoring, 10(4), 207–213. https://doi.org/10.1097/01.mbp.0000172708.97534.15

Saad, M. F., & Knowler, W. C. (2007). Population studies of diabetic kidney disease. Diabetes Spectrum, 20, 74–80.

Saran, R., Robinson, B., Abbott, K. C. *et al.* (2021). US renal data system 2020 annual report. American Journal of Kidney Diseases, 77, A7–A8.

Sattar, N., Petrie, M. C., Zinman, B. *et al.* (2021). Cardiorenal outcomes with SGLT2 inhibitors: Expected and unexpected benefits. Diabetologia, 64, 2103–2109.

Sawaf, H., Thomas, G., Taliercio, J. J. *et al.* (2015). Chronic kidney disease: Global impact. Kidney International Supplements, 5, 149–160.

Schievink, B., & Groop, P. H. (2019). Albuminuria: A hallmark of diabetic nephropathy. Journal of Internal Medicine, 286, 467–493.

Schmid, H., Boucherot, A., Yasuda, Y., Henger, A., Brunner, B., Eichinger, F., Nitsche, A., Kiss, E., Bleich, M., Gröne, H.-J., Nelson, P. J., Schlöndorff, D., Cohen, C. D., Kretzler, M., & European Renal cDNA Bank (ERCB) Consortium. (2006). Modular activation pattern of NF-κB in DKD. Diabetes, 55(11), 2993–3003. https://doi.org/10.2337/db06-0477

Schupp, M., Clemenz, M., Gineste, R. *et al.* (2004). Selective PPAR-γ modulators with AT1 blocking activity. Diabetes, 53, 2242–2251.

Sharma, S., & Haffner, S. (2013). Lipid abnormalities and DKD. Kidney International Supplements, 3(3), 303–305. https://doi.org/10.1038/kisup.2013.42

Shin, S. J., Chung, S., Kim, S. J. *et al.* (2020). Telmisartan protects podocytes via PPAR-γ. Scientific Reports, 10, 8786–8796.

Stangier, J., Su, C. A., & Roth, W. (2000). Pharmacokinetics of telmisartan in healthy volunteers. The Journal of International Medical Research, 28(4), 149–167. https://doi.org/10.1177/147323000002800401

Thomas, M. C., Cooper, M. E., & Zimmet, P. (2015). Changing epidemiology of type 2 diabetes and DKD. Nature Reviews. Nephrology, 12, 73–81.

Tobe, S. W., Clase, C. M., Gao, P., McQueen, M., Grosshennig, A., Wang, X., Teo, K. K., Yusuf, S., Mann, J. F. E., & ONTARGET, and TRANSCEND Investigators. (2011). Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: Results from the ONTARGET and Transcend studies. Circulation, 123(10), 1098–1107. https://doi.org/10.1161/CIRCULATIONAHA.110.964171

Tokunaga, M., Kabashima, N., Serino, R., Shibata, T., Matsumoto, M., Miyamoto, T., Miyazaki, M., Furuno, Y., Nakamata, J., Fujimoto, Y., Takeuchi, M., Abe, H., Okazaki, M., Otsuji, Y., & Tamura, M. (2010). Renoprotective effects of telmisartan in patients with advanced chronic kidney disease. Clinical Nephrology, 73(2), 139–146. https://doi.org/10.5414/cnp73139

Tuttle, K. R., Bakris, G. L., Bilous, R. W., Chiang, J. L., de Boer, I. H., Goldstein-Fuchs, J., Hirsch, I. B., Kalantar-Zadeh, K., Narva, A. S., Navaneethan, S. D., Neumiller, J. J., Patel, U. D., Ratner, R. E., Whaley-Connell, A. T., & Molitch, M. E. (2014). Diabetic kidney disease: A report from ADA consensus conference. Diabetes Care, 37(10), 2864–2883. https://doi.org/10.2337/dc14-1296

Umino, T., Hasegawa, K., Minakuchi, H. *et al.* (2018). Dapagliflozin and telmisartan additively suppress diabetic nephropathy in db/db mice. Physiological Reports, 6, Article e13871.

Vallon, V., & Thomson, S. C. (2017). Targeting renal glucose reabsorption to treat hyperglycemia. Diabetologia, 60(2), 215–225. https://doi.org/10.1007/s00125-016-4157-3

Van Bommel, E. J., Muskiet, M. H., Tonneijck, L. *et al.* (2017). SGLT2 inhibition in the diabetic kidney. Trends in Endocrinology and Metabolism, 28, 493–503.

