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Role of SGLT-2 Inhibitors In Diabetic Nephropathy

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Abstract

Diabetic nephropathy refers to a set of structural and functional changes in kidneys in patients with diabetes and is a leading cause of morbidity and mortality world-wide. Sodium glucose co-transporter 2 (SGLT-2) inhibitors are a newly group of oral anti-diabetic medications having a unique mechanism of action. SGLT-2 inhibitors not only help in glycaemic control but have actions on cardiovascular mortality, renal disease progression and mortality from other causes. The reno-protective effects of SGLT-2 inhibitors are studied in patients with or without diabetes as well as kidney disease. This article focuses on literature review around evidence of beneficial actions of SGLT-2 inhibitors in terms of diabetic nephropathy.

KeyWords: Diabetes Mellitus, Diabetic Nephropathy, Proteinuria, Diabetic Kidney Disease, SGLT-2 Inhibitors, Canagliflozin, Dapagliflozin, Empagliflozin

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نبذة مختصرة

يشير اعتلال الكلية السكري إلى مجموعة من التغيرات الهيكلية والوظيفية في الكلى لدى مرضى السكري وهو سبب رئيسي للمراضة والوفيات في جميع أنحاء العالم. مثبطات ناقل جلوكوز الصوديوم 2 (SGLT-2) هي مجموعة جديدة من الأدوية المضادة للسكري عن طريق الفم والتي لها آلية عمل فريدة. لا تساعد مثبطات SGLT-2 في التحكم في نسبة السكر في الدم فحسب ، بل لها تأثير أيضًا على معدل وفيات القلب والأوعية الدموية ، وتطور أمراض الكلى ، والوفيات من أسباب أخرى. تمت دراسة التأثيرات الواقية للرينو لمثبطات SGLT-2 في المرضى الذين يعانون من مرض السكري أو بدونه وكذلك أمراض الكلى. تركز هذه المقالة على مراجعة الأدبيات حول الأدلة على الإجراءات المفيدة لمثبطات SGLT-2 فيما يتعلق باعتلال الكلية السكري.

الكلمات الرئيسية: داء السكري ، اعتلال الكلية السكري ، بيلة بروتينية ، مرض الكلى السكري ، مثبطات SGLT-2 ، كاناجليفلوزين ، داباجليفلوزين ، إمباغليفلوزين

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Introduction

Sodium glucose co-transporter 2 (SGLT-2) inhibitors are one of the newer anti-diabetic medications and are commonly used in the treatment of diabetes mellitus (DM). Over the last three years there has been significant progress in both the safety and efficacy of this class of medication. SGLT-2 inhibitors have a mechanism of action which is independent of insulin. SGLT-2 inhibitors work by blocking sodium glucose co-transporter in proximal renal tubule, hence inhibiting the reabsorption of glucose back into the blood stream. This helps in lowering blood glucose levels by excreting extra glucose in urine (Diabetes.co.uk Editor, 2019) (Hsia et al., 2017). To date the U.S food and drug administration (FDA) has approved four type of SGLT-2 inhibitors to treat type 2 diabetes mellitus (T2DM). These are Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin. There are few more types of SGLT-2 inhibitors which are being developed and are in clinical trials (*SGLT2 Inhibitors*, 2019).

Apart from regulating blood sugar levels in diabetic patients, SGLT-2 inhibitors have shown benefits beyond glycaemic control which include improving cardiovascular disease and mortality, diabetic nephropathy and heart failure in diabetics. Patients with diabetes, especially with T2DM have higher risk of cardiovascular disease, renal disease, heart failure and death. SGLT-2 inhibitors have gained attention owing to the discovery of their beneficial actions on cardiovascular disease, renal disease and mortality (Carolina, n.d.) ('Association of Cardiometabolic Multimorbidity With Mortality', 2015). Diabetes mellitus is a common condition, especially in middle east which is one of the highest regions in terms of DM indices. It is estimated that by the year 2045, the cases of DM will rise from 39 million to 67 million in Middle East and North Africa (MENA) and this will increase the diabetes expenditure to 37.1 billion USD (Shahwan et al., 2019). This article focuses mainly on the role of SGLT-2 inhibitors in diabetic nephropathy (DN).

