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REVIEW

Role of Finerenone in the Treatment of Diabetic Kidney Disease: Patient Selection and Clinical Perspectives

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Abstract: Diabetes is the leading cause of chronic and end stage kidney disease globally. Despite recent advances in therapies for diabetic kidney disease (DKD), there remains a critical need for additional options to improve renal and cardiovascular outcomes. Mineralocorticoid overactivation contributes to inflammation and fibrosis which in turn leads to progression of DKD. Finerenone, a novel non-steroidal mineralocorticoid receptor antagonist, has shown promising cardiac and renoprotective benefits in DKD. The utility of finerenone in the real world will require appropriate patient selection and patient monitoring by clinicians.

Keywords: finerenone, diabetes, chronic kidney disease

Introduction

Type 2 diabetes mellitus (T2DM) affects more than 400 million people worldwide and the prevalence is expected to reach 700 million by the year 2045.[1] T2DM accounts for over 90% of all diabetes mellitus cases[2] and diabetic kidney disease (DKD) develops in approximately 40% of cases.[3] T2DM is associated with significant cardiovascular mortality causing many patients with DKD to die prematurely before progressing to end stage kidney disease.[4,5] Mitigation of cardiovascular disease and chronic kidney disease burden is therefore the cornerstone of T2DM management.

Diabetic kidney disease is a clinical diagnosis defined as decreased estimated glomerular filtration rate (<60 mL/min/1.73 m^2) or presence of albuminuria (≥30 mg/g of creatinine or mg/day) or both in patients with diabetes mellitus. On the other hand, diabetic nephropathy refers to the renal histologic findings related to diabetes mellitus. The histological findings of diabetic nephropathy include a wide array of glomerular lesions as well as tubulointerstitial disease.[6,7]

For almost two decades, therapeutic interventions for slowing progression of diabetic kidney disease were limited to glycemic control and inhibition of the renin angiotensin aldosterone system (RAAS).[8–10] Recently sodium glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP-1 RA) have emerged as promising therapeutic options for management of T2DM, with benefits extending beyond glycemic control. SGLT2is have demonstrated benefit in slowing progression of kidney disease in patients with diabetic and non-diabetic proteinuric kidney disease.[11,12] Furthermore, SGLT2is lower risk of heart failure hospitalization, myocardial infarction, and cardiovascular death.[13–15] GLP-1 RA use is associated with lower risk of cardiovascular death, myocardial infarction, and stroke in patients with T2DM.[16,17] GLP-1 RAs also lower albuminuria, but their role in attenuating the decline in glomerular filtration rate remains unclear.[18–20]

The CREDENCE and the DAPA-CKD trials have changed the paradigm of DKD management and have established a new standard of care: combination of RAAS blocker and SGLT2i.[11,12] Although the combination of RAAS blockers and SGLT2i therapy decreases progression of DKD, it does not completely halt it. This is not surprising given the complex and still poorly understood heterogeneity of DKD involving glomerular hyperfiltration and activation of

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proinflammatory and profibrotic pathways.[21–23] Mineralocorticoid receptor signaling through glucocorticoid activation is an important driver of inflammation and fibrosis in DKD. The recent regulatory approval of the nonsteroidal mineralocorticoid receptor antagonist finerenone increases the options for DKD management. The aim of this review is to summarize the pharmacologic basis for finerenone use while providing clinical context for patient selection in the rapidly evolving clinical management landscape in the DKD space.

