Renal Outcomes with Anti-Diabetic Medications and Clinical Implications in Type 2 Diabetes

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Abstract

After the invention of Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers (ACE-i/ARB), for nearly two decades, there has not been another drug to prevent the progression of diabetic kidney disease. Recent trials have indicated that some of the anti-hyperglycemic drug classes have positive renal outcomes thus potentially changing the course of renal disease. Here, we summarized the relevant evidence with medications used in diabetes mellitus, especially focusing on the most recent innovations predominantly used in type-2 diabetes.

Keywords: Diabetes mellitus; Diabetic nephropathy; Albuminuria; Chronic kidney disease; SGLT-2 inhibitors; GLP-1 agonists

Introduction

Diabetes Mellitus (DM) is associated with both micro and macro vascular complications. It is the major cause of chronic kidney disease [1-3]. Diabetic Kidney Disease (DKD) develops in approximately 30% of individuals with Type 1 Diabetes Mellitus (T1DM), up to 50% of those with Type 2 Diabetes Mellitus (T2DM), and is associated with poor outcomes [4-5]. Despite this, early diagnosis and management of DKD has remained elusive. The global number of deaths due to DKD rose by 94% between the years 1990 to 2012, showing that preventive measures for DKD development and progression remain a global healthcare challenge [6]. Here, we discuss the important trials with emphasis on renal outcomes related to anti-diabetic medications mainly focusing on the novel therapies including Dipeptidyl Peptidase-4 inhibitors (DPP4-i), Glucagon like Peptide-1 (GLP-1) agonists and Sodium Glucose Coransporter Type-2 inhibitors (SGLT-2i). Detailed review of glycemic management guidelines, pathogenesis of DKD and the effect of deteriorating kidney function on insulin/glucose metabolism is beyond the scope of this review.

Epidemiology

The number of individuals with DKD is rising worldwide and is associated with increasing mortality [1]. According to U.S. Renal Data System (USRDS) 2020, 14.9% of the U.S. adult population surveyed in 2015 to 2018 had CKD stages 1 to 5, based on low eGFR or proteinuria. CKD stage 3 is the most prevalent among these [3]. In UK, 3.9 million people have been diagnosed with diabetes as of 2019 [7]. In England, it is estimated that up to 2.6 million people aged 16 years and older have CKD stage 3 to 5. This is equivalent to 6.1% of the population of this age group.CKD is innately linked to Cardiovascular (CV) disease and an independent risk factor for CV mortality and morbidity.

Pathophysiology of DKD

Factors that play a key role in pathogenesis of DKD include renal hemodynamic changes, inflammation, ischemia and overactive Renin-Angiotensin-Aldosterone System (RAAS) [8]. One of the avidly used, easily available markers of DKD is albuminuria, which can be associated with disease progression and cardiovascular events. Therefore, slowing the development of, or preventing kidney disease should be part of holistic care provision plan for persons living with diabetes [9,10].

Evidence to suggest improvement in renal outcomes with better glycemic control

The United Kingdom Prospective Diabetes Study (UKPDS) is a watershed moment in the management of T2DM. It demonstrated that intensive glucose control (target fasting glucose of <6 mmol/L, mean HbA1c of 7.0%) reduces microvascular outcomes by a quarter (primarily due to a

lower rate of retinopathy) as compared to conventional therapy (target glucose of <15 mmol/L, mean HbA1c of 7.9%) [11]. This was followed a decade later by a cluster of trials – ADVANCE, 12 ACCORD, 13 and VADT [14]. In a meta-analysis, Zoungas et al. [15] analyzed four randomized controlled trials (VADT, UKPDS, ACCORD and ADVANCE) looking at 27,049 adults with type 2 diabetes with a median follow up of 5.0 years who were categorized to either more intensive glucose control group or less intensive glucose control group. It was found that improvement in glycemic control reduced the incidence and progression of microvascular complications. Intensive glucose control was associated with a relative risk reduction of the composite primary kidney outcome of 20% (HR: 0.80, 95% CI 0.72 to 0.88; p<0.0001) and composite primary eye outcome of 13% (HR: 0.87, 95% CI 0.76 to 1.00; p=0.042), but did not reduce the risk of the composite primary nerve outcome (HR: 0.98, 95% CI 0.87 to 1.09; p=0.68) [15].