Literature Review

Diabetic nephropathy (DN) is one of the major complications of DM and is a leading cause of renal failure and mortality in patients with T2DM (Kassab et al., 2008). DN is characterized by increased urinary albumin excretion (UAE) and progresses through micro-albuminuria then macro-albuminuria and eventually towards end stage renal disease (ESRD) (Ayodele et al., 2004). As per statistics of American Diabetes Association (ADA), 20% to 40% of patients with T2DM develop diabetic nephropathy. It is seen that microalbuminuria precedes macroalbuminuria by 5 to 10

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years interval and reducing the albuminuria offers greater renal protection and is positively proportional to renal protection (Association, 2010) (Jerums & Maclsaac, 2002).

A series of studies have shown the beneficial effects of SGLT-2 inhibitors in terms of diabetic nephropathy. These agents improve glomerular filtration, reduce production of extracellular matrix and decrease inflammation and oxidative stress within kidneys (Figure-1) (Kawanami et al., 2017).

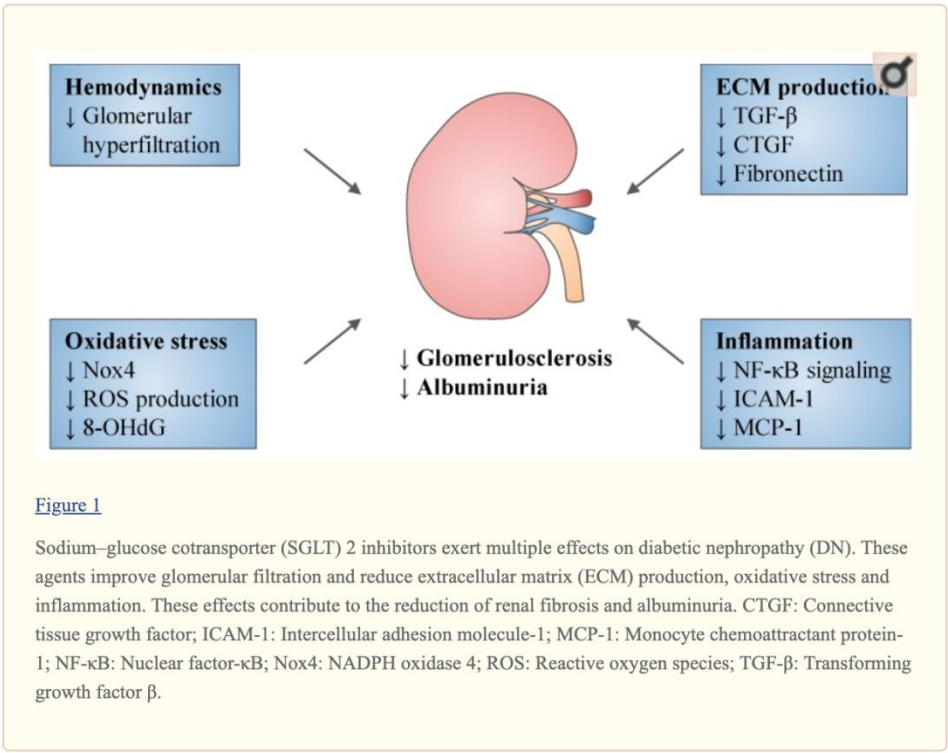

Figure 1

Sodium–glucose cotransporter (SGLT) 2 inhibitors exert multiple effects on diabetic nephropathy (DN). These agents improve glomerular filtration and reduce extracellular matrix (ECM) production, oxidative stress and inflammation. These effects contribute to the reduction of renal fibrosis and albuminuria. CTGF: Connective tissue growth factor; ICAM-1: Intercellular adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1; NF-κB: Nuclear factor-κB; Nox4: NADPH oxidase 4; ROS: Reactive oxygen species; TGF-β: Transforming growth factor β.