Mineralocorticoid Receptor Antagonists

The mineralocorticoid receptor (MR) is an intracellular steroid hormone receptor and member of the nuclear receptor protein superfamily. MRs in the distal nephron are activated by aldosterone and play a critical role in maintenance of blood pressure and extracellular fluid volume. MR receptors can also be activated by glucocorticoids and they tend to have similar affinity for both mineralocorticoids and glucocorticoids. MR expression is not limited to the distal nephron as these receptors are also expressed in the podocytes, fibroblasts, vascular cells, and macrophages.[24] Unlike the distal tubule, these cells may not co-express 11-β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) allowing for additional MR activation by cortisol that leads to increased expression of pro-inflammatory and profibrotic genes, and generation of reactive oxygen species culminating in inflammation and fibrosis.[25–28] Collectively, this inflammation and fibrosis leads to chronic kidney disease progression.[29–31] There is evidence that MR activation in myeloid cells rather than podocytes is responsible for driving proinflammatory gene expression, tubular damage and progressive renal fibrosis.[32] MR activation in non-renal cells such as cardiomyocytes, endothelial cells and vascular smooth muscle cells has been shown to contribute to poor cardiovascular and kidney outcomes.[33] Absence of 11β-HSD2 expression in cardiomyocytes also makes them susceptible to glucocorticoid mediated MR activation. Taken together, these observations provide a strong rationale for the potential anti-inflammatory and anti-fibrotic effects of MR antagonism in the treatment of cardiorenal diseases.[24]

Spironolactone and Eplerenone are steroidal MR antagonists. The beneficial effects of spironolactone and eplerenone in patients with cardiovascular disease, particularly in heart failure, are well established.[34,35] These agents have also been shown to lower proteinuria in DKD, but the associated risk of hyperkalemia has limited their use in patients with advanced chronic kidney disease.[36–40] Finerenone and Esaxerenone are two recently developed non-steroidal MRAs.[41,42] This article will focus on finerenone, recently approved by the Food and Drug Administration and European Medicines Agency for chronic kidney disease in adults with T2DM.

Finerenone has distinct pharmacologic characteristics that differentiate it from steroidal MRAs. Nuclear receptors like MRs exert their action by binding to coregulators that define cell-specific transcriptional responses.[43] Steroidal MRAs such as spironolactone and eplerenone exhibit partial agonism on cofactor recruitment,[41] while finerenone is a bulky, passive antagonist, inhibiting cofactor binding in the absence of aldosterone.[44] While the first-generation MRA spironolactone is potent but nonselective and the second-generation MRA eplerenone more selective but less potent, finerenone is potent and selective.[41] The pharmacokinetics of finerenone and steroidal MRAs also differs. Finerenone has minimal urinary excretion, a short half-life (2–3 hours) and no active metabolites. Conversely, spironolactone has multiple biologically active metabolites with long half lives that accumulate in patients with impaired kidney function.[45] While spironolactone and eplerenone have much higher drug-equivalent concentration accumulation in the kidney versus heart, finerenone has balanced kidney-heart distribution.[46,47] In deoxycorticosterone acetate-/salt-challenged rats, finerenone reduced cardiac hypertrophy, plasma prohormone of brain natriuretic peptide and proteinuria more efficiently than eplerenone when comparing equinatriuretic doses.[46] A mouse model of cardiac fibrosis also showed distinct finerenone-induced anti-fibrotic gene expression profiling from that of eplerenone. Taken together, nonsteroidal MRAs such as finerenone have distinct biochemical, pharmacokinetic, tissue distribution and downstream signaling properties that make it an attractive therapeutic option.

Patient Selection and Clinical Perspectives

It is useful to review recent clinical trial data for finerenone. In 2020, the FIDELIO-DKD trial was published.[48] This was a randomized, double-blind, placebo-controlled, multicenter trial in adult participants with CKD associated with T2DM. The inclusion criteria were defined as either having a urine albumin creatinine ratio (UACR) of 30 to

