Emerging data from EMPA-KIDNEY study

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SGLT2 inhibitors, also called gliflozins or flozins, were first introduced into practice as glucose-lowering agents. This medication class modulate sodium-glucose transport proteins in renal tubules, thus preventing glucose reabsorption from glomerular ultrafiltrate. Several flozins were approved for managing adult patients with type 2 diabetes mellitus (T2DM) adjunct to diet and exercise. However, it soon emerged that these agents also have appeared to have several nonglycemic benefits, including a reduction in risk of cardiovascular diseases and a delay in the progression of kidney disease in patients with T2DM. This triggered several trials aiming to further investigate the possible cardioprotective and renoprotective effects of SGLT2 inhibitors (Figure 1).

The EMPA-KIDNEY trial

The EMPA-KIDNEY trial was initiated, designed, conducted, and analyzed by the University of Oxford. The trial was envisaged in 2016 and registered in 2018. The trial was designed to assess the effects of SGLT2 inhibition in a broad range of patients with chronic kidney disease (CKD) at risk of progression, including those with and without DM. The target population were adults with glomerular filtration rate (GFR) between 20 and 45 mL/min/1.73m^2 estimated with CKD-EPI equation or between 45 and 90 mL/min/1.73m^2 with urinary albumin to creatinine ratio of ≥200mg/g (≥22.6mg/mmol). Patients with polycystic kidney disease or transplanted kidneys were excluded, but intolerance of a RAS inhibition was not an exclusion criterion. The primary outcome was a composite of cardiovascular death and kidney disease progression, defined as end-stage kidney disease, a sustained decrease in eGFR to <10 mL/min/1.73 m^2, a sustained decline in eGFR of ≥40% from baseline, or death from renal causes.

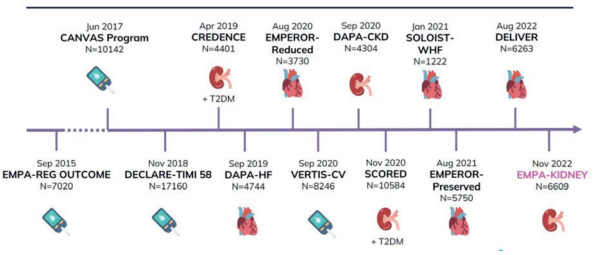

Figure 1.
Completed large placebo-controlled SGLT2-inhibitor trials

There were 6609 patients randomly assigned to receive empagliflozin (10mg once daily) or a matching placebo. The mean age was 64 years, about two-thirds (67%) were men, 56% of patients had DM (predominantly type 2), 27% reported a history of heart disease, and 85% were on a RAS inhibitor. Mean eGFR was 37.4mL/min/1.73m^2 and one-third of patients had eGFR <30mL/min/1.73m^2. The median follow-up time was two years. The adherence to study treatment was excellent, even though the COVID-19 pandemic significantly interfered with face-to-face visits during the trials conduct.

The primary composite outcome occurred in 13.1% of patients on empagliflozin and 16.9% on placebo. The study drug significantly reduced the risk for kidney disease progression by 28%, regardless of diabetes, level of eGFR, and RAS inhibitors use. Clear evidence of benefit in patients

with an eGFR <30mL/min importantly expanding understanding of how these drugs work in this previously underinvestigated group of patients. In tertiary slope analyses, empagliflozin slowed the chronic rate of eGFR decline by about half compared to the placebo (Figure 2). Patients with higher levels of albuminuria appeared to experience large benefits. There was less information on the primary outcome in patients with low levels of albuminuria, but eGFR slope analyses suggested kidney benefits are predicted for even those at lower risk of CKD progression. All-cause hospitalizations were also significantly reduced in the empagliflozin group. Secondary cardiovascular endpoints were limited by low power (due to lower than expected event rates).

