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Renin-angiotensin system blockers-SGLT2 inhibitors-mineralocorticoid receptor antagonists in diabetic kidney disease: A tale of the past two decades!

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Abstract

Several pharmacological agents to prevent the progression of diabetic kidney disease (DKD) have been tried and tested in patients with type 2 diabetes mellitus (T2DM) in the past two decades. Except for the renin-angiotensin system blockers (RASB) that have shown a significant reduction in the progression of DKD in 2001, no other pharmacological agent so far has shown any meaningful result until recently. Recently, an SGLT-2 inhibitor (SGLT-2i) canagliflozin has shown a significant reduction in the composite of hard renal and cardiovascular (CV) endpoints including progression of end-stage kidney disease in people with DKD with T2DM at the top of RASB use. Another SGLT-2i, dapagliflozin has also shown a significant reduction in the composite of renal and CV endpoints including death in people with chronic kidney disease, regardless of T2DM. Very recently, a novel non-steroidal mineralocorticoid receptor antagonist, finerenone has also shown a significant reduction in the composite of hard renal and CV endpoints in people with DKD and T2DM.

Key Words: Renin-angiotensin system blockers; SGLT-2 inhibitors; Mineralocorticoid receptor antagonist; Diabetic kidney disease; Chronic kidney disease; Renal outcomes; Cardiovascular outcomes

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Core Tip: Angiotensin receptor blockers (ARBs) were the first drug class that has shown a conclusive benefit in preventing the progression of diabetic kidney disease (DKD). In the year 2001, two randomized trials with ARB's irbesartan (IDNT) and losartan (RENAAL) showed a significant reduction in hard renal composite endpoints compared to the placebo, in people with DKD having type 2 diabetes mellitus. Notably, for the past 20 years, several newer pharmacological agents have been tried in DKD

without much success. In 2019, a renal outcome trial with SGLT-2 inhibitor (SGLT-2i) canagliflozin (CREDENCE) showed a significant reduction in hard renal composite endpoint in people with DKD at the top of ARBs uses. In 2020, another trial of SGLT-2i dapagliflozin (DAPA-CKD) replicated the positive renal outcomes observed in CREDENCE but additionally lowered the progression of chronic kidney disease due to non-diabetic cause. Recently, in 2021 a newer pharmacological agent, finerenone, a selective non-steroidal mineralocorticoid receptor antagonist has been tested in people with DKD. Two trials of finerenone (FIDELIO-DKD and FIGARO-DKD) have shown a significant improvement in the composite renal endpoints, at the top of ARBs uses.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) remains the leading cause of both chronic kidney disease (CKD) and end-stage kidney disease (ESKD), worldwide[1]. The exact incidence and prevalence of CKD and ESKD from T2DM is difficult to assess: (1) Due to infrequently performed invasive procedure of kidney biopsies [the gold standard for diagnosis of diabetic kidney disease (DKD)]; and (2) Because most of the patients with DKD die before requiring renal replacement therapy. DKD affects nearly 20% of patients with T2DM[2-4]. Several factors that may lead to DKD include: (1) formation of advanced glycation end-products; (2) Generation of reactive oxygen species; (3) activation of intercellular signals for proinflammatory and profibrotic gene expression causing cellular inflammation, injury, and fibrosis; (4) alterations in glomerular hemodynamics; and (5) hyperinsulinemia and insulin resistance further inciting these pathogenic mechanisms[5]. Although the time to development of DKD in T2DM depends on multiple risk factors, its incidence is about 2% of patients per year and affects nearly 25% of patients within 10 years of diagnosis[6]. Classically, DKD progresses from three stages of albuminuria based on urinary albumin excretion: (1) normal to mildly increased [< 30 mg/d or albumin/creatinine ratio (ACR) of < 30 mg/g]; (2) moderately increased (formerly called microalbuminuria—30 to 300 mg per day or ACR 30-300 mg/g); and (3) severely increased (formerly called

macroalbuminuria—> 300 mg per day or ACR >300 mg/g) albuminuria. Importantly, the presence of severe albuminuria increases the annual risk of mortality by 4.6% compared with the risk of progression to ESKD by 2.3%[6]. These findings necessitate the role of pharmacological agents other than glycemic control in the management of DKD in people with T2DM.

