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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

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ABSTRACT

Chronic kidney disease (CKD) is a major public health issue affecting an estimated 850 million people globally. The leading causes of CKD is diabetes and hypertension, which together account for >50% of patients with end-stage kidney disease. Progressive CKD leads to the requirement for kidney replacement therapy with transplantation or dialysis. In addition, CKD, is a risk factor for premature cardiovascular disease, particularly from structural heart disease and heart failure (HF). Until 2015, the mainstay of treatment to slow progression of both diabetic and many non-diabetic kidney diseases was blood pressure control and renin-angiotensin system inhibition; however, neither angiotensin-converting enzyme inhibitors (ACEIs) nor angiotensin receptor blockers (ARBs) reduced cardiovascular events and mortality in major trials in CKD. The emergence of cardiovascular and renal benefits observed with sodium-glucose cotransporter-2 inhibitors (SGLT2i) from clinical trials of their use as anti-hyperglycaemic agents has led to a revolution in cardiorenal protection for patients with diabetes. Subsequent clinical trials, notably DAPA-HF, EMPEROR, CREDENCE, DAPA-CKD and EMPA-KIDNEY have demonstrated their benefits in reducing risk of HF and progression to kidney failure in patients with HF and/or CKD. The cardiorenal benefits—on a relative scale—appear similar in patients with or without diabetes. Specialty societies' guidelines are continually adapting as trial data emerges to support increasingly wide use of SGLT2i. This consensus paper from EURECA-m and ERBP highlights the latest evidence and summarizes the guidelines for use of SGLT2i for cardiorenal protection focusing on benefits observed relevant to people with CKD.

Keywords: cardiorenal syndrome, cardiovascular, chronic renal failure, diabetic kidney disease, heart failure

EPIDEMIOLOGY OF CKD

Approximately 850 million patients in the world have chronic kidney disease (CKD), with ~4 million receiving kidney replacement therapy [1]. Diabetic kidney disease (DKD) is the foremost cause of CKD globally [2]. In 2015, there were ~415 million people living with diabetes mellitus with the prevalence predicted to rise to 642 million by 2040, largely driven by an ageing population and lifestyle factors [2, 3]. DKD develops in ~40% of patients with diabetes mellitus and the incidence is increasing with the growing prevalence of diabetes [2]. Until recently the mainstay of renal protection in patients with type 2 diabetes mellitus (T2DM) and proteinuric CKD has been the use of renin-angiotensin system inhibitors (RASi) based on the Reduction of Endpoints with the Angiotensin II Antagonist Losartan (RENAAL) [4] and the Irbesartan in Diabetic Nephropathy Trial (IDNT) [5] with both studies published >20 years ago. Similarly, RASi was the mainstay of treatment for hypertensive kidney disease, the second most common cause of CKD, based mainly of the results of the African American Study on Kidney Disease [6]. However, the residual renal risk remained very high [2, 7]. Furthermore, in all outcome trials in DKD, the use of RASi was not associated with reduction in cardiovascular events and mortality [8].

Cardiovascular events and mortality increase exponentially with decreasing glomerular filtration rate or increasing albuminuria independent of age, sex, and other risk factors [9, 10]. Furthermore, as kidney function decreases, there is a shift from predominantly atherosclerotic/thrombo-embolic/vasculo-occlusive cardiovascular diseases to a proportionally increasing incidence of heart failure (HF) and sudden cardiac death [11]. In a large United States study (1998–2006) of 15 762 patients aged >20 years, the 10-year cumulative cardiovascular mortality for patients without neither diabetes or CKD, with diabetes and no CKD, and with CKD and no diabetes was 3.4%, 6.7%, and 9.9% respectively [12]. However, for patients with both diabetes and CKD the 10-year cumulative mortality was a staggering 19.6% [12]. Until 2015, although several novel agents had emerged for managing hyperglycaemia in T2DM, limited progress had been made in reducing the incidence of kidney failure due to diabetes [13]. The emergence of sodium-glucose cotransporter-2 inhibitors (SGLT2i) as a beneficial evidence-based therapy for improving cardiovascular and renal outcomes potentially revolutionizes therapy in this group of patients. This position paper integrates the current evidence base for therapy with SGLT2i with professional societies guidelines for their use.

CARDIOVASCULAR AND RENAL BENEFITS OF SGLT2i IN THE ORIGINAL CARDIOVASCULAR OUTCOME TRIALS

The cardiovascular and kidney benefits of SGLT2i were initially observed in cardiovascular outcomes trials (CVOT) mandated by the US Food and Drug Administration to assess cardiovascular (CV) safety in T2DM. Three CVOT shared a common three-point major adverse cardiovascular events (MACE) primary outcome and additionally had secondary kidney outcomes. Table 1 summarizes the major CVOTs and as well the renal outcome trials with SGLT2i.

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial studied empagliflozin versus placebo (81% subjects on RASi at baseline) in T2DM with established atherosclerotic cardiovascular disease (ASCVD) (coronary, peripheral vascular, or cerebral artery disease). During median follow up of 3.1 years, empagliflozin reduced risk of MACE and kidney disease outcomes [14]. A *post hoc* analysis of new onset or worsening nephropathy in 2250 patients with prevalent CKD at baseline demonstrated the benefit of empagliflozin on cardiovascular risk reduction by 29% [hazard ratio (HR), 0.71; 95% confidence interval (CI), 0.52–0.98] independently of estimated glomerular filtration rate (eGFR) category and urinary albumin-creatinine ratio (uACR) baseline status [14, 15].

The Canagliflozin Cardiovascular Assessment Study (CANVAS) programme assessed canagliflozin versus placebo in T2DM, with 66% of patients with established ASCVD. Canagliflozin reduced risk of primary MACE outcome, and also found similar reductions in kidney disease progression outcomes to EMPA-REG OUTCOME. *Post hoc* analyses of CANVAS reported consistency of effects on cardiovascular and renal outcomes at different albuminuric stages [16]. An increased risk of lower limb amputation risk led to regulatory warnings, but this observation has not been replicated in subsequent trials of canagliflozin [17, 18] or other SGLT2i [19].

The Dapagliflozin Effect on Cardio-vascular Events–Thrombolysis in Myocardial Infarction 58 trial (DECLARE-TIMI 58) included T2DM patients at high risk of cardiovascular disease, ~60% of patients without previous ASCVD (59%). During median follow up of 4.2 years, compared to placebo, dapagliflozin did not reduce risk of MACE but did reduce risk of its co-primary outcome of CV death or hospitalization for HF (4.9 vs. 5.8%, HR 0.83; 95% CI, 0.73 to 0.95), as well as the composite kidney outcomes [20].