300 mg/g, eGFR of 25 to 60 mL/min/1.73 m^2 and diabetic retinopathy, or as having an UACR of ≥300 mg/g and an eGFR of 25 to 75 mL/min/1.73 m^2. In FIDELIO-DKD, the baseline mean eGFR was 44 mL/min/1.73 m^2 and median UACR was 852 mg/g. All participants needed to have a serum potassium of ≤4.8 mEq/L and were required to be on maximum tolerated dose of an ACEi or ARB before being randomized to finerenone or placebo. FIDELIO-DKD trial demonstrated that in 5734 patients randomized and followed over a median 2.6 years, finerenone was associated with a lower incidence of the primary composite outcome of sustained decline in eGFR of ≥40%, kidney failure, or renal death (504 patients, 17.8%) compared with placebo (600 patients, 21.1%, hazard ratio 0.82; 95% confidence interval [CI], 0.73 to 0.93; P = 0.001). Finerenone use was also associated with reduced the incidence of the secondary composite CV endpoint of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke and hospitalization for heart failure compared to placebo and lowered albuminuria by 30%. Of note, the risk of hyperkalemia was noted to be twice as high with finerenone compared to placebo (18.3% vs 9.0%), and hyperkalemia led to discontinuation of finerenone therapy in 2.3% of the trial participants.[48]

While FIDELIO-DKD demonstrated that finerenone slowed the progression of diabetic kidney disease, the efficacy of finerenone in reducing cardiovascular events in patients with early stages of diabetic kidney disease was not known until the publication of FIGARO-DKD trial.[49] This was a randomized, double-blind, placebo-controlled, multicenter trial in 7437 adult participants with predominantly stage 3 or 4 CKD associated with T2DM. The inclusion criteria were defined as UACR of 30 to <300 mg/g and an eGFR of 25 to 90 mL/min/1.73 m^2 (stage 2 to 4 CKD) or a UACR of 300 to 5000 mg/g and an eGFR of at least 60 mL/min/1.73 m^2 (stage 1 or 2 CKD). In this trial, 45% participants had established cardiovascular disease, baseline mean eGFR was 68 mL/min/1.73 m^2 and the median UACR was 308 mg/g. All patients were required to be on maximum tolerated dose of an ACEi or ARB before being randomized to finerenone or placebo. FIGARO-DKD showed that finerenone lowered the risk of primary cardiovascular composite outcome of cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure (458 patients, 12.4%) compared to placebo (519 patients, 14.2%; hazard ratio 0.87; 95% confidence interval [CI], 0.76 to 0.98; P = 0.03). This benefit was mainly driven by decreased incidence in hospitalization for heart failure. The secondary kidney composite outcome of decline in eGFR of ≥40% or renal death was not statistically different between the finerenone and the placebo groups. Hyperkalemia was again more common in the finerenone group compared to the placebo group (10.8% vs 5.3%), and hyperkalemia led to discontinuation of finerenone in 1.2% of the trial participants. The overall risk of hyperkalemia with finerenone use was lower in FIGARO-DKD than in FIDELIO-DKD, and this difference was likely due to the higher mean eGFR in the FIGARO-DKD trial (68 vs 44 mL/minute/1.73 m^2).[49]

The FIDELITY pooled analysis, which included 13,026 participants from the FIDELIO-DKD and FIGARO-DKD trials, demonstrated that finerenone lowered cardiovascular outcomes by 14% and kidney outcomes by 23% compared to placebo in participants with CKD and T2DM.[50] Hyperkalemia led to permanent discontinuation of finerenone in 1.7% participants in that pooled analysis compared to 0.6% in the placebo group.

Finerenone and Blood Pressure

The FIDELIO-DKD and FIGARO-DKD trials demonstrate that finerenone has a minimal impact on lowering systolic blood pressure in participants with DKD. In FIDELIO-DKD, finerenone lowered the mean systolic blood pressure by 2.13 mmHg at 12-month follow-up, and in FIGARO-DKD, finerenone lowered the mean systolic blood pressure by 2.85 mmHg at 12-month follow-up. This highlights the fact that the cardioprotective and kidney protective effects of finerenone in DKD are independent of its blood pressure lowering effect.

