Nephrol Dial Transplant, 2025, **40**, i3–i17
https://doi.org/10.1093/ndt/gfae212

REVIEW

Combination therapy: an upcoming paradigm to improve kidney and cardiovascular outcomes in chronic kidney disease

Radica Z. Alicic [1,2], Joshua J. Neumiller[1,3] and Katherine R. Tuttle [1,2,4]

[1]Providence Medical Research Center, Providence Inland Northwest Health, Spokane, WA, USA
[2]Department of Medicine, University of Washington, Seattle, WA, USA
[3]College of Pharmacy and Pharmaceutical Sciences, Washington State University, Spokane, WA, USA
[4]Kidney Research Institute and Institute of Translational Health Sciences, University of Washington, Seattle, WA, USA
Correspondence to: Radica Z. Alicic; E-mail: Radica.Alicic@providence.org

PLAIN ENGLISH SUMMARY

In this article the authors review recent advances in the treatment of chronic kidney disease (CKD) with diabetes, and summarize evidence supporting combination therapy approaches to improve patient outcomes. Driven by the global rise in diabetes, the worldwide burden of CKD has nearly doubled since the 1990s. People with CKD have notably increased risks for premature cardiovascular disease (heart and blood vessels disease), kidney failure and death. CKD, diabetes, obesity and cardiovascular disease are closely interrelated and share common risk factors. These health conditions therefore comprise what is now known as cardiovascular–kidney–metabolic (CKM) syndrome. Recently approved medications, including sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the non-steroidal mineralocorticoid receptor antagonist (ns-MRA) finerenone, represent agents capable of reducing metabolic, kidney and cardiovascular risk through complementary mechanisms of action. Current evidence supports use of these therapies in combination. Besides providing additive protective effects, combination therapy may also help reduce side effects. For instance, using an SGLT2 inhibitor in combination with finerenone helps decrease the risk for high potassium levels. Through the multipronged approach, combination therapy allows tailoring treatment for the individual patient characteristics and needs. Several planned and ongoing clinical trials continue to study the benefits of combination therapy in people with CKM syndrome. With building evidence supporting the use of combination therapy, it is crucial to raise awareness of the importance of this treatment approach and develop processes to incorporate new therapies into every day practice to support optimal care and improved outcomes.

ABSTRACT

The global burden of chronic kidney disease (CKD) increased by nearly 90% in the period spanning 1990 to 2016, mostly attributed to an increase in the prevalence of CKD in diabetes. People living with CKD have an elevated lifetime risk for cardiovascular disease (CVD) when compared with the general population, with risk increasing in parallel with albuminuria and kidney function decline. Metabolic disease, CKD and CVD share common risk factors including neurohumoral activation, systemic inflammation and oxidative stress, thus prompting the introduction of a broader construct of cardiovascular–kidney–metabolic (CKM) syndrome. An important rationale for the introduction of this concept are recent and ongoing therapeutic advancements fundamentally changing CKM management. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the non-steroidal mineralocorticoid receptor antagonist (ns-MRA) finerenone have shifted the therapeutic paradigm for patients with CKD and have emerged in rapid succession as cornerstones of guideline-directed medical therapy (GDMT). Recently completed clinical trials of aldosterone synthase inhibitors and endothelin receptor antagonists have additionally reported additive antiproteinuric effects on the background of renin–angiotensin system and SGLT2 inhibition, with acceptable safety profiles. The sum of current evidence from both preclinical and clinical studies support combination therapy in the setting of CKD to achieve additive and potentially synergistic kidney and heart protection by addressing metabolic, hemodynamic, and pro-inflammatory and pro-fibrotic mechanistic pathways. This narrative review will discuss available evidence supporting combination GDMT in CKD with diabetes and additionally discuss ongoing and future trials evaluating the efficacy and safety of combination therapies for CKD with or without diabetes.

Keywords: albuminuria, cardiovascular, CKD, diabetes mellitus, inflammation

INTRODUCTION

With over 800 million people worldwide affected, and the incidence more than doubling between the years 1990 and 2019, chronic kidney disease (CKD) represents a pressing public health concern [1–3]. These concerning trends are largely attributable to the diabetes pandemic, with obesity representing the most important risk factor linked to more than 50% of new cases of diabetes every year [4]. The highest rates of age-standardized CKD incidence and disability-adjusted life years are reported in North Africa, the Middle East, South Asia, Central Latin America and North America [3]. In the USA, CKD rates are disproportionately high in racially minoritized populations when compared with the

Received: April 10, 2024; Editorial decision: June 28, 2024

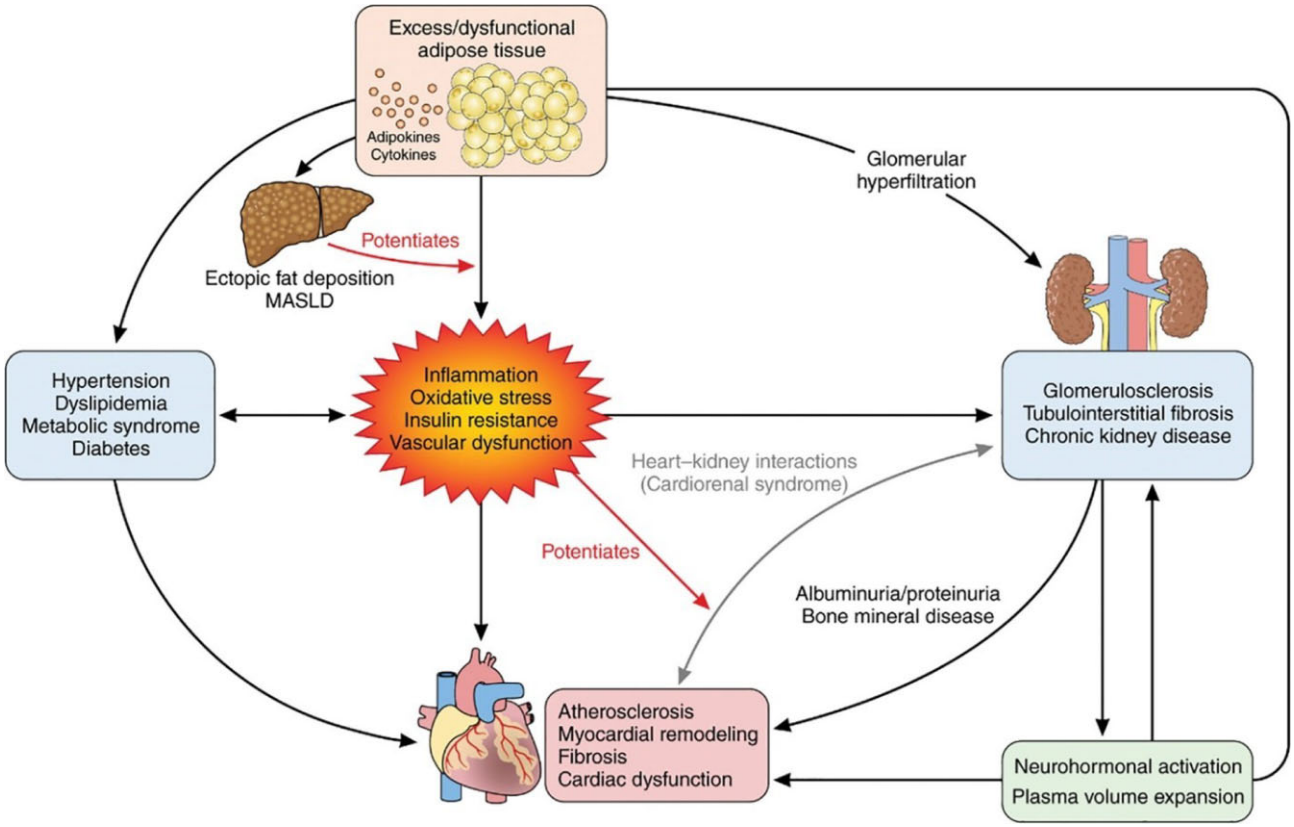

Figure 1: Conceptual representation of CKM syndrome. The image displays the pathophysiology underlying CKM syndrome. CKM syndrome most commonly originates from excess adipose tissue, dysfunctional adipose tissue or both. Multiple pathological processes related to dysfunctional adipose tissue result in insulin resistance and eventual hyperglycemia. Inflammation, oxidative stress, insulin resistance and vascular dysfunction are highlighted as central processes leading to the development of metabolic risk factors, to the progression of kidney disease, to the potentiation of heart–kidney interactions and to the development of CVD. Metabolic risk factors and CKD further predispose to CVD through multiple direct and indirect pathways. MASLD indicates metabolic dysfunction–associated steatotic liver disease. Source: Ndumele *et al.* [17].

white population [4]. CKD is present in nearly half of people with type 2 diabetes (T2D) and one-third of those with type 1 diabetes (T1D) [2, 5]. Together, T2D and hypertension account for 85% of global growth in CKD burden [3, 4, 6, 7]. CKD is associated with increased risks for adverse kidney, cardiovascular (CV) and mortality outcomes [8–10]. Although CKD in diabetes is a global leading cause of kidney failure and need for kidney replacement therapy, due to the competing risk of death only a minority of persons with diabetes survive to progress to kidney failure [11]. Death, mainly due to heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD), is a major competing risk of CKD [12, 13]. Importantly, both increased albuminuria and reduced estimated glomerular filtration rate (eGFR) are independent and additive risk factors for CV events, CV-related mortality and all-cause mortality [10].

Recent therapeutic advancements, including the sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and aldosterone inhibition with non-steroidal mineralocorticoid antagonists (ns-MRAs) have emerged as guideline-directed medical therapies (GDMT) capable of improving kidney and CV outcomes in patients with CKD on top of renin–angiotensin system (RAS) blockade given at the highest approved or tolerated dose [14, 15]. The recognition of interconnectivity and shared risk factors among metabolic conditions (e.g. diabetes, obesity), CKD and cardiovascular disease (CVD) served as the impetus to formulate the concept of cardiovascular–kidney–metabolic (CKM) syndrome. The introduction of CKM syndrome as an overarching model helps to establish a theoretical framework for the treatment that focuses on identifying and managing shared risk factors and conditions through a multipronged approach that addresses the complex biology involved in the development and progression of CKM conditions (Fig. 1) [16, 17]. A "pillar approach" to management of CKD has been proposed to holistically address kidney and CVD risks [18, 19]. Recently completed and ongoing studies continue to inform the use of these therapies in non-diabetic forms of CKD [20, 21]. This narrative review will discuss evidence supporting combination GDMT in CKD with diabetes as well as ongoing and future studies evaluating the efficacy and safety of combination therapies for CKD with or without diabetes.

