Defining the Role of SGLT2 Inhibitors in Primary Care: Time to Think Differently

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ABSTRACT

Disease burden in people with diabetes is mainly driven by long-term complications such as cardiovascular disease, heart failure and chronic kidney disease. This is a consequence of the interconnection between the cardiovascular, renal and metabolic systems, through a continuous chain of events referred to as 'the cardiorenal metabolic continuum'. Increasing

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evidence suggests that sodium–glucose cotransporter 2 inhibitors (SGLT2is) have beneficial effects across all stages of the cardiorenal metabolic continuum, reducing morbidity and mortality in a wide range of individuals, from those with diabetes and multiple risk factors to those with established heart failure and chronic kidney disease, regardless of the presence of diabetes. Despite this robust evidence base, the complexity of label indications and misconceptions concerning potential side effects have resulted in a lack of clear understanding in primary care regarding the implementation of SGLT2is in clinical practice. With this in mind, we provide an overview of the clinical and economic benefits of SGLT2is across the cardiorenal metabolic continuum together with practical considerations in order to help address some of these concerns and clearly define the role of SGLT2is in primary care as a holistic outcomes-driven treatment with the potential to reduce disease burden across the cardiorenal metabolic spectrum.

Keywords: Cardiorenal metabolic continuum; Chronic kidney disease; Diabetes; Heart failure; SGLT2 inhibitors; Primary care

Key Summary Points

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) have demonstrated clinical and economic value across all stages of the cardiorenal metabolic continuum by reducing morbidity and mortality in a wide range of individuals, from those with diabetes and multiple risk factors to those with established heart failure and chronic kidney disease, regardless of the presence of diabetes.

SGLT2is are well tolerated, with a low risk of serious adverse effects that should not overshadow the significant cardioprotective benefits.

SGLT2is should be considered as cornerstones of integrated care strategies in primary care in order to reduce disease burden over the patient lifetime by maximising outcome benefits across the cardiorenal metabolic continuum, rather than according to the traditional approach of controlling each risk factor or comorbidity as a separate entity.

A person-centred, outcomes-driven approach that recognises the holistic role of SGLT2is offers an opportunity to significantly improve clinical outcomes for people with cardiorenal metabolic disease.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2is), including dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin, are now widely approved antihyperglycaemic therapies that can reduce glucose levels independent of insulin, when estimated glomerular filtration rate (eGFR) is sufficient. Their main mechanism of action is the inhibition of SGLT2 function which results in a reduction of glucose absorption from the glomerular filtrate in the proximal renal tubule, and an increase in urinary glucose excretion [1, 2] (Fig. 1). Given their glucose-lowering effects, SGLT2is were firstly licensed as treatments for the management of glycaemic control in type 2 diabetes mellitus (T2DM) [3] and as such are increasingly employed for this purpose in primary care. Beyond the glucose control benefits, in recent years there has been a wealth of evidence indicating that SGLT2is exert cardiac and renal protective effects across the cardiorenal metabolic continuum [4–7].

This has led to new treatment paradigms for SGLT2is including secondary prevention of cardiovascular (CV) disease and delaying progression of chronic kidney disease (CKD) in people with T2DM, as well as managing heart failure (HF) and CKD, regardless of the presence of diabetes [8–12].
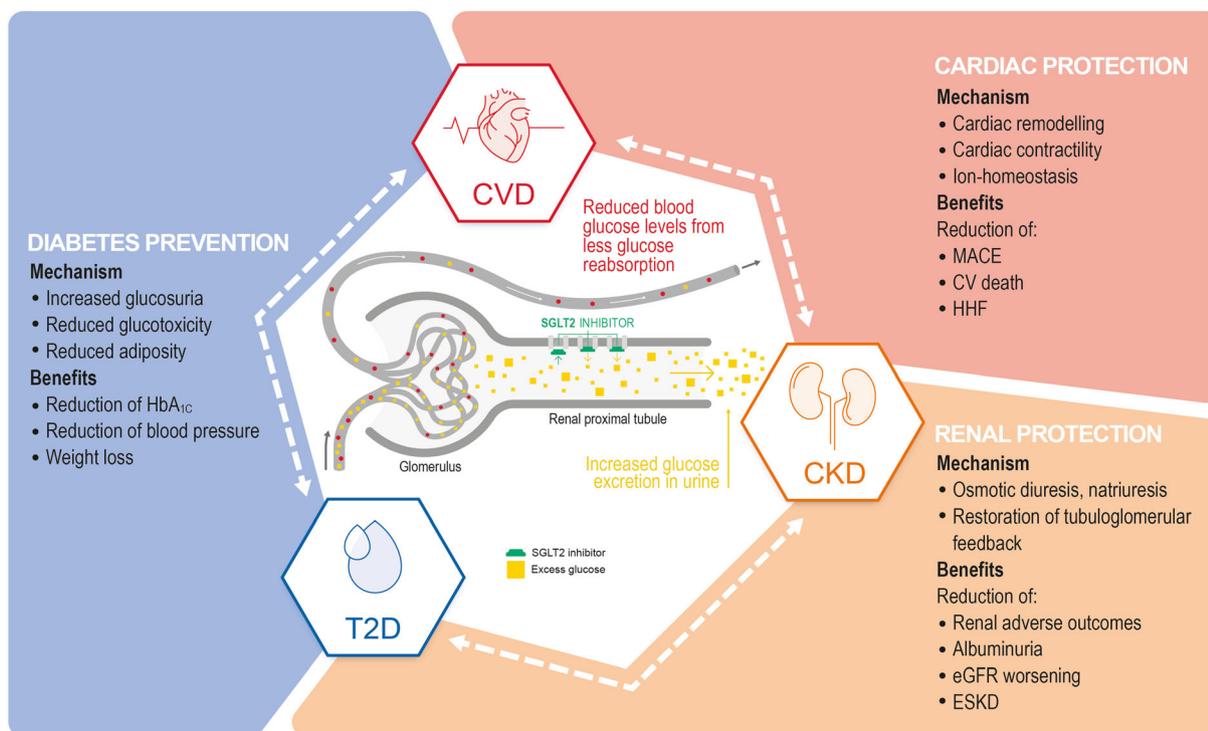
Fig. 1 SGLT2 inhibitor cardiorenal metabolic effects. The figure summarizes main mechanisms of action and beneficial effects of SGLT2 inhibitors across the cardiorenal metabolic spectrum, including reduction of CV events, renal protection, and improvement of metabolic control in diabetes. *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *HbA1c* glycated haemoglobin, *HHF* hospitalisation for heart failure, *MACE* major adverse cardiovascular event, *T2DM* type 2 diabetes mellitus