MANAGEMENT OF DKD IN T2DM

The general approach to managing DKD is similar to all people with T2DM which include smoking cessation, weight loss, regular exercise, individualized glycemic targets, and statins. However, certain specific considerations are additionally needed in DKD which include: (1) more intensive blood pressure lowering [to prevent ESKD and cardiovascular (CV) morbidity in patients with severe albuminuria and to reduce mortality]; and (2) mandatory use of renin-angiotensin system blockers (RASB) either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) but not both. Since most individuals with DKD and hypertension require combination therapy, either a combination of an ACEIs or ARBs plus a dihydropyridine calcium channel blocker is the preferred regime except in patients with severe albuminuria where either a non-dihydropyridine CCB or a diuretic may be more suitable with RASB[7].

RASB era

Although there are several randomized controlled trials (For instance, landmark studies: MICRO-HOPE, IRMA-2, and ADVANCE) that found RASB prevented progression from normal to microalbuminuria and micro- to macro-albuminuria in T2DM, reduction of albuminuria has been generally considered as only a soft renal surrogate endpoint[8-10]. The first convincing evidence that suggested RASB could significantly reduce hard renal endpoints and prevent the progression of CKD to ESKD in people with T2DM with severe albuminuria, dates back to 2001. The Irbesartan Diabetic Nephropathy Trial (IDNT) randomized 1715 T2DM patients (having urine

protein excretion ≥ 0.9 g/d and mean serum creatinine of 1.7 mg/dL) to either irbesartan or amlodipine or placebo. At 2.6 years, the primary composite renal outcome (doubling of serum creatinine, development of ESKD or death from any cause) with irbesartan was 20% lower than placebo [Hazard ratio (HR), 0.80; 95% Confidence interval (CI), 0.66-0.97; *P* = 0.02) and 23% lower than amlodipine (HR, 0.77; 95%CI, 0.63-0.93; *P* = 0.006). However, neither any significant reduction in secondary CV endpoint [CV death, non-fatal myocardial infarction (MI), non-fatal stroke, heart failure hospitalization (HHF), or lower limb amputation] nor any reduction in all-cause death was noted with irbesartan, compared to either placebo or amlodipine[11]. The Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial randomized 1513 T2DM patients (having albuminuria > 300 mg/d and mean serum creatinine of 1.9 mg/dL) to either losartan or placebo or both, in addition to conventional antihypertensive drugs (but not ACEI). At 3.4 years, the primary outcome (doubling of serum creatinine, development of ESKD, or death from any cause) was reduced by 16% (HR, 0.84; 95%CI, 0.72-0.98; *P* = 0.020) in losartan *vs* placebo group. However, no reduction in all-cause death was noted between losartan *vs* placebo[12]. Moreover, despite the positive renal outcomes with ARBs, a substantial residual risk did remain in both IDNT (residual risk-32.6%) and RENAAL trials (residual risk-43.5%). These findings necessitate additional safe pharmacological agents along with RASBs to further reduce the remaining risks in people with DKD.

Experimental combination therapy and novel drug era

From 2001 until the year 2018, several combinations of RASB [ACEI plus ARB such as lisinopril plus losartan (VA NEPHRON-D trial) or telmisartan plus ramipril (ONTARGET trial)] were tried without any success. Few older agents such as atorvastatin (4D trial) and several newer novel pharmacological agents [such as protein-kinase-C β (PKC-β) inhibitor: Ruboxistaurin; Darbepoetin-alfa; non-selective endothelin A receptor antagonist: Avosentan; tumor growth factor-β (TGF-β) inhibitor: Pirfenidine; Pyridoxamine; a mixture of natural glycosaminoglycans polysaccharide: Sulodexide;

direct renin inhibitor: Aliskiren; nuclear factor erythroid 2-related factor 2 (NRF-2) activator: Bardoxolone methyl; and Pentoxyphylline] were also tried in DKD with T2DM, without much success. Indeed, some of these studies showed harm and were stopped prematurely [Avosentan (ASCEND trial), Aliskiren (ALTITUDE trial), VA NEPHRON-D trial, and Bardoxolone (BEACON trial)][13-25].

