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EDITORIAL

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 tested in patients with type 2 diabetes mellitus (T2DM) in the past two decades. With the exception of renin-angiotensin system blockers that have shown a significant reduction in the progression of DKD in 2001, no other pharmacological agent tested in the past two decades have shown any clinically meaningful result. Recently, the sodium-glucose cotransporter-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 patients with DKD with T2DM at the top of renin-angiotensin system blocker use. Another SGLT-2i, dapagliflozin, has also shown a significant reduction in the composite of renal and CV endpoints including death in patients with chronic kidney disease (CKD), regardless of T2DM status. Similar positive findings on renal outcomes were recently reported as a top-line result of the empagliflozin trial in patients with CKD regardless of T2DM. However, the full results of this trial have not yet been published. While the use of older steroidal mineralocorticoid receptor antagonists (MRAs) such as spironolactone in DKD is associated with a significant reduction in albuminuria outcomes, a novel non-steroidal MRA finerenone has additionally shown a significant reduction in the composite of hard renal and CV endpoints in patients with DKD and T2DM, with reasonably acceptable side effects.

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

Core Tip: Angiotensin receptor blockers were the first drug class to show a conclusive benefit in preventing diabetic kidney disease (DKD) progression through two randomized trials IDNT and RENAAL in 2001. Several newer pharmacological agents have been tested in DKD in the past 20 years without much success. Notably, recently conducted renal outcome trials of sodium-glucose cotransporter-2 inhibitors in patients with DKD such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY have shown significant improvement in disease progression. Similarly, recent trials of the non-steroidal mineralocorticoid receptor antagonist finerenone (FIDELIO-DKD and FIGARO-DKD) have shown significant improvement in both renal and cardiac endpoints in DKD.

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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 due to infrequently performed invasive procedure of kidney biopsies (the gold standard for diagnosis of diabetic kidney disease [DKD]); and because most patients with DKD die before requiring renal replacement therapy. However, DKD affects nearly 20% of patients with T2DM[2-4]. Several factors that may lead to DKD include: the formation of advanced glycation end-products; generation of reactive oxygen species; activation of intercellular signals for proinflammatory and profibrotic gene expression causing cellular inflammation, injury, and fibrosis; alterations in glomerular hemodynamics; and associated hyperinsulinemia and insulin resistance further activating 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: normal to mildly increased (< 30 mg/d or albumin/creatinine ratio [ACR] of < 30 mg/g), moderately increased (formerly called microalbuminuria-30 to 300 mg per day or ACR 30-300 mg/g), and 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 patients with T2DM.

MANAGEMENT OF DKD IN T2DM

The general approach to managing DKD is similar to that in all patients with T2DM, which includes smoking cessation, weight loss, regular exercise, individualized glycemic targets, and statins. However, certain specific considerations are additionally needed in DKD which include: more intensive blood pressure lowering to prevent ESKD and cardiovascular (CV) morbidity in patients with severe albuminuria and to reduce mortality; and mandatory use of renin-angiotensin system blockers (RASBs), 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 ACEI or ARB plus a dihydropyridine calcium channel blocker is the preferred regimen, 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 (*e.g.*, landmark studies: MICRO-HOPE, IRMA-2, and ADVANCE), which showed that RASB prevented progression from normal to microalbuminuria and micro- to macro-albuminuria in T2DM, reduction of albuminuria has generally been considered only a soft renal surrogate endpoint[8-10]. The first convincing evidence suggesting that RASB can significantly reduce hard renal endpoints and prevent the progression of CKD to ESKD in patients 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* the placebo group. However, no reduction in all-cause death was noted between losartan *vs* placebo[12]. Importantly, 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 residual risks in patients with DKD.

Experimental combination therapy and novel drug era

From 2001 until 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 (*e.g.*, 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 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 patients with CKD and T2DM, at the top of RASB use. The SONAR (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 a 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 patients 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 patients with CKD although no conclusive evidence is yet available suggesting 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 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 showed 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 (Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease trial, commonly known as MiREnDa) that assessed the safety and CV outcomes with spironolactone and another RCT (Spironolactone in Dialysis-Dependent ESRD, commonly known as SPin-D)-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 indicated 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 patients 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, to 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 (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD]) was 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 patients with T2DM, to 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 patients 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 patients with CKD due to either T2DM or 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]. It should be noted however that 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 patients with T2DM.