CKD PATHOPHYSIOLOGY AS A FRAMEWORK FOR COMBINATION THERAPY APPROACHES

The pathophysiology of CKD in diabetes is quite complex, involving intricate interplay between metabolic derangements, hemodynamic changes, and progression of inflammation and fibrosis. Obesity, dysglycemia, dyslipidemia and hypertension contribute to the development and progression of diabetes, CKD, and major CVD subtypes [22]. Obesity, especially visceral adiposity, is strongly associated with insulin resistance, dyslipidemia and hypertension, and is recognized as a state of chronic inflammation with enhanced production of pro-inflammatory cytokines such as

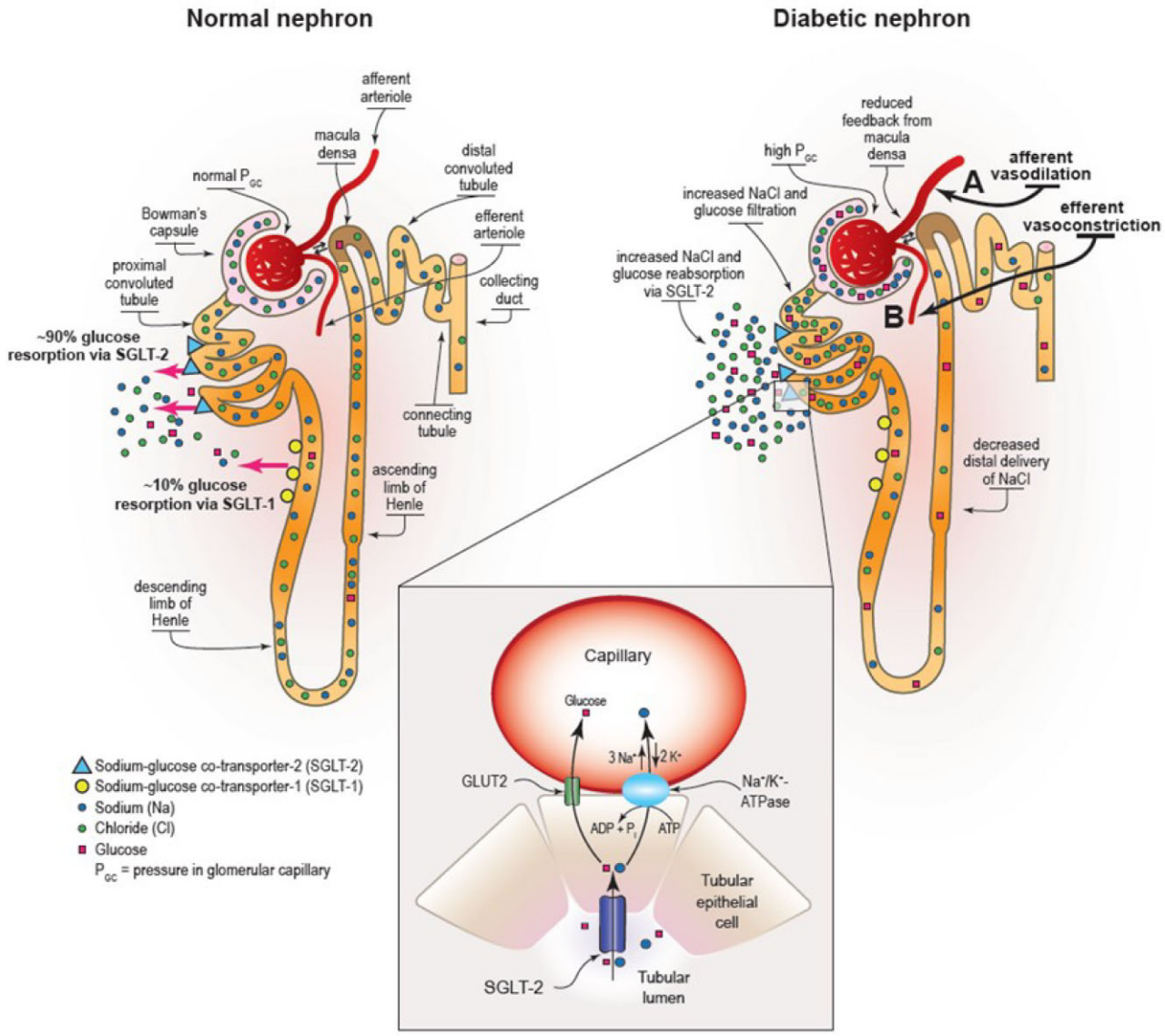

Figure 2: Normal and diabetic nephron with altered hemodynamics. (**A**) Afferent vasodilation is promoted by hyperglycemia, hyperinsulinemia, elevated level of circulating amino acids, COX-2 prostanoids, reduction of tubule glomerular feedback. Tubuloglomerular feedback is a kidney intrinsic autoregulatory mechanism which helps regulate the rate of glomerular filtration rate. Because of increased reabsorption of glucose and sodium via SGLTs in diabetes, sodium chloride delivery to macula densa cells of juxtaglomerular apparatus is decreased, resulting in lower production of adenosin and consequent relative vasodilation of afferent arteriolar. (**B**) Efferent vasoconstriction is promoted by high local angiotensin II level, endothelin I, reactive oxygen species, thromboxane A2. Source: Alicic *et al.* [33].

tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 [23]. Furthermore, unhealthy adipose tissue is linked to an imbalance in secretion of adipokines (adiponectin and leptin), resulting in increased vascular tone and overactivity of the sympathetic nervous system, and RAS activation [23, 24]. Higher aldosterone production and upregulation of mineralocorticoid receptors (MRs) accelerate kidney and CV injury through multiple pathways activating inflammation and fibrosis [25]. Aldosterone also promotes sodium and volume retention by the kidney, which in turn increases cardiac preload, HF worsening and atrial fibrosis [26, 27].

At the level of the kidney, high levels of glucagon and amino acids decrease afferent arteriolar resistance (vasodilation) and increase glomerular perfusion, while increased production of angiotensin II and endothelin-1 and increase efferent arteriolar resistance (vasoconstriction) [28–31]. With persistent hyperglycemia, enhanced glucose and sodium chloride uptake in the proximal tubule via upregulated SGLT2 transporters reduces solute delivery to the macula densa, thus inhibiting tubuloglomerular feedback and adenosine-mediated vasoconstriction of the afferent arteriole, further augmenting hyperperfusion. These imbalances in glomerular vascular tone and perfusion tip the balance toward increased glomerular pressure and hyperfiltration (Fig. 2) [32–34].

Advanced glycation end products (AGE), formed by the interaction of glucose and associated metabolites with proteins and amino acids, reacts with its membrane-bound receptor (RAGE) [35]. RAGE is found on multiple cells in the kidney, including podocytes, mesangial cells, endothelial cells, tubular epithelial cells and macrophages [35]. AGE-RAGE activation is implicated in multiple signaling pathways, including immune pathways

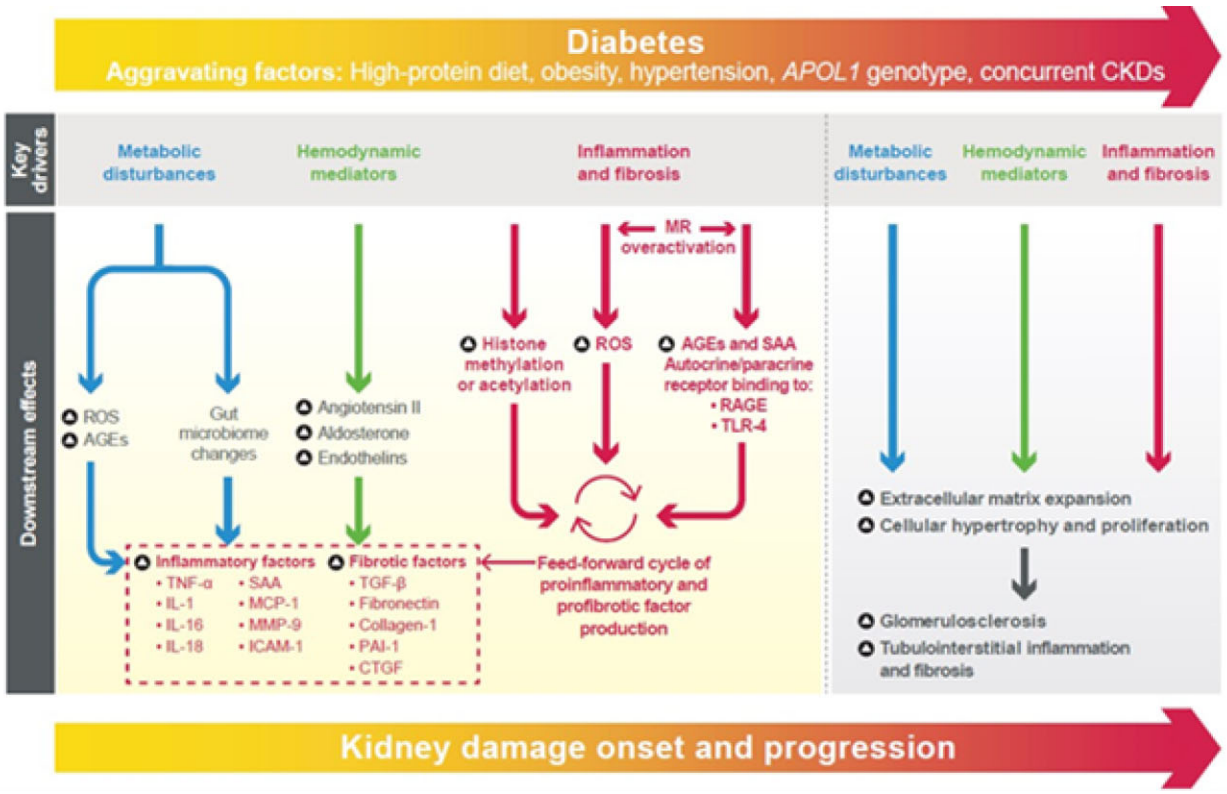

Figure 3: Diagram showing the interrelation of mechanistic drivers in early though advanced stages of kidney damage and disease progression in diabetes. CTGF, connective tissue growth factor; DKD, diabetic kidney disease; ICAM-1, intracellular adhesion molecule 1; MCP-1, monocyte chomoattractant protein-1; MMP-9, matrix metalloproteinase 9; PAI-1, plasminogen activator inhibitor; SAA, serum amyloid A; TLR-4, toll-like preceptor-4. Source: Tuttle *et al.* [41].

and transcription factors, macrophage migration, production of pro-inflammatory cytokines [e.g. IL 6, TNF-α and vascular cell adhesion molecule-1 (VCAM-1)], increased expression of pro-fibrotic transforming growth factor-β (TGF-β), and oxidative stress via generation of reactive oxygen species (ROS) through stimulation of nicotinamide adenine dinucleotide phosphate (NADPH) [35–40]. As a result, the resident network of macrophages in the kidney release proinflammatory cytokines and activate inflammatory pathways, with subsequent recruitment of additional inflammatory cells, and further upregulated production of inflammatory cytokines, chemokines, and ultimately pro-fibrotic cells and pathways (Fig. 3) [41–45].

REVIEW OF GDMT IN CKD

RAS inhibitors

RAS inhibition with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) has been a long-term standard-of-care for patients with diabetes, hypertension and albuminuria [46–48]. Accordingly, contemporary guidelines recommend first-line treatment with a maximally tolerated dose of a RAS inhibitor for patients with diabetes, CKD and hypertension [14, 15]. ACEis and ARBs reduce efferent arteriolar vasoconstriction leading to a reduction in glomerular pressure [5], and possibly anti-inflammatory benefits [49]. Notably, more recently established GDMTs have demonstrated kidney benefit as add-on to RAS inhibitor therapy, providing proof of concept for combination therapy to improve CKD outcomes.