Nevertheless, after a failure of any favorable outcomes for nearly two decades, the year 2019 ushered a new hope for the management of DKD. A series of recent trials have shown a positive renal outcome including a reduction of death in people with CKD and T2DM, at the top of RASB use. The Study of Diabetic Nephropathy with Atrasentan, a selective endothelin A receptor antagonist, randomized 2648 patients of CKD (eGFR 25-75 mL/min/1.73 m^2 and urinary ACR of 300-5000 mg/g) with T2DM who were receiving maximum tolerated dose of RASB to either atrasentan 0.75 mg daily or placebo. At a median follow-up of 2.2 years, the primary composite renal endpoint (doubling of serum creatinine or ESKD) was reduced by 35% (HR, 0.65; 95%CI, 0.49-0.88; P = 0.005) in atrasentan *vs* placebo. However, a higher frequency of HHF (33%) and death (9%) was also noted with atrasentan compared to the placebo[26]. Meanwhile, several cardiovascular outcome trials (CVOTs) conducted with SGLT-2 inhibitors (SGLT-2i) in people with T2DM, with or without DKD (EMPA-REG, CANVAS Program, and DECLARE-TIMI conducted with empagliflozin, canagliflozin, and dapagliflozin, respectively), have also shown a significant reduction in prespecified renal composite endpoints including progression to ESKD, albeit the renal outcomes were exploratory in nature in all these studies[27-29]. Similarly, studies conducted with non-selective steroidal mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone have shown a significant reduction in proteinuria in people with CKD although no conclusive evidence is yet available that suggests that these drugs prevent the progression of DKD. While a meta-analysis of 16 RCTs conducted with spironolactone in CKD at the top of RASB showed a significant reduction in proteinuria (although at the increased risk of hyperkalemia[30], a recent (2020) proteomic prediction and renin-angiotensin-aldosterone system inhibition

prevention of early diabetic nephropathy in type 2 diabetic patients with normoalbuminuria study has failed to show prevention of progression to microalbuminuria with spironolactone, at the end of 2.5 years of follow-up[31]. Another recently updated (2020) Cochrane meta-analysis involving 44 trials of steroidal MRA (spironolactone and eplerenone) in early stage-CKD (mild-to-moderate proteinuria) showed a significant reduction in proteinuria but an increased risk of hyperkalemia (2.17-fold), acute kidney injury (2.04-fold) and gynecomastia (5.14-fold) was noted with spironolactone[32]. Moreover, the latest (2021) Cochrane meta-analysis of 16 trials of steroidal MRA in late-stage CKD requiring dialysis has shown a significant reduction in CV- and all-cause mortality but with a significant 6-fold increased risk of gynecomastia and 1.4-fold increased trend of hyperkalemia[33]. However, the major limitations of these meta-analyses include smaller numbers, shorter duration of studies, and potential risk of bias. Indeed, one RCT of spironolactone MiREnDa (Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease) trial that assessed the safety and CV outcomes with spironolactone and another RCT SPin-D (Spironolactone in Dialysis-dependent ESRD)—both failed to show any benefit on the left ventricular mass index (LVMI) over 40 wk, or diastolic function or LVMI over 36-wk, respectively along with a dose-dependent increased risk of hyperkalemia[34,35]. Similarly, an eplerenone pilot trial PHASE (Hemodialysis patients undergoing Aldosterone antagonism with Eplerenone) failed to show any CV benefit and had a 4.5-fold increased risk of hyperkalemia against placebo[36].