Renal outcome studies with anti-diabetic medications

Biguanides (Metformin): Metformin (MTF) is one of the oldest antidiabetic drugs and is recommended as first-line pharmacological therapy in virtually all guidelines for type 2 diabetes [16]. Studies have shown that intensive glucose control with metformin, compared with the conventional group, had risk reduction of 32% (p=0.002) for any diabetes-related endpoint, 42% for diabetes-related death (p=0.017), and 36% for all-cause mortality (p=0.011) in overweight individuals with type 2 diabetes. It is also associated with less weight gain and fewer hypoglycemic episodes than with insulin and sulphonylureas [17]. There are no RCT to date to our knowledge specifically looking at renal endpoints with MTF.

Sulphonylurea (SU): No concrete evidence of reno-protective effects attributable to SUs has been recognized. In ADVANCE trial, 11,140 participants with type 2 diabetes were randomized into either intensive glucose control group (receiving Gliclazide MR and any other additional therapy) or standard glucose control group (receiving therapy according to local guidelines). After a median follow-up of 5 years, fewer microvascular events were noted in the intensive control group (14% relative risk reduction, P=0.01), essentially a reduction in diabetic nephropathy at the cost of severe hypoglycemia (2.7% in the intensive-control group vs. 1.5% in the standard-control group) [18]. As patients with worsening CKD are at higher risk of hypoglycemia, it is recommended that predominantly renally excreted sulfonylureas should be reviewed (either dose reduced or stopped) in advanced CKD (stage 4 and 5) patients [19].

Thaizolidinedione (TZD): TZDs may have a potential benefit preserving renal function in early stages of DKD and decreasing progression of albuminuria in persons with T2DM [20,21]. Two RCTs found that TZDs were associated with improved kidney outcomes (reduced proteinuria or improved eGFR) compared to metformin while two observational studies found no differences between them [22-25].

Alpha glucosidase inhibitors (ACARBOSE): A multi-centered randomized study was carried out in 762 newly diagnosed drug naïve patients with T2DM. Baseline urine Albumin/Creatinine Ratio (ACR) was measured (elevated ACR ≥ 30 mg/g in 21.9% of all participants). The patients were randomized to receive either acarbose or metformin and were followed up for 48 weeks for change in ACR. It was found that there was a significant reduction in urine ACR in both the acarbose and metformin groups at 24 and 48 weeks (P<0.001). The reduction in urine ACR was greater with acarbose compared to

metformin. Neither treatment affected eGFR [26]. Acarbose is rarely used in clinical practice these days.

Insulin: A systematic review analyzed the long-term efficacy of insulin on clinical outcomes (all-cause mortality, cardiovascular mortality, death by cancer, microvascular complications). The review involved all Randomized Clinical Trials (RCT), published between 1950 and 2013, analyzing insulin vs. hypoglycemic drugs or diet/placebo in individual's ≥ 18 years with T2DM. There was no significant effect of insulin on any of the above-mentioned clinical outcomes [27].

Three classes of novel anti-glycemic drugs approved in the past 15 years include DPP-4 inhibitors, GLP-1agonistsand SGLT-2 inhibitors, which are primarily used in T2DM. Clinical trials have highlighted the safety and efficacy of these newer therapies across the spectrum of renal impairment [28-30]. Unless specifically stated, the trials are conducted in individuals with T2DM.

Dipeptidyl peptidase-4 inhibitors (DPP-4i): DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme which destroys the incretin, an endogenous GLP-1 (Glucagon LikePeptide-1) and thus increase the concentration of native GLP-1, resulting in reduction of glucose concentrations [31].

There are several published and ongoing large-scale clinical trials with cardiovascular endpoints for DPP-4i in individuals with T2DM. In terms of renal effects, experimental studies from various animal models have suggested reno-protective effects through various mechanisms independent of glucose and blood pressure reduction [32,33].

Data from the cardiovascular outcomes trial SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) showed a significant mean reduction in Urinary Albumin/Creatinine Ratio (UACR) compared to placebo after 2 years of treatment with saxagliptin, mainly driven in individuals with UACR>300 mg/g at baseline. Furthermore, even after stratifying by baseline eGFR, saxagliptin treatment was associated with a decrease in albuminuria in all categories after 2 years, with − 19.3 mg/g for eGFR>50 mL/min/1.73 m², − 105 mg/g for eGFR 30 to 50 mL/min/1.73 m² and − 245.2 mg/g for eGFR<30 mL/min/1.73 m². However, saxagliptin did not affect other renal or cardiovascular outcomes [34].