Figure-1: Taken from Kawanami et al., 2017- Actions of SGLT-s inhibitors on Kidneys

The first renal outcome trial to publish on Canagliflozin was CREDENCE in 2019. This trial looked at the actions of Canagliflozin vs placebo in high-risk patients with an average period of diabetes of 15.8 years and estimated glomerular filtration rate (eGFR) between 30 to < 90 ml/min of 1.73 m^2 with albuminuria (albumin creatinine ration > 300- 5000). The trial was stopped early due to its positive findings as it demonstrated a 30% relative risk reduction (RRR) in primary outcomes of doubling of serum creatinine, end stage renal disease (ESRD) and all-cause mortality. The risk of renal failure and cardiovascular events was lower in Canagliflozin group vs placebo group over a median follow up of 2.62 years (Figure-2) (Perkovic et al., 2019) (*CREDENCE*, n.d.). The results of CREDENCE trial made American Diabetes

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Association (ADA) to update " Living Standards of Medical Care" suggesting suing SGLT-2 inhibitor in T2DM with DN with albuminuria > 300mg/g and eGFR > 30 to reduce the risk of cardiovascular events, chronic kidney disease (CKD) or both (*ADA Updates Its "living" Guidelines Based on CREDENCE Trial*, n.d.).

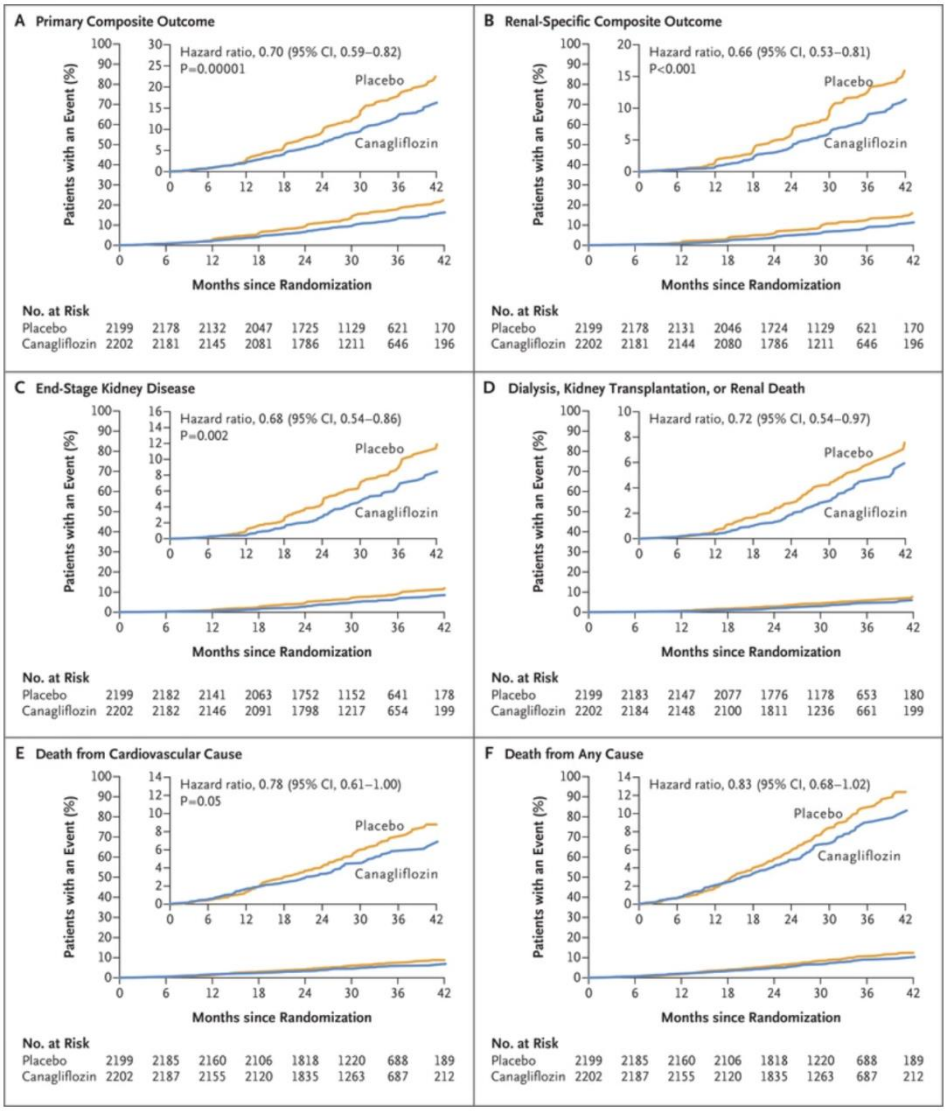

Figure-2: CREDENCE Trial - Primary Composite, Renal and Mortality outcomes (Perkovic et al., 2019).