MRA era

While several studies of steroidal MRA (spironolactone and eplerenone) have shown a significant reduction in soft surrogates of proteinuria in patients 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 the ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (commonly known as ALCHEMIST; NCT01848639) is evaluating the primary composite endpoint of non-fatal MI, acute coronary syndrome, HHF, nonfatal stroke, or CV death; the Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease (commonly known as ACHIEVE; NCT03020303) trial is evaluating the composite of CV death or HHF, in patients on maintenance dialysis. The 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. The Mineralocorticoid Receptor Antagonist Tolerability Study in Diabetic Nephropathy (ARTS-DN) study, which evaluated various doses of finerenone, showed a dose-dependent significant reduction in UACR (24% and 38% reduction with 10 and 20 mg, respectively) in patients 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 the Esaxerenone in Patients with Type 2 Diabetes and Microalbuminuria (ESAX-DN) study and apararenone study in patients with DKD and T2DM[42,43]. Nevertheless, the conclusive evidence to prevent progression of DKD with MRA was first noted only with finerenone in The Finerenone in Reducing Kidney Failure and Disease Progression in DKD (FIDELIO-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

Table 1 Studies (in chronological order) that evaluated hard renal or cardiovascular composites in patients having diabetic kidney disease and type 2 diabetes mellitus with various pharmacological agents

Ref.	*n*	Comparator	Duration (mean/median)	Primary endpoints	Results	Remarks
Lewis *et al* [11], 2001, IDNT	1715	Irbesartan 75-300 mg *vs* Amlodipine 2.5-10 mg *vs* PBO	2.6 yr	Composite of doubling of serum Cr, development of ESKD or death from any cause	The primary outcome with IRBE was 20% lower than PBO and 23% lower than AMLO. Doubling of Cr was significantly 33% lower in IRBE *vs* PBO ($P = 0.003$) and 37% lower with IRBE *vs* AMLO ($P < 0.001$). The risk of ESKD was non-significantly 23% lower *vs* both PBO and AMLO ($P = 0.07$, for both comparisons). No difference in CV- or all-cause death was noted	Similar BP control with IRBE and AMLO. Protection is independent of reduction in BP
Brenner *et al* [12], 2001, RENAAL	1513	Losartan 50-100 mg *vs* PBO	3.4 yr	Composite of doubling of serum Cr, development of ESKD or death from any cause	Primary outcome reduced by 16% risk in LOSA *vs* PBO ($P = 0.020$). LOSA reduced the doubling of Cr by 25% ($P = 0.006$) and ESKD by 28% ($P = 0.002$) *vs* PBO but no effect on death was noted. HHF was reduced by 32% in LOSA ($P = 0.005$) while proteinuria was reduced by 35% ($P < 0.001$) *vs* PBO	There was no active comparator, and the mean blood pressure throughout the study was lower among those assigned losartan
Wanner *et al* [13], 2005, 4D	1255	Atorvastatin 20 mg *vs* PBO (receiving hemodialysis)	4.0 yr	Composite of 3P-MACE (death from CV causes, nonfatal MI, and stroke)	No benefit in 3P-MACE (RR: 0.92; 95%CI: 0.77-1.10; $P = 0.37$) but significant increase in fatal stroke (RR: 2.03; $P = 0.04$)	An increase in stroke could be a chance finding, given the data from the CARDS trial that showed atorvastatin lowers the incidence of stroke (HR: 0.52; 95%CI: 0.31-0.89)
Tuttle *et al* [14], 2007, PKC-DRS, PKC-DMES and PKC-DRS 2 study	1157	Ruboxistaurin *vs* PBO	33-39 mo	Composite of doubling of serum Cr, development of advanced chronic kidney disease (stages 4 to 5), and death	No difference between the two group	-
Pfeffer *et al* [15], 2009, TREAT	4038	Darbepoetin alfa *vs* PBO	4.0 yr	Composite outcomes of death or a CV event (nonfatal MI, CHF, stroke, or hospitalization for myocardial ischemia) and of death or ESKD	No difference in the composite of death or ESKD (HR: 1.06; 95%CI: 0.95-1.19; $P = 0.29$) or ESKD (HR: 1.02; 95%CI: 0.87-1.18; $P = 0.83$) between darbepoetin alfa and PBO. An increase in stroke (fatal or nonfatal stroke) occurred in darbepoetin alfa compared with PBO (HR: 1.92; 95%CI: 1.38-2.68; $P < 0.001$)	-
Mann *et al*[16], 2010, ASCEND	1392	Avosentan 25/50 mg *vs* PBO	4 mo	Composite of doubling of serum Cr, ESKD, or death	No difference in primary outcome (25 mg 8.1% *vs* PBO 9.6%; $P = 0.46$; 50 mg 8.6% *vs* PBO 9.6%; $P = 0.79$) but a significant increase in CHF with avosentan (25 mg 5.9% *vs* PBO 2.2%; $P = 0.008$; 50 mg 6.1% *vs* PBO 2.2%; $P = 0.05$) compared with PBO	The trial terminated prematurely after a median follow-up of 4 mo (maximum 16 mo) because of an excess of CV events with avosentan
Sharma *et al* [17], 2011	77	Pirfenidone 1200/2400 mg *vs* PBO	1 yr	Change in eGFR	Mean eGFR significantly increased the pirfenidone 1200-mg/d group *vs* PBO (+3.3 *vs* -2.2 mL/min; $P = 0.03$) but no improvement in 2400-mg/d group	-
Pergola *et al* [18], 2011, BEAM	227	Bardoxolone 25/75/150 mg OD *vs* PBO	12 mo	Change in eGFR at 6 mo	Significant increase in mean eGFR both at 6-mo (8.2-11.4 mL/min; $P < 0.001$) and 12-mo (5.8-10.5 mL/min) against PBO	Muscle spasms were the MC observed S/E with BDX
Lewis *et al* [19], 2012	317	Pyridoxamine 150/300 mg BID *vs* PBO	52-wk	Change in serum Cr	No difference in outcome observed	-