In the TECOS trial, which primarily evaluated cardiovascular outcomes with sitagliptin, renal outcomes for patient with CKD stages 1 to 3b were analyzed. There was no significant impact in either delay in CKD progression or UACR reduction compared to placebo over 4 years. Sitagliptin had no clinically significant impact on cardiovascular outcomes as well, irrespective of baseline eGFR [35].

CARMELINA trial, another randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes and high cardio-renal risk, a total of 6,979 patients were randomized to either linagliptin or placebo for a median of 2.2 years. In this study, linagliptin treatment resulted in a less frequent progression of albuminuria than placebo (35.3% vs. 38.5%). Sustained End-Stage Renal Disease (ESRD) or death due to renal failure was not statistically different among groups (linagliptin 3.9% vs. 4.4% placebo) [36].

A systematic review and meta-analysis found that DPP-4 inhibitors had renal benefits mainly by reducing the risk of development or progression of albuminuria as compared to placebo

Table 1: Renal outcomes reported for DPP4i.

PARAMETERS	SAVOR-TIMI 53 TRIAL	TECOS trial	CARMELINA trial
Type of study	Randomized control trial	Randomized control trial	Randomized control trial
Medication assessed	Saxagliptin *vs.* placebo	Sitagliptin *vs.* placebo	Linagliptin *vs.* placebo
Number of participants	16492 participants (8280 active *vs.* 8212 placebo)	14671 participants (7332 active *vs.* 7339 placebo)	6979 participants (3494 active *vs.* 3485 placebo)
Follow-up period	2.1 years	3 years	2.2 years
RESULTS			
Baseline mean eGFR (mL/min per 1.73 m^2)	72.5 (+/- 22.6)	74.9 (+/- 21.3)	54.6 (+/-25.0)
Baseline UACR (mg/g)	203.6 (79.2-848.4)	10.3 (3.5-34.6)	162 (44-728)
New onset persistent macro	2.2% *vs.* 2.8%	NA (micro: 7.8% *vs.* 7.9%)	NA
Doubling of serum creatinine	1.1 (0.89-1.36) NS	NA	0.98 (0.82-1.18) P=0.87
Progression to ESKD requiring RRT	0.7% *vs.* 0.9%, 0.90 (0.61-1.32), NS	1.4% *vs.* 1.5%	0.87 (0.69-1.10) P=0.24
Composite renal outcome	1.08 (0.88-1.32), P=0.46	NA	1.04 (0.89-1.22)
Death from any cause[a]	1.05 (0.74–1.50) P=0.79	1.01 (0.90-1.14) P=0.88	0.98 (0.84-1.13) P=0.74

Results are expressed as hazard ratios (95% confidence interval)
eGFR: estimated Glomerular Filtration Rate; UACR: Urinary Albumin/Creatinine Ratio; macro/micro: macroalbuminuria/microalbuminuria; ESKD: End-Stage Kidney Disease; RRT: Renal Replacement Therapy; NA: Not Available; NS: Not Significant
[a]: Includes renal death

or other antidiabetic agents [37].

Above results are summarized in Table 1.

Glucagon-like peptide-1 receptor agonists (GLP-1RA): GLP-1 agonists have beneficial effects on various organs including kidneys [38]. They improve insulin sensitivity, potentiate insulin secretion and contribute to glucose metabolism through a wide range of physiological actions [39].

There are no published GLP-1RA trials primarily examining renal end points. Insights into the renal impact of GLP-1RA were obtained by analyzing their dedicated cardiovascular outcomes trials.

A systematic review and meta-analysis screened the findings of 27 publications for cardiovascular mortality and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes. Seven trials, with a combined 56,004 participants, were included. Overall, GLP-1 receptor agonist treatment reduced all-cause mortality by 12% and a broad composite kidney outcome (development of new-onset macroalbuminuria, decline in estimated Glomerular Filtration Rate [or increase in creatinine], progression to end-stage kidney disease, or death attributable to kidney causes) by 17% mainly due to a reduction in urinary albumin excretion [40].