The CANVAS program looked at data from two trials, involving a total of 10,142 patients with T2DM and high cardiovascular risk. Participants were assigned to Canagliflozin vs placebo and were followed for a mean period of 188.2 weeks. The primary outcome was composite of death from cardiovascular causes, nonfatal stroke and nonfatal myocardial infarction. The secondary outcomes were death from

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any cause, death from cardiovascular cause, progression of diabetic nephropathy and hospitalisation for heart failure. The rate of primary outcome in Canagliflozin group was lower than the placebo group i.e 26.9 vs 31.5 participants/1000 patient-years. Albuminuria progression happened less frequently in Canagliflozin group as compared to placebo (89.4 vs 128.7 participants). Also, there was more regression of albuminuria in Canagliflozin group vs placebo group (293.4 vs 187.5 participants). Overall the reduction in eGFR, need of renal replacement therapy (RRT) and death from renal causes occurred less among Canagliflozin group. (Neal et al., 2017) (Perkovic et al., 2018) (Neuen Brendon L. et al., 2018).

The EMPA-REG trial looked at the effects of Empagliflozin on renal and cardiovascular outcomes in patients with T2DM. The trails showed that Empagliflozin in addition to standard of care reduced the risk of cardiovascular death significantly by 38%, heart failure related hospitalisations by 35% and worsening of nephropathy by 39% and also the progression of nephropathy was decreased when compared to placebo in patients with established T2DM and cardiovascular risk. The incidence of worsening of nephropathy was 12.7 % in Empagliflozin group vs 18.8% in placebo group, a significant RRR of 39% (Figure-3) (Levin et al., 2020) (Wanner et al., 2016).

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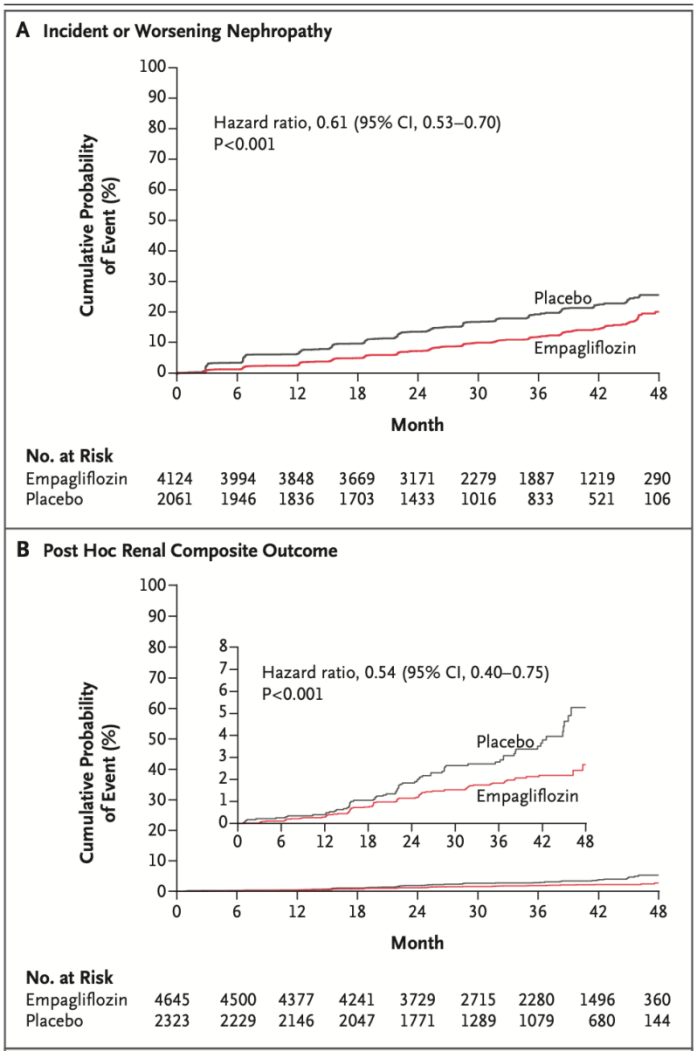