SGLT-2i era

While SGLT-2i hinted at improved renal outcomes in CVOTs of empagliflozin, canagliflozin, and dapagliflozin (EMPA-REG, CANVAS Program, and DECLARE-TIMI, respectively), the results of the first dedicated renal outcome study CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) in people with DKD became available in the year 2019. CREDENCE trial randomized 4402 patients with CKD (eGFR 30 to <90 mL/min/1.75 m^2 and urinary

ACR 300-5000 mg/g) and T2DM already receiving RASB, either canagliflozin 100 mg daily or placebo. At a median follow up of 2.62 years, the relative risk reduction of primary composite outcome (composite of ESKD, a doubling of the serum creatinine level, or death from renal or CV causes) was 30% (HR, 0.70; 95%CI, 0.59-0.82; P = 0.00001) lower with canagliflozin compared to placebo. ESKD reduced by 31% (HR 0.68; 95%CI, 0.54-0.86; P = 0.002) with canagliflozin compared to placebo. The secondary CV outcome, a composite of 3P-MACE (CV death, non-fatal MI and non-fatal stroke) was found to reduce by 20% (HR, 0.80; 95%CI, 0.67-0.95; P = 0.01), while HHF reduced by 39% (HR, 0.61; 95%CI, 0.47-0.80; P < 0.001) with canagliflozin when compared to placebo[37]. The results of the second kidney outcome trial DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) got published in the year 2020. DAPA-CKD randomized 4304 patients with CKD (eGFR 25 to 75 mL/min/1.73 m^2 and urinary ACR of 200 to 5000 mg/g) having 2906 people with T2DM, on either dapagliflozin 10 mg or placebo. Over a median of 2.4 years, the primary outcome (composite of the sustained decline of eGFR of at least 50%, ESKD, or death from renal or cardiovascular cause) was 39% (HR, 0.61; 95%CI, 0.51-0.72; P < 0.001) lower with dapagliflozin compared to placebo. Reduction in primary renal composite was similar in people both with (HR, 0.64; 95%CI, 0.52-0.79) or without (HR, 0.50; 95%CI, 0.35-0.72) T2DM with dapagliflozin *vs* placebo. The secondary CV endpoints (composite of CV death or HHF) were reduced by 29% (HR, 0.71; 95%CI, 0.55-0.92; P = 0.009), while all-cause death was reduced by 31% (HR, 0.69; 95%CI, 0.53-0.88; P = 0.004) with dapagliflozin compared to placebo[38]. Ongoing empagliflozin renal outcome trial (EMPA-KIDNEY) in people with CKD due to T2DM and the non-diabetic cause has been recently (March 16, 2022) stopped owing to the positive results which met the prespecified threshold for early termination against placebo[39]. However, the residual risk of CKD progression or kidney failure was still evident in CREDENCE and DAPA-CKD in about 10% of patients despite a full dose of concomitant RASB use after a median follow-up of nearly 2.5 years[37,38]. This necessitates further strategies to combat the progression of DKD in people with T2DM.

MRA era

While several studies of steroidal MRA (spironolactone and eplerenone) have shown a significant reduction in soft surrogates of proteinuria in people with DKD albeit, at increased risk of hyperkalemia and gynecomastia (spironolactone), no conclusive evidence of benefit is yet available with these MRAs concerning prevention of ESKD progression. Two ongoing phase 3b RCTs of spironolactone are currently evaluating the CV effect in patients with CKD on dialysis. While ALCHEMIST (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial, NCT01848639) is evaluating the primary composite endpoint of non-fatal MI, acute coronary syndrome, HHF, nonfatal stroke, or CV death, ACHIEVE (Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease, NCT03020303) trial is evaluating the composite of CV death or HHF, in patients on maintenance dialysis. Results of both studies are expected in 2023[40].

Meanwhile, several newer, selective, non-steroidal MRA such as finerenone, esaxerenone, and apararenone have also been tried in DKD. ARTS-DN (Mineralocorticoid Receptor Antagonist Tolerability Study in Diabetic Nephropathy) study that evaluated various doses of finerenone showed a dose-dependent significant reduction in UACR (24% and 38% reduction with 10 and 20 mg, respectively) in people with T2DM having albuminuria (UACR ≥ 30 mg/g) and eGFR of > 30 mL/min/1.73 m^2 at the top of RASB use, although no difference in ≥ 30% decline in eGFR (secondary outcome) was noted against placebo[41]. Significant reduction in proteinuria was also exhibited by esaxerenone in ESAX-DN (Esaxerenone in Patients with Type 2 Diabetes and Microalbuminuria) study and apararenone study in people with DKD and T2DM[42,43]. Nevertheless, the conclusive evidence to prevent progression of DKD with MRA was first noted only with finerenone in FIDELIO-DKD (The Finerenone in Reducing Kidney Failure and Disease Progression in DKD) trial that become available in the year 2020. FIDELIO-DKD randomized 5734 patients with CKD (eGFR 25 to < 60 mL/min/1.73 m^2, urinary ACR of 30 to < 300 mg/g and diabetic retinopathy, or urinary

