SGLT2 inhibitors for evidence-based cardiorenal protection in diabetic and non-diabetic chronic kidney disease: A comprehensive review by EuReCa-M and ERBP Working Groups of ERA

Speaker:
Patrick Mark,
United Kingdom

Panellists:
Evangelia Dounousi,
Greece

Panellists:
Sokratis Stoumpos,
United Kingdom

Moderator:
Pantelis Sarafidis,
Greece

Sodium-glucose transport protein 2 inhibitors (SGLT2i) are novel oral antihyperglycemic agents which have swiftly changed the landscape not only of diabetes care but also among several other large patient populations. The observed cardiovascular and renal benefits of these therapeutics in clinical trials have led to a revolution in cardiorenal protection, even regardless of the presence of diabetes. Their ability to improve kidney outcomes has been an eagerly awaited breakthrough in the renal community ever since the introduction of the renin-angiotensin-aldosterone (RAAS) blockade. These striking developments prompted the European Renal Association working groups for Renal and Cardiovascular Medicine (EuReCa-M) and European Renal Best Practice (ERBP) to publish a comprehensive review addressing the crucial issues related to cardiorenal benefits of SGLT2 inhibition in chronic kidney disease (CKD).

The emergence of SGLT2 inhibitors

Diabetic kidney disease (DKD) is the major cause of CKD worldwide with diabetes affecting up to 40% of people with CKD. Given the growing prevalence of diabetes and the global population trend of ageing, the number of DKD patients is expected to further increase in the following decades. This population exhibits an increased risk of cardiovascular events and mortality that is exponentially related to the loss of glomerular filtration rate or rising proteinuria. Initial efforts to reverse this trend with the use of ACE inhibitors and ARBs yielded rather moderate results. Several novel hypoglycaemic agents that have been introduced over the last years also insufficiently contributed to improving renal and cardiovascular outcomes in this group of patients. The first compelling results in this area have been achieved in the clinical trials with SGLT2 inhibitors canagliflozin, empagliflozin and dapagliflozin. Besides demonstrating superiority over placebo in improving glycaemic control in type 2 diabetes mellitus (T2DM), all three consistently reduced cardiovascular risk, while canagliflozin and dapagliflozin also improved renal outcomes in patients with established DKD in the CREDENCE and DAPA-CKD trials. Further breakthrough was seen with the EMPA-KIDNEY trial which revealed salutary effects of empagliflozin on renal function in a broad range of CKD patients even without T2DM. This without a doubt established all three currently available SGLT2 inhibitors as effective treatment options to preserve renal function among patients with and without T2DM. Nevertheless, a recent meta-analysis of SGLT2i trials went even further. After analysing 13 trials involving over 90,000 participants, of whom 17.3% were without diabetes, it concluded that compared to placebo SGLT2i reduced the risk of kidney disease progression by 37% with similar relative risk, regardless of the presence of diabetes, primary kidney disease or kidney function. They also reduced the risk of cardiovascular death, but not of non-cardiovascular death. The safety profile of SGLT2i has also been a much-debated issue. They seem to be associated with a doubled risk of ketoacidosis in patients with diabetes although the absolute risk is small. Besides the recognized excess risk of mycotic genital infections, there is no overall increased risk of other safety outcomes with these agents, including serious urinary tract infections, amputations, and fractures. Therefore, the absolute harms of SGLT2i in patients with and without diabetes are definitely lower than the substantial absolute benefits, particularly in patients with CKD, and especially those without diabetes.