Liraglutide, a once daily GLP1 analogue was evaluated for renal outcomes in addition to cardiovascular endpoints in the LEADER trial [41]. In this randomized controlled trial, liraglutide was compared with placebo in patients with type 2 diabetes and high cardiovascular risk who were receiving usual care. A total of 9,340 patients underwent randomization, and the median follow-up was 3.84 years. It was reported that the composite renal outcome (persistent doubling of serum creatinine, persistent macro-albuminuria, ESKD and death caused by renal disease) occurred in fewer participants in the liraglutide group than in the placebo group (268 of 4,668 patients *vs.* 337 of 4,672 respectively; HR: 0.78; 95% CI: 0.67 to 0.92; P=0.003). Above benefit was mainly derived from a 26% significant risk reduction in new onset macro-albuminuria (HR= 0.74, 95% CI: 0.60 to 0.91; P=0.004) without any significant changes in eGFR [42].

ELIXA trial evaluating lixisenatide in acute coronary syndrome showed no inferiority in cardiovascular outcome, but reported lower albuminuria with treatment *vs.* placebo [43,44].

For exenatide, the EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering Trial) demonstrated a reduction in new-onset macroalbuminuria (2.8% *vs.* 2.2%; P=0.03) in persons with type 2 diabetes, 70% of whom had pre-existing CVD [45]. Bethel et al. [46] investigated the renal outcomes of EXSCEL trial and reported that a composite of 40% eGFR decline, renal replacement, renal death or new macroalbuminuria was better through the addition of exenatide in people with T2DM with a hazard ratio of 0.85 (0.73 to 0.98; p=0.027). This was predominantly due to the reduction in new macroalbuminuria.

REWIND was a multicenter, randomized, double-blind, placebo-controlled trial where persons aged 50 or above with T2DM who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1.5 mg) or placebo [47]. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes. Renal component of the composite microvascular outcome, defined as the first occurrence of new macroalbuminuria, a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy were investigated in an exploratory analysis. During a median follow-up of 5.4 years, the renal outcome developed in 848 (17.1%) participants in the dulaglutide group and in 970 (19.6%) participants in the placebo group (Hazard Ratio [HR]: 0.85, 95% CI 0.77 to 0.93; p=0.0004) [48]. The clearest effect was for new macroalbuminuria (HR: 0.77, 95% CI 0.68 to 0.87; p<0.0001) whilst non-significant effect was observed in sustained decline in eGFR and for chronic renal replacement therapy.

The results of SUSTAIN-6 clinical trial (Semaglutide and Cardiovascular outcomes in patients with T2DM) were also similar. Out of total 3,297 patients who underwent randomization, new or worsening nephropathy occurred in 62 patients (3.8%) in the semaglutide group and 100 patients (6.1%) in the placebo group (P=0.005). Progression of albuminuria occurred in 2.7% of semaglutide group compared to 4.9% of the placebo group (HR: 0.54; 95% CI: 0.37 to 0.77, P<0.001) with no significant differences in the

rate of a doubling of serum creatinine or the rate of initiation of Renal Replacement Therapy (RRT) [49].

In the AWARD-7, which is a multi-center, open label trial, participants with T2DM and moderate to severe CKD were randomly assigned to receive dulaglutide (at doses of 0.75 mg or 1.5 mg once a week) and insulin glargine. Nearly 2/3rd of study participants had an eGFR<45 mL/min/1.73 m², 30% had stage 4 CKD. At 52 weeks, eGFR was higher with dulaglutide 1.5 mg (34.0 mL/min per 1.73 m², p=0.005 vs. insulin glargine) and dulaglutide 0.75 mg (33.8 mL/min per 1.73 m²; p=0.009 vs. insulin glargine) than with insulin glargine (31.3 mL/min per 1.73 m²). Dulaglutide group had reduced decline in eGFR but there was no difference in UACR in comparison with patients receiving insulin glargine [50,51].

The most common adverse effects reported with GLP-1 agonists are diarrhea, nausea, and vomiting which are often self-limiting for most of the patients. Other rare side effects include tachyphylaxis, pancreatitis, and thyroid C-cell hyperplasia. Hypoglycemia is rare except when used in combination with insulin or insulin secretagogues [52].

In summary, data from clinical trials suggest that GLP-1RA improve albuminuria and may have protective role in DKD [53]. The mechanism might involve a direct effect of GLP-1RA in the kidneys promoting antioxidant, anti-inflammatory, and anti fibrotic effects in the diabetic kidney [54]. They also have indirect metabolic and hemodynamic actions that favorably affect major CKD risk factors namely hypertension, hyperglycemia and obesity [55,56].

However, given the fact that albuminuria is not a robust prognostic marker in DKD, whether such reductions in albuminuria translate into clinically relevant patient outcomes remains unclear. Further studies looking at dedicated renal outcomes with GLP-1RA in individuals with T2DM and more advanced CKD at baseline are required to answer this question. On that note, there are three ongoing studies evaluating kidney outcomes as primary endpoint: 1. Liraglutide on DKD (NCT01847313); 2. Lixisenatide on the Renal System (ELIXIRS) (NCT02276196); 3. The FLOW study (Effect of semaglutide versus placebo on the progression of renal impairment in subjects with T2DM and CKD) (NCT03819153).

Key trials with GLP-1 agonists are summarized in Table 2.

SGLT-2 inhibitors: Sodium Glucose Cotransporter-2 inhibitors (SGLT2i) are a novel class of glucose-lowering agents with potential renoprotective effects [57]. They work by inhibiting glucose and sodium reabsorption, by reducing tubuloglomerular feedback, which leads to reduced glomerular hyper filtration and glomerular hypertension [58,59]. Chronic hypoxia is a final common pathway to end-stage kidney disease [60]. SGLT2 inhibitors also improve renal oxygenation and decrease intra-renal inflammatory and fibrotic responses of proximal tubular cells leading to a reduction in albuminuria as well as slowing the progression of kidney function decline [61]. Glucose-independent hemodynamic effects, such as blood pressure lowering also have renoprotective action [58].

Clinical trials conducted in T2DM patients have shown that SGLT2 inhibitors can reduce relevant CV and renal adverse outcomes. These include CREDENCE, DAPA-CKD (which are the dedicated renal trials), CANVAS, and CANVAS-R, DECLARE-TIMI and EMPA-REG OUTCOME trials.

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), is a randomized, double-blind, placebo controlled, multi-center study included subjects with type 2 diabetes mellitus and diabetic nephropathy. Participants had an eGFR of 30 to <90 ml/min/1.73 m² of body-surface area, albuminuria (ACR>300 to 5000 mg/g) and received standard care including a maximum tolerated daily dose of ACE-i or ARB. They were randomized to receive either canagliflozin 100 mg once daily or matching placebo. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m²), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. By this time, 4,401 patients had undergone randomization, with a median follow-up of 2.62 years. There was a 30% relative risk reduction in primary outcome in canagliflozin group compared to placebo (Hazard Ratio: 0.70; 95% CI: 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney

Table 2: Renal outcomes reported for glucagon-like peptide-1 receptor agonists (GLP-1RAs).

Parameters	LEADER Trial	EXSCEL Trial	SUSTAIN-6 Trial	Rewind Trial
Type of study	Randomized controlled trial	Randomized controlled trial	Randomized control trial	Randomized control trial
Medicines assessed	Liraglutide vs. placebo	Exenatide ER vs. placebo	Semaglutide vs. placebo	Dulaglutide vs. placebo
Dose of the medicine	1.8 mg per day	2 mg per week	0.5 or 1 mg per week	1.5 mg per week
Number of participants	9340 participants (4668 active vs. 4672 placebo)	14,752 participants (7356 active vs. 7396 placebo)	3297participants (1648 active vs. 1649 placebo)	9901 participants (4949 active vs. 4952 placebo)
Follow-up period	3.84 years	3.2 years	2 years	5.4 years
Results				
Baseline mean eGFR (mL/ min per 1.73 m²)	80.4	76.6	NA	76.9
Doubling of serum creatinine	0.89 (0.67-1.19) P=0.43	NA	1.28 (0.64-2.58) P=0.48	NA
Composite renal outcome	0.78 (0.67-0.92) P=0.003	NA	0.64 (0.46-0.88) P=0.005	NA
Death from any cause[a]	0.85 (0.74-0.97) P=0.02	0.86 (0.77-0.98) P not tested	1.05 (0.74-1.50) P=0.79	0.90 (0.8–1.01) P=0.067

Results are expressed as hazard ratios (95% confidence interval)
eGFR: estimated Glomerular Filtration Rate (mL/min/1.73 m²); UACR: Urinary Albumin/Creatinine Ratio; ESKD: End-Stage Kidney Disease; RRT: Renal Replacement Therapy; Micro/Macro: Microalbuminuria/Macroalbuminuria; NA: Not Available; ER: Extended Release
[a]: Includes renal death

disease, a doubling of the creatinine level, or death from renal causes was lower by 34% in canagliflozin group (hazard ratio: 0.66; 95% CI: 0.53 to 0.81; P<0.001). Thus, it concluded that canagliflozin safely reduces the rate of progression of DKD and prevents Cardiovascular (CV) events in people with T2DM and DKD [62].