ACR 300-5000 mg/g and eGFR 25 to < 75 mL/min/1.73 m^2) and T2DM on maximum licensed dose of RASB, to either finerenone 10 mg (< 60 mL/min/1.73 m^2) or 20 mg (≥ 60 mL/min/1.73 m^2) once daily, or placebo. At the median follow-up of 2.6 years, FIDELIO-DKD showed an 18% reduction (HR, 0.82; 95%CI, 0.73-0.93; *P* = 0.001) in primary renal outcome (composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) with finerenone compared to placebo. A significant reduction of 14% (HR, 0.86; 95%CI, 0.75-0.99; *P* = 0.03) in secondary CV outcome (composite of CV death, nonfatal MI, and nonfatal stroke, or HHF) was also shown with finerenone compared to placebo. Although adverse events were similar in both arms, hyperkalemia-related drug discontinuation was 2.5 times higher with finerenone (2.3%) compared to placebo (0.9%)[44]. Another study conducted with Finerenone in Reducing Cardiovascular Mortality and Morbidity in DKD (FIGARO-DKD trial) has been published recently in 2021. FIGARO-DKD randomized 7437 patients with CKD (eGFR 25 to 90 mL/min/1.73 m^2 and urinary ACR of 30 to <300 mg/g, or urinary ACR 300 to 500 mg/g and eGFR ≥ 60 mL/min/1.73 m^2) and T2DM on the maximum licensed dose of RASB. On a median follow-up of 3.4 years, the primary CV outcome (composite of CV death, nonfatal MI, and nonfatal stroke, or HHF) was significantly reduced by 13% (HR, 0.87; 95%CI, 0.76-0.98; *P* = 0.03) primarily driven by 29% reduction (HR, 0.71; 95%CI, 0.56-0.90) in HHF with finerenone compared to placebo. Interestingly, no significant difference (HR, 0.87; 95%CI, 0.76-1.01) was noted in secondary renal outcome (composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal cause) with finerenone compared to placebo. Overall, no difference in the adverse events was noted in the two arms, however hyperkalemia-related drug discontinuation was 3-times higher with finerenone (1.2%) compared to placebo (0.4%)[45]. Table 1 summarizes the results from all these studies (in chronological order) which have been conducted in patients with T2DM having CKD that evaluated hard renal or cardiovascular composite endpoint as the primary objective[11-26,37,38,44,45]. Figure 1 is a schematic representation of timelines and outcomes from all these cardio-renal outcome trials.