Packham *et al* [20], 2012, Sun-MACRO	1248	Sulodexide *vs* PBO	11 mo	Composite of a doubling of serum Cr, development of ESKD, or serum Cr ≥6.0 mg/dl	No difference in the outcome	The trial was stopped prematurely due to futility
Parving *et al* [21], 2012, ALTITUDE	8561	Aliskiren *vs* PBO	32.9 mo	Composite of CV death or the first occurrence of cardiac arrest with resuscitation; nonfatal MI; nonfatal stroke; unplanned HHF; ESKD, death attributable to kidney failure, or the need for RRT with no dialysis or transplantation available or initiated; or doubling of Cr level	Results of the primary endpoint were no different between the two arms (HR: 1.08; 95% 0.98-1.20; $P = 0.12$)	The trial was stopped prematurely after the second interim efficacy analysis because of significantly higher (11.2% *vs* 7.2%; $P < 0.001$) hyperkalemia (Serum K level ≥ 6 mmol/L) and hypotension (12.1% *vs* 8.3%; $P < 0.001$ in the aliskiren group *vs* PBO
Fried *et al*[22], 2013, VA NEPHRON-D	1448	Losartan plus lisinopril *vs* losartan plus PBO	2.2 yr	Composite of change in the eGFR, ESKD, or death	No difference in outcome (HR: 0.88; 95%CI: 0.70 to 1.12; $P = 0.30$). Combination therapy increased the risk of hyperkalemia ($P < 0.001$) and acute kidney injury ($P < 0.001$) compared to monotherapy	The trial was stopped prematurely
Mann *et al*[23], 2013, ONTARGET	3163	Ramipril 10 mg *vs* telmisartan 80 mg *vs* ramipril plus telmisartan (10 + 80)	56-mo	Composite of dialysis, doubling of serum Cr, and death	Combination therapy was associated with a non-significantly higher ESKD or doubling of serum creatinine (5.3% *vs* 4.8 %), but a similar death rate (2.3% *vs* 2.2 %) *vs* monotherapy. Combination therapy had higher rates of acute kidney injury requiring dialysis (1.4% *vs* 0.8 %)	This is the data of 3163 people having DKD from a total of 9628 patients with diabetes
de Zeeuw *et al* [24], 2013, BEACON	2185	Bardoxolone 20 mg OD *vs* PBO	9.0 mo	Composite of ESKD or CV death	No difference (HR: 0.98; 95%CI: 0.70-1.37; $P = 0.92$). Significant increase in HHF and death due to HHF with bardoxolone (HR: 1.83; 95%CI: 1.32-2.55; $P < 0.001$) *vs* PBO	The trial was stopped prematurely
Navarro-Gonzalez *et al* [25], 2015, PREDIAN	169	Pentoxyphylline 600 mg BID *vs* PBO	2-yr	Change in eGFR	Significant less decrease in eGFR in PTF *vs* PBO (-2.1 *vs* -6.5 mL/min; Group difference -4.3 mL/min; $P < 0.001$)	Open-label design and envelope (rather than computer-generated) randomization could have biased the results
Heerspink *et al* [26], 2019, SONAR	2648	Atrasentan 0.75 mg *vs* PBO	2.2 yr (Median)	Composite of doubling of serum Cr or ESKD or death from kidney failure	35% reduction in primary composite renal endpoint event (HR: 0.65; 95%CI: 0.49-0.88; $P = 0.005$)	HHF was insignificantly higher in atrasentan (HR: 1.33; 95%CI: 0.85-2.07; $P = 0.208$) *vs* PBO
Perkovic *et al* [37], 2019, CREDENCE	4401	Canagliflozin 100 mg *vs* PBO	2.6 yr	Composite of ESKD, doubling of serum Cr, or death from renal or CV causes	30% reduction in primary composite (HR: 0.70; 95%CI: 0.59-82; $P = 0.00001$), 34% reduction (HR: 0.66; 95%CI: 0.53-0.81; $P < 0.001$) in renal-specific composite (of ESKD, doubling of Cr, renal death) and 32% reduction in ESKD (HR: 0.68; 95%CI: 0.54-0.86; $P = 0.002$) in CANA *vs* PBO. Reduction in composite of 3P-MACE was 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; $P < 0.001$) in CANA arm *vs* PBO	The trial was stopped prematurely due to efficacy
Heerspink *et al* [38], 2020, DAPA-CKD	4304	Dapagliflozin 10 mg *vs* PBO	2.4 yr	Composite of ESKD, sustained decline in eGFR of at least 50%, or death from renal or CV causes	39% reduction in primary composite (HR: 0.61; 95%CI: 0.51-0.72; $P < 0.001$), 44% reduction (HR: 0.56; 95%CI: 0.45-0.68; $P < 0.001$) in renal-specific composite (of ESKD, decline in eGFR of at least 50%, or renal death), 29% reduction (HR: 0.71; 95%CI: 0.55-0.92; $P = 0.009$) in composite of CV death of HHF and 31% reduction in death (HR: 0.69;	The trial stopped prematurely due to efficacy