Another dedicated renal trial, DAPA-CKD ("A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease"), has been reported recently. This is an international, multi-center, randomized, double-blinded trial designed to evaluate the efficacy of Dapagliflozin 10mg, compared with placebo, in patients with CKD stages 2 to 4 (eGFR between 25 to 75 ml/min/1.73 m^2 of body-surface area) and elevated UACR (200 mg/g to 5000 mg/g), with and without T2DM. A total of 4,304 patients were studied. The primary composite endpoint is worsening of renal function (defined as a composite of an eGFR decline ≥ 50%, onset of ESKD and death from CV or renal cause). Over a median of 2.4 years, a primary outcome event occurred in 197 of 2,152 participants (9.2%) in the dapagliflozin group and 312 of 2,152 participants (14.5%) in the placebo group (hazard ratio: 0.61; 95% CI: 0.51 to 0.72; P<0.001). There was a statistically significant 39% Relative Risk Reduction (RRR) in this composite endpoint for the DAPA group, with a Number Needed to Treat (NNT) being 19 to prevent one event. The effect was consistent across subgroups, and importantly, the result was similar and statistically significant both in patients with T2DM (36% RRR) and without T2DM (RRR 50%). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI: 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI: 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group. The trial was halted early as independent data monitoring committee recommended stopping the trial because of efficacy [63].

Empagliflozin Cardiovascular Outcome Event Trial in T2DM patients (EMPA-REG Outcome), enrolled 7,020 patients with established cardiovascular disease and an eGFR of >30 mL/min/1.73 m^2 who were followed for a median of 3.1 years. Long-term renal effects, an analysis that was a prespecified component of the secondary microvascular outcome of the trial, were looked into and the results showed that in the empagliflozin group, there was 55% relative risk reduction of initiation of renal replacement therapy compared to placebo (0.3% vs. 0.6%) [64,65]. Empagliflozin treatment was shown to result in a relative risk reduction in new onset or worsening of nephropathy by 39%, progression to macroalbuminuria by 38%, doubling of serum creatinine by 44% [64].

The Canagliflozin Cardiovascular Assessment Study trial (CANVAS) program comprised randomized control trial comparing canagliflozin to placebo in 10,142 participants with T2DM at high cardiovascular risk (i.e., previous symptomatic coronary artery disease or age over 50 with two risk factors). Participants were followed for a mean of 2.4 years. Results showed a reduction in major cardiovascular events, heart failure, and composite renal endpoint of sustained doubling of serum creatinine, ESKD, or death from renal causes, which occurred at a rate of 1.5 vs. 2.8 per 1,000 patient-years [66]. Patients randomized to canagliflozin had a 40% relative risk reduction in a composite renal outcome of reduction in eGFR, End-Stage Kidney Disease (ESKD), or renal death (5.5 vs. 9.0 per 1,000 patient), and a 47% relative risk reduction in a composite of

doubling of serum creatinine, ESKD, or renal death (1.5 vs. 2.8 per 1,000 patient-years) compared with placebo. Renal function was also stabilized in those on canagliflozin (once the initial 3.1 mL/min/1.73 m^2 decrease in eGFR was accounted for), with a mean annual change in eGFR of +0.3 mL/min/1.73 m^2 vs. −0.9 mL/min/1.73 m^2 in those on placebo, suggesting and supporting a renoprotective effect in DKD [67].

The Dapagliflozin Effect on Cardiovascular Events (DECLARE) study, another randomized study, evaluated 17,160 patients, who were followed up for a median of 4.2 years. The effect of dapagliflozin primarily on cardiovascular outcomes when added to current background therapy in patients with T2DM (and either established CV disease, or CV risk factors) was analyzed. Secondary kidney outcomes were also compared. The study showed that renal events (>40% relative risk reduction in eGFR, end-stage renal disease, or death due to renal or CV causes) occurred in 4.3% in the dapagliflozin group compared to 5.6% in the placebo (p<0.05) group and death from any cause occurred in 6.2% and 6.6%, respectively [68].

Some commonly reported side-effects of SGLT-2i are vulvovaginal candidiasis, mycotic infections and osmotic diuresis. Rarely, diabetic ketoacidosis, acute kidney injury, bone fractures have been reported [69]. Prescribing SGLT2 inhibitors should be guided by specialists in case of T1DM or ketosis prone T2DM.