SGLT2 inhibitors

In addition to the benefits described for secondary kidney outcomes in SGLT2 inhibitor cardiovascular outcome trials (CVOTs) [50–52], three dedicated kidney outcome trials of SGLT2 inhibitor therapy in CKD have been completed to date (Table 1) [20, 21, 53]. The first trial published was the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [53]. CREDENCE reported a 30% relative risk reduction for its primary kidney composite outcome (Table 1) [53]. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) trials quickly followed, thus establishing a class effect of SGLT2 inhibitors for kidney protection [20, 21]. Importantly, DAPA-CKD and EMPA-KIDNEY included participants without diabetes, with lower eGFRs (baseline eGFRs down to 20 mL/min/1.73 m^2) and with wide variations in baseline albuminuria (Table 1) [20, 21]. Subgroup analyses from the EMPA-KIDNEY trial found no heterogeneity of relative effect based on CKD cause or baseline eGFR [21, 54]. Similarly, a meta-analysis of large SGLT2 inhibitor outcome trials reported kidney benefit in patients with CKD or HF irrespective of baseline diabetes status or kidney function [55]. In consideration of these remarkably consistent findings of kidney and CV benefit, SGLT2 inhibitors are recommended as first-line therapy for CKD by organizations including the American Diabetes Association (ADA), Kidney Disease: Improving Global Outcomes (KDIGO) and the American Association of Clinical Endocrinology (AACE) [14, 15, 56, 57]. SGLT2 inhibitors are currently recommended in people with eGFR $\geq$20 mL/min/1.73 m^2. Discontinuation of SGLT2 inhibition is

Table 1: SGLT2 inhibitor dedicated kidney outcome trials [20, 21, 53].

Trial	CREDENCE ($n = 4401$)	DAPA-CKD ($n = 4304$)	EMPA-KIDNEY ($n = 6609$)
Treatment	Canagliflozin	Dapagliflozin	Empagliflozin
Mean participant age (years)	63	62	64
Key inclusion criteria	• T2D • eGFR 30 to <90 mL/min/1.73 m^2 • UACR >300 to 5000 mg/g • Treated with RAS inhibitor for ≥4 weeks prior to randomization	• eGFR 25 to 75 mL/min/1.73 m^2 • UACR of 200 to 5000 mg/g • Treated with RAS inhibitor for ≥4 weeks prior to screening	• eGFR 20 to <45 mL/min/1.73 m^2 regardless of albuminuria, or • eGFR 45 to <90 mL/min/1.73 m^2 with UACR ≥200 mg/g • Treated with RAS inhibitor unless deemed inappropriate by the investigator
Baseline diagnosis of T2D (%)	100	67	46
Median follow-up (years)	2.6	2.4	2.0
Primary outcome HR (95% CI)	ESKD, doubling of SCr, or renal or CV death: 0.70 (0.59–0.82)	≥50% decline in eGFR, ESKD or renal or CV death: 0.61 (0.51–0.72)	ESKD, ≥40% decline in eGFR, sustained eGFR of <10 mL/min/1.73 m^2, or renal or CV death: 0.72 (0.64–0.82)
Key secondary outcome Progression to ESKD; HR (95% CI)	0.68 (0.54–0.86)	0.64 (0.50–0.82)	N/R

ESKD, end-stage kidney disease; HR, hazard ratio; N/R, data not reported; SCr, serum creatinine.

currently recommended once a patient progresses to dialysis or kidney transplant. However, a potential therapeutic role of SGLT2 inhibitors for patients treated by dialysis or kidney transplant is under study [58, 59]. The Renal Lifecycle Trial (NCT05374291) will assess the effects of dapagliflozin on kidney failure, HF, mortality and safety in patients with eGFR ≤25 mL/min/1.73 m^2, chronic dialysis or kidney transplant with an eGFR ≤45 mL/min/1.73 m^2.

While SGLT2 inhibitor therapy results in reduced glycemia, weight and blood pressure [60, 61], the kidney and heart protective effects of SGLT2 inhibition are independent of metabolic effects [62]. A principal therapeutic mechanism is reduction of glomerular hyperfiltration by restoring tubuloglomerular feedback through increased distal delivery of solutes including sodium and chloride along with glucose (Fig. 4) [41]. SGLT2 inhibition may also reduce oxidative stress and inflammation in kidney, heart and endothelial cells [62–70]. Another plausible mechanisms responsible for improved kidney and CV outcomes are augmented delivery of efficient fuels and oxygen in the setting of SGLT2 inhibition induced ketonemia and erythrocytosis [71, 72]. However, data on role of the increased hematocrit in reduction of CV risk are inconsistent, underscoring the need for ongoing research [73].

ns-MRA: finerenone

Overactivation of the MR is an important mechanism for CKD progression and CVD (Fig. 3) [41, 74, 75]. The ns-MRA finerenone selectively antagonizes the MR [74]. The finerenone–MR complex in turn transits to the nucleus and downregulates pro-inflammatory and profibrotic gene transcription (Fig. 4) [76]. The benefits of finerenone treatment as an add-on to RAS inhibitor therapy in the setting of T2D and CKD were reported in two primary outcome trials: the Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD) trial and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial (Table 2) [77, 78]. After median follow-ups of 2.6 and 3.4 years, the FIDELIO-DKD and FIGARO-DKD trials reported relative risk reductions of 18% and 13% for their primary composite kidney and CV outcomes, respectively [77, 78]. Together, FIDELIO-DKD and FIGARO-DKD included participants with a range of baseline eGFR and urine albumin to creatinine ratio (UACR) values. FIDELITY analyses (inclusive of pooled data from both primary trials) reported benefits on kidney and CV outcomes across a broad range of baseline eGFR and albuminuria levels [79], with treatment benefits realized regardless of prevalent ASCVD [80]. Other MRAs such as spironolactone also convey antialbuminuric effects, but have not been studied for efficacy or safety in dedicated kidney outcomes trials among patients with CKD [81]. Therefore, based on the available evidence, ADA and KDIGO recommend use of finerenone in patients with T2D and CKD with persistent albuminuria (UACR ≥30 mg/g) despite treatment with first-line therapies [14].

GLP-1RAs

GLP-1RAs, like SGLT2 inhibitors, were initially developed as glucose-lowering therapies [82]. Secondary kidney outcome findings from CVOTs and a clinical trial (inclusive of participants with eGFRs as low as 15 mL/min/1.73 m^2) suggested benefits of GLP-1 receptor agonism on kidney disease [83–86]. Pooled GLP-1RA CVOT analyses reported that GLP-1RA therapy reduced albuminuria and slowed eGFR decline compared with placebo, with the greatest benefits observed in those with baseline eGFR <60 mL/min/1.73 m^2 [87, 88]. The first dedicated kidney outcome trial performed with a GLP-1RA, the "Effects of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease" (FLOW) enrolled 3533 participants with T2D and CKD. After median follow-up of 3.4 years, treatment with subcutaneous semaglutide 1.0 mg weekly reduced the risk of the primary composite outcome by 24% [89]. Both the kidney and CV components of the composite endpoint contributed to the reduction in risk, with a 21% risk reduction observe for the kidney-specific components of the primary outcome, and a 29% reduction in death from CV causes.