Vassalotti, J. A., Li, S., Chen, S. C. *et al.* (2013). Kidney early evaluation program (KEEP) and diabetes. American Journal of Kidney Diseases, 61, S46–S57.

Verma, S., Mazer, C. D., Yan, A. T. *et al.* (2021). SGLT2 inhibitors and cardio-renal benefits. Journal of Cardiac Failure, 27, 453–466.

Villarreal, G., Martínez-de la Torre, A., & Méndez, J. D. (2020). AGEs and diabetic nephropathy. World Journal of Diabetes, 11, 115–129.

Wanner, C., Inzucchi, S. E., Lachin, J. M., Fitchett, D., von Eynatten, M., Mattheus, M., Johansen, O. E., Woerle, H. J., Broedl, U. C., Zinman, B., & EMPA-Reg OUTCOME Investigators. (2016). Empagliflozin and progression of kidney disease in type 2 diabetes. The New England Journal of Medicine, 375(4), 323–334. https://doi.org/10.1056/NEJMoa1515920

Weir, M. R. (2011). RAAS inhibition and potassium homeostasis in CKD. Kidney International Supplements, 79 (Suppl uppl S20-S27.

Wiviott, S. D., Raz, I., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Silverman, M. G., Zelniker, T. A., Kuder, J. F., Murphy, S. A., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., Ruff, C. T., Gause-Nilsson, I. A. M., Fredriksson, M., Johansson, P. A., Langkilde, A.-M., DECLARE–TIMI 58 Investigators. (2019). Dapagliflozin and cardiovascular outcomes in type 2 diabetes. The New England Journal of Medicine, 380(4), 347–357. https://doi.org/10.1056/NEJMoa1812389

World Health Organization. (2016). Global report on diabetes. WHO press.

Xu, C., Ha, X., Yang, S., Tian, X., & Jiang, H. (2023). Advances in understanding and treating diabetic kidney disease: Focus on tubulointerstitial inflammation mechanisms. Frontiers in Endocrinology, 14, Article 1232790. https://doi.org/10.3389/fendo.2023.1232790

Xu, L., Ng, H. Y., & Pianta, T. (2018). Biomarkers of DKD progression. Nephrology, 23, 699–708.

Yamada, T., Shojima, N., Yamauchi, T., & Kadowaki, T. (2021). SGLT2 inhibitors and albuminuria. Diabetologia, 64, 692–703.

Yang, W., Xie, X., Curhan, G. *et al.* (2018). DKD and mortality in NHANES III. Kidney International, 93, 195–207.

Yang, Y., & Xu, G. (2022). Update on pathogenesis of glomerular hyperfiltration in early diabetic kidney disease. Frontiers in Endocrinology, 13, Article 872918. https://doi.org/10.3389/fendo.2022.872918

Yoon, K. H., & Ko, S. H. (2011). Exercise and DKD. Diabetes Research and Clinical Practice, 93, S54–S59.

Yoshida, A., Nakamura, J., Akanuma, Y. *et al.* (2014). Telmisartan suppresses renal fibrosis via PPAR-γ. Kidney International, 86, 360–370.

Yuyun, M. F., Khaw, K. T., Luben, R. *et al.* (2004). Proteinuria and cardiovascular risk. Journal of Human Hypertension, 18, 177–181.

Zeni, L., Norden, A. G., Cancarini, G., & Unwin, R. J. (2017). Why do SGLT2 inhibitors protect the kidney? Kidney International, 91, 1290–1302.

Zhang, Q., & Zhou, S. P. (2019). PPAR-γ and kidney fibrosis. Frontiers in Pharmacology, 10, 672–679.

Zheng, S. L., Zhang, Q., Zhang, S. *et al.* (2020). Real-world effectiveness of SGLT2 inhibitors. The BMJ, 371, m4166–m4172.

Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., Mattheus, M., Devins, T., Johansen, O. E., Woerle, H. J., Broedl, U. C., Inzucchi, S. E., & EMPA-Reg OUTCOME Investigators. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. The New England Journal of Medicine, 373(22), 2117–2128. https://doi.org/10.1056/NEJMoa1504720

Zou, H. W., Yang, C. H., Che, W. Q. *et al.* (2019). Telmisartan improves insulin resistance and reduces kidney injury in DKD. Endocrine Research, 44, 176–185.

Zoungas, S., de Galan, B., Ninomiya, T. *et al.* (2010). Combined effect of blood pressure and glycemic control on DKD risk. New England Journal of Medicine, 363, 1909–1917.

Zuo, L., Liu, F., & Zhang, M. (2021). Inflammation and fibrosis biomarkers in DKD. Renal Failure, 43, 1156–1167.

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