RENAL MECHANISMS OF ACTION OF SGLT2i

A key concept that may explain both acute and long-term SGLT2i protective effects on renal function is linked to the decreased re-absorption of glucose and sodium (Na) in the S1 and S2 portions of the proximal tubule where SGLT2i have their intended mechanism of action. Higher Na delivery to the macula densa stimulates adenosine release, inducing vasoconstriction of the afferent and vasodilatation of the efferent arterioles, reducing intraglomerular pressure and restoring tubuloglomerular feedback [21]. This effect leads to an initial dip in eGFR and reduced albuminuria but preserves renal function in the longer term [22]. A natriuretic effect associated to the inhibition of the Na/H^+ exchanger (NHE3) has been also described [23]. The increase in diuresis and reduction in blood pressure (BP) confers extra beneficial long-term effects than usual diuretics as fluid redistribution between intracellular and extracellular compartments is achieved [24]. Furthermore, the reduction in BP does not increase heart rate, so a direct inhibition of sympathetic activity is suggested [25]. Decreases in the tubular transport workload reduce glucotoxicity and oxygen consumption, increasing cortical oxygen tension in this highly aerobic part which may explain the mechanism by which acute kidney injury (AKI) is reduced by these agents [26]. The increased glucose delivery to subsequent tubular segments, increases SGLT1 activity decreasing oxygen tension in the outer medulla and stimulating erythropoietin production [27]. Another beneficial effect of SGLT2i is the increased uricosuria, due to a decrease in urate absorption by competition of the excess glucose delivered with urate in the urate transporter [28]. A direct effect in podocytes with a potential of decreasing proteinuria has been also described [29].

Indirect effects are mainly metabolic, as SGLT2i induce weight loss, perirenal fat, and obesity-induced inflammation [30]. SGLT2i have been associated with increases in adiponectin and ketogenesis, and decreases in leptin release, mimicking a fasting-like state [31]. This will lead to an increase in sirtuin-1 and adenosine monophosphate-activated protein kinase (AMPK), which in turn decrease oxidative and endoplasmic reticulum

Table 1: Main: clinical trials evaluating cardiorenal outcomes in patients treated with SGLT2i. CKD: chronic kidney disease; MACE: major adverse cardiovascular event (CV death, nonfatal MI, or nonfatal stroke); CV: cardiovascular; eGFR: estimated GFR; EF: ejection fraction; HHF: hospitalised heart failure; HF: heart failure; ESKD: end-stage kidney disease; T2DM Type 2 Diabetes mellitus.

Trials (ref)	Year of completion	SGLT2i	Patient population	Number of patients	Median follow up	Mean eGFR (ml/min/1.73 m²)	Median uACR mg/g (IQR)	CV outcome	SGLT2i vs. placebo group	HR (95%CI)	Renal outcome	SGLT2i vs. placebo group	HR (95%CI)
EMPA-REG OUTCOME [48]	2015	empagliflozin (10 or 25 mg)	T2DM and CVD	7020	3.1 years (2.6 treatment)	74 ± 21	NA (28.7% microalbuminuria and 11% macroalbuminuria)	MACE	10.5% vs. 12.1%	0.86 (0.74–0.99)	(Post hoc)	16.2% vs. 23.6%	0.61 (0.55–0.69)
								HF or CV death (excluding fatal stroke)	5.7% vs. 8.5%	0.66 (0.55–0.79)	Incident or worsening nephropathy or CV death		
								CV death	3.7% vs. 5.9	0.62 (0.49–0.77)	incident or worsening nephropathy	12.7% vs 18.8%	0.61 (0.53–0.7)
											doubling of the serum creatinine	1.5% vs. 2.6%	0.56 (0.39–0.79)
											initiation of renal-replacement therapy	0.3% vs. 0.6%	0.45 (0.21–0.97)
CANVAS [17]	2017	canagliflozin (100 or 300 mg)	T2D and high CVD risk	10 142	2.6 years	76.5 ± 20.5	12.3 (6.65–42.1)	MACE	26.9% vs. 31.5%	0.86 (0.75–0.97)	progression of albuminuria	89.4 128.7 per 1000 patient-years	0.73 (0.67–0.79)
								Hospitalization for HF	5.5 vs. 8.68 per 1000 patient-years	0.67 (0.52–0.87)	sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes	5.5 vs. 9.0	0.60 (0.47–0.77)
DECLARE-TIMI58 [20]	2018	Dapagliflozin (10 mg)	T2DM and ≥ 1 CVD risk factor	17.160	4.2years	85.2 ± 16	NA	MACE	8.8 vs. 9.4%	0.93 (0.84–1.03)	≥40% reduction in eGFR, ESKD >90 days, (dialysis, sustained eGFR <15 ml/min/1.73 m², or kidney transplantation), or renal/CV death	4.3% vs. 5.6%	0.76 (0.67–0.87)
								CV death or hospitalization for HF	4.9% vs. 5.8%	0.83 (0.73–0.95)			
CREDENCE [18]	2019	canagliflozin (100 mg)	T2DM and CKD	4401	2.6 years	56.2 ± 18.2	927 [463–1833]	MACE	9.9 vs. 12.2%	0.80 (0.67–0.95)	doubling of serum creatinine, ESKD (dialysis, renal transplantation, or sustained eGFR <15 ml/min/1.73 m²), or renal/CV death	11.1% vs. 15.4%	0.70 (0.59–0.82)
								HHF or CV death	8.1 vs. 11.5%	0.69 (0.57–0.83)			

Table 1: Continued.