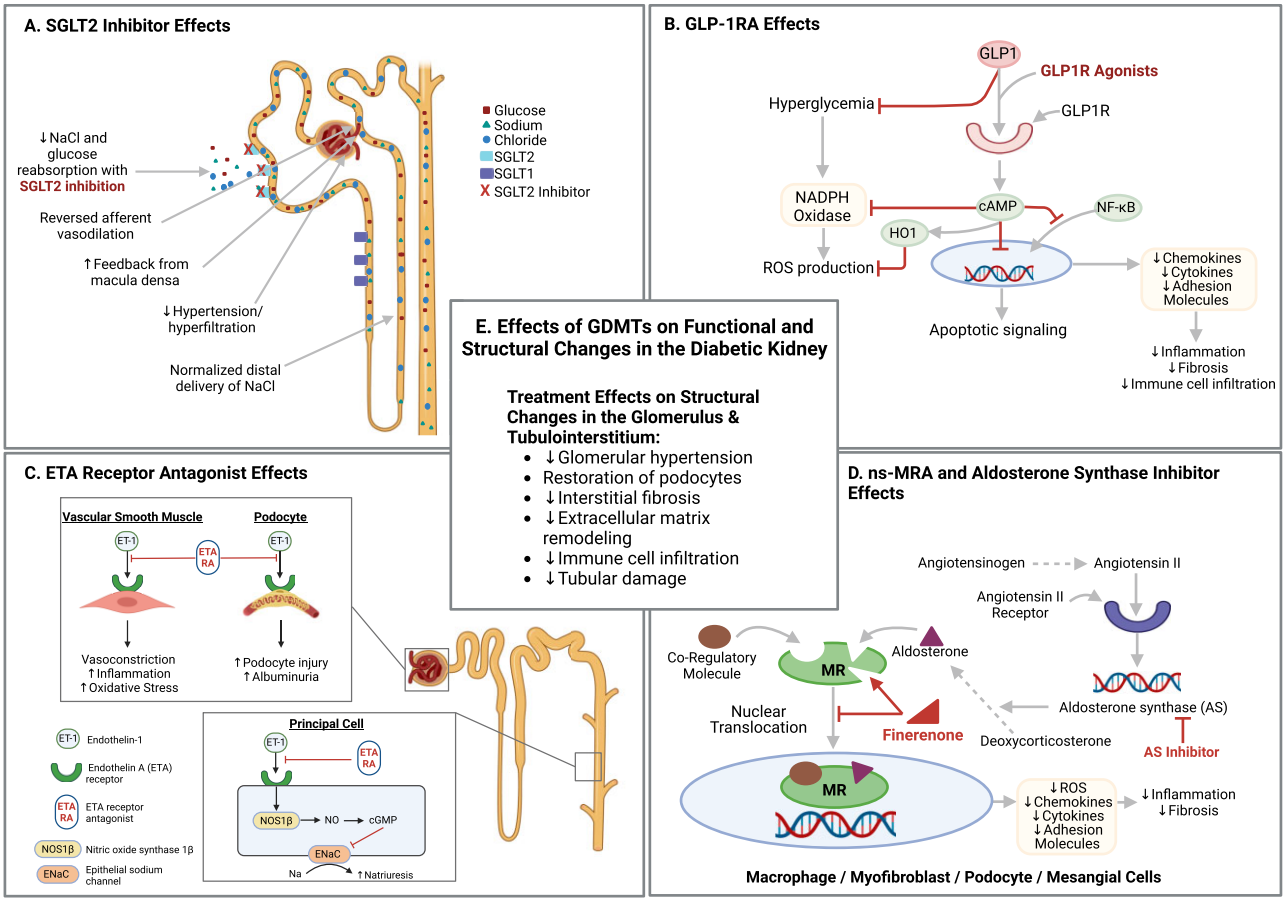

Figure 4: Mechanisms of GDMT benefit in CKD. Mechanisms of kidney protection with SGLT2 inhibitors, GLP-1RAs and an ns-MRA. (**A**) Hemodynamic changes in the diabetic kidney are reversed with SGLT2 inhibition. In diabetes, the resorptive capacity for glucose in the proximal tubule is increased via upregulation of SGLT2 and SGLT1. As a result of enhanced glucose and sodium chloride uptake in the proximal tubule, solute delivery to the macula densa cells of the juxtaglomerular apparatus is diminished resulting in altered tubuloglomerular feedback. Adenosine release is subsequently decreased resulting in vasodilation of afferent arteriola, glomerular hyperfiltration and hypertension. SGLT2 inhibition deceases glucose/sodium reabsorption, thus increasing solute delivery to the distal tubule. These effects help restore tubuloglomerular feedback with a resulting increase in production of adenosine leading to vasoconstriction of afferent arteriola, with improvement of glomerular hyperfiltration and hypertension. (**B**) The proposed effects of GLP-1RAs in kidney are predominantly mediated through activation of the GLP1R. Beneficial effects are principally related to suppression of inflammation and oxidative stress, reduced immune cell infiltration, and reduced fibrosis. Activation of the GLP1R reduces production of ROS via HO1, and reduces production of proinflammatory chemokines, cytokines, adhesion molecules and pro-fibrotic factors via inhibition of NF-κB binding. ROS production is also reduced through a non-receptor mediated reduction in NADPH oxidase. (**C**) In kidney, ET_A activation causes predominantly efferent arteriolar vasoconstriction contributing to the glomerular hypertension, podocyte injury with loss of nephrin, cytoskeleton disruption and detachment from glomerular basement membrane, mesangial cell proliferation and matrix accumulation, and inflammatory cell infiltration. Selective ET_A antagonists inhibit arteriolar vasoconstriction overall reducing glomerular hypertension, decrease mesangial matrix accumulation and inflammatory cell infiltration and help restore podocyte morphology. As a result, there is a reduction in albuminuria and amelioration of inflammatory and fibrotic changes. ET_A antagonist may (to a lesser degree than nonselective ET_A/ET_B antagonist) still induce exaggerated fluid retention through ET_B receptor overstimulation causing vascular permeability, upregulation of aldosterone and vasopressin-mediated water reabsorption. (**D**) Overactivation of the aldosterone production and MR expression in obesity, diabetes has further been implicated in the promotion of inflammation and fibrosis. Aldosterone synthase inhibition blocks production of aldosterone, and antagonism of the MR with steroidal (e.g. spironolactone), and non-steroidal (finerenone) MRAs suppresses expression of pro-inflammatory and pro-fibrotic genes in macrophages, myofibroblasts, podocytes and mesangial cells. (**E**) Structural changes observed in patients with diabetes and CKD include glomerular hypertrophy, thickening of the glomerular basement membrane, podocyte detachment and foot process effacement, expansion of glomerular mesangial cell matrix, immune cell infiltration and interstitial fibrosis. Treatment with SGLT2 inhibitors, GLP-1RAs and ns-MRA helps restore podocytes and decreases extracellular mesangial matrix remodeling, immune cell infiltration, tubular damage, and interstitial inflammation and fibrosis. cAMP, cyclic adenosine monophosphate; GLP1R, glucagon-like peptide 1 receptor; HO1, haem-oxygenase 1; NaCl, sodium chloride; NF-κB, nuclear factor-κB; SGLT-1, sodium-glucose cotransporter 1. Created with BioRender.com.

Importantly, the risk of death from any cause was 20% lower in the semaglutide group compared with placebo. The number of persons who would need to be treated over 3 years to prevent one primary outcome event was 20 [89]. Therefore, the FLOW results are likely to elevate semaglutide as another foundational GDMT for treatment of CKD in persons with T2D.

In addition to robust reductions in glycemia and weight, GLP-1RAs suppress oxidative stress, reduce activation and infiltration of inflammatory cells into the kidney and heart, and reduce inflammation and fibrosis (Fig. 4) [90–96]. Notably, early findings with the dual GLP-1/glucose-dependent insulinotropic peptide (GIP) receptor agonist, tirzepatide, suggest benefits on both albuminuria and eGFR decline [97]. The ongoing Study of Tirzepatide (LY3298176) in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes (TREASURE-CKD; NCT05536804) is examining the effect

Table 2: Finerenone outcome trials [77, 78].

Trial	FIDELIO-DKD ($n = 5734$)	FIGARO-DKD ($n = 7437$)
Mean participant age (years)	66	64
Key inclusion criteria	• T2D • eGFR 25 to <60 mL/min/1.73 m^2 and UACR 30 to <300 mg/g, or • eGFR 25 to <75 mL/min/1.73 m^2 and UACR 300 to 5000 mg/g • Treated with RAS inhibitor at maximum tolerated dose	• T2D • eGFR 25 to 90 mL/min/1.73 m^2 and UACR 30 to <300 mg/g, or • eGFR >60 mL/min/1.73 m^2 and UACR 300 to 5000 mg/g • Treated with RAS inhibitor at maximum tolerated dose
Mean baseline A1C (%)	7.7	7.7
Median follow-up (years)	2.6	3.4
Primary outcome		
HR (95% CI)	Kidney failure, ≥40% decline in eGFR or renal death: 0.82 (0.73–0.93)	CV death, non-fatal MI, non-fatal stroke or hospitalization for HF: 0.87 (0.76–0.98)
Key secondary outcomes		
Key secondary composite; HR (95% CI)	CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF: 0.86 (0.75–0.99)	Kidney failure, ≥40% decline in eGFR, or renal death: 0.87 (0.76–1.01)
Progression to ESKD; HR (95% CI)	0.86 (0.67–1.10)	0.64 (0.41–0.995)

A1C, glycated hemoglobin A1c; ESKD, end-stage kidney disease; HR, hazard ratio; MI, myocardial infarction.

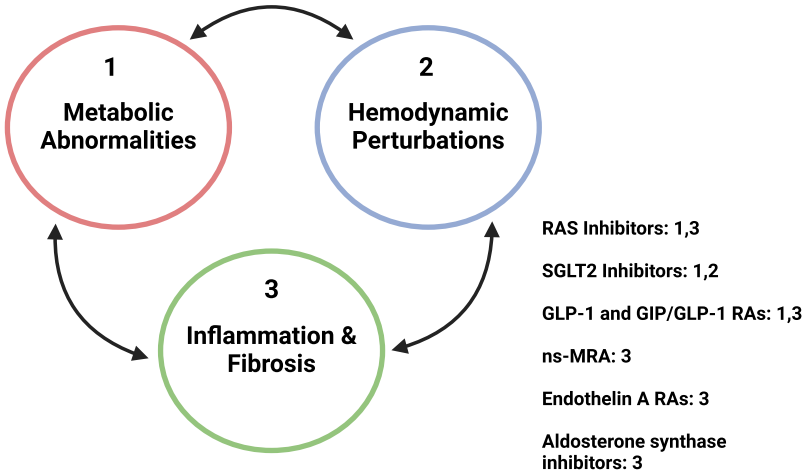

Figure 5: Summary of GDMT complimentary effects in CKD. Proposed mechanisms of kidney and CV protection. RAS inhibitors, SGLT2 inhibitors, incretin therapies (GLP-1RAs, GIP/GLP-1RAs), aldosterone blockade with the ns-MRA finerenone and aldosterone synthase inhibition address multiple pathophysiological drivers of CKD and CVD. Created with BioRender.com.

of tirzepatide on kidney oxygenation and fibrosis on magnetic resonance imaging in addition to multiple secondary clinical outcomes (e.g. eGFR and UACR change from baseline).

COMBINATION GDMT IN CKD

The availability of several classes of drugs with different, yet complimentary mechanism of action poses important questions surrounding the efficacy and safety of combination therapy for CKD (Fig. 5) [98].

Preclinical studies

Combination therapy with an SGLT2 inhibitor and RAS inhibitor in a rat model of diabetic kidney disease reported additive benefits, greater than either drug class alone, on glomerular injury, outer medullar fibrosis and blood pressure lowering [99]. Similarly, combination treatment with the finerenone and empagliflozin in nondiabetic rats demonstrated longer survival, reductions in proteinuria, plasma creatinine, uric acid and blood pressure, along with amelioration of heart and kidney fibrosis [100]. Elucidation of the mechanism behind the observed antifibrotic effects of SGLT2 inhibitors is an area of active inquiry [101]. An *in vitro* study on network-based molecular models of proximal tubular cells reported a reduction of plasma levels of TNF receptor 1, IL-7, matrix metalloproteinase 7 and fibronectin 1 with canagliflozin treatment [70]. In another study utilizing the mouse model of kidney disease in T2D, a combination of the endothelin-1 type A (ET_A) receptor antagonist atrasentan and losartan increased glomerular podocyte numbers and reduced proteinuria compared with the group treated with atrasentan alone [102]. Additionally, in a study using a model of non-diabetic CKD (Ren-2 transgenic rats after

5/6 renal ablation) combination treatment with a RAS inhibitor and ET_A receptor antagonist had additive effects on reducing proteinuria and glomerular damage [103].

Clinical studies

In persons with T1D and mean baseline GFR of 121 mL/min/1.73 m^2, ramipril plus empagliflozin reduced directly measured measured GFR by 8 mL/min/1.73 m^2 and urinary 8-isoprostane levels compared with placebo or ramipril, suggestive of reductions glomerular hyperfiltration and oxidative stress [104]. Similarly, in persons with T2D, combination treatment with empagliflozin and losartan demonstrated small additive reductions in directly measured GFR compared with empagliflozin or losartan monotherapy [105]. In both studies, combination therapy was also associated with greater reductions in systolic blood pressure [104, 105]. Taken together, these data support additive effects of ARBs and SGLT2 inhibition on glomerular and systemic hemodynamics in both T1D and T2D [104, 105].

The Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial was a CV outcome trial with the GLP-1RA efpeglenatide [106]. Approximately 15% of participants in AMPLITUDE-O were on background SGLT2 inhibitor therapy with a subgroup analysis finding that the benefits of efpeglenatide were independent of background SGLT2 inhibitor use. The combined use of the ns-MRA finerenone with a GLP-1RA was explored in a *post hoc* FIDELITY analysis [107]. Approximately 7% of participants in the FIDELIO and FIGARO trials used GLP-1RAs at baseline. The *post hoc* analysis reported significantly greater reduction in UACR at 4 months in patients treated with a GLP-1RA at baseline (–38%) when compared with those not taking a concomitant GLP-1RA treatment (–31%) (*P*-interaction = .03) [107]. The observations from this analysis suggest that use of finerenone and a GLP-1RA in combination may provide additional kidney protection in patients with CKD and T2D. Additionally, combined use of MRAs and SGLT2 inhibitors was explored in *post hoc* analyses of DAPA-CKD and FIDELIO-DKD [108, 109]. These analyses found that dapagliflozin in baseline users of a conventional MRA (spironolactone or eplerenone) or finerenone in users of an SGLT2 inhibitor at baseline resulted in potential additive kidney and CV effects [108, 109]. Subgroup analyses from FIDELITY further examined concomitant baseline treatment with an SGLT2 inhibitor on composite kidney (time to first event of kidney failure, sustained ≥57% decline in eGFR, or kidney disease death) and CV (time to first event of CV death, non-fatal myocardial infarction, non-fatal stroke or HF hospitalization) outcomes with finerenone treatment. Hazard ratios (HRs) with finerenone versus placebo for the kidney composite outcome were 0.80 [95% confidence interval (CI) 0.69–0.92] and 0.42 (95% CI 0.16–1.08) in patients not receiving and receiving an SGLT2 inhibitor at baseline, respectively [110]. For the CV composite outcome, the HRs were 0.87 (95% CI 0.79–0.96) and 0.67 (95% CI 0.42–1.07) without and with treatment with an SGLT2 inhibitor at baseline, respectively [110]. Patients receiving an SGLT2 inhibitor at baseline additionally had a lower incidence of hyperkalemia in both the placebo and finerenone treatment groups, which may improve safety of aldosterone antagonism [110]. It is important to recognize that analyses of treatment effects by baseline MRA, GLP-1 RA or SGLT2 inhibitor use must be interpreted cautiously, as study participants patients were not randomized by baseline use of these agents.

