The emerging pillars of chronic kidney disease: no longer a bystander in metabolic medicine

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ABSTRACT

Chronic kidney disease (CKD) represents an enormous healthcare burden, the management of which has been stagnant for the last couple of decades, with blockade of the renin–angiotensin–aldosterone system (RAAS) the most potent tool available to retard kidney disease progression. In the new cardiometabolic era, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as forerunners in addressing combined cardiorenal risk. This review summarises the evidence for SGLT2i use in diabetic and non-diabetic CKD and examines the risk:benefit profile in this population. Novel non-steroidal mineralocorticoid receptor antagonists are also considered as an emerging pillar of CKD management, and their role in optimising the cardiorenal health of patients with diabetic kidney disease is discussed.

Introduction

Chronic kidney disease (CKD) represents a major health burden, with annual costs to the NHS exceeding £1.45 billion.[1] Individuals with type 2 diabetes mellitus and CKD have a high risk of cardiovascular disease (CVD), and are at greater risk of dying from cardiovascular (CV) complications than progressing to end-stage kidney disease (ESKD).[2] Even in the absence of diabetes, albuminuria confers a higher rate of CKD progression and is an independent risk factor for CVD.[3]

In the early 2000s, large trials of renin–angiotensin–aldosterone system (RAAS) inhibitors[4,5] demonstrating reductions in proteinuria and progression to ESKD shaped what was to become the gold standard of care in proteinuric CKD for the next 20 years. Anti-fibrotic drugs, aiming to target the final common pathway in CKD, yielded disappointing results in clinical trials.[6] Newer anti-diabetic agents, such as GLP-1 receptor agonists, show reduction in albuminuria, but no translation to hard clinical endpoints such as ESKD or renal death.[7] So when CV safety trials of the novel-acting, sodium-glucose cotransporter-2 inhibitors (SGLT2i) demonstrated apparent improvements in renal outcomes in addition to superior CV results,[8–10] the nephrology community waited impatiently for results of renal-dedicated SGLT2i trials, and were not disappointed.

Here, we summarise three SGLT2i trials that have evolved CKD management (all of which were terminated early on the grounds of overwhelming efficacy) and the emergence of novel mineralocorticoid receptor antagonists (MRAs) in DKD.

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SGLT2i in diabetic kidney disease (DKD)

Three large randomised controlled trials (RCTs) provide the evidence for SGLT2i as cardiorenal-protective agents in a DKD population (Table 1). The CREDENCE trial enrolled exclusively patients with T2DM and demonstrated a 30% reduction in the primary composite outcome of ESKD, doubling of creatinine or death from renal/CV cause.[11] DAPA-CKD[12] and EMPA-KIDNEY[13] additionally included non-diabetic participants and reported primary outcome risk reductions of 39% and 28%, respectively. Due to the reduced filtration of glucose when eGFR <45 ml/min, the HbA1c lowering effect is lost; however, subanalyses in low eGFR groups demonstrate equivalent cardiorenal benefits to those with higher eGFRs, indicating that cardiorenal benefits are independent of any glucose-lowering effect.

Key points

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) significantly reduce the risk of renal progression, cardiovascular death and hospitalisation for heart failure and are now considered to be a gold standard treatment in the management of proteinuric chronic kidney disease (CKD).

SGLT2i-derived cardiorenal benefit is equivalent in diabetic kidney disease (DKD) and non-diabetic, proteinuric CKD.

The glucose-lowering effects of SGLT2i are lost at lower eGFR (<45 ml/min/1.73m^2) but cardiorenal benefits persist.

The safety profile of SGLT2i means their risk:benefit ratio is highly favourable even in low eGFR groups, but all prescribers should be alert to the increased risk of ketoacidosis and have a low threshold for blood ketone testing during illness episodes.

Finerenone, a non-steroidal mineralocorticoid receptor antagonist (MRA), has demonstrated improved cardiovascular and renal outcomes in patients with DKD.