Figure-3: EMPA-REG Trial – Renal Outcomes of Empagliflozin (Wanner et al., 2016)

A web search of 42 articles which included 40 randomised controlled trials (RCTs) from various online resources compared the actions of SGLT-2 inhibitors with placebo in people with renal impairment. The review of RCTs showed an improvement in eGFR levels. SGLT-2 inhibitors were associated with preservation of serum creatinine levels , decrease in urinary albumin excretion , improvement in albuminuria and a delayed progression to macroalbuminuria, reduced risk of decline in renal impairment (Seidu et al., 2018).

The DAPA-CKD trial looked at the effects of Dapagliflozin vs placebo in a randomised double blinded trail involving 4304 adult patients, with or without type 2

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diabetes, eGFR of 25 – 75 ml/min and a urinary albumin creatinine ratio of 200 to 5000. Participants were randomised to receive Dapagliflozin 10mg daily or matching placebo. The trial was followed up for a median period of 2.4 years. The primary composite outcomes were a sustained decline in eGFR of at least 50%, ESRD or death from a renal or cardiovascular cause and occurred in 9.2% (n=197) of participants taking Dapagliflozin vs 14.5% (n=312) participants in placebo group. A summary of primary and secondary outcomes and adverse events is shown in Figure-4 (Heerspink et al., 2020).