Trials (ref)	Year of completion	SGLT2i	Patient population	Number of patients	Median follow up	Mean eGFR (ml/min/1.73 m²)	Median uACR mg/g (IQR)	CV outcome	SGLT2i vs. placebo group	HR (95%CI)	Renal outcome	SGLT2i vs. placebo group	HR (95%CI)
VERTIS CV [80]	2019	ertugliflozin (5 or 15 mg)	T2D and established CVD	8246	3.5 years	76.1 ± 20.9 (75.7 ± 20.8 placebo group)	NA	hospitalization for heart failure	11.9% vs. 11.9%	0.97 (0.85–1.11)	death from renal causes, renal-replacement therapy, or doubling of the serum creatinine	3.2% vs. 3.9%	0.81 (0.63–1.04)
								Death from CV causes or hospitalization for HF	8.1% vs. 9.1%	0.88 (0.75–1.03)			
EMPEROR reduced [50]	2020	empagliflozin (10 mg)	HF with reduced EF	3730	16 months	61.8 ± 21.7 (62.2 ± 21.5 placebo group)	NA	death from CV causes or hospitalization for HF	19.4% vs 24.7%	0.75 (0.65–0.86)	dialysis or renal transplantation or sustained reduction in the eGFR	1.6% s 3.1%	0.50 (0.32–0.77)
								hospitalization for HF	20.8% vs. 29.6%	0.70 (0.58–0.85)	eGFR decline	−0.93 vs. −4.21 ml per minute per 1.73 m²	(95%CI −1.97–0.11) and(95% CI, −5.26 to −3.17)
EMPEROR –preserved [51]	2021	empagliflozin (10 mg)	HF with preserved EF	5988	26.2 months	60.6 ± 19.8	NA	death from CV causes or hospitalization for HF	13.8% vs. 17.1%	0.79 (0.69–0.90)	Rate of decline in the eGFR	(−1.25 vs. − 2.62 ml per minute per 1.73 m² per year)	
								hospitalization for HF	8.6% vs. 11.8%	0.73 (0.61–0.83)			
DAPA-CKD [35]	2020	dapagliflozin (10 mg)	CKD (T2D and non-diabetics)	4304	2.4 years	43.1 ± 12.4	965 (472–1903) 934 (482–1868) for the placebo group	Death CV causes or hospitalization for HF	4.6% vs. 6.4%	0.71 (0.55–0.92)	decline in e-GFR of at least 50%, ESKD, or death from renal, or CV causes	9.2% vs. 14.5%	0.61 (0.51 −0.72)
											sustained decline in the eGFR of at least 50%, ESKD or death from renal causes	6.6% vs. 11.3%	0.56 (0.45–0.68)
EMPA-KIDNEY [58]	2022	Empagliflozin (10 mg)	CKD (T2D and non-diabetics)	6609	2.0 years	37.5 ± 14.8	412 (94–1190)	hospitalization for HF or cardiovascular death	4.0% vs. 4.6%	0.84 (0.67–1.07)	ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of ≥ 40% in eGFR from randomization) or (ii) Cardiovascular death	13.1% vs. 16.9%	0.72 (0.64–0.82)

stress and inflammation [32, 33]. Furthermore, a decrease in epithelial-mesenchymal transition has been demonstrated [34]. All those changes lead to a decrease in renal damage and fibrosis.

RENAL OUTCOME TRIALS- CREDENCE AND DAPA-CKD

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) was the first trial evaluating the effect of an SGLT2i on major renal outcomes in CKD [18], randomizing 4401 patients with T2DM, eGFR 30 to <90 ml/min/1.73 m^2 and uACR 300–5000 mg/g already on maximum tolerated dose of an ACEI or ARB to canagliflozin or placebo. The primary outcome was end-stage kidney disease (ESKD) defined as dialysis, transplantation, or sustained eGFR <15 ml/min/1.73 m^2; doubling of serum creatinine; or death from renal or cardiovascular causes. Mean eGFR was 56.2 ml/min/1.73 m^2; median uACR 927 mg/g; mean age of participants 63 years; and 33.9% of patients were women. The study was stopped early for efficacy (median follow up 2.62 years). The relative risk of the primary outcome was 30% lower with canagliflozin, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR 0.70; 95%CI 0.59–0.82). The risk of the renal-specific composite of ESKD, doubling of creatinine, or death from renal causes was lower by 34% (HR 0.66; 95%CI 0.53–0.81), and that of ESKD by 32% (HR 0.68; 95%CI 0.54–0.86) with canagliflozin. Furthermore, the geometric mean of uACR was 31% lower with canagliflozin (95%CI, 26 to 35%), while the eGFR slope was typical of an acute eGFR dip with canagliflozin during the first 3 weeks (−3.72 ± 0.25 vs. −0.55 ± 0.25 ml/min/1.73 m^2), followed by slower eGFR decline thereafter (−1.85 ± 0.13 vs. −4.59 ± 0.14 ml/min/1.73 m^2 for canagliflozin versus placebo) [18].

The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with CKD (DAPA-CKD) evaluated the effect of dapagliflozin versus placebo in addition to a maximum tolerated dose of an ACEI or ARB in patients with eGFR ≥ 25 and ≤75 ml/min/1.73 m^2, and uACR ≥ 200 and ≤5000 mg/g. The primary outcome was a composite of ≥50% sustained decline in eGFR, ESKD, or cardiovascular or renal death [35]. DAPA-CKD recruited 4304 participants with mean eGFR 43.1 ml/min/1.73 m^2 and median uACR of 949 mg/g. Here, 2906 participants (67.5%) had T2DM, but in 396 of them CKD was ascribed to causes different than DKD [36]. DAPA-CKD was also stopped early (median of 2.4 years) due to overwhelming efficacy. The primary endpoint occurred in 9.2% versus 14.5% of the participants in the dapagliflozin and the placebo groups, respectively (HR 0.61; 95% CI 0.51–0.72). The renal component of the primary composite outcome of ≥50% sustained decline in eGFR, ESKD and renal death was reduced with dapagliflozin (HR 0.56; 95% CI, 0.45–0.68), including reductions in each component of this renal composite. Dapagliflozin reduced geometric mean uACR by 29.3% (95% CI −33.1 to −25.2; $P < 0.0001$) [37], a typical eGFR dip during the first 2 weeks was evident with dapagliflozin (−3.97 ± 0.15 vs. −0.82 ± 0.15 ml/min/1.73 m^2), which was followed by a smaller annual eGFR loss thereafter (−1.67 ± 0.11 vs. −3.59 ± 0.11 ml/min/1.73 m^2) [35].
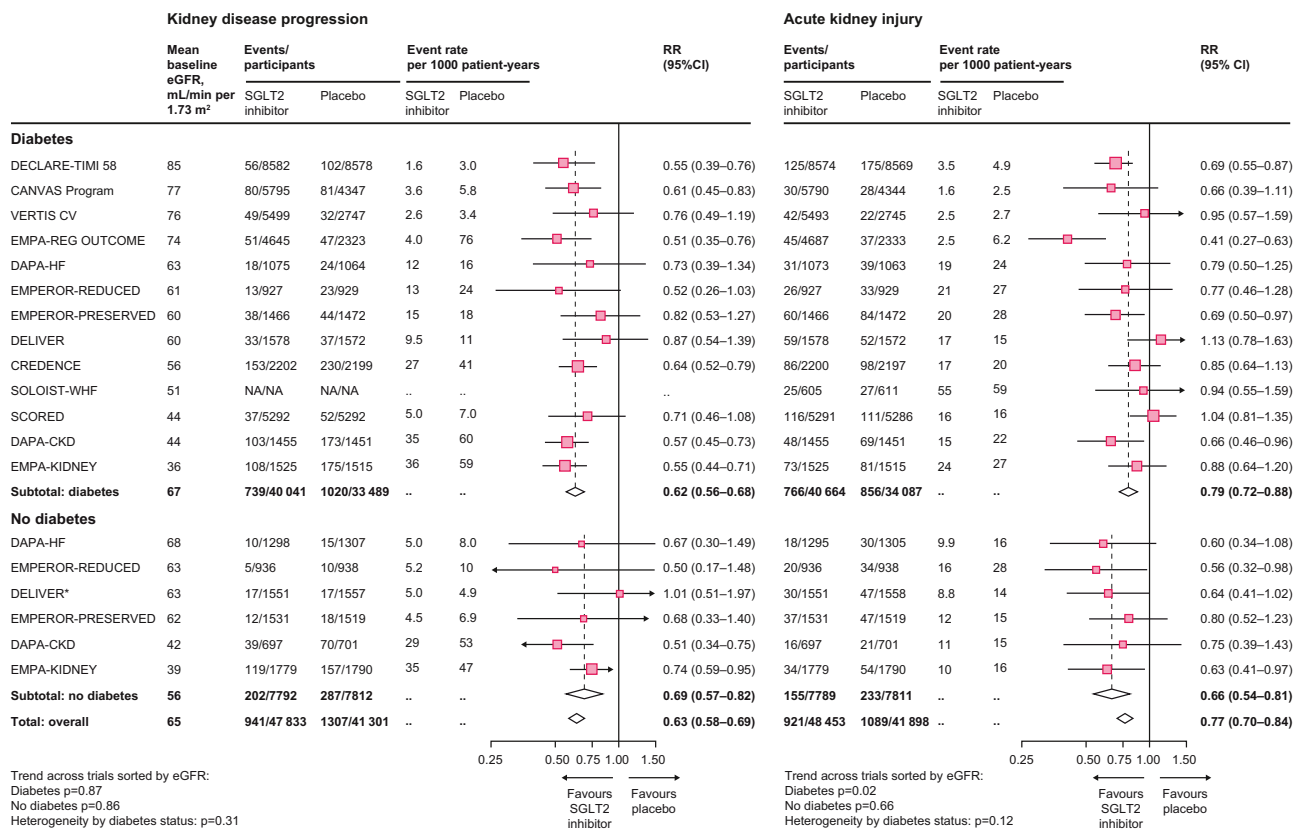
SGLT2i IN NON-DIABETIC CKD