KEYWORDS: SGLT2i, MRA, CKD, diabetes, cardiovascular

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Table 1. Summary of randomised controlled trials of SGLT2i and finerenone in CKD

Trial Drug name Size	Key inclusion criteria	Median follow-up (yrs)	% T2DM	Mean eGFR (SD)	Median uACR mg/g	Key findings	NNT
SGLT2i trials in CKD							
CREDENCE[10] Canagliflozin n = 4,401	> T2DM > eGFR 30–90 > uACR 300–5,000 mg/g > Max tolerated RAASi	2.6	100	56 (18)	927	30% ↓ ESKD, doubling of sCr or death from renal/CV cause (HR 0.70; CI 0.59–0.82) Secondary outcome: 31% ↓ HHF or CV death (HR 0.69; CI 0.57–0.83)	22
DAPA-CKD[11] Dapagliflozin n = 4,304	> eGFR 25–75 > ACR 200–5,000 mg/g > Max tolerated RAASi	2.4	68	43 (12)	949	39% ↓ ESKD, sustained >50% eGFR decline or death from renal/CV cause (HR 0.61; CI 0.51–0.72) Secondary outcome: 29% ↓ HHF or CV death (HR 0.71; CI 0.55–0.92)	19
EMPA-KIDNEY[13] Empagliflozin n = 6,609	> eGFR 20–45, OR > eGFR 45–90 with uACR ≥200 mg/g	2.0	46	37 (14)	329	28% ↓ ESKD, sustained >40% eGFR decline or sustained decrease in eGFR to <10 ml, death from renal/CV cause (HR 0.72; CI 0.64–0.82)	26
MRA trials in CKD							
FIDELIO-DKD[20] Finerenone n = 5,734	> T2DM, K<4.8 mmol/L > Max tolerated RAASi > eGFR 25–60 + ACR 30–300 mg/g + DR > eGFR 25–70 + ACR 300–5,000 mg/g	2.6	100	44 (13)	852	18% ↓ kidney failure, sustained >40% eGFR decline, renal death (HR 0.82; CI 0.73–0.93) Secondary outcome: 14% ↓ CV death, NF-MI, HHF, NF-CVA (HR 0.86; CI 0.75–0.99)	29
FIGARO-DKD[19] Finerenone n = 7,437	> T2DM, K <4.8 mmol/L > Max tolerated RAASi > eGFR 25–90 + ACR 30–300 mg/g > eGFR >60 + ACR 300–5,000 mg/g	3.4	100	68 (22)	308	13% ↓ CV death, NF-MI, HHF, NF-CVA (HR 0.87; CI 0.76-0.98) Secondary outcome: 13% ↓ kidney failure, sustained >40% eGFR decline, renal death (HR 0.87; CI 0.76–1.01)	47
FIND-CKD Finerenone	> Non-diabetic on max tolerated RAASi > eGFR 25–90, ACR 200–3,500 mg/g, K <4.8 mmol/L	*In recruitment, results to be announced 2026*					

CI = confidence interval, CV = cardiovascular, DR = diabetic retinopathy, eGFR = estimated glomerular filtration rate, ESKD = end stage kidney disease, HHF = hospitalisation for heart failure, HR = hazard ratio, K = potassium, NF-CVA = non-fatal cerebrovascular accident, NF-MI = non-fatal myocardial infarction, NNT = number needed to treat (to prevent one primary outcome event), SCr = serum creatinine, SD = standard deviation, RAASi = renin-angiotensin-aldosterone system inhibitor, T2DM = type 2 diabetes mellitus, uACR = urinary albumin creatinine ratio.

SGLT2i in non-diabetic CKD

DAPA-CKD and EMPA-KIDNEY provide the evidence for SGLT2i use in non-diabetic CKD. An important distinction between these trial populations was the inclusion of an advanced CKD cohort (eGFR 20–45 ml/min/1.73m^2) with no proteinuria requirement in EMPA-KIDNEY, versus a minimum ACR of 200 mg/g in DAPA-CKD. Both trials reported equivalent reductions in primary outcomes for non-diabetic and diabetic cohorts. A meta-analysis of 13 SGLT2i RCTs across diabetes, CKD and heart failure concluded that there was an overall 37% reduction in kidney disease progression (RR 0.63; CI 0.58–0.69) and 23% reduction in composite of CV death or hospitalisation for heart failure (HHF) (RR 0.77; CI 0.74–0.81) with no evidence of heterogeneity on account of diabetes status (or baseline eGFR).[14]

Although meta-analyses suggest that all aetiologies of non-diabetic CKD benefit from SGLT2i, a pre-specified secondary analysis of 270 participants with IgA nephropathy in DAPA-CKD demonstrated a 76% reduction in ESKD, >50% eGFR decline and renal death (HR 0.24; CI 0.09–0.65), with the caveat of small event rates in this group.[15] Equivalent data from EMPA-KIDNEY are not yet available.