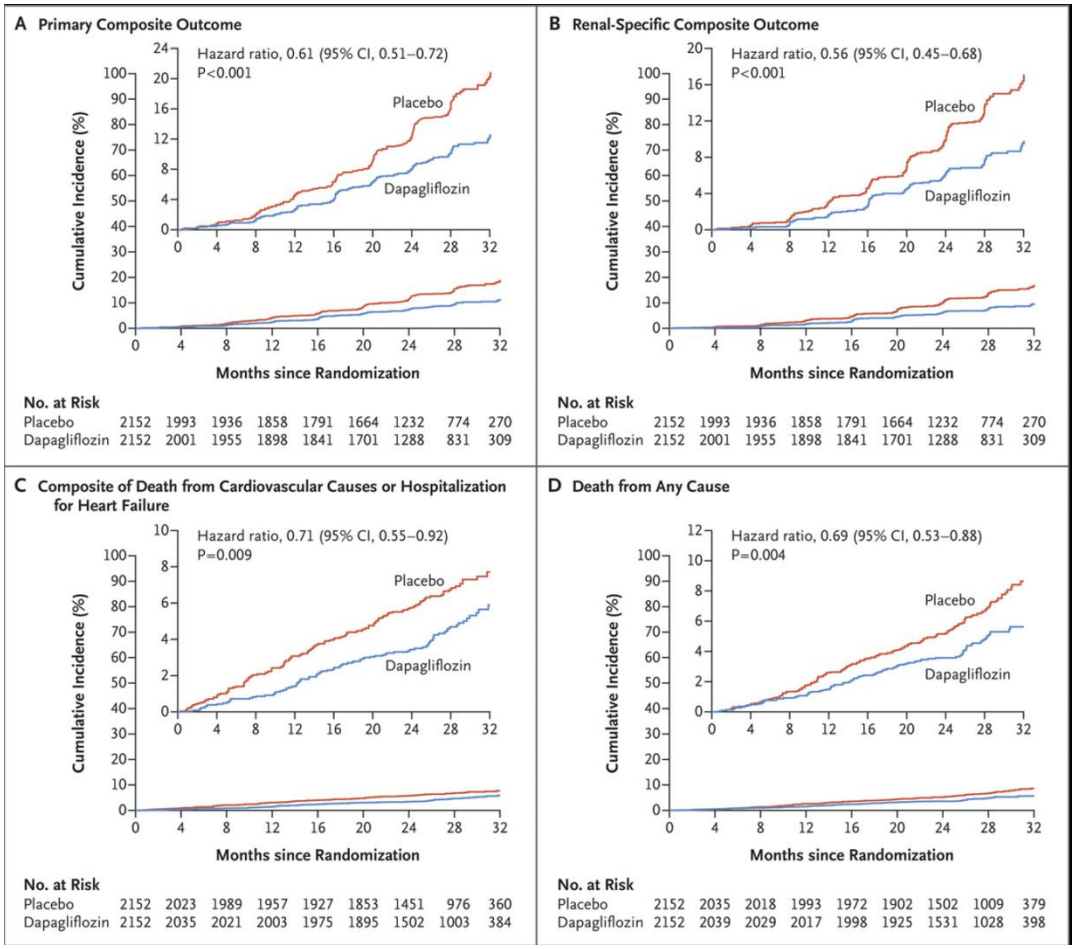

Figure-4: DAPA-CKD Trial – Primary & Secondary outcomes of Dapagliflozin (Heerspink et al., 2020)

Discussion

Diabetic nephropathy or diabetic kidney disease is a leading cause of end stage renal disease worldwide. Diabetes mellitus accounts for 30% to 50% cases of ESRD

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in US alone (Umanath & Lewis, 2018). The incidence and prevalence of DN is rapidly growing worldwide due to a rise in obesity and poor control of diabetes itself. Patients with type 1 diabetes as well as type 2 diabetes are at increased risk of mortality and cardiovascular disease (González-Pérez et al., 2020). SGLT-2 inhibitors are a newly developed group of oral anti-diabetic medications with a unique and different mechanism of action. The first SGLT-2 inhibitor "Phlorizin" was discovered from apple tree bark but given its non-selective nature and side effects its development was discontinued. The newer selective SGLT-2 inhibitors work on the sodium glucose co-transporter in proximal convoluted tubule (PCT) of kidneys preventing the reabsorption of glucose and increasing its excretion in urine (Kalra, 2014). The clinical pharmacology of various SGLT-2 inhibitors in clinical use is given in Figure-5.

Molecule	Dose range	Oral bioavailability (%)	Elimination pathway	Dose modifications
Dapagliflozin	5–10 mg once daily	78	Hepatic and renal UGT1A9	Should not be initiated in patients with eGFR <60 ml/mt/1.73 m^2 No dose adjustment in patients with eGFR >60 ml/min/1.73 m^2
Canagliflozin	100–300 mg once daily	65	UGT1A9 and 2B4	Dose limited to 100 mg once daily in patients with eGFR >45 <60 ml/min/1.73 m^2 Stopped in patients with eGFR <45 ml/min/ 1.73 m^2
Empagliflozin	10–25 mg once daily	N/a	UGT1A3, UGT1A8, UGT1A9, and UGT2B7	Dose adjustment in patients with creatinine clearance <60 ml/min Contraindicated in patients with creatinine clearance <45 ml/min No adjustment in hepatic failure
Ipragliflozin	100–300 mg once daily	65	UGT1A9 and UGT2B4	Dose limited to 100 mg once daily in patients with eGFR >45 <60 ml/min/1.73 m^2 Not recommended in patients with eGFR <45 ml/min/1.73 m^2

Figure-5: Clinical pharmacology of various SGLT-2 inhibitors in use (Kalra, 2014)

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The beneficial actions of SGLT-2 inhibitors are beyond glycaemic control and include cardiovascular benefits, renal benefits and decreased mortality. These have been proven in various clinical trials involving various SGLT-2 inhibitors. The EMPA-REG trial has shown a 11.2% of patients on Empagliflozin group had progression to macroalbuminuria as compared to 16.2% in placebo group with a 39% RRR. The doubling of serum creatinine occurred in 1.5% participants treated with Empagliflozin as compared to 2.3% in placebo group (Rabizadeh et al., 2019). The CANVAS trial also showed a 27% reduction in albuminuria progression as compared to placebo. There was a 40% reduction in composite renal outcomes including requirement of renal replacement therapy (Rabizadeh et al., 2019).

A meta-analysis of 40 RCTs in 2018 including 29,954 patients showed using SGLT-2 inhibitors more particularly Empagliflozin and Canagliflozin to patients with or without renal failure improved albuminuria significantly, delayed the rate of progression to macroalbuminuria, reduced the risk of worsening renal dysfunction, requirement of renal transplant and death from a renal cause (Seidu et al., 2018). A summary of SGLT-2 inhibitors kidney outcome trials in patients with type 2 diabetes is shown in Figure-6.