Several small pilot trials have been conducted to assess the safety and additive benefit of kidney protective therapies in patients in CKD. ROTATE-3 enrolled patients with CKD with and without T2D [111] to assess the albuminuria-lowering effect of dapagliflozin and the MRA eplerenone individually and in combination. After 4 weeks, the mean changes from baseline in UACR with dapagliflozin, eplerenone, and dapagliflozin plus eplerenone treatment were –19.6% (95% CI –34.3 to –1.5), –33.7% (95% CI –46.1 to –18.5) and –53% (95% CI –61.7 to –42.4) ($P < .001$ versus dapagliflozin; $P = .01$ versus eplerenone). These data support that the albuminuria-lowering effects of SGLT2 inhibitor plus MRA combination therapy may be additive. Additionally, the incidence of hyperkalemia was significantly less with combination treatment compared with eplerenone alone [111]. Another pilot open-label, randomized clinical trial investigated the short-term effects of finerenone and dapagliflozin separately and in combination on albuminuria in patients with non-diabetic, proteinuric CKD [112]. Combination therapy produced an additive reduction in albuminuria of –36% (95% CI –46% to –24%) from baseline to Week 8. A secondary outcome was change in directly measured GFR, which was most pronounced in the combination therapy group (mean decrease of 7 mL/min by Week 8) [112].

The Dapagliflozin, Exenatide and Combination for Albuminuria reduction in Diabetes (DECADE) study examined effects of dapagliflozin plus exenatide on albuminuria [113]. The mean change in UACR from baseline was –21.9% (95% CI –34.8% to –6.4%) with dapagliflozin, –7.7% (95% CI –23.5% to 11.2%) with exenatide, and –26.0% (95% CI –38.4% to –11.0%) with dapagliflozin plus exenatide combination treatment over 6 weeks from baseline [113]. A prespecified analysis of the Dapagliflozin plus Exenatide on Central REgulation of Appetite in diabeteS typeE 2 (DECREASE) trial tested the effects of dapagliflozin and exenatide alone or in combination, versus placebo, on UACR and cystatin C–estimated GFR in obese patients with T2D compared with placebo, the UACR difference in the exenatide plus dapagliflozin treatment group was –32.2% (95% CI –60.7 to 16.9; $P = 0.159$). Combination therapy also resulted in a greater dip in cystatin C–estimated GFR (–10.4 mL/min/1.73 m^2) [114].

Recently completed phase II trials further tested additive effects of SGLT2 inhibition with an aldosterone synthase inhibitor and an ET_A receptor antagonist on CKD with or without T2D. A trial of BI 690517 (an aldosterone synthase inhibitor) conducted in people with eGFR <30 to <90 mL/min/1.73 m^2 and UACR >200 to <5000 mg/g found that treatment resulted in substantial dose-dependent reductions in UACR when used concurrently with a RAS inhibitor and with or without empagliflozin [115]. The percentage change in UACR measured in first morning void urine with placebo was –6%, –12% with BI 690517 3 mg, –43% with BI 690517 10 mg and –39% with BI 690517 20 mg in once daily doses. Notably, in the BI 690517 10 mg dose group, a reduction of ≥30% UACR was reported in 51% and 70% of participants with monotherapy or in combination with empagliflozin, respectively, supporting a benefit with combination therapy added to background standard-of-care without unexpected safety signals [115].

Clinical development of the endothelin-1 receptor antagonist class has been hindered by adverse events of fluid retention and HF. In the Zibotentan and Dapagliflozin for the Treatment of CKD (ZENITH-CKD) trial, while the higher dose of zibotentan 1.5 mg daily was associated with fluid retention–associated adverse events compared with the 0.25 mg dose, the risk of HF was mitigated by addition of dapagliflozin [116]. After 12 weeks, the UACR reduction with zibotentan plus dapagliflozin versus dapagliflozin alone was –33.7% (90% CI –42.5 to –23.5; $P < .001$) for high dose (1.5 mg zibotentan plus dapagliflozin 10 mg) and –27.0% (90% CI –38.4 to –13.6; $P = .002$) for low dose (0.25 mg zibotentan plus dapagliflozin 10 mg), suggesting that combination

Table 3: GLP-1RA dedicated kidney outcomes trial [89].

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes (FLOW) (3533 participants)
Intervention: semaglutide 1.0 mg weekly vs placebo
Key inclusion criteria: T2D; CKD (eGFR 50 to 75 mL/min/1.73 m^2 and UACR >300 and <5000 mg/g or eGFR of 25 to <50 mL/min/1.73 m^2 and UACR >100 and <5000 mg/g)
Mean participant age (in years): 66.6 ± 9.0
Median follow-up (in years): 3.4
Participant characteristics: eGFR 46.9 ± 15.6 mL/min/1.73 m^2 (12.3% with eGFR <30 mL/min/1.73 m^2); median UACR 582.3 mg/g [68% (3533/1205) with A3, macroalbuminuria)
Primary outcome: the major kidney disease events [a composite of the onset of kidney failure (dialysis, transplantation or an eGFR of <15 mL/min/1.73 m^2)], at least a 50% reduction in the eGFR from baseline or death from kidney-related or CV causes: 24% lower relative risk in in semaglutide vs placebo group: 331 first events [5.8 per 100 patient-years of follow-up] vs 410 first events (7.5 per 100 patient-years) (HR 0.76; 95% CI 0.66–0.88; $P = .0003$)
Confirmatory secondary outcomes:
(i) Total eGFR slope (the annual rate change in eGFR from randomization to the end of trial): −2.19 vs −3.36 mL/min/1.73 m^2 per year in semaglutide and placebo group respectively (between-group difference 1.16; 95% CI 0.86 to 1.47; $P < .001$)
(ii) Major CV events (a composite of nonfatal myocardial infarction, nonfatal stroke or death from CV causes): 18% lower in semaglutide group (212 vs 254 events; HR 0.82; 95% CI 0.68 to 0.98; $P = .029$)
(iii) Death from any cause: 20% lower in semaglutide group (227 vs 279 events; HR 0.80; 95% CI 0.67 to 0.95, $P = .01$)

eGFR shown as mean (SD); mL/min/1.73 m^2; UACR in median mg/g.
HR, hazard ratio.

therapy improved upon monotherapy for reducing albuminuria (Fig. 4; Table 3) [116].

COMBINATION THERAPY IN CKD: CLINICAL TRIALS IN PROGRESS

The COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with CKD and T2D using a UACR Endpoint (CONFIDENCE, NCT05254002) study is an ongoing randomized, double-blind, multicenter, parallel-group, phase 2 study enrolling 807 adults with T2D, stage 2–3 CKD and 100 ≤UACR <5000 mg/g . CONFIDENCE is exploring the effect of dual therapy with finerenone and empagliflozin on reducing albuminuria versus either agent alone [117].

Following successful completion of the phase 2 trial of aldosterone synthase inhibition with and without empagliflozin for CKD, EASi-KIDNEY (Studies of Heart & Kidney Protection with BI 690517 in combination with empagliflozin: A multicenter, international, randomized, double-blind, placebo-controlled clinical trial of the aldosterone synthase inhibitor BI 690517 in combination with empagliflozin in patients with CKD) will compare BI 690517 10 mg once daily versus placebo given in addition to empagliflozin 10 mg once daily and standard-of-care RAS inhibition. EASi-KIDNEY will enroll an estimated 11 000 participants with eGFR ≥20 to <45 mL/min/1.73 m² or eGFR ≥45 to <90 mL/min/1.73 m^2 with UACR ≥200 mg/g. The primary outcome is the first occurrence of a composite of ≥40% eGFR decline, kidney failure, HF hospitalization or CV death.

CLINICAL IMPLICATIONS OF COMBINATION THERAPY

Initiation of an SGLT2 inhibitors is associated with an acute reversible decline in GFR. Following an initial GFR "dip," kidney function typically stabilizes with ongoing SGLT2 inhibitor therapy [118]. Initially findings of an eGFR dip with SGLT2 inhibitor therapy raised concerned of possible acute kidney injury (AKI) in patients receiving combination therapy with RAS and SGLT2 inhibitors [119]. However, a meta-analysis of over 90 000 study participants reported that SGLT2 inhibition actually reduces risk of AKI by 23% (relative risk 0.77; 95% CI 0.70 to 0.84) [120]. Thus, the dip in eGFR is more commonly attributable to acute reduction in glomerular hyperfiltration [118]. Larger dips in GFR have been observed in combination therapy trials. In ROTATE-3, a reduction of directly measured GFR from baseline to 8 weeks was observed with finerenone and dapagliflozin, which was largest with combination therapy (–7 mL/min/1.73 m^2; 95% CI –8 to –5; $P < .001$) [112]. In ZENITH-CKD, there was also an acute reduction with the largest eGFR dip observed in the zibotentan 1.5 mg plus dapagliflozin group [116]. Two weeks after discontinuation of dapagliflozin and zibotentan, eGFR returned to baseline [116]. The acute eGFR decrease typically levels off after the 3 months, and the chronic eGFR slope following the dip becomes less steep compared with placebo, which is expected to result in a long-term slowing of CKD progression [118]. Additionally, an ongoing clinical trial is evaluating SGLT2 inhibition for prevention of postoperative AKI in cardiac surgery patients (MERCURI-2; NCT05590143), which is mechanistically plausible considering the acute reduction in glomerular hyperfiltration and proximal tubular metabolic stress [104].

Overall, evidence continues to build for combination therapy in the setting of diabetes and CKD. A recently published analysis posits that combination therapy with SGLT2 inhibitors, GLP-1 receptor agonists and finerenone will improve long-term kidney, CV and mortality outcomes [121]. An "accelerated, risk-based approach" to initiation of combination GDMT has been suggested for patients with T2D in high- or very-high-risk CKD categories [122], with thoughtful application of risk mitigation strategies recommended to ensure patient safety [14].

CONCLUSIONS

Findings from kidney and CV outcome trials have dramatically shifted the standard-of-care for CKD with or without diabetes. Recommendations from major guideline-forming organizations stress early initiation and intensification of kidney and heart protective therapies to improve outcomes in this high-risk population. While traditionally kidney and CV complications of

Table 4: Summary of key findings from studies of combination therapy in CKD.