The mechanisms behind the CV and renal protection associated with SGLT2is are likely to be multifactorial and are not yet fully elucidated. However, it has been suggested that osmotic diuresis and natriuresis, with subsequent reduction in volume overload and reduced blood pressure, together with a reduction in intraglomerular pressure and glomerular hyperfiltration, may play a role [2, 13]. In addition, metabolic effects (e.g. increases in glucosuria and reductions in HbA1c, glucotoxicity, weight gain and adiposity), improved cardiac remodelling, cardiac contractility and ion-homeostasis, as well as reductions in inflammation and oxidative stress are also likely to contribute to the observed cardiorenal benefits [14, 15] (Fig. 1).

The broad range of benefits of SGLT2is for both people with and without diabetes has led to differing licence indications, which has the potential to result in confusion as to the prescribing of these agents and which may be a contributing factor to the slow uptake of these drugs. With this in mind, it may now be time to challenge the paradigm of SGLT2is in clinical practice and implement a holistic approach to reduce the burden of disease across the cardiorenal metabolic spectrum, instead of focusing on single comorbidities or conditions. A person-centred outcomes-driven approach that considers the presence of T2DM, high risk for atherosclerotic cardiovascular disease (CVD), CKD, and HF, as well as individuals' needs and preferences (e.g. weight loss in overweight or obese people, desire to avoid hypoglycaemia), alongside HbA1c, may now be considered the best approach in deciding whether the management plan of those with cardiorenal

metabolic disease should include SGLT2is [16–18]. As such, healthcare professionals involved in the care and management of people with cardiorenal metabolic disease should be encouraged to change their thinking from 'is there an indication for an SGLT2i in this person with cardiorenal metabolic disease?' to 'why is this person with cardiorenal metabolic disease not on an SGLT2i?' Since the majority of people with cardiorenal metabolic disease are managed in primary care it is important that healthcare professionals working in primary care are fully aware of the role of SGLT2is in clinical practice as a holistic outcomes-driven treatment with the potential to reduce disease burden and associated costs across the cardiorenal metabolic spectrum. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

SGLT2IS IN T2DM

Clinical Value of SGLT2is in T2DM

Historically, therapeutic efforts for people with T2DM have focused on achieving optimal glycaemic targets, to prevent microvascular and macrovascular complications. However, although glycaemic control with diabetes treatments such as metformin, thiazolidinediones (TZD), sulfonylureas (SU) and dipeptidyl peptidase inhibitors (DPP4is) has been associated with decreased risk of microvascular complications, a similar reduction has not been observed for macrovascular complications or CV events [19, 20]. Consequently a large proportion of people with T2DM remain at high residual risk for renal/CV disease progression [21]. In fact, some of these drugs may actually increase the risk of CV events, as well as being associated with additional side effects such as hypoglycaemia and weight gain [22–24]. For example, although pioglitazone was associated with reduced risk of major adverse cardiovascular events (MACE), the risks of heart failure, bone fracture, oedema and weight gain were increased [25]. Consequently, there is a need for novel treatments that provide both glycaemic

and non-glycaemic benefits. In this context, SGLT2is have emerged as an interesting therapeutic option, demonstrating multiple effects including glycaemic control, weight and blood pressure lowering, as well as cardiorenal protection.

The beneficial impact of SGLT2is in T2DM is supported by a large body of evidence. Several randomised controlled studies have demonstrated that SGLT2is (dapagