Implementation, not hesitation, for sodium glucose co-transporter-2 inhibition as foundational therapy for chronic kidney disease

Despite the increasing burden of ill health attributable to chronic kidney disease, appropriate pharmacotherapy has been inadequate. Based on trials in the 1990s and 2000s,[1] guidelines recommend renin angiotensin system (RAS) inhibition to reduce progression of chronic kidney disease and its associated cardiovascular risk. However, the global burden of chronic kidney disease continues to increase. Furthermore, data from the US CURE-CKD registry highlights that uptake of chronic kidney disease management strategies is low, with only around 21% of patients prescribed RAS inhibitors 2006-2017[2].

Largely unexpectedly, evidence that sodium glucose co-transporter-2 (SGLT2) inhibitors might substantially slow progression of chronic kidney disease in people with type 2 diabetes **[A: type 2 diabetes?]** first emerged in 2015 from the seminal EMPA-REG OUTCOME trial.[3,4] Now, in *The Lancet*, the Nuffield Department of Population Health Renal Studies Group and the SGLT2 Meta-Analysis Cardio-Renal Trialists' Consortium report an updated meta-analysis of 13 placebo-controlled trials of SGLT2 inhibition in type 2 diabetes, stable heart failure**]**, and chronic kidney disease.[5] Data were incorporated from 90 413 people, with more than 15 000 people without diabetes, including 4967 patients without diabetes in chronic kidney disease trials. Mean age of the trial populations ranged from 62 to 72 years, and 23–45% of participants were women. Results of the meta-analysis comprehensively show that SGLT2 inhibitors meaningfully effect robust kidney endpoints, including a standardised, composite definition of kidney disease progression applied to all trials. Compared with placebo, allocation to an SGLT2 inhibitor reduced the risk of kidney disease progression by 37% (relative risk [RR] 0·63, 95% CI 0·58–0·69) and near identical kidney benefits in those with or without diabetes were noted. The consistent magnitude of benefit on the progression of kidney disease across the populations recruited, including trials specific to chronic kidney disease, suggests SGLT2 inhibition should be a foundational therapy for chronic kidney disease including in patients without diabetes. Furthermore, SGLT2 inhibition reduced the risk a composite outcome of cardiovascular death or hospitalisation for heart failure by 23% (RR 0·77, 0·74–0·81) compared with placebo, which is particularly pertinent as the risk of these events increases as estimated glomerular filtration rate (eGFR) decreases.[6] Concerns around acute kidney injury risk with SGLT2 inhibition based on theoretical risk of volume depletion have also been rebuffed, with SGLT2 inhibition being shown to protect against acute kidney injury in the trials, with risk lowered by 23% (RR 0·77, 0·70–0·84). In people without diabetes, the authors observed no excess risk of ketoacidosis or lower limb amputation with SGLT2 inhibitors, and such outcomes were minimally increased in people with diabetes, such that benefits substantially exceeded harms.

This meta-analysis is expected to change chronic kidney disease guidelines with its robust findings on the benefits of SGLT2 inhibition in a wide range of patients with chronic kidney disease, including many without diabetes, although outstanding questions remain. For instance, is there a threshold of albuminuria at initiation of therapy below which SGLT2 inhibition does not show benefits in renal (or other) outcomes? The EMPA-KIDNEY trial recruited more than 1000 participants with a urinary albumin to creatinine ratio of less than 30 mg/g, and should help address this unknown.[7] Additionally, no robust data are available on the safety and benefits of this class in end-stage kidney

disease, nor on the effects on cardiovascular and kidney outcomes in type 1 diabetes. Further work to elucidate the mechanisms by which SGLT2 inhibition conveys kidney benefits is important, given that these mechanisms must be largely or completely independent of the glucose lowering actions. Mechanistic results to date suggest the importance of both haemodynamic perturbances[8] and loosely defined cellular stress pathways,[9] however further research into mechanisms should improve pathogenic understanding of cardiorenal diseases and inform future preventative methods **[A: sentence ok as edited?]**.

In many of the included trials, use of RAS inhibitors as antihypertensive and /or kidney protective agents was widespread, for example, in around 80% of participants in both groups in EMPA-REG and 98% of participants in DAPA-CKD.[3,10] However, unlike RAS inhibition, SGLT2 inhibitors do not require dose titration for the prevention of chronic kidney disease progression and do not potentiate hyperkalaemia.[11] Given the magnitude of benefit of SGLT2 inhibitor on kidney progression and their easier dosing regimens with no titration required, earlier prescription of SGLT2 inhibition should be considered, either before or in parallel to RAS inhibitor initiation and in preference to prolonged dose titration of RAS inhibitors, analogous to recent opinions in heart failure.[12]

In addition to the headline results, this new meta-analysis indicates comprehensive benefit with SGLT2 inhibition across a spectrum of primary glomerulonephritides, most notably IgA nephropathy. Thus, early instigation of SGLT2 inhibitors might be in order irrespective of chronic kidney disease subtype (with the exception of polycystic kidney disease, not studied in the trials). Nevertheless, the need to diagnose specific primary renal diseases remains. For example, biopsy diagnosis helps identify patients who might require specific targeted therapy for glomerular disease in addition to SGLT inhibition and RAS inhibition, and might benefit from the chance to participate in clinical trials of novel drugs.

Nephrologists have long-awaited the expansion of evidence-based therapies to slow the overall global increase in kidney failure, which is detrimental to length and quality of life, and places substantial financial burden on health-care systems. Nephrologists should now work with and empower primary health-care providers to ensure that SGLT2 initiation is implemented as a foundational therapy for chronic kidney disease, with early initiation in individuals at risk of chronic kidney disease progression to minimise the risk of kidney failure and its associated cardiovascular complications. The robust cardiorenal benefits now being observed were not widely predicted when the first SGTL2 inhibitors were being trialled (appendix), showing once again the importance of randomised trials and scientific humility in medicine. Ongoing trials with SGLT2 inhibitors suggest their clinical reach might expand further.

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*Patrick B Mark, *Naveed Sattar*
naveed.sattar@glasgow.ac.uk
School of Cardiovascular and Metabolic Health, College of Medical and Veterinary Sciences, University of Glasgow, Glasgow G12 8TA, UK (PBM, NS)

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