Regarding the unique, non-proteinuric inclusion of EMPA-KIDNEY, subanalysis by ACR level demonstrated a –0.78 ml/min/1.73m^2 difference in eGFR decline in those with ACR <30mg/g, but no significant differences in hard outcomes of ESKD or renal/CV death compared to placebo. It may be argued that, by virtue of non/low-proteinuric status, participants in this trial were at lower risk of primary outcome events and therefore significant differences between groups would be difficult to demonstrate during the short 2-year trial period. While it is reasonable to expect that reductions in eGFR slopes will translate into future hard outcomes, the trial evidence in this group is currently the least convincing and it remains to be seen whether NICE will consider a non-proteinuric, non-diabetic CKD indication for SGLT2i to be cost effective enough to recommend it alongside the existing recommendation for the use of dapagliflozin in non-diabetic CKD with albuminuria.

Safe prescribing of SGLT2i in CKD

Meta-analysis data have demonstrated that SGLT2i are safe across a broad range of comorbidities.[14] Early concerns regarding excess incidence of hypovolaemia, bone fracture and hypoglycaemia (only possible if additionally using insulin/insulin secretagogues) have not been borne out by RCT data. The commonest side effect is a 3.5-fold increased incidence of thrush, episodes of which may be treated as usual with no indication to discontinue SGLT2i.[16]