Finerenone and Hyperkalemia

Patients with CKD are at risk for developing hyperkalemia and clinical trials have demonstrated that finerenone increases the risk of hyperkalemia due to mineralocorticoid receptor antagonism.[48–50] High baseline serum potassium, low baseline eGFR and high UACR were identified as risk factors for development of hyperkalemia with finerenone use.[51] Clinicians should be aware of the recommendations for finerenone dosing based on eGFR and serum potassium as outlined in the US FDA label and shown in Figure 1.[52]

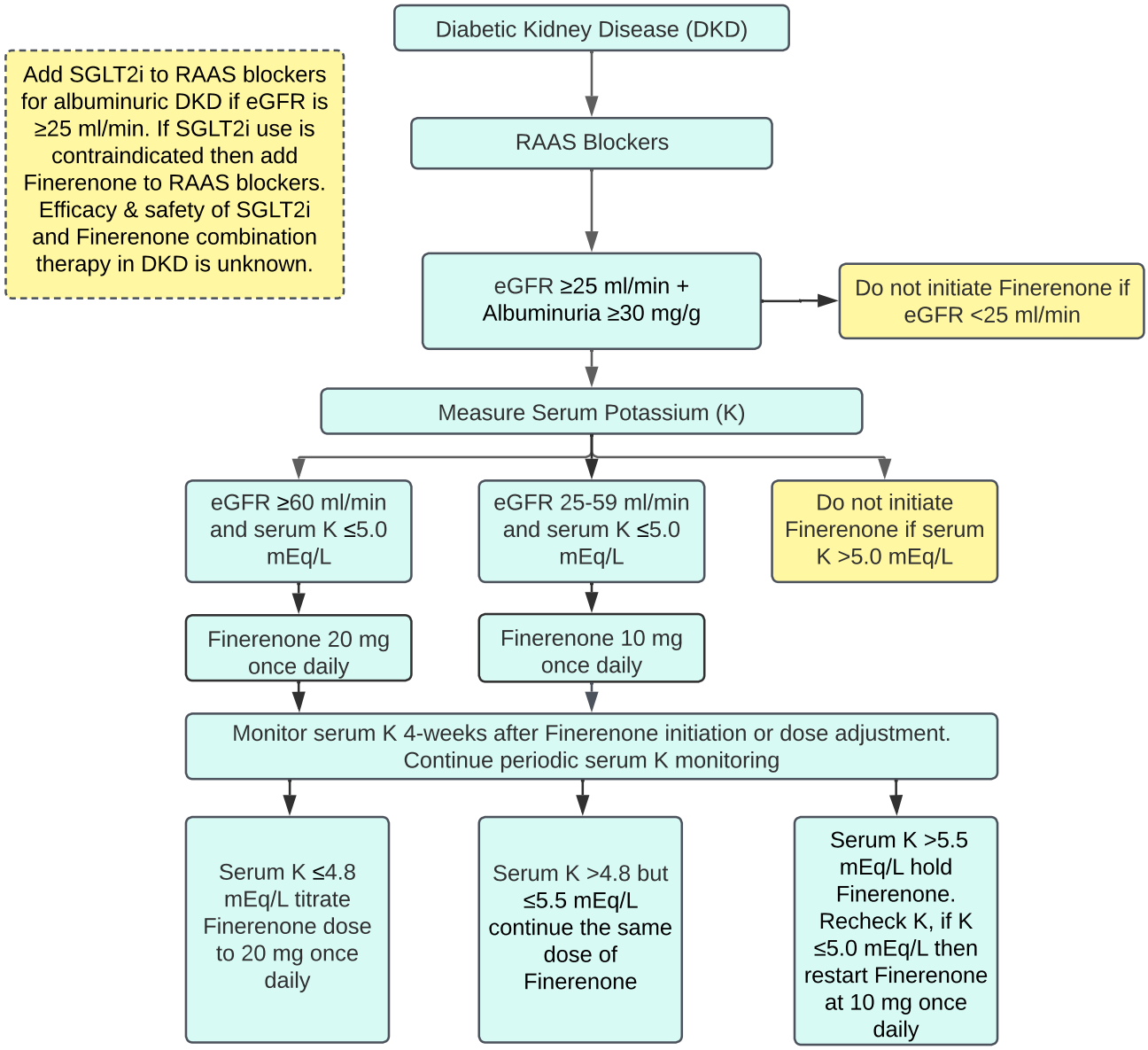

Figure 1 Finerenone dosing based on estimated glomerular filtration rate (eGFR) and serum potassium (K).