DAPA-CKD and the Multicentre International Randomized Parallel Group Double-blind Placebo-controlled Clinical Trial of EM-PAgliflozin Once Daily to Assess Cardio-renal Outcomes in Patients With Chronic KIDNEY Disease trial (EMPA-KIDNEY) enrolled, among other non-diabetic diseases, patients with IgA nephropathy (IgAN) and focal segmental glomerulosclerosis (FSGS) with or without diabetes (Table 1) [38]. DAPA-CKD provided pre-specified analyses of 270 participants with IgAN (94% biopsy confirmed) and 104 with biopsy-confirmed FSGS [39, 40]. The size of DAPA-CKD compares favourably with phase 2 and 3 (Supplementary Table S1) and recent trials in IgAN, such as Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study (TESTING) and Supportive Versus Immunosuppressive Therapy for the Treatment Of Progressive IgA Nephropathy (STOP-IgAN). IgAN patients in DAPA-CKD had lower baseline eGFR and similar proteinuria but were older and were more frequently diabetic than patients in TESTING and STOP-IgAN (Supplementary Table S2) [41–44].

In DAPA-CKD, mean eGFR slopes for IgAN patients on dapagliflozin and placebo were −3.5 and −4.7 ml/min/1.73 m^2/year, respectively, and dapagliflozin reduced the uACR by 26% relative to placebo [39]. The primary outcome occurred in six (4%) participants on dapagliflozin and 20 (15%) on placebo (HR, 0.29; 95% CI, 0.12, 0.73). EMPA-KIDNEY has confirmed important kidney benefits in IgAN, adding a further 80 such outcomes. Once pooled, SGLT2i appeared to reduce kidney disease progression substantially compared to placebo (37/550 vs. 68/537; HR 0.49, 95% CI 0.32–0.74) [45]. Data are more limited in FSGS, with only 28 kidney disease progression outcomes when DAPA-CKD and EMPA-KIDNEY are combined [40, 45]. However, when considered as a group of diseases, pooled analysis of DAPA-CKD and EMPA-KIDNEY suggest SGLT2i reduce risk of kidney disease progression by about 40% compared to placebo (HR 0.60, 95% CI 0.46–0.78) [45]. It is now proposed that IgAN and podocytopathy trials should include SGLT2i as background therapy and assess GFR decline as primary outcome [46, 47]. Clinical guidelines for the treatment of these conditions should be updated to include combined RASi plus SGLT2i as the recommended new standard of care.

CARDIOVASCULAR BENEFITS OF SGLT2i IN HEART FAILURE

Following the observation of major clinical benefits of HF outcomes in the initial CVOTs [20, 48], recent trials of SGLT2i as an adjunctive therapy in HF have demonstrated significant benefits with these agents, both in people with and without diabetes. In DAPA-HF trial of 4744 people with HF with reduced ejection fraction (HFrEF) with and without diabetes, compared to placebo, dapagliflozin was associated with reduced incidence of the of primary outcome of worsening HF or cardiovascular death [49]. Similarly, in the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR Reduced) trial of 3730 people with HFrEF empagliflozin with or without diabetes, empagliflozin reduced risk of the primary composite outcome of cardiovascular death or hospitalization for worsening HF compared to placebo [50]. Moreover, in the EMPEROR with Preserved Ejection Fraction (EMPEROR-Preserved) trial, empagliflozin reduced the incidence of the composite of cardiovascular death or hospitalization for HF in patient with and without diabetes considered separately [51], and the drug now has a US licence for the treatment of HF regardless of ejection fraction—the first therapy to demonstrate clear efficacy in HF with preserved ejection fraction (HFpEF). The benefits of empagliflozin were consistent across the range of eGFR in HF patients in EMPEROR Reduced [52].