Name of the study	Type of the study	Participants	Kidney function	Combination therapy	Outcome
FIDELITY [107]	*Post hoc* analysis (944 of 12 082 with baseline GLP1-RA use)	T2D CKD	eGFR 58.7 (21.6); UACR 483.5 (180–1052)	Finerenone, GLP1 RA	↓ Albuminuria reduction In combination group –31% (east squares mean treatment ratio 0.69, 95% CI 0.66–0.71) vs 38% (least squares mean treatment ratio 0.62, 95% CI 0.57–0.67), *P*-interaction = .03
FIDELIO-DKD [109]	*Post hoc* analysis (250 or 5674 with baseline SGLT2 inhibitor use)	T2D CKD	eGFR 51.1 (11.9) UACR 619 (370–1258)	Finerenone, SGLT2i	Albuminuria reduction 31% (95% CI 0.66–0.71) vs 25% (95% CI 0.62–0.90) with SGLT2 inhibitor (*P*-interaction: 0.31)
FIDELITY [110]	*Post hoc* analysis (877 with baseline SGLT2-i/13 026)	T2D CKD	eGFR 66.3 ± 21 UACR 448 (185–945) in SGLT2i group; eGFR 57.0 ± 21.6 UACR 521 (199–1161) no SLGT2i	Finerenone, SGTL2i	[a]Kidney composite outcome: HR 0.80 (95% CI 0.69–0.92) without SGLT2i and 0.42 (95% CI 0.16–1.08) with SGLT2i [b]CV composite outcome: HR 0.87 (95% CI 0.79–0.96) without SGLT2i and 0.67 (95% CI 0.42–1.07) with SGLT2i
DAPA-CKD [108]	*Post hoc* analysis (229/4304)	CKD with and w/o T2D	eGFR 25–75; UACR 200–5000	Dapagliflozin, MRA	Consistent outcome with and w/o MRA independent of baseline use of nsMRA Lower rates of hyperkalemia with SGLTi
Tuttle *et al.* 2024 [115]	Clinical trial	CKD with and w/o T2D	eGFR 51.9 (17.7); UACR 426 mg/g (205 to 889)	BI 690517 3 mg, 10 mg, 20 mg; Empa 10 mg + BI690517 3, 10, 20 mg	BI 690517: Placebo –3% (–19 to –17) 3 mg –20% (–39 to 3) 10 mg –37% (–52 to –18) 20 mg –35% (–51 to –14) Combination: Placebo –11 (–23 to 4) 3 mg BI –19% (–31 to –5) 10 mg –46% (–54 to –36) 20 mg –40 (–49 to –30)
ROTATE-3 [111]	Clinical trial	CKD with and w/o T2D	eGFR58.1 (18.6); UACR 401 (225, 629)	Dapagliflozin, eplerenone, combination (dapagliflozin + eplerenone)	UACR change 19.3% dapagloflozin 33.7% eplerenone 53% combination Combination vs dapagloflozin, $P < .001$ Combination vs eplerenone, $P = .127$
Marup *et al.* 2023 [112]	Clinical trial	CKD w/o dia-betes	eGFR 34; UACR 469	Finerenone vs dapagloflozin vs combination (finerenone + dapa)	Change in UACR: Finerenone ↓24% Dapa ↓8% Combination ↓36% Change of mGFR: Finerenone ↓3 mL/min Dapa ↓2 mL/min Combinatinon ↓7 mL/min
ZENITH-CKD [116]	Clinical trial	CKD w and w/o T2D	eGFR 46.7; UACR 565.5	Zibotentan 1·5 mg plus dapagliflozin, zibotentan 0·25 mg plus dapagliflozin, dapagliflozin plus placebo	Change in UACR with: Dapa: –28.3% (90% CI –37.8 to –17.4) Dapa/zibotentan 1.5 mg: –52.5% (90% CI –59.0 to –44.9) Dapa/zibotentan 0.25 mg: –47.7% (90% CI –55.7 to –38.2)

[a]Fifty percent decline in eGFR, kidney failure or death from kidney causes.
[b]First occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF.
eGFR shown as mean (SD) (mL/min/1.73 m^2); mGFR, measured GFR in mL/min; UACR in median (IQR) mg/g.
SGLT2i, SGLT2 inhibitor; HR, hazard ratio; w, with; w/o, without.

diabetes have been addressed in isolation, increased recognition of shared common pathways and the availability of therapies that improve CKM outcomes is shepherding change to the delivery of clinical care and trial design. Current data support additive therapeutic effects that allow targeting distinct pathways involved in the onset and progression of CKD that can be tailored to an individual patient's phenotype and clinical needs. Notably, protective effects of SGLT2 inhibition against occurrence of ns-MRA-related hyperkalemia or fluid retention with endothelin-1 receptor antagonist could enable patients to safely stay on combination therapies. As the evidence supporting combination GDMT in CKD continues to build, dissemination and implementation efforts will be critical to ensure optimal patient care and clinical outcomes (Table 4).

FUNDING

This paper was published as part of a supplement financially supported by Bayer AG and the scientific content has not been influenced in any way by the sponsor.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

R.Z.A. is supported by National Institutes of Health (NIH) research grants OT2HL161847, OT2OD032581 and U24TR001608, and Centers for Disease Control (CDC) project numbers 75D301-21-P-12254 and 75D301-23-C-18264; and reports other support from Travere Therapeutics Inc. and the Doris Duke Foundation outside the submitted work, and consultancy fees from Boehringer Ingelheim and Bayer; and other support from Bayer AG, AstraZeneca, Novo Nordisk, The George Institute for Global Health and CareDx, Inc. J.J.N. is supported by NIH research grant OT2OD032581, and reports personal fees and other support from Bayer AG, Sanofi, Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Proteomics International and Dexcom outside the submitted work. K.R.T. is supported by NIH research grants R01MD014712, U2CDK114886, UL1TR002319, U54DK083912, U01DK100846, OT2HL161847 and UM1AI109568, OT2OD032581, and CDC project numbers 75D301-21-P-12254 and 75D301-23-C-18264. She has also received investigator-initiated grant support from Travere, Bayer and the Doris Duke Foundation outside of the submitted work. She reports consultancy fees from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Bayer, AstraZeneca, ProKidney, Travere, Mineralys and Pfizer; and speaker fees from Novo Nordisk, Bayer and AstraZeneca.

REFERENCES

1. Vallianou NG, Mitesh S, Gkogkou A *et al.* Chronic kidney disease and cardiovascular disease: is there any relationship? *Curr Cardiol Rev* 2019;**15**:55–63. https://doi.org/10.2174/1573403X14666180711124825
2. (CDC) CfDCaP. *Chronic Kidney Disease in the United States*. 2021. https://www.cdc.gov/kideny-disesae (31 March 2024, date last accessed).
3. Ying M, Shao X, Qin H *et al.* Disease burden and epidemiological trends of chronic kidney disease at the global, regional, national levels from 1990 to 2019. *Nephron* 2024;**148**:113–23. https://doi.org/10.1159/000534071
4. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet North Am Ed* 2023;**402**:203–34. https://doi.org/10.1016/S0140-6736(23)01301-6
5. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol* 2017;**12**:2032–45. https://doi.org/10.2215/CJN.11491116
6. Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet North Am Ed* 2020;**396**:1204–22. https://doi.org/10.1016/S0140-6736(20)30925-9
7. Liu Y, He Q, Li Q *et al.* Global incidence and death estimates of chronic kidney disease due to hypertension from 1990 to 2019, an ecological analysis of the global burden of diseases 2019 study. *BMC Nephrol* 2023;**24**:352. https://doi.org/10.1186/s12882-023-03391-z
8. Levin A, Tonelli M, Bonventre J *et al.* Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet North Am Ed* 2017;**390**:1888–917. https://doi.org/10.1016/S0140-6736(17)30788-2
9. Afkarian M, Sachs MC, Kestenbaum B *et al.* Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013;**24**:302–8. https://doi.org/10.1681/ASN.2012070718
10. Fox CS, Matsushita K, Woodward M *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet North Am Ed* 2012;**380**:1662–73. https://doi.org/10.1016/S0140-6736(12)61350-6
11. United States Renal Data System. 2022; *USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
12. Tuttle KR, Wong L, St Peter W *et al.* Moving from evidence to implementation of breakthrough therapies for diabetic kidney disease. *Clin J Am Soc Nephrol* 2022;**17**:1092–103. https://doi.org/10.2215/CJN.02980322
13. Luyckx VA, Tuttle KR, Abdellatif D *et al.* Mind the gap in kidney care: translating what we know into what we do. *Kidney Int* 2024;**105**:406–17. https://doi.org/10.1016/j.kint.2023.12.003
14. de Boer IH, Khunti K, Sadusky T *et al.* Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2022;**102**:974–89. https://doi.org/10.1016/j.kint.2022.08.012
15. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2022;**102**:S1–127.
16. Ndumele CE, Rangaswami J, Chow SL *et al.* Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation* 2023;**148**:1606–35. https://doi.org/10.1161/CIR.0000000000001184
17. Ndumele CE, Neeland IJ, Tuttle KR *et al.* A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation* 2023;**148**:1636–64. https://doi.org/10.1161/CIR.0000000000001186
18. Naaman SC, Bakris GL. Diabetic nephropathy: update on pillars of therapy slowing progression. *Diabetes Care* 2023;**46**:1574–86. https://doi.org/10.2337/dci23-0030