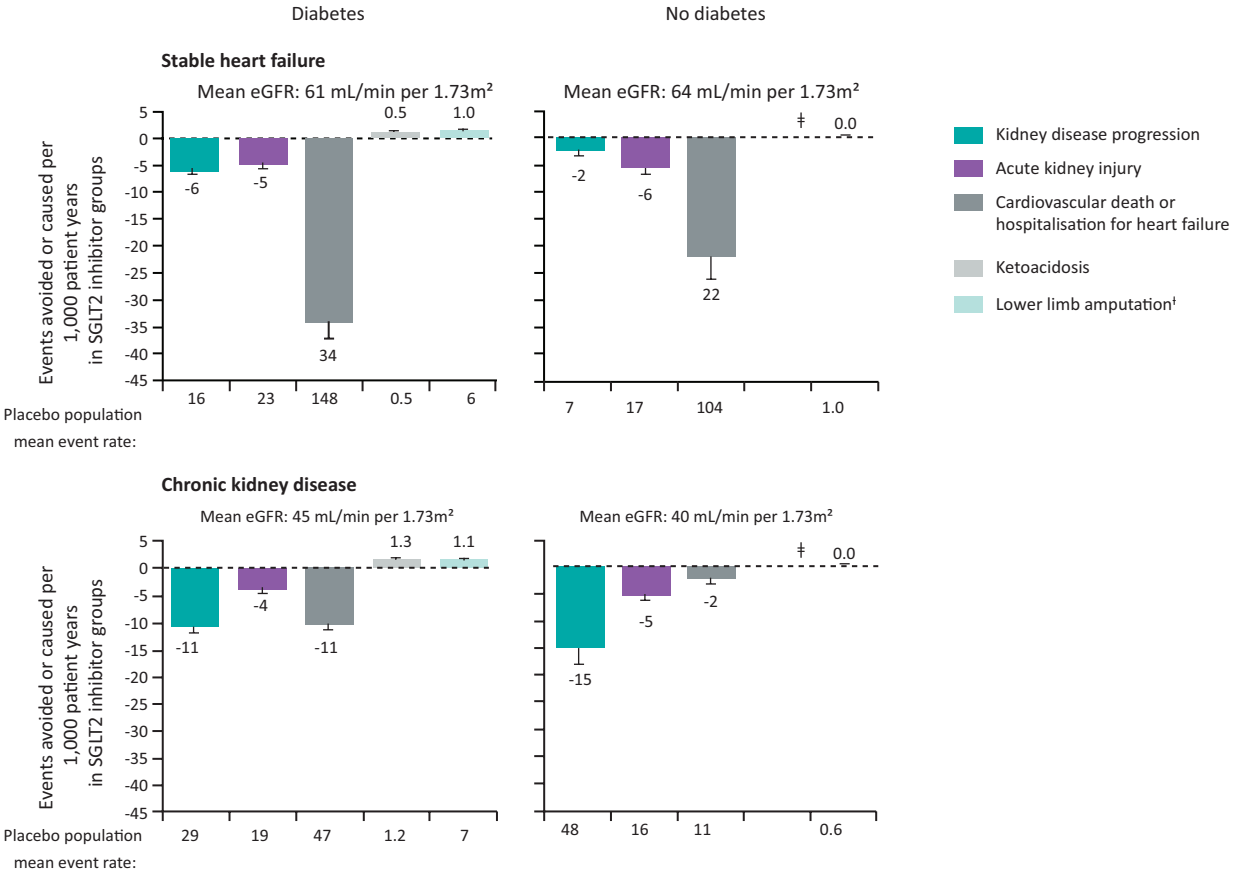

Fig 1. Absolute benefits and harms of SGLT2 inhibition per 1,000 patient-years by diabetes status and patient group. Adapted from Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium 2022.[14] Patient-group-specific absolute effects estimated by applying the diabetes subgroup specific risk ratio (RR) to the average event rate in the placebo arms (first event only). Negative numbers indicate events avoided by SGLT2i per 1,000 patient-years. Error bars represent standard error in the numbers of events avoided or caused, estimated from uncertainty in the RRs. Mean eGFR values are given for combined trial populations by patient group and diabetes status. Placebo population mean event rates are the absolute numbers of events per 1.000 patient-years in the placebo groups of all trials in the relevant subpopulation. ‡Too few ketoacidosis events to estimate absolute effects.

Only one trial detected a significant signal for amputation;[10] however many trials have shown numerically more cases of amputation in the SGLT2i groups, and guideline bodies unanimously recommend avoiding SGLT2i in the presence of active diabetic foot disease. However, patients with diabetes, CKD and peripheral vascular disease are likely to derive significant CV benefit from SGLT2i and hence clinical pragmatism must be employed in assessing individual risk:benefit.

A two-fold increase in ketoacidosis episodes[14] warrants close attention, particularly the appreciation that SGLT2i-associated DKA may present with lower than usual blood sugars, and rarely euglycaemia, given the urinary glucose 'outlet' afforded by these medications. Fig 1 depicts the absolute benefits versus harms from amputation or ketoacidosis per 1,000 patient years in the heart failure and CKD trials. Patients without diabetes have no increased risk of either amputation or ketoacidosis (one ketoacidosis event out of 7,788 non-diabetic trial participants).

From a CKD-specific perspective, it must be appreciated that SGLT2i will result in a temporary reduction in eGFR (~4 weeks) which is reflective of haemodynamic modulation that reduces intraglomerular hypertension, and hence filtration rate. This initial dip is followed by a period of stabilisation followed by long-term eGFR preservation that results in fewer renal deaths and dialysis starts. Renal blood tests following initiation are not required, and UK Kidney Association guidance recommends that bloods performed incidentally during the 4-week 'dip' period must be interpreted in the context of an expected drug effect to prevent knee-jerk discontinuation or erroneous AKI diagnoses.[16] In fact, metaanalyses have demonstrated that SGLT2i are protective against AKI (HR 0.77; CI 0.70–0.84),[14] postulated to be a consequence of inhibiting the high energy demands of the sodium glucose co-transporter in the proximal tubule, rendering it hardier against hypoxic tubular injury.[17]

Finerenone in diabetic kidney disease

Finerenone is a novel, non-steroidal, selective mineralocorticoid receptor antagonist (MRA) that causes less hyperkalaemia and fewer sexual side effects compared to steroidal MRAs[18] such as spironolactone.

FIGARO-DKD[19] tested the CV outcomes of patients with DKD, demonstrating a 13% reduction in CV death, hospitalisation for heart failure (HHF), non-fatal MI and CVA, while FIDELIO-DKD[20] demonstrated an 18% reduction in a renal primary composite outcome of kidney failure, sustained >40% eGFR decline and renal death (Table 1).

While somewhat overshadowed by the results of the flozin trials, these risk reductions still far exceed that seen with use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) alone, potentially owing to additional targeting of aldosterone escape, plus anti-fibrotic and anti-inflammatory effects conferred by MRAs. However, pooled analysis of both trials[21] confirmed a 14% incidence of hyperkalaemia compared with 7% among placebo-treated patients in those with eGFR <60 ml/min/1.73m^2.

Conclusion

SGLT2i are now firmly established as a joint-first-line treatment to modify CV risk and retard kidney disease progression in patients with DKD. SGLT2i use in non-diabetic CKD is building momentum, with increasing RCT evidence of safety and efficacy in this group. What is currently lacking are CKD population-level data assessing the additive effects of additional agents such as MRAs and GLP-1 receptor agonists, so that nephrologists can begin to emulate the heart failure optimisation strategy and build our own 'pillars' on the solid foundations of RAASi and SGLT2i in the management of CKD. ■

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