	Mean baseline eGFR, mL/min per 1.73 m²	Kidney disease progression Events/participants		Event rate per 1000 patient-years		RR (95%CI)	Acute kidney injury Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo		SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Diabetes											
DECLARE-TIMI 58	85	56/8582	102/8578	1.6	3.0	0.55 (0.39–0.76)	125/8574	175/8569	3.5	4.9	0.69 (0.55–0.87)
CANVAS Program	77	80/5795	81/4347	3.6	5.8	0.61 (0.45–0.83)	30/5790	28/4344	1.6	2.5	0.66 (0.39–1.11)
VERTIS CV	76	49/5499	32/2747	2.6	3.4	0.76 (0.49–1.19)	42/5493	22/2745	2.5	2.7	0.95 (0.57–1.59)
EMPA-REG OUTCOME	74	51/4645	47/2323	4.0	76	0.51 (0.35–0.76)	45/4687	37/2333	2.5	6.2	0.41 (0.27–0.63)
DAPA-HF	63	18/1075	24/1064	12	16	0.73 (0.39–1.34)	31/1073	39/1063	19	24	0.79 (0.50–1.25)
EMPEROR-REDUCED	61	13/927	23/929	13	24	0.52 (0.26–1.03)	26/927	33/929	21	27	0.77 (0.46–1.28)
EMPEROR-PRESERVED	60	38/1466	44/1472	15	18	0.82 (0.53–1.27)	60/1466	84/1472	20	28	0.69 (0.50–0.97)
DELIVER	60	33/1578	37/1572	9.5	11	0.87 (0.54–1.39)	59/1578	52/1572	17	15	1.13 (0.78–1.63)
CREDENCE	56	153/2202	230/2199	27	41	0.64 (0.52–0.79)	86/2200	98/2197	17	20	0.85 (0.64–1.13)
SOLOIST-WHF	51	NA/NA	NA/NA	..	..	..	25/605	27/611	55	59	0.94 (0.55–1.59)
SCORED	44	37/5292	52/5292	5.0	7.0	0.71 (0.46–1.08)	116/5291	111/5286	16	16	1.04 (0.81–1.35)
DAPA-CKD	44	103/1455	173/1451	35	60	0.57 (0.45–0.73)	48/1455	69/1451	15	22	0.66 (0.46–0.96)
EMPA-KIDNEY	36	108/1525	175/1515	36	59	0.55 (0.44–0.71)	73/1525	81/1515	24	27	0.88 (0.64–1.20)
Subtotal: diabetes	**67**	**739/40 041**	**1020/33 489**	..	..	**0.62 (0.56–0.68)**	**766/40 664**	**856/34 087**	..	..	**0.79 (0.72–0.88)**
No diabetes											
DAPA-HF	68	10/1298	15/1307	5.0	8.0	0.67 (0.30–1.49)	18/1295	30/1305	9.9	16	0.60 (0.34–1.08)
EMPEROR-REDUCED	63	5/936	10/938	5.2	10	0.50 (0.17–1.48)	20/936	34/938	16	28	0.56 (0.32–0.98)
DELIVER*	63	17/1551	17/1557	5.0	4.9	1.01 (0.51–1.97)	30/1551	47/1558	8.8	14	0.64 (0.41–1.02)
EMPEROR-PRESERVED	62	12/1531	18/1519	4.5	6.9	0.68 (0.33–1.40)	37/1531	47/1519	12	15	0.80 (0.52–1.23)
DAPA-CKD	42	39/697	70/701	29	53	0.51 (0.34–0.75)	16/697	21/701	11	15	0.75 (0.39–1.43)
EMPA-KIDNEY	39	119/1779	157/1790	35	47	0.74 (0.59–0.95)	34/1779	54/1790	10	16	0.63 (0.41–0.97)
Subtotal: no diabetes	**56**	**202/7792**	**287/7812**	..	..	**0.69 (0.57–0.82)**	**155/7789**	**233/7811**	..	..	**0.66 (0.54–0.81)**
Total: overall	**65**	**941/47 833**	**1307/41 301**	..	..	**0.63 (0.58–0.69)**	**921/48 453**	**1089/41 898**	..	..	**0.77 (0.70–0.84)**

Trend across trials sorted by eGFR:
Diabetes p=0.87
No diabetes p=0.86
Heterogeneity by diabetes status: p=0.31

Favours SGLT2 inhibitor — Favours placebo

Trend across trials sorted by eGFR:
Diabetes p=0.02
No diabetes p=0.66
Heterogeneity by diabetes status: p=0.12

Favours SGLT2 inhibitor — Favours placebo

Figure 1: Effect of sodium-glucose cotransporter-2 inhibition on kidney disease outcomes from meta-analysis of large placebo-controlled randomized controlled trials. Figure adopted from [45]. eGFR: estimated glomerular filtration rate; SGLT2i: sodium-glucose cotransporter-2 inhibitor; RR: relative risk; NA: not available.

These data has been followed by the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial in 6263 patients with HF and a left ventricular ejection fraction >40%, where compared to placebo, dapagliflozin significantly reduced the incidence of a primary outcome (composite of worsening HF or cardiovascular death) (HR, 0.82; 95% CI, 0.73 to 0.92; P < 0.001) [53].

Given the high prevalence of HF in general and more specifically HFpEF in patients with CKD, these observations should herald a new era of SGLT2i for cardiorenal protection where people with CKD may stand to experience considerable benefit [54]. For example, it is estimated from event rates from the CKD trials, that each 1000 patient-years of treatment with an SGLT2i is predicted to prevent 11 first hospitalization for HF or cardiovascular deaths in patients with diabetes, and many more if they have pre-existing heart failure (Supplementary Fig. S1, see the online supplementary material for a colour version of this figure) [45].

HOW EMPA-KIDNEY AND ONGOING TRIALS ARE PUSHING THE EVIDENCE IN CKD

With the growing number of large placebo-controlled SGLT2i confirming their efficacy in increasingly broad populations [19], certainty about their safety is increasing and the opportunity for new placebo-controlled trials in CKD has diminished rapidly. CREDENCE and DAPA-CKD provide clear evidence of cardiorenal benefits among patients with T2DM and DKD [18, 35], and other trials suggest renal benefits extend to those with T2DM without albuminuria [55]. Nevertheless, it is important for the renal community to see more randomized data in patients without T2DM and with low eGFR.