Finerenone initiation is not recommended for patients with eGFR of <25 mL/min/m^2 or with serum potassium of >5.0 mEq/L. The initial dose of finerenone is 20 mg daily for eGFR of ≥60 mL/minute/1.73 m^2 and 10 mg daily for eGFR of ≥25–59 mL/minute/1.73 m^2. Finerenone dose can be titrated from 10 mg daily to 20 mg daily (maximum dose) if the serum potassium remains ≤4.8 mEq/L. Finerenone must be held if the serum potassium exceeds 5.5 mEq/L, and it should not be restarted until the serum potassium decreases to ≤5.0 mEq/L. Serum potassium and eGFR should be monitored in 4-weeks following finerenone initiation, and any time the finerenone dose is increased. In the setting of hyperkalemia, therapies to lower serum potassium such as oral potassium binders and diuretics can be utilized to facilitate the use of finerenone.

Concomitant Use of Finerenone with SGLT2i

The FIDELIO-DKD and FIGARO-DKD trials were initiated before the approval of SGLT2i for the management of diabetic kidney disease, therefore only 6.7% of the participants in these two trials received SGLT2i. The sub-group analyses of these trials show that the cardiorenal benefits of finerenone in participants on SGLT2i were comparable to

those not on SGLT2i, however the efficacy and safety of SGLT2i and finerenone combination therapy in DKD is not known. Animal studies demonstrate that finerenone and empagliflozin combination therapy conferred cardiorenal protection in a rat model of hypertension-induced end organ damage.[53] Therefore, it is plausible that the SGLT2i and finerenone combination therapy could be beneficial in slowing progression of DKD, and future trials and analysis will shed further light on this. The magnitude of kidney outcome benefit observed with SGLT2i trials was larger than the benefits observed with finerenone in FIDELIO-DKD. However, these trials differed in study population and trial design thereby limiting the accuracy of direct comparison of the trial outcomes (Table 1).[11,48]

It is worth noting that post hoc analysis of the CREDENCE trial showed that canagliflozin lowered the risk of hyperkalemia by 22% compared to placebo.[54] The underlying mechanism for this finding is unclear but it could be

Table 1 Baseline Characteristics and Primary Kidney Outcomes in SGLT2i and Finerenone Trials

	CREDENCE	DAPA-CKD	FIDELIO-DKD
Study Population	T2DM and albuminuric diabetic kidney disease	1. T2DM and albuminuric diabetic kidney disease 2. Non-diabetic albuminuric chronic kidney disease	T2DM and albuminuric diabetic kidney disease
Key Inclusion Criteria	UACR 300 to ≤ 5000 mg/g and eGFR 30 to ≤90 mL/min/1.73m^2	UACR 200 to ≤5000 mg/g and eGFR 25 to ≤75 mL/min/1.73m^2	UACR 30 to <300 mg/g, eGFR 25 to <60 mL/min/1.73m^2 and diabetic retinopathy OR UACR ≥300 to ≤5000 mg/g and eGFR of 25 to ≤ 75 mL/min/1.73m^2
Study Drug	Canagliflozin vs. Placebo	Dapagliflozin vs. Placebo	Finerenone vs. Placebo
Background RAS Blockade	Yes	Yes	Yes
Baseline eGFR	56 mL/min/1.73m^2	43 mL/min/1.73m^2	44 mL/min/1.73m^2
Baseline Urine Albumin Creatinine Ratio (UACR)	927 mg/g	950 mg/g	852 mg/g
Duration (Median)	2.6 years	2.4 years	2.6 years
Primary Renal Endpoint	Composite of kidney failure (end-stage kidney disease or kidney transplantation or eGFR of <15 mL/minute/1.73 m^2), doubling of the serum creatinine from baseline or death from renal or cardiovascular causes	Composite of kidney failure (end-stage kidney disease or kidney transplantation or eGFR of <15 mL/minute/1.73 m^2), sustained decline of at least 50% in the eGFR, or death from renal or cardiovascular causes	Composite of kidney failure (end-stage kidney disease or kidney transplantation or eGFR of <15 mL/minute/1.73 m^2), sustained decline of at least 40% in the eGFR, or death from renal causes
Primary Outcome	30% lower risk of primary kidney outcome in the canagliflozin group versus placebo, (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P = 0.00001)	39% lower risk of primary kidney outcome in the dapagliflozin group versus placebo, (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P <0.001)	18% lower risk of primary kidney outcome in the finerenone group versus placebo, (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P = 0.001)
Number Needed Treat to Prevent One Primary Outcome	22	19	29
Adverse Effect of the Study Drug	Diabetic ketoacidosis	Volume depletion	Hyperkalemia