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Summary of kidney outcomes from completed placebo-controlled SGLT2 inhibitor outcome trials in patients with Type 2 Diabetes (4-9)

	CANVAS program (n = 10,142)	DECLARE-TIMI 58 (n = 17,160)	EMPA-REG outcome (n = 7020)	CREDENCE (n = 4401)
Intervention	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin
A1C inclusion criteria	A1C 7.0-10.5%	A1C 6.5-12.0%	A1C 7.0-10.0%	A1C 6.5-12.0%
Additional inclusion criteria	Preexisting cardiovascular disease if ≥30 years of age or >2 cardiovascular risk factors if ≥50 years of age	Preexisting cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease	Preexisting cardiovascular disease	eGFR of 30 to <90 mL/min/1.73m² UACR>300-5,000 mg/g Receiving a stable dose of an ACE inhibitor or ARB for ≥4 weeks prior to randomization
% with history of cardiovascular disease	65.6	40.6	99	50.4
Mean eGFR (mL/min/1.73m²)	76.5	85.3	74.1	56.2
UACR group (mg/g)	<30: 70% 30-300: 22% >300: 8%	<30: 69% 30-300: 24% >300: 7%	<30: 60% 30-300: 29% >300: 11%	<30: 1% 30-300: 11% >300: 88%
Primary outcome(s) (HR [95% CI])	3-point MACE 0.86 (0.75-0.97)	3-point MACE 0.93 (0.84-1.03)	3-point MACE 0.86 (0.74-0.99)	Primary composite kidney and cardiovascular outcome[a] 0.70 (0.59-0.82)
Key kidney outcomes (HR [95% CI])	Progression of albuminuria[b] 0.73 (0.67-0.79)	≥40% decrease in eGFR to <60, end-stage kidney disease, or kidney-related death 0.53 (0.43-0.66)	Doubling of serum creatinine accompanied by eGFR of ≤45, initiation of kidney replacement therapy, or kidney-related death 0.54 (0.40-0.75)	End-stage kidney disease, doubling of serum creatinine level, or renal death 0.66 (0.53-0.81)
	40% reduction in eGFR, kidney replacement therapy, or kidney-related death 0.60 (0.47-0.77)	End-stage kidney disease 0.31 (0.13-0.79)	Incident or worsening nephropathy 0.61 (0.53-0.70)	End-stage kidney disease 0.68 (0.54-0.86)
		End-stage kidney disease or kidney-related death 0.41 (0.20-0.82)	Initiation of kidney replacement therapy 0.45 (0.21-0.97)	Dialysis, kidney transplantation, or renal death 0.72 (0.54-0.97)

A1C, glycated hemoglobin; ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; UACR, urine albumin-to-creatinine ratio.

[a] The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73m²), a doubling of serum creatinine level, or death from renal or cardiovascular causes.
[b] On the basis of prespecified outcomes, the outcome is not viewed as statistically significant.

Figure-6: Summary of SGLT-2 inhibitors Renal outcome trials in patients with Type 2 Diabetes Mellitus (Neumiller & Kalyani, 2019).

Conclusion:

SGLT-2 inhibitors play a vital role not only in the blood glucose regulation in patients with diabetes but also offer benefits in terms of cardiovascular mortality, renal mortality, renal disease and mortality from other causes. Their actions are independent of insulin and have been shown by various trials and studies. In terms of diabetic nephropathy and diabetic kidney disease their benefits are quite evident and have shown to improve albuminuria and decline in eGFR. SGLT-2 inhibitors can be used as treatment options for diabetic nephropathy and those with worsening renal functions. The emerging data has suggested that SGLT-2 inhibitors preserve renal functions in diabetes, with or without renal impairment and also prevent further decline of renal disease and death from renal or any other cause. This novel class of anti-diabetic medicine will certainly help large number of people with diabetes in terms of glucose control, renal disease, cardiovascular disease and make these

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agents an attractive choice for add-on therapy in people not controlled on other medications.

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