					95%CI: 0.53-0.88; *P* = 0.004) in DAPA arm *vs* PBO	
Bakris *et al* [44], 2020, FIDELIO-DKD	5734	Finerenone 10/20 mg *vs* PBO	2.6 yr	Composite of kidney failure, sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes	18% reduction (HR: 0.82; 95%CI: 0.73-0.93; *P* = 0.001) in primary composite in FINE *vs* PBO arm. 14% reduction (HR: 0.86; 95%CI: 0.75-0.99; *P* = 0.03) in secondary outcome composite (CV death, non-fatal MI, non-fatal stroke, or HHF) in FINE *vs* PBO arm	Hyperkalemia-related discontinuation of the drug was higher in the FINE *vs* PBO (2.3% *vs* 0.9%) arm
Pitt *et al*[45], 2021, *FIGARO*-DKD	7437	Finerenone 10/20 mg *vs* PBO	3.4 yr	Composite of CV death, nonfatal MI, nonfatal stroke, or HHF. The secondary outcome was a composite of a decrease of eGFR by at least 40%, ESKD, or death from renal causes	13% reduction (HR: 0.87; 95%CI: 0.76-0.98; *P* = 0.03) in primary cardiac composite primarily driven due to 29% reduction (HR: 0.71; 95%CI: 0.56-0.90) in HHF with FINE *vs* PBO. Non-significant 13% reduction (HR: 0.87; 95%CI: 0.76-1.01) in secondary renal composite with FINE *vs* PBO	Hyperkalemia-related discontinuation of the drug was higher in the FINE *vs* PBO (1.2% *vs* 0.4%) arm