The EMPA-KIDNEY trial assessed the effect of 10 mg of empagliflozin versus placebo on a composite primary outcome of kidney disease progression or cardiovascular death in an even broader range of patients with CKD at risk of progression. In total, 6609 patients with eGFRs as low as 20 ml/min/1.73 m² were screened, and by the time of randomization 254 had eGFRs 15–20 ml/min/1.73 m² [45, 56]. The types of patient recruited into EMPA-KIDNEY who were under-represented in previously reported SGLT2i trials including a large proportion without diabetes (54%), with an eGFR <30 ml/min/1.73 m² (35%), and with a uACR <300 mg/g at recruitment (48%). The trial also included 1669 people with glomerular disease, of which 817 (49%) had IgAN, plus 68 patients with type 1 diabetes [57]. Empagliflozin had beneficial effect on the primary renal outcome in EMPA-KIDNEY (HR 0.72, 95% CI 0.64–0.82) (Table 1) [58]. All the reported large SGLT2i trials in CKD excluded patients with polycystic kidney disease or a kidney transplant. Patients with extremely low eGFR and on dialysis are still being studied in the RENAL LifeCycle trial (NCT05374291). The cumulative of impact of SGLT2i on renal outcomes is highlighted in an updated meta-analysis with SGLT2i use having 37% lower risk of kidney disease progression (HR 0.63, 95% CI 0.58–0.69) (Fig. 1), with consistent effects in patients with and without diabetes, across primary kidney diagnoses and with different SGLT2 inhibitors [45].
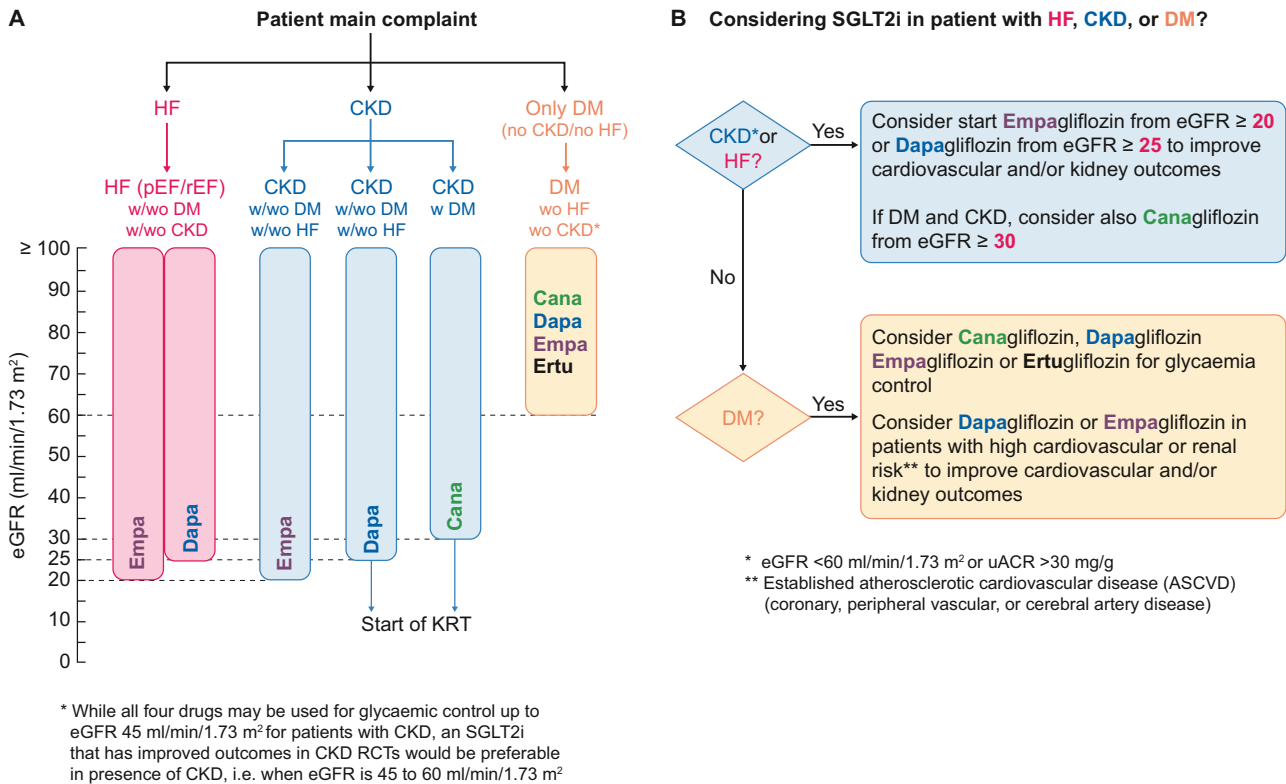
Figure 2: Proposed algorithm for selection of SGLT2i based on large clinical trial evidence/indication and threshold of eGFR for initiation based on patient's main complaint (A) and clinical indication (B). Note that current prescribing licences for agents may not apply in all regions. CKD: chronic kidney disease, defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² or urine albumin-creatinine ratio (uACR) >30 mg/g; HF: heart failure; pEF: preserved ejection fraction; rEF: reduced ejection fraction; DM: Type 2 diabetes mellitus: eGFR values expressed in ml/min/1.73 m², w/: with; wo: without, RCT: randomized controlled trials; KRT: kidney replacement therapy, SGLT2i: sodium-glucose cotransporter-2 inhibitor; ASCVD: atherosclerotic cardiovascular disease.

ROLE OF SGLT2i COMPARED TO/COMBINED WITH OTHER NEPHROPROTECTIVE THERAPY-NOW AND IN FUTURE

In parallel to the advent of SGLT2i as foundational therapy for CKD, contemporary data from the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) and Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) trials suggest the novel non-steroidal mineralocorticoid receptor antagonist (ns-MRA) finerenone on top of standard of care RAS inhibition can also significantly improve a range of both kidney and cardiovascular outcomes [59, 60]. FIDELIO-DKD ($n = 5674$) and FIGARO-DKD ($n = 7352$) trials determined the effect of finerenone on CKD progression and CV mortality and morbidity in patients with CKD and T2DM and a combined analysis termed FIDELIO-DKD and FIGARO-DKD Trial programme analYsis (FIDELITY) has been published [59–61]. Both trials randomized patients receiving a standard of care with the maximum tolerated dose of RASi.

In FIDELIO-DKD, finerenone in combination with maximal tolerated RASi significantly reduced the risk of the kidney and CV composite endpoints by 23% (0.77, 95%CI 0.67–0.88) and 14% (0.86, 95%CI 0.78–0.95), respectively [59]. In the FIDELITY analysis, just 6.7% of participants received an SGLT2i at baseline and 8.5% initiated one during the trial [62]. Baseline SGLT2i use did not affect risk reduction for the cardiovascular or kidney composites with finerenone. Indeed, numerically, the lowest risk corresponded to patients with combined SGLT2i and finerenone: for the cardio-

vascular composite, the HRs were 0.87 (95% CI 0.79–0.96) without SGLT2i and 0.67 (95% CI 0.42–1.07) with SGLT2i; for the kidney composite, the HRs were 0.80 (95% CI 0.69–0.92) without SGLT2i and 0.42 (95% CI 0.16–1.08) with SGLT2i [62].

Combination of ns-MRA and SGLT2i seems to be very attractive not only for efficacy but also as the potential risk of hyperkalaemia when adding MRA to ACEIs/ARBs might be counteracted by the potassium lowering effect of SGLT2i [63].