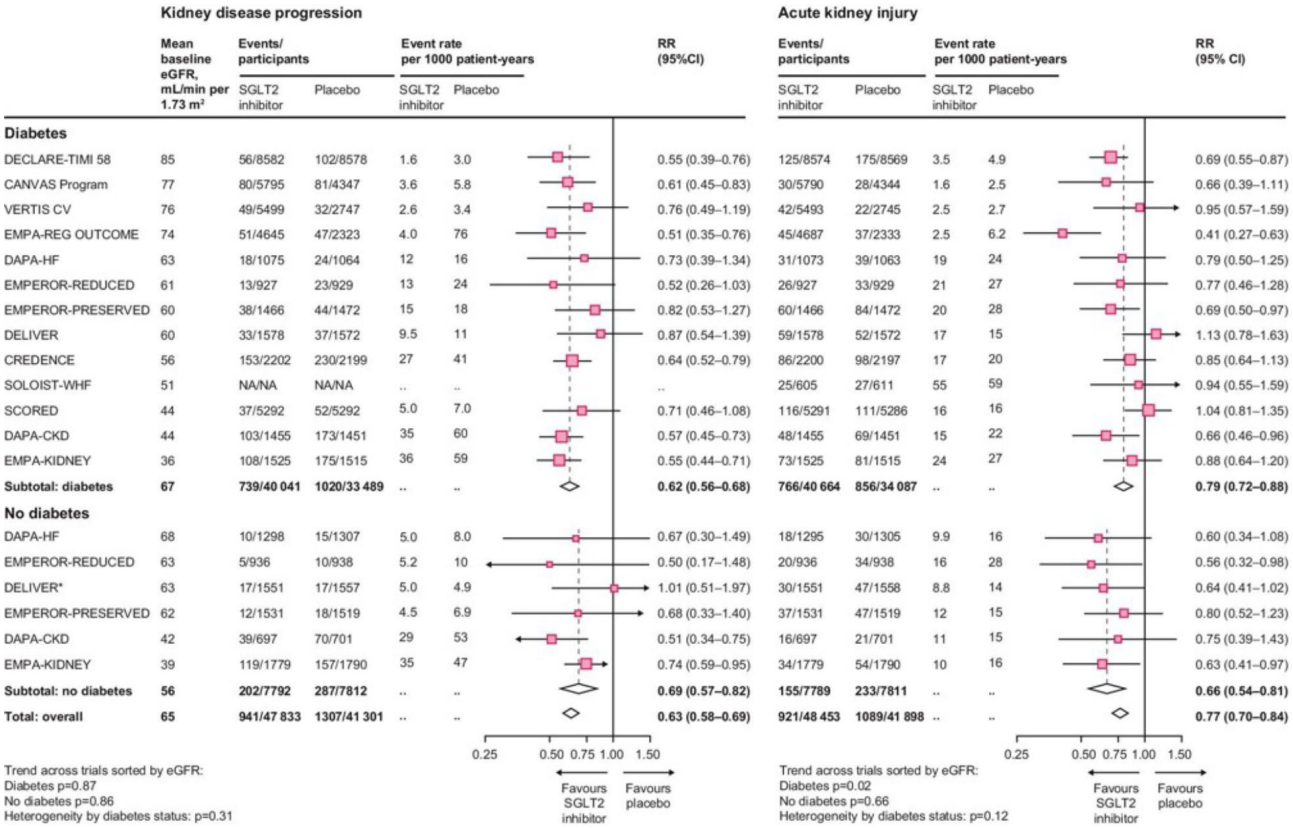

Figure 1.
Effect of SGLT2i on kidney disease progression and acute kidney injury outcomes by diabetes status (Mark et al. *Nephrol Dial Transplant.* 2023;gfad112).

Current recommendations for the use of SGLT2i in CKD

The good performance and favourable safety profile of SGLT2i led to their prompt implementation in the official guidelines. In 2018 the Canadian Diabetes Association recommended their use in CKD patients with eGFR>30mL/min/1.73m^2 and T2DM. European Society of Cardiology soon followed and included SGLT2i as a recommended glucose-lowering treatment in patients with T2DM and cardiovascular disease in the 2019 revised guidelines. In the same year, the EuReCa-M and DIABESITY working groups of the ERA-EDTA recommended SGLT2i for patients with T2DM and CKD who failed to achieve target HbA1c with metformin or for whom metformin was contraindicated or not tolerated. Last year KDIGO published an updated guideline on diabetes management in CKD establishing SGLT2i as a first-line treatment option for patients with T2DM and CKD with an eGFR≥20mL/min/1.73m^2. Concurrently, the National Institute for Health and Care Excellence in the UK recommended dapagliflozin as an option for treating CKD in addition to RAAS blockade in patients with T2DM or albuminuria. The UK Kidney Association guidelines suggest expanding this recommendation to all members of the class. Based on the recent trials, future recommendations might introduce SGLT2i for certain patients with glomerular disease.