3P-MACE: 3-point major adverse cardiac events; AMLO: Amlodipine; BDX: Bardoxolone; BID: Twice daily; BP: Blood pressure; CANA; Canagliflozin; CHF: Congestive heart failure; CI: Confidence interval; Cr: Creatinine; CV: Cardiovascular; DAPA; Dapagliflozin; DKD: Diabetic kidney disease; eGFR: Estimated glomerular filtration rate; ESKD: End-stage kidney disease; FINE: Finerenone; HHF: Heart failure hospitalization; HR; Hazard ratio; IRBE: Irbesartan; LOSA: Losartan; MC: Most common; MI: Myocardial infarction; OD: Once daily; PBO: Placebo; PTF; Pentoxyphylline; RR: Relative risk; RRT: Renal replacement therapy; S/E: Side effects.

Finerenone FIGARO-DKD (Reducing Cardiovascular Mortality and Morbidity in DKD) has been published recently in 2021. FIGARO-DKD trial 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 to either finerenone 10 mg (25 to < 60 mL/min/1.73 m^2) or 20 mg (≥ 60 mL/min/1.73 m^2) once daily, or placebo 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.

In summary, several agents have been tried in the past two decades in patients 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 m^2/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 and Drug Administration in the year 2020[46]. This cut-off seems to have primarily originated from at least two meta-analyses[47,48]. While the Reducing Albuminuria as Surrogate Endpoint (REASSURE) 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 due to the following: (1) The 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.

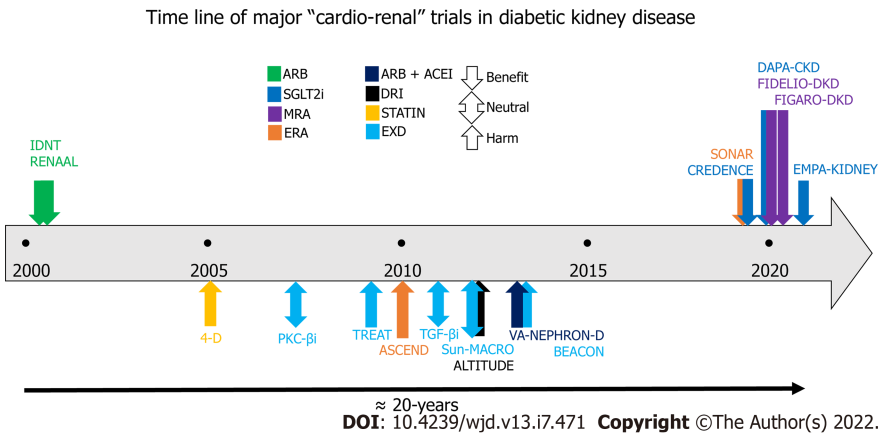

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Figure 1 Major cardio-renal outcome trials in patients with diabetic kidney disease and type 2 diabetes mellitus. ARB: Angiotensin-receptor blocker; ACEI: Angiotensin converting enzyme inhibitors; DRI: Direct renin inhibitors; ERA: Endothelin A receptor antagonists; EXD: Experimental drugs; MRA: Mineralocorticoid receptor antagonists; PKC-βi: Protein-kinase C β inhibitor; SGLT-2i: Sodium-glucose co-transporter 2 inhibitors; TGF-βi: Tumor growth factor β inhibitor.

In FIDELIO-DKD, 4.6% (259/5674) patients were receiving SGLT-2i at the baseline and reduction in primary renal composite was similar ($P_{\text{Interaction}}$ = 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 patients 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 clearly 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 patients 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 patients 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 patients 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.

FOOTNOTES

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