due to canagliflozin-induced kaliuresis due to high urine flow from osmotic diuresis and natriuresis. It could also be due to better kidney function preservation in the canagliflozin group compared to the placebo group. It is therefore conceivable that combination therapy with SGLT2i could lower the hyperkalemia risk associated with finerenone. Indeed, the post-hoc analysis of FIDELIO-DKD demonstrated that use of SGLT2i with finerenone lowered risk of hyperkalemia by 55%, however these results should be interpreted with caution as only 4.6% of the trial participants received SGLT2i.[51] Furthermore, an in-depth profiling of volume status and electrolyte changes associated with empagliflozin use in patients with T2DM and chronic, stable heart failure, found no impact of SGLT2i use on 6-hour urinary potassium excretion.[55]

In summary, the efficacy and safety of SGLT2i and finerenone combination therapy is not known. RAAS blockers and SGLT2i are currently the standard of care for management of diabetic kidney disease. Finerenone offers an alternative treatment option for patients with DKD and albuminuria in whom SGLT2i are contraindicated or not tolerated (Figure 1).

Future Directions

The advancements in therapeutic drug development for DKD are happening at a faster pace than ever before. Several ongoing clinical trials may offer additional options for management of DKD. The FLOW trial is the first long-term kidney outcome trial, studying the efficacy of the GLP-1 RA, semaglutide, on kidney outcomes.[56] This study includes patients with T2DM and eGFR 50 to 75 mL/min/1.73m^2 and UACR 300–5000 mg/g or eGFR 25 to <50 mL/min/1.73m^2 and UACR 100–5000 mg/g. All patients must be on maximally tolerated dose of RAAS blockers.

The EMPA-KIDNEY study is a Phase 3 primary kidney outcome trial testing the efficacy of empagliflozin in patients with diabetic and non-diabetic kidney disease.[57] This study, designed to shed more light on the use of SGLT2i in over 6600 diabetic and non-diabetic CKD patients, includes participants with DKD with eGFR 20 to <45 mL/min/1.73m^2 or DKD & Non-DKD with eGFR 45 to <90 mL/min/1.73m^2 and UACR ≥200 mg/g. In contrast to the previous SGLT2i kidney outcome trials, EMPA-KIDNEY includes patients with eGFR as low as 20 mL/min/1.73m^2 and those with normal, or mildly increased albuminuria.[58] This trial was stopped early due to clear positive efficacy based on interim analysis, with pending published results expected to broaden our understanding of the role of SGLT2i across the full spectrum of eGFR and albuminuria.

Conclusion

The FIDELIO-DKD and FIGARO-DKD trials have demonstrated the renal and cardiovascular benefits of finerenone on background RAAS blockade therapy with the associated risk of hyperkalemia significant, but lower than historically observed with steroidal MRAs. The potential benefits of finerenone and SGLT2i combination therapy in DKD are unknown. Several ongoing trials will assist in identifying additional therapeutic agents for DKD. The rapid emergence of new therapeutic options for DKD is exciting, and now more than ever, clinicians must tailor therapy to the individual needs of their patients.

Disclosure

The authors have no relevant conflicts to declare.

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