

TRANSFORMING KIDNEY DISEASE OUTCOMES; THE REVOLUTIONARY IMPACT OF SGLT2 INHIBITORS

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It can be said that the utilization of inhibitors glucose sodium cotransporters as a remedy for renal ailments is a tale consisting of extraordinary happenstance. Rossetti, and associates presented a groundbreaking study in the *Journal of Clinical Investigation* in 1987¹, which introduced the notion of obstructing in the tubules of kidney, the sodium glucose cotransporter-2 (SGLT2) to stimulate glucose in urine. This mechanism could potentially reduce blood glucose levels and rectify insulin resistance. Although they experimented with an oral agent called phlorizin, it proved impractical for clinical use due to gastrointestinal degradation and the hindrance of gut SGLT1, which resulted in diarrhea. In year 1835, it was first time that phlorizin was extracted from an apple tree's bark by Petersen² then 50 years later, von Mering explored that it has characteristic to cause glucose in urine³.

During period of 1990s, Tsujihara and colleagues conducted research on multiple derivatives of phlorizin while doing job at Tanabe Seiyaku, a pharmaceutical firm in Japan.⁴ Their efforts resulted in the creation of sodium glucose cotransporter-2 (SGLT2) which can taken by mouth, which was the foremost manufactured blocker of its kind to decrease

in rats having high blood sugar the risk of diabetes⁵. it was proposed that this blocker can provide a up to date treatment approach for type 2 diabetes by Oku and colleagues in 1999⁶. This breakthrough prompted other pharmaceutical companies to develop their own SGLT2 inhibitors.⁷

Tests of cardiovascular results (CVOTs) regarding harmlessness after administrative agreement of agents that lower down blood glucose level were required by US drug and food administration, which began in 2008 as drug development continued for hyperglycemia.⁸ The first successful CVOT was the REG-EMPA OUTCOME trial.⁹ which revealed both efficacy and harmlessness of sodium glucose cotransporter-2 inhibitor for crucial harmful events related to CVS in patients with insulin independent diabetes. Furthermore, it was foremost trial for demonstrating benefits of an agent that can lower glucose in protecting from end points of kidney disease that result secondarily, such as start of development of albuminuria, serum creatinine doubling with approximate (eGFR) of lower than 45 milliliter per minute per 1.73 m², with collapse of renal system and mortality due to ailment related to renal system. Other CVOTs conducted with canagliflozin, dapagliflozin, and ertugliflozin also demonstrated same outcomes on end points related to kidney diseases resulting secondarily.¹⁰⁻¹²

These CVOT trials were followed by tests with end points of renal ailments as main results, namely EMPA-KIDNEY, DAPA-CKD, CREDENCE, further

verified these benefits. When analyzed together with heart failure trials and Cardiovascular outcomes, these trials showed that Sodium glucose cotransporter inhibitors were clearly superior to inert drugs, with a 40% lowering of harm for renal disease development with or without insulin independent diabetes in patients.

A trial known as CREDENCE¹³ registered four thousand four hundred and one patients with arteriosclerotic cardiovascular disease and insulin independent diabetes with related renal disease with albuminuria showed a considerable advantage in patients with Type-2 diabetes mellitus and CKD of canagliflozin having approximate eGFR of thirty to less than 90 milliliter per minute per 1.73m² and drastic amount of albumin in urine (urine albumin: creatinine ratio: urine albumin >33-565mg/mmol). Canagliflozin causes lowering of thirty percent in the compound danger of failure of renal system(estimated glomerular filtration rate less than fifteen milliliter per min per 1.73 m² or transplantation or dialysis intervention), level of serum creatinine doubles, or mortality by renal or cardiovascular reasons (confidence interval [CI]: 0.59-0.82 and hazard ration 0.70, 95%) Their was considerably less danger of end-stage renal ailment (by 95% CI: 0.53-0.81, 32%, HR: 0.66) in the canagliflozin cohort, as was the acute heart attack's danger , stroke, or cardiovascular death (CI: 0.67-0.95, HR: 0.68, 95%).

CKD - DAPA trial¹⁴, involving 4,304 participants, investigated the efficacy of dapagliflozin compared to placebo in people with more advanced renal disease of prolonged nature (estimated glomerular filtration rate of twenty-five to less than seventy-five milliliter per minute per 1.73 m² plus albumin in urine (uACR 22-565 mg/mmol [200-5000mg/gm]) with or without T2DM. This trial was stopped early because of profuse efficiency of the study drug. The rate of estimated glomerular filtration rate was declined, development to end-stage kidney disease was slowed, plus mortality from renal or cardiovascular ailment by Dapagliflozin. (CI: 0.51-0.72, HR: 0.61, 95%), regardless of diabetes status. In all grades of CKD, cardio renal benefits were observed (inclusive of stage 4 CKD with 624 patients in this cohort), all degrees of albuminuria, and HbA1C measurements (in diabetic individuals).

A randomized double-blind placebo-controlled test of matching vs empagliflozin placebo was EMPA-KIDNEY in six thousand six hundred and nine people having renal disease of chronic nature, with or without high blood sugar level with GFR between 20 to 45 milliliter/min: 1.73 m² with any creatinine-albumin

ratio and those with a GFR between forty-five to ninety ml/min/ 1.73 m² with an ACR at least 200. A median follow-up of two years showed that considerably less rates of CKD development and mortality by Cardiovascular reasons occurred in those treated with empagliflozin in contrast to the placebo group (13.1% vs. 16.9% respectively<0.001, hazard ratio [HR] 0.72 [0.64 to 0.82]).

SGLT2i have been proven to show enormous benefits in both cardiovascular disease and protein uric renal disease with presence or absence of diabetes. Their safety profile has also been established over nearly a decade of clinical use. (KDIGO) suggestions strongly guide sodium glucose co transporters use for patients with CKD and T2D regardless of their glycemic levels. Moreover, trials involving non-diabetic participants¹⁶ have shown similar benefits to those with T2D, indicating non-glycemic mechanisms for the kidney and cardiovascular benefits. SGLT2 inhibitors are effective and safe regardless of glycemic control, and can be used with renin-angiotensin system inhibitors or metformin. Based on this evidence, KDIGO now considers SGLT2 inhibitors to be a cornerstone of pharmacologic therapy for patients with CKD and T2D. After approximately hundred years of clinical use, the harmlessness profile of sodium glucose cotransport inhibitors is promising. The2022 KDIGO¹⁶ recommendations more strongly emphasize for patients with CKD and T2D, sodium glucose cotransporter inhibitors should be used, despite of high blood sugar level. Many Sodium glucose cotransport inhibitors¹⁶ trials comprised of subclasses of people not having diabetes, who showed same advantages like with type two diabetes mellitus and rising proof bolsters up Nonglycemic mechanisms cardiovascular and kidney advantages. Based on this evidence, KDIGO considers SGLT2i as understructure of pharmaceutical intervention for patients with CKD and T2D.

Key words: SGLT2 inhibitors, chronic kidney disease, cardiovascular

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