Summarily, several agents have been tried in the past two decades in people with DKD and T2DM, but only three drug classes (RASB, SGLT-2i, and MRA especially finerenone) have conclusively shown both ≥ 30% reduction in albuminuria and a significant lowering in renal disease progression. It should be recalled that a cut-off of 30% geometric mean albuminuria reduction within 6 mo or an eGFR slope reduction of 0.5-1.0 mL/min/1.73 m²/year over 2-3 years has been adopted as a surrogate renal endpoint for CKD progression for clinical trials by National Kidney Foundation, European Medicines Agency, and US Food Drug Administration in the year 2020[46]. This cut-off seems to have primarily originated from at least two meta-analyses[47,48]. While REASSURE (Reducing Albuminuria as Surrogate Endpoint) Consortium showed each 30% reduction in albuminuria lowered the risk of ESKD by 24%, a meta-analysis of observational studies involving nearly 700000 individuals found that a 30% reduction of albuminuria over 2 years lowered ESKD by 22%, regardless of drug class tested[47,48]. However, the pressing question which remains unanswered conclusively is whether the addition of MRA including finerenone to the patients who are already receiving SGLT-2i and RASB would help prevent further progression of kidney disease[49]. Mechanistically, the action of both SGLT-2i and MRA including finerenone appears to be complementary owing to: (1) Differential mechanism of action: While SGLT-2i reduces glomerular hyperfiltration and could have direct beneficial cellular and metabolic effect, finerenone reduces inflammation and fibrosis by inhibiting mineralocorticoid receptor pathway; and (2) Hyperkalemia induced by finerenone (the commonest reason for drug discontinuation) can be counterbalanced by SGLT-2i. A recent meta-analysis from the pooled data of five RCTs (n = 8296) in patients with reduced ejection fraction showed SGLT-2i plus MRA to significantly reduce both cardiovascular composite of CV death or HHF (HR, 0.73; 95%CI, 0.66-0.80; P < 0.00001) and composite renal endpoints (HR 0.56; 95%CI, 0.39-0.81; P = 0.002) but with a significantly lower risk of hyperkalemia (HR 0.60; 95%CI, 0.42-0.87; P = 0.007), compared to MRA alone[50]. However, renal outcomes were exploratory endpoints in

these RCTs included in this meta-analysis. In FIDELIO-DKD, 4.6% (259/5674) patients were receiving SGLT-2i at the baseline and reduction in primary renal composite was similar ($P_{Interaction}$ = 0.21), regardless of the SGLT-2i use (SGLT-2i users: HR, 1.38, 95%CI, 0.61-3.10; SGLT-2i non-users: HR, 0.82, 95%CI, 0.72-0.92). Similarly, in FIGARO-DKD, 8.4% patients (618/7352) were receiving SGLT-2i at baseline and benefit in primary CV composite was similar, regardless of SGLT-2i use (SGLT-2i users: HR, 0.49, 95%CI, 0.28-0.86; SGLT-2i non-users: HR, 0.89, 95%CI, 0.78-1.01). Importantly, a recent subgroup analysis of FIDELIO-DKD found that finerenone caused a 25% reduction in UACR in people receiving SGLT-2i at the baseline, and patients on SGLT-2i also had fewer hyperkalemia events. Indeed, this subgroup analysis stratified on the baseline SGLT-2i use reported a lesser episode of treatment-emergent hyperkalemia of both moderate (> 5.5 mmol/L) and severe (> 6.0 mmol/L) nature in combined SGLT-2i plus finerenone users (7% and 0%, respectively), compared with finerenone alone (22% and 5%, respectively)[51]. Notably, a recent meta-analysis of six cardio-renal trials involving 49875 individuals has found a 16% lower risk (HR, 0.84; 95%CI, 0.76-0.93) of serious hyperkalemia (> 6.0 mmol/L) with SGLT-2i without any higher risk of hypokalemia[52]. Collectively, these finding hints that combination therapy of SGLT-2i and finerenone would likely reduce the risk of hyperkalemia. Whether combining MRA to SGLT-2i would enhance the CV or renal outcome is not known due to: (1) low number of events in a small population of baseline SGLT-2i users in both FIDELIO-DKD and FIGARO-DKD trial (number of events 24 and 61, respectively); and (2) absence of any dedicated RCT that has assessed the renal or CV outcome with the combination therapy in people with CKD and T2DM. Efficacy and safety of finerenone plus empagliflozin compared with either finerenone or empagliflozin in 807 participants with CKD and T2DM (CONFIDENCE Trial, NCT05254002) is currently planned and expected to be complete by end of 2023[53].

CONCLUSION

While optimal glucose control, intensive blood pressure control, and use of RASB have been the traditional foundation of treatment in slowing the progression of kidney disease in people with albuminuria and T2DM for the past two decades, the addition of SGLT-2i to this foundational treatment has further shown to reduce the disease progression including death (DAPA-CKD). Finerenone would be a welcome addition to the list of novel drugs that have been able to reduce the progression of CKD successfully in people with T2DM along with RASB. It is also possible that finerenone plus SGLT-2i combination can further prevent the progression of DKD in T2DM but that has to be proved through dedicated RCTs.

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