19. Morales J, Dagogo-Jack S, Fonseca V *et al.* Perspectives on chronic kidney disease with type 2 diabetes and risk management: practical viewpoints and a paradigm shift using a pillar approach. *Clin Diabetes* 2023;**41**:553–66. https://doi.org/10.2337/cd22-0110
20. Heerspink HJL, Stefánsson BV, Correa-Rotter R *et al.* Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–46. https://doi.org/10.1056/NEJMoa2024816
21. Herrington WG, Staplin N, Wanner C *et al.* Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;**388**:117–27.
22. Lingvay I, Sumithran P, Cohen RV *et al.* Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet North Am Ed* 2022;**399**:394–405. https://doi.org/10.1016/S0140-6736(21)01919-X
23. Saxton SN, Clark BJ, Withers SB *et al.* Mechanistic links between obesity, diabetes, and blood pressure: role of perivascular adipose tissue. *Physiol Rev* 2019;**99**:1701–63. https://doi.org/10.1152/physrev.00034.2018
24. Nakamura T, Girerd S, Jaisser F *et al.* Nonepithelial mineralocorticoid receptor activation as a determinant of kidney disease. *Kidney Int Suppl* 2022;**12**:12–18. https://doi.org/10.1016/j.kisu.2021.11.004
25. Epstein M. Aldosterone and Mineralocorticoid receptor signaling as determinants of cardiovascular and renal injury: from Hans Selye to the present. *Am J Nephrol* 2021;**52**:209–16. https://doi.org/10.1159/000515622
26. Akhtar Z, Leung LW, Kontogiannis C *et al.* Arrhythmias in chronic kidney disease. *Eur Cardiol* 2022;**17**:e05. https://doi.org/10.15420/ecr.2021.52
27. House AA, Wanner C, Sarnak MJ *et al.* Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019;**95**:1304–17. https://doi.org/10.1016/j.kint.2019.02.022
28. Tuttle KR, Bruton JL, Perusek MC *et al.* Effect of strict glycemic control on renal hemodynamic response to amino acids and renal enlargement in insulin-dependent diabetes mellitus. *N Engl J Med* 1991;**324**:1626–32. https://doi.org/10.1056/NEJM199106063242304
29. Tuttle KR, Bruton JL. Effect of insulin therapy on renal hemodynamic response to amino acids and renal hypertrophy in non-insulin-dependent diabetes. *Kidney Int* 1992;**42**:167–73. https://doi.org/10.1038/ki.1992.274
30. Kanbay M, Copur S, Bakir CN *et al.* Glomerular hyperfiltration as a therapeutic target for CKD. *Nephrol Dial Transplant* 2024;**39**:1228–38. https://doi.org/10.1093/ndt/gfae027
31. Chung EYM, Badve SV, Heerspink HJL *et al.* Endothelin receptor antagonists in kidney protection for diabetic kidney disease and beyond? *Nephrology* 2023;**28**:97–108. https://doi.org/10.1111/nep.14130
32. Tuttle KR. Back to the future: glomerular hyperfiltration and the diabetic kidney. *Diabetes* 2017;**66**:14–16. https://doi.org/10.2337/dbi16-0056
33. Alicic RZ, Neumiller JJ, Johnson EJ *et al.* Sodium-glucose cotransporter 2 inhibition and diabetic kidney disease. *Diabetes* 2019;**68**:248–57. https://doi.org/10.2337/dbi18-0007
34. Tuttle KR, Puhlman ME, Cooney SK *et al.* Effects of amino acids and glucagon on renal hemodynamics in type 1 diabetes. *Am J Physiol Renal Physiol* 2002;**282**:F103–12. https://doi.org/10.1152/ajprenal.00155.2001
35. Steenbeke M, Speeckaert R, Desmedt S *et al.* The role of advanced glycation end products and its soluble receptor in kidney diseases. *Int J Mol Sci* 2022;**23**:3439. https://doi.org/10.3390/ijms23073439
36. Berthier CC, Zhang H, Schin M *et al.* Enhanced expression of Janus kinase-signal transducer and activator of transcription pathway members in human diabetic nephropathy. *Diabetes* 2009;**58**:469–77. https://doi.org/10.2337/db08-1328
37. Salazar J, Navarro C, Ortega Á *et al.* Advanced glycation end products: new clinical and molecular perspectives. *Int J Environ Res Public Health* 2021;**18**:7236. https://doi.org/10.3390/ijerph18147236
38. Jin X, Yao T, Zhou Z *et al.* Advanced Glycation end products enhance macrophages polarization into M1 phenotype through activating RAGE/NF-κB pathway. *Biomed Res Int* 2015;**2015**:1. https://doi.org/10.1155/2015/732450
39. Chuang PY, Yu Q, Fang W *et al.* Advanced glycation endproducts induce podocyte apoptosis by activation of the FOXO4 transcription factor. *Kidney Int* 2007;**72**:965–76. https://doi.org/10.1038/sj.ki.5002456
40. Ki HJ, Kim SY, Lee SH *et al.* Transforming growth factor-β receptor 2 gene polymorphisms are associated with end-stage renal disease. *Kidney Res Clin Pract* 2015;**34**:93–7. https://doi.org/10.1016/j.krcp.2015.05.002
41. Tuttle KR, Agarwal R, Alpers CE *et al.* Molecular mechanisms and therapeutic targets for diabetic kidney disease. *Kidney Int* 2022;**102**:248–60. https://doi.org/10.1016/j.kint.2022.05.012
42. Pichler R, Afkarian M, Dieter BP *et al.* Immunity and inflammation in diabetic kidney disease: translating mechanisms to biomarkers and treatment targets. *Am J Physiol Renal Physiol* 2017;**312**:F716–31. https://doi.org/10.1152/ajprenal.00314.2016
43. Ferenbach D, Kluth DC, Hughes J. Inflammatory cells in renal injury and repair. *Semin Nephrol* 2007;**27**:250–9. https://doi.org/10.1016/j.semnephrol.2007.02.001
44. Alicic RZ, Johnson EJ, Tuttle KR. Inflammatory mechanisms as new biomarkers and therapeutic targets for diabetic kidney disease. *Adv Chronic Kidney Dis* 2018;**25**:181–91. https://doi.org/10.1053/j.ackd.2017.12.002
45. Humphreys BD. Mechanisms of renal fibrosis. *Annu Rev Physiol* 2018;**80**:309–26. https://doi.org/10.1146/annurev-physiol-022516-034227
46. Brenner BM, Cooper ME, de Zeeuw D *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9. https://doi.org/10.1056/NEJMoa011161
47. Lewis EJ, Hunsicker LG, Bain RP *et al.* The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**:1456–62. https://doi.org/10.1056/NEJM199311113292004
48. Lewis EJ, Hunsicker LG, Clarke WR *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**:851–60. https://doi.org/10.1056/NEJMoa011303
49. Cantero-Navarro E, Fernández-Fernández B, Ramos AM *et al.* Renin-angiotensin system and inflammation update. *Mol Cell Endocrinol* 2021;**529**:111254. https://doi.org/10.1016/j.mce.2021.111254
50. Zinman B, Wanner C, Lachin JM *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–28. https://doi.org/10.1056/NEJMoa1504720
51. Neal B, Perkovic V, Mahaffey KW *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–57. https://doi.org/10.1056/NEJMoa1611925
52. Wiviott SD, Raz I, Bonaca MP *et al.* Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–57. https://doi.org/10.1056/NEJMoa1812389
53. Perkovic V, Jardine MJ, Neal B *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N*

Engl J Med 2019;**380**:2295–306. https://doi.org/10.1056/NEJMoa1811744
54. EMPA-KIDNEY Collaborative Group. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial. *Lancet Diabetes Endocrinol* 2024;**12**:51–60. https://doi.org/10.1016/S2213-8587(23)00322-4
55. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet North Am Ed* 2022;**400**:1788–801. https://doi.org/10.1016/S0140-6736(22)02074-8
55. Samson SL, Vellanki P, Blonde L *et al.* American Association of Clinical Endocrinology Consensus Statement: comprehensive type 2 diabetes management algorithm–2023 update. *Endocr Pract* 2023;**29**:305–40. https://doi.org/10.1016/j.eprac.2023.02.001
57. American Diabetes Association Professional Practice Committee. Standards of care in diabetes–2024. *Diabetes Care* 2024;**47**:S1–4. https://doi.org/10.2337/dc24-SINT
58. Oliveras L, Montero N, Cruzado JM. Searching in the maze: sodium-glucose cotransporter-2 inhibitors in kidney transplant recipients to improve survival. *Clin Kidney J* 2023;**16**:909–13. https://doi.org/10.1093/ckj/sfad045
59. Medicine NLo. *meChANisms and sAfety of SGLT2 Inhibition in peRitoneal dialYsis (CANARY)*. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05715814 (31 March 2024, date last accessed).
60. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia* 2017;**60**:215–25. https://doi.org/10.1007/s00125-016-4157-3
61. Tuttle KR, Brosius FC, III, Cavender MA *et al.* SGLT2 inhibition for CKD and cardiovascular disease in type 2 diabetes: report of a scientific workshop sponsored by the National Kidney Foundation. *Am J Kidney Dis* 2021;**77**:94–109. https://doi.org/10.1053/j.ajkd.2020.08.003
62. Tuttle KR. Digging deep into cells to find mechanisms of kidney protection by SGLT2 inhibitors. *J Clin Invest* 2023;**133**:e167700. https://doi.org/10.1172/JCI167700
63. Blazek O, Bakris GL. Slowing the progression of diabetic kidney disease. *Cells* 2023;**12**:1975. https://doi.org/10.3390/cells12151975
64. Tanaka S, Sugiura Y, Saito H *et al.* Sodium-glucose cotransporter 2 inhibition normalizes glucose metabolism and suppresses oxidative stress in the kidneys of diabetic mice. *Kidney Int* 2018;**94**:912–25. https://doi.org/10.1016/j.kint.2018.04.025
65. Szwed A, Kim E, Jacinto E. Regulation and metabolic functions of mTORC1 and mTORC2. *Physiol Rev* 2021;**101**:1371–426. https://doi.org/10.1152/physrev.00026.2020
66. Kogot-Levin A, Hinden L, Riahi Y *et al.* Proximal tubule mTORC1 is a central player in the pathophysiology of diabetic nephropathy and its correction by SGLT2 inhibitors. *Cell Rep* 2020;**32**:107954. https://doi.org/10.1016/j.celrep.2020.107954
67. Rabanal-Ruiz Y, Korolchuk VI. mTORC1 and nutrient homeostasis: the central role of the lysosome. *Int J Mol Sci* 2018;**19**:818. https://doi.org/10.3390/ijms19030818
68. Layton AT, Laghmani K, Vallon V *et al.* Solute transport and oxygen consumption along the nephrons: effects of Na+ transport inhibitors. *Am J Physiol Renal Physiol* 2016;**311**:F1217–29. https://doi.org/10.1152/ajprenal.00294.2016
69. Zhou B, Tian R. Mitochondrial dysfunction in pathophysiology of heart failure. *J Clin Invest* 2018;**128**:3716–26. https://doi.org/10.1172/JCI120849
70. Heerspink HJL, Perco P, Mulder S *et al.* Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. *Diabetologia* 2019;**62**:1154–66. https://doi.org/10.1007/s00125-019-4859-4
71. Doi Y, Hamano T, Yamaguchi S *et al.* Mediators between canagliflozin and renoprotection vary depending on patient characteristics: insights from the CREDENCE trial. *Diabetes Obes Metab* 2023;**25**:2944–53. https://doi.org/10.1111/dom.15191
72. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation* 2022;**146**:1383–405. https://doi.org/10.1161/CIRCULATIONAHA.122.061732
73. Inzucchi SE, Zinman B, Fitchett D *et al.* How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care* 2018;**41**:356–63. https://doi.org/10.2337/dc17-1096
74. Agarwal R, Kolkhof P, Bakris G *et al.* Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J* 2021;**42**:152–61. https://doi.org/10.1093/eurheartj/ehaa736
75. Agarwal R, Pitt B, Rossing P *et al.* Modifiability of composite cardiovascular risk associated with chronic kidney disease in type 2 diabetes with finerenone. *JAMA Cardiol* 2023;**8**:732–41. https://doi.org/10.1001/jamacardio.2023.1505
76. Gerisch M, Heinig R, Engelen A *et al.* Biotransformation of finerenone, a novel nonsteroidal mineralocorticoid receptor antagonist, in dogs, rats, and humans, in vivo and in vitro. *Drug Metab Dispos* 2018;**46**:1546–55. https://doi.org/10.1124/dmd.118.083337
77. Bakris GL, Agarwal R, Anker SD *et al.* Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–29. https://doi.org/10.1056/NEJMoa2025845
78. Pitt B, Filippatos G, Agarwal R *et al.* Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;**385**:2252–63. https://doi.org/10.1056/NEJMoa2110956
79. Agarwal R, Filippatos G, Pitt B *et al.* Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;**43**:474–84. https://doi.org/10.1093/eurheartj/ehab777
80. Filippatos G, Anker SD, Pitt B *et al.* Finerenone efficacy in patients with chronic kidney disease, type 2 diabetes and atherosclerotic cardiovascular disease. *Eur Heart J Cardiovasc Pharmacother* 2022;**9**:85–93. https://doi.org/10.1093/ehjcvp/pvac054
81. Oiwa A, Hiwatashi D, Takeda T *et al.* Efficacy and safety of low-dose spironolactone for chronic kidney disease in type 2 diabetes. *J Clin Endocrinol Metab* 2023;**108**:2203–10. https://doi.org/10.1210/clinem/dgad144
82. Alicic RZ, Cox EJ, Neumiller JJ *et al.* Incretin drugs in diabetic kidney disease: biological mechanisms and clinical evidence. *Nat Rev Nephrol* 2021;**17**:227–44. https://doi.org/10.1038/s41581-020-00367-2
83. Marso SP, Bain SC, Consoli A *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**:1834–44. https://doi.org/10.1056/NEJMoa1607141
84. Marso SP, Daniels GH, Brown-Frandsen K *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–22. https://doi.org/10.1056/NEJMoa1603827
85. Gerstein HC, Colhoun HM, Dagenais GR *et al.* Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*