SAFETY PROFILE OF SGLT2i

The renal safety profile of SGLT2i has been quantified by meta-analysis [45, 64]. Data from 13 studies of 90 413 participants showed that beyond the known excess risk of mycotic genital infections (RR, 3.57; 95% CI, 3.14–4.06), there was no overall increased risk of other safety outcomes, including serious urinary tract infections, amputations, and fractures [45]. In patients with diabetes, the risk of ketoacidosis is approximately doubled, but the risk is higher for states of insulin deficiency and T1 diabetes mellitus and patients with T2DM in the trials remained at low absolute risk. In the trial populations studies to date, the absolute harms of SGLT2i in patients with and without diabetes are clearly lower than the substantial absolute benefits [45]. This is particularly the case in patients with CKD, and especially those without diabetes [19, 45]. Furthermore, meta-analysis of the large placebo-controlled SGLT2i trials show they reduce the risk of AKI (HR 0.77, 0.70–0.84) [45] and reduce risk of serious adverse events of hyperkalaemia by 16% (0.84, 95% CI 0.76–0.93) [19, 63]. Although there is a risk of ketoacidosis and hypoglycaemia with

these agents, there were no differences in the incidence of these events between placebo and control groups [35, 45].

Reductions in serious hyperkalaemia were consistent across the trials and a range of subgroups, including baseline kidney function, history of HF, and use of RASi, diuretic, and MRA. Of note, SGLT2i did not increase the risk of hypokalaemia [HR, 1.04 (95% CI, 0.94–1.15)] [64]. In the HFrEF setting, beneficial effects of empagliflozin were unmodified in a secondary analysis of EMPEROR Reduced when those prescribed an MRA at baseline or not were compared, and allocation to empagliflozin was associated with less discontinuation of MRAs (perhaps due to less severe hyperkalaemia with empagliflozin [65]). In DAPA-HF moderate/severe hyperkalaemia (potassium >6.0 mmol/l) was less common among patients assigned to dapagliflozin, compared with placebo in patients taking an MRA at baseline [HR 0.50 (0.29–0.85); $P = 0.01$, P value for interaction 0.08] [66].

In the HFpEF setting, the benefit of empagliflozin to reduce the primary outcome was not significantly different between steroidal MRA nonusers and steroidal MRA users [67]. The effect of empagliflozin to reduce first and recurrent HF hospitalizations was more pronounced in MRA nonusers [HR: 0.60 (95% CI: 0.47–0.77) compared to MRA users HR: 0.90 (95% CI: 0.68–1.19); interaction $P = 0.038$]. Empagliflozin reduced hyperkalaemia or initiation of potassium binders, with no significant treatment-by-MRA subgroup interaction. Multiple mechanisms have been proposed to explain the mechanism by which SGLT2i reduce hyperkalaemia [63].

REVIEW OF GUIDELINES AND RECOMMENDATIONS ON THE USE SGLT2I BY DIFFERENT SPECIALTIES (SUPPLEMENTARY TABLE S3)
Diabetology guidelines

In 2018 the Canadian Diabetes Association [68] published its recommendations for antihyperglycemic medication selection and dosing in CKD. In this guideline, SGLT2i are used as 'antihyperglycaemic drugs' in people who cannot achieve glycaemic targets. The authors recommend using SGLT2i with proven renal benefits for reducing the risk of CKD progression in people with T2DM, cardiovascular disease and CKD who have eGFR >30 ml/min/1.73 m^2 with a level for recommendation '2B for empagliflozin' and '3C for canagliflozin'.

The most recent 2022 joint American Diabetes Association (ADA) European Association for Study of Diabetes (EASD) consensus statement regarding the choice of glucose-lowering therapy in patients with T2DM. The recommendation is that the therapy should be based on assessment of established ASCVD, CKD or HF with goals of glycaemic control and cardiorenal protection considered in partnership [69]. SGLT2i are indicated in people with T2DM independently of baseline HbA1c or individualized HbA1c target to reduce cardiac events, HF, cardiovascular death, and progression of CKD. In particular, SGLT2i were recommended for people with HF with moderately reduced ejection fraction or CKD (eGFR 30 to 60 ml/min/1.73 m^2) or T2DM and HFrEF because they reduce cardiac events and cardiovascular death. As a distinct recommendation, for patients with high risk for amputation, SGLT2i should be prescribed after risks are explained and with comprehensive education on foot care. The 2023 updated ADA ADA guideline on Standards of Medical Care in Diabetes suggests that both cardiorenal risk and glycaemic control should be assessed in parallel with SGLT2i first line therapy for cardiorenal risk [70].

Cardiology guidelines

In 2019, the revised version of the European Society of Cardiology (ESC) guidelines on diabetes, pre-diabetes, and cardiovascular diseases first mentioned the use of SGLT2i as recommended for glucose-lowering treatment in patients with T2DM [71]. This guideline recognized the paradigm shift in glucose-lowering treatment demonstrated by several cardiovascular outcome trials that indicate cardiovascular benefits from the use of SGLT2i and GLP-1-receptor agonists (GLP-1RA) in patients with ASCVD or at very high/high cardiovascular risk.

SGLT2i are indicated as glucose-lowering agents in patients with cardiovascular disease or high cardiovascular risk to reduce cardiovascular events with class of recommendation 'I' and level of evidence 'A'. Also, SGLT2i are recommended to lower the risk of HF hospitalization with class of recommendation 'I' and level of evidence 'A'. Finally, empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death with a class I recommendation and level B of evidence.

The ESC guideline for acute and chronic HF [72] described a four-pillar approach in managing HFrEF patients irrespective of presence of T2DM. These four pillars are represented by four classes of medication that are used to reduce mortality: beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor-neprilysin inhibitor, MRA, and SGLT2i. The main SGLT2i are dapagliflozin and empagliflozin. They are recommended to reduce hospitalization for HF and to reduce death with class of recommendation 'I' and level of evidence 'A'.

ERA AND KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES (KDIGO) GUIDELINES

The first mention of SGLT2i was in the ERBP Clinical Practice Guideline on management of patients with diabetes and CKD stage 3b or higher (eGFR <45 ml/min), published in 2015 [73]. There, SGLT2i were used as anti-hyperglycaemic drugs. The recommendation of use for SGLT2i was for CKD stage 3B or less, but the authors mention a 'limited experience'. On this topic, this guideline is outdated and undergoing revision.

In 2019 the EURECA-m and the DIABESITY working groups of the ERA-EDTA made a consensus statement recommending that patients with T2DM and CKD, that are not on HbA1c target on recommended Metformin therapy or for whom Metformin is not tolerated or is contraindicated, to use SGLT2i with evidence for cardio and renal protection [74]. Therefore, SGLT2i were historically recommended for patients with T2DM and CKD with eGFR >60 ml/min/1.73 m^2 or with eGFR <60 ml/min/1.73 m^2 but above the licensed range who have either micro- or macro-albuminuria who do not achieve glycaemic targets under Metformin or do not tolerate Metformin. While these guidelines emphasized the role of SGLT2i in glycaemic control, we have moved to an era of SGLT2i for kidney protection rather than glycaemic control in isolation, and, in reality, the effect of SGLT2i on glycaemia is limited when eGFR <45 ml/min/1.73 m^2.