Overall, clinical trials conducted in T2DM patients have shown that SGLT2i have renoprotective benefits and can reduce renal adverse outcomes. With CREDENCE and DAPA-CKD, it is clear that improvement is not merely in numbers (like ACR) but also in hard renal outcomes, including progression to dialysis and renal death.

In view of dedicated renal trial data, US Food and Drug Administration (FDA) and EMA (European Medicines Agency) have approved canagliflozin to reduce the risk of worsening kidney function, ESKD in adults with T2DM and DKD. FDA has also granted "Breakthrough Therapy" designation to dapagliflozin for patients with chronic kidney disease, with and without Type 2 Diabetes (T2DM), to reduce the risk of kidney failure and cardiovascular or renal death. In line with this, guidelines across the world are changing for the usage of SGLT-2i in patients with chronic kidney disease [70]. The glucose-independent hemodynamic mechanisms of SGLT-2 inhibitors opened the door for extending their usage in the context of non-diabetic kidney disease as well.

Results of key clinical trials with SGLT-2i are summarized (Table 3).

Conclusion

Correction of hyperglycemia, hypertension, dyslipidemia, and lifestyle modification are the interventions that have a role in modifying the trajectory of DKD in a positive way [71].

Progression of DKD to ESKD can be delayed if glycemic control is optimal with glycosylated Hemoglobin (HbA1c) targets around 7.0%, as recommended by the American Diabetes Association (ADA) [70,71]. Given a wide variety of choices in anti-diabetic medications, it is crucial for clinicians to be aware of cardiovascular as well as renal outcomes to ensure the individualized management strategy is chosen. So far, reduction in albuminuria is confirmed with DPP-4i, GLP-1 agonists and SGLT-2i. But, albuminuria does not always correlate well with development and progression of DKD. Non-proteinuric DKD entity is increasingly recognized especially in T2DM and a

Table 3: Renal outcomes trials reported for SGLT-2i.

Parameters	Credence trial	Dapa-CKD	Empa-reg outcome trial
Type of study	Randomized control trial	Randomized control trial	Randomized control trial
Medicines assessed	Canagliflozin *vs.* placebo	Dapagliflozin *vs.* placebo	Empagliflozin *vs.* placebo
Dose of the medicine	100 mg, once daily	10 mg	10 or 25 mg
Number of participants	4401 (2202 active *vs.* 2199 placebo)	4304 (2152 active *vs.* 2152 placebo)	7020 (4687 active *vs.* 2333 placebo)
Follow-up period	2.62 years	2.4 years	3.1 years
Mean Hba1c at baseline (%)	8.3	-	8.1
Results			
Baseline mean GFR(mL/min per 1·73 m²)	56.2 +/- 18.2	43.2 +/- 12.3 (Dapa) 43.0 +/- 12.4 (Placebo)	74.2
Baseline UACR (mg/g)	927	Median: 965 Dapa group and 934 Placebo group	Micro: 29%, micro: 11%
Progression to ESKD requiring RRT	0.74 (0.55-1.00)	0.66 (0.48-0.90)	0.45 (0.21–0.97)
	P=NA	P=NA	P=0.04
Composite renal outcome	0.70 (0.59–0.82)	0.61 (0.51–0.72)	0.61 (0.53–0.70)
	P=0.00001	P<0.001	P<0.001
Death from any cause[a]	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.68 (0.57–0.82)
	P=NA	P=0.004	P<0.001

Results are expressed as hazard ratios (95% confidence interval)

eGFR: estimated Glomerular Filtration Rate; UACR: Urinary Albumin/Creatinine Ratio; ESKD: End-Stage Kidney Disease; RRT: Renal Replacement Therapy; NA: Not Available

[a]: Includes renal death

lot remains elusive regarding DKD progression including genetic factors, circulating and histopathological biomarkers.

However, dedicated renal studies with two of the SGLT-2i (Canagliflozin and Dapagliflozin) showed improvement not only in albuminuria but also in clinically relevant hard renal outcomes (doubling of serum creatinine, dialysis and renal death). It is imperative that clinicians are aware of this evolving evidence to provide maximum benefit for their patients and also to curb the economic burden related to ESKD.

There are several ongoing RCT's examining renal endpoints as primary outcome. It is an exciting arena to watch for all the physicians in general but the diabetologists and the nephrologists in particular.

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