North Am Ed 2019;**394**:121–30. https://doi.org/10.1016/S0140-6736(19)31149-3
86. Tuttle KR, Lakshmanan MC, Rayner B *et al.* Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018;**6**:605–17. https://doi.org/10.1016/S2213-8587(18)30104-9
87. Tuttle KR, Bosch-Traberg H, Cherney DZI *et al.* Post hoc analysis of SUSTAIN 6 and PIONEER 6 trials suggests that people with type 2 diabetes at high cardiovascular risk treated with semaglutide experience more stable kidney function compared with placebo. *Kidney Int* 2023;**103**:772–81. https://doi.org/10.1016/j.kint.2022.12.028
88. Shaman AM, Bain SC, Bakris GL *et al.* Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. *Circulation* 2022;**145**:575–85. https://doi.org/10.1161/CIRCULATIONAHA.121.055459
89. Perkovic V, Tuttle KR, Rossing P *et al.* Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med* 2024;**391**:109–21. https://doi.org/10.1056/NEJMoa2403347
90. Zhao YY, Chen LH, Huang L *et al.* Cardiovascular protective effects of GLP-1: a focus on the MAPK signaling pathway. *Biochem Cell Biol* 2022;**100**:9–16. https://doi.org/10.1139/bcb-2021-0365
91. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab* 2016;**24**:15–30. https://doi.org/10.1016/j.cmet.2016.06.009
92. Hendarto H, Inoguchi T, Maeda Y *et al.* GLP-1 analog liraglutide protects against oxidative stress and albuminuria in streptozotocin-induced diabetic rats via protein kinase A-mediated inhibition of renal NAD(P)H oxidases. *Metabolism* 2012;**61**:1422–34. https://doi.org/10.1016/j.metabol.2012.03.002
93. Sancar-Bas S, Gezginci-Oktayoglu S, Bolkent S. Exendin-4 attenuates renal tubular injury by decreasing oxidative stress and inflammation in streptozotocin-induced diabetic mice. *Growth Factors* 2015;**33**:419–29. https://doi.org/10.3109/08977194.2015.1125349
94. Kodera R, Shikata K, Kataoka HU *et al.* Glucagon-like peptide-1 receptor agonist ameliorates renal injury through its anti-inflammatory action without lowering blood glucose level in a rat model of type 1 diabetes. *Diabetologia* 2011;**54**:965–78. https://doi.org/10.1007/s00125-010-2028-x
95. Park CW, Kim HW, Ko SH *et al.* Long-term treatment of glucagon-like peptide-1 analog exendin-4 ameliorates diabetic nephropathy through improving metabolic anomalies in db/db mice. *J Am Soc Nephrol* 2007;**18**:1227–38. https://doi.org/10.1681/ASN.2006070778
96. Neumiller JJ, Alicic RZ, Tuttle KR. Incorporating evidence and guidelines for personalized care of diabetes and chronic kidney disease. *Semin Nephrol* 2023;**43**:151427. https://doi.org/10.1016/j.semnephrol.2023.151427
97. Heerspink HJL, Sattar N, Pavo I *et al.* Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. *Lancet Diabetes Endocrinol* 2022;**10**:774–85. https://doi.org/10.1016/S2213-8587(22)00243-1
98. van Raalte DH, Bjornstad P, Cherney DZI *et al.* Combination therapy for kidney disease in people with diabetes mellitus. *Nat Rev Nephrol* 2024;**20**:433–46 . https://doi.org/10.1038/s41581-024-00827-z
99. Kojima N, Williams JM, Takahashi T *et al.* Effects of a new SGLT2 inhibitor, luseogliflozin, on diabetic nephropathy in T2DN rats. *J Pharmacol Exp Ther* 2013;**345**:464–72. https://doi.org/10.1124/jpet.113.203869
100. Kolkhof P, Hartmann E, Freyberger A *et al.* Effects of finerenone combined with empagliflozin in a model of hypertension-induced end-organ damage. *Am J Nephrol* 2021;**52**:642–52. https://doi.org/10.1159/000516213
101. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. *Nat Rev Nephrol* 2021;**17**:319–34. https://doi.org/10.1038/s41581-021-00393-8
102. Hudkins KL, Wietecha TA, Steegh F *et al.* Beneficial effect on podocyte number in experimental diabetic nephropathy resulting from combined atrasentan and RAAS inhibition therapy. *Am J Physiol Renal Physiol* 2020;**318**:F1295–305. https://doi.org/10.1152/ajprenal.00498.2019
103. Certikova Chabova V, Vernerova Z, Kujal P *et al.* Addition of ET(A) receptor blockade increases renoprotection provided by renin-angiotensin system blockade in 5/6 nephrectomized Ren-2 transgenic rats. *Life Sci* 2014;**118**:297–305. https://doi.org/10.1016/j.lfs.2013.12.018
104. Lytvyn Y, Kimura K, Peter N *et al.* Renal and vascular effects of combined SGLT2 and angiotensin-converting enzyme inhibition. *Circulation* 2022;**146**:450–62. https://doi.org/10.1161/CIRCULATIONAHA.122.059150
105. Scholtes RA, Hesp AC, Mosterd CM *et al.* Kidney hemodynamic effects of angiotensin receptor blockade, sodium-glucose cotransporter-2 inhibition alone, and their combination: a crossover randomized trial in people with type 2 diabetes. *Circulation* 2022;**146**:1895–7. https://doi.org/10.1161/CIRCULATIONAHA.122.061033
106. Lam CSP, Ramasundarahettige C, Branch KRH *et al.* Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. *Circulation* 2022;**145**:565–74. https://doi.org/10.1161/CIRCULATIONAHA.121.057934
107. Rossing P, Agarwal R, Anker SD *et al.* Finerenone in patients across the spectrum of chronic kidney disease and type 2 diabetes by glucagon-like peptide-1 receptor agonist use. *Diabetes Obes Metab* 2023;**25**:407–16. https://doi.org/10.1111/dom.14883
108. Provenzano M, Jongs N, Vart P *et al.* The kidney protective effects of the sodium-glucose cotransporter-2 inhibitor, dapagliflozin, are present in patients with CKD treated with mineralocorticoid receptor antagonists. *Kidney Int Rep* 2022;**7**:436–43. https://doi.org/10.1016/j.ekir.2021.12.013
109. Rossing P, Filippatos G, Agarwal R *et al.* Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose cotransporter-2 inhibitor therapy. *Kidney Int Rep* 2022;**7**:36–45. https://doi.org/10.1016/j.ekir.2021.10.008
110. Rossing P, Anker SD, Filippatos G *et al.* Finerenone in patients with chronic kidney disease and type 2 diabetes by sodium-glucose cotransporter 2 inhibitor treatment: the FIDELITY analysis. *Diabetes Care* 2022;**45**:2991–8. https://doi.org/10.2337/dc22-0294
111. Provenzano M, Puchades MJ, Garofalo C *et al.* Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with chronic kidney disease: a randomized crossover clinical trial. *J Am Soc Nephrol* 2022;**33**:1569–80. https://doi.org/10.1681/ASN.2022020207
112. Marup 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* 2023;**17**:sfad249. https://doi.org/10.1093/ckj/sfad249

113. van der Aart-van der Beek AB, Apperloo E, Jongs N *et al.* Albuminuria-lowering effect of dapagliflozin, exenatide, and their combination in patients with type 2 diabetes: a randomized cross-over clinical study. *Diabetes Obes Metab* 2023;**25**:1758–68. https://doi.org/10.1111/dom.15033
114. van Ruiten CC, van der Aart-van der Beek AB, RG IJ *et al.* Effect of exenatide twice daily and dapagliflozin, alone and in combination, on markers of kidney function in obese patients with type 2 diabetes: a prespecified secondary analysis of a randomized controlled clinical trial. *Diabetes Obes Metab* 2021;**23**:1851–8. https://doi.org/10.1111/dom.14410
115. Tuttle KR, Hauske SJ, Canziani ME *et al.* Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial. *Lancet North Am Ed* 2024;**403**:379–90. https://doi.org/10.1016/S0140-6736(23)02408-X
116. Heerspink HJL, Kiyosue A, Wheeler DC *et al.* Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial. *Lancet North Am Ed* 2023;**402**:2004–17. https://doi.org/10.1016/S0140-6736(23)02230-4
117. A Study to Learn How Well the Treatment Combination of Finerenone and Empagliflozin Works and How Safe it is Compared to Each Treatment Alone in Adult Participants With Long-term Kidney Disease (Chronic Kidney Disease) and Type 2 Diabetes (CONFIDENCE). Available from: https://clinicaltrials.gov/study/NCT05254002?term=CONFIDENCE&intr=finerenone&rank=1#participation-criteria (16 January 2025, date last accessed).
118. Heerspink HJL, Cherney DZI. Clinical implications of an acute dip in eGFR after SGLT2 inhibitor initiation. *Clin J Am Soc Nephrol* 2021;**16**:1278–80. https://doi.org/10.2215/CJN.02480221
119. Phadke G, Kaushal A, Tolan DR *et al.* Osmotic nephrosis and acute kidney injury associated with SGLT2 inhibitor use: a case report. *Am J Kidney Dis* 2020;**76**:144–7. https://doi.org/10.1053/j.ajkd.2020.01.015
120. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet North Am Ed* 2022;**400**:1788–801. https://doi.org/10.1016/S0140-6736(22)02074-8
121. Neuen BL, Heerspink HJL, Vart P *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**:450–62. https://doi.org/10.1161/CIRCULATIONAHA.123.067584
122. Neuen BL, Tuttle KR, Vaduganathan M. Accelerated risk-based implementation of guideline-directed medical therapy for type 2 diabetes and chronic kidney disease. *Circulation* 2024;**149**:1238–40. https://doi.org/10.1161/CIRCULATIONAHA.123.068524

Received: April 10, 2024; Editorial decision: June 28, 2024