KDIGO published an updated guideline on Diabetes Management in CKD in 2022 in which it recommends a comprehensive treatment of patients with diabetes and CKD to reduce risks of kidney disease progression and CV disease [75]. SGLT2i are now considered a first line drug for patients with T2DM and CKD. The target population for SGLT2i were people with T2DM and CKD who
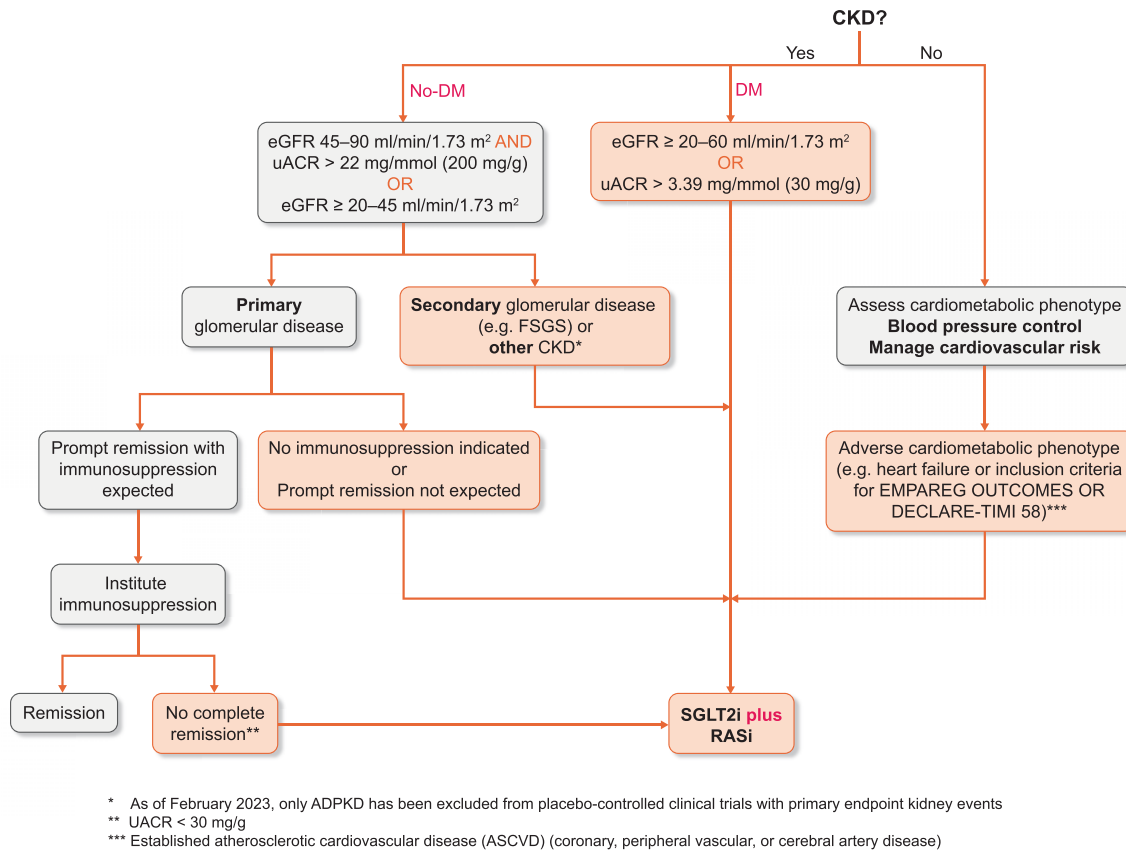
Figure 3: Broad schematic to support clinical use of SGLT2i in as foundational therapy for CKD considering need for specific treatment in both cardiometabolic and glomerular disease. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate (eGFR); FSGS: focal segmental glomerulosclerosis; DM: type 2 diabetes mellitus; SGLT2i: sodium-glucose cotransporter-2 inhibitor; uACR: urine albumin-creatinine ratio; ASCVD: atherosclerotic cardiovascular disease; RASi renin-angiotensin system inhibition.

have eGFR ≥ 20 ml/min/1.73 m^2. The level of recommendation for the SGLT2 administration was '1A'.

UPDATED UNITED KINGDOM GUIDANCE SPECIFIC TO KIDNEY INDICATIONS OF SGLT2i

The guideline from the National Institute for Health and Care Excellence (NICE) focused on drug treatment of T2DM, specifically on 'anti-hyperglycaemic drugs' was published in February 2022 [76]. For SGLT2i, the target population are patients with T2DM and one other disease: HF, ASCVD, or people at risk for development cardiovascular disease. Also, SGLT2i are suggested as anti-hyperglycaemic drug if people have contraindication for Metformin in chronic HF, atherosclerotic cardiovascular disease, or in people at risk for development cardiovascular disease. Perhaps more importantly, in CKD, a NICE update now recommends use of dapagliflozin, in addition to RASi, in patients with T2DM, or patients with a uACR of 22.6 mg/mol or more (irrespective of diabetes) [77]. This is consistent with the UK Kidney Association recommendations, with the exception that there is an effort to simplify the summary of where there is clear evidence for use of an SGLT2i, suggesting any member of the SGLT2i class could be used in CKD. To facilitate implementation, the UK Kidney Association guideline also has a full lay summary and template patient information leaflets [78]. A pragmatic algorithm for using SGLT2i across the range of indications is proposed in Fig. 2.

CONCLUSIONS AND FUTURE GUIDELINES

The emergence of SGLT2i represents a major leap forward in the evidence base for cardiorenal protection in CKD. DAPA-CKD has shown the renal benefits of SGLT2i, clearly proven in patients with T2DM with proteinuric CKD, appear to extend to patients with non-diabetic proteinuric CKD and EMPA-KIDNEY trial has provided more evidence on benefits in patients without diabetes, and included one-third of participants with an eGFR <30 ml/min/1.73 m^2 and those without albuminuria. Nephrologists are required to assimilate existing evidence and guidelines and apply these to the broad spectrum of patients with CKD, including those with primary glomerular diseases. Recent proposals for integrating SGLT2i into the management of glomerular disease have been proposed [79] (Fig. 3). We propose that this broad pragmatic approach is appropriate, as SGLT2i appears to be safe in CKD, particularly in patients without diabetes and potentially highly effective. Further efforts are required by nephrologists and aligned professional organizations to ensure that these agents with evidence-based benefits for reducing rate of progression of CKD to kidney failure are prescribed to eligible patients to address the global burden of CKD and its cardiovascular complications.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

CONFLICT OF INTEREST STATEMENT

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