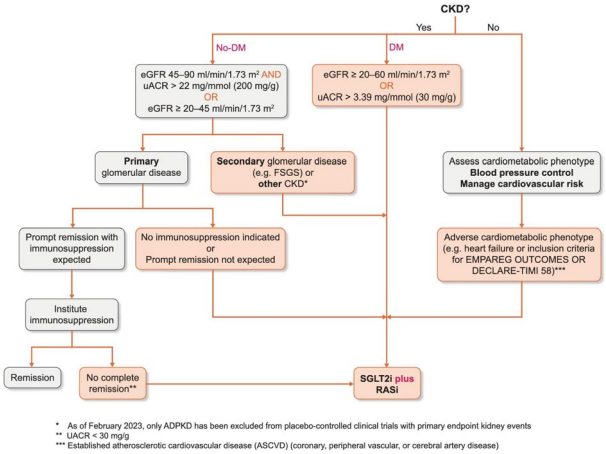

Figure 2.
Proposed algorithm for SGLT2i use in CKD patients (Mark et al. *Nephrol Dial Transplant.* 2023;gfad112).

NEPHROLOGY EDUCATION PORTAL

Specific renal patient groups for future considerations

Despite the growing list of indications for SGLT2i use in various patient groups including the CKD population, dialysis and transplant patients remain under investigated in this regard. Given the well-known enhanced cardiovascular risk in the dialysis population, these patients might significantly benefit from this drug class. On the other hand, it is dubious whether there are pathophysiological grounds to expect the cardioprotective effect of this therapy in anuric patients as it primarily relies on natriuresis. Another major limitation of SGLT2i use is insufficient safety data which are lacking in both the dialysis and the transplant settings. In the transplant population, their employment is limited by the context of a solitary kidney, abnormal genitourinary anatomy and concurrent immunosuppression predisposing the patients to urinary infections. Furthermore, they might be best avoided in the immediate posttransplant period, when polyuria is common, due to their natriuretic and diuretic effect. Nevertheless, several observational trials suggest that SGLT2i are safe in transplanted diabetic patients, thus paving the way for further investigation of whether they could improve cardiovascular and graft survival. The RENAL LIFECYCLE Trial which is currently underway is planning to recruit up to 1,500 patients with advanced CKD, dialysis patients with preserved diuresis and transplanted patients with eGFR≤45 mL/min/1.73m^2 at least 6 months after transplantation to assess reno- and cardioprotective efficacy and safety of dapagliflozin. The follow-up period is set at 30 months and the results are expected in 2027 to, hopefully, provide insight into these sensitive patient groups.

KEY POINTS

1. CKD management has seen little progress since the introduction of RAAS blockade as the standard of care.
2. SGLT2 inhibitors are a novel class of drugs with the potential to improve outcomes in the CKD population.
3. EuReCa-M and ERBP working groups of ERA have comprehensively explored evidence for cardiorenal protection of these agents in diabetic and non-diabetic CKD populations in a recently published review.
4. Dialysis and transplant populations should be more thoroughly investigated for the safety and possible benefits of SGLT2i.

Written by: Jasna Trbojevic-Stankovic.
The author reviewed and approved the content

Further readings

1. Mark PB, Sarafidis P, Ekart R, et al. SGLT2i for evidence based cardiorenal protection in diabetic and non-diabetic chronic kidney disease: a comprehensive review by EuReCa-M and ERBP working groups of ERA. *Nephrol Dial Transplant.* 2023;gfad112. doi:10.1093/ndt/gfad112
2. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816.
3. 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)02074-8Rossing P, Anker SD, Filippatos G, et al. Finerenone in Patients with Chronic Kidney Disease and Type 2 Diabetes by Sodium-Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis. Diabetes Care. 2022;45(12):2991-2998. doi:10.2337/dc22-0294.
4. McQuarrie EP, Gillis KA, Mark PB. Seven suggestions for successful SGLT2i use in glomerular disease - a standalone CKD therapy?. *Curr Opin Nephrol Hypertens.* 2022;31(3):272-277. doi:10.1097/MNH.0000000000000786.