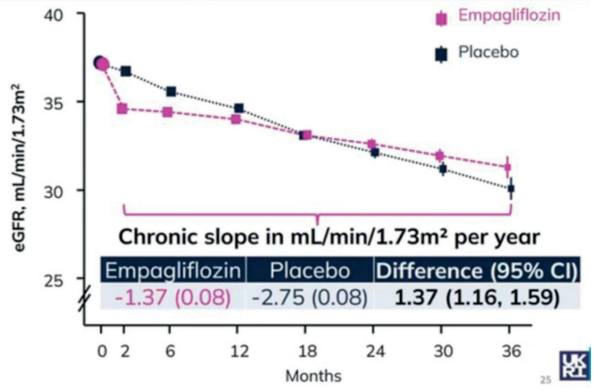

Figure 2.
The annual rate of change of eGFR with empagliflozin and placebo

Empagliflozin was generally well tolerated in this trial. The rate of adverse events, which included urinary tract infection, hyperkalemia, acute kidney injury, and lower limb amputation, did not differ significantly between allocated treatment groups. The know effect on ketoacidosis was observed but event rates were exceedingly low (6 vs 1 events). The Steering Committee has decided to continue follow up of participants (observational only) for an additional 2 years to estimate the full effect of 2 years of treatment with empagliflozin over 4 years.

Meta-analysis of large placebo-controlled trials

As the EMPA-KIDNEY trial was closing, the trialists formed a team with members of other SGLT2-inhibitors-related trials, the SMART-C consortium, to perform a 2-stage trial-level meta-analysis of 13 large (>500 participants/arm) placebo-control trials conducted in the last seven years. The trials included in the analysis were CANVAS, CREDENCE, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-CKD, DAPA-HF, SOLOIST-WHF, DELIVER, DECLARE-TIMI, VERTIS-CV, SCORED, EMPA-REG OUTCOME and EMPEROR-Preserved. The main aim of this collaborative analysis was to compare the effects of SGLT-2 inhibitors on kidney disease progression outcome, which was standardized to 50% sustained eGFR decline from randomization, in patients with and without diabetes.

A total of 90,413 participants were included and 18% of them did not have diabetes. Median follow-up ranged from 0.8 to 4.2 years. Over 2000 participants had a kidney disease progression outcome, including 450 without diabetes. The results demonstrated an impressive reduction of risk for renal disease progression by 40%, regardless of the presence of diabetes or underlying primary kidney disease. Furthermore, SGLT2 inhibitors demonstrated an overall 27% risk reduction for acute kidney injury and 23% risk reduction for cardiovascular death or hospitalization for heart failure, regardless of the presence of diabetes. This meta-analysis also confirmed a favourable safety profile for investigated SGLT2 inhibitors, with acknowledged risks for ketoacidosis (and perhaps lower limb amputation), which are substantially outweighed by the benefits in terms of attenuating cardiovascular risk, kidney disease progression and acute kidney injury prevention (Figure 3).

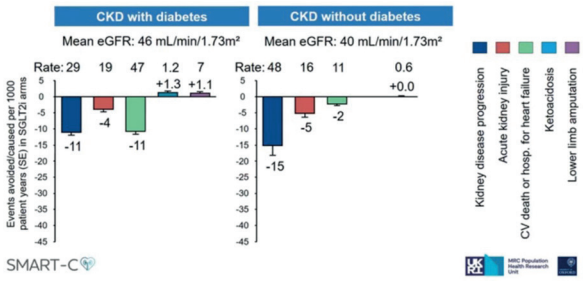

Figure 3.
Predicted absolute effects with SGLT2-inhibitors therapy per 1000 patients/years

Written by Jasna Trbojevic-Stankovic.
The speaker approved the content.

KEY POINTS

1 Empagliflozin reduced the primary composite endpoint of kidney disease progression or cardiovascular death versus placebo by 28%, with consistent findings irrespective of preexisting cardiovascular disease, presence of diabetes and eGFR level (to at least 20 mL/min).

2 Empagliflozin slowed chronic eGFR decline in all albuminuria subgroups.

3 Empagliflozin was well-tolerated and exhibited a safety profile in CKD which is similar to that observed in other studied populations.

4 SGLT2 inhibitors safely reduce the risk of kidney disease progression and acute kidney injury, irrespective of diabetes status, underlying primary kidney disease, or level of eGFR.

Further readings

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3. Levey AS, Gansevoort RT, Coresh J, et al. Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD: A Scientific Workshop Sponsored by the National Kidney Foundation in Collaboration With the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis.* 2020;75(1):84-104. doi:10.1053/j.ajkd.2019.06.009
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5. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400(10365):1788-1801. doi: 10.1016/S0140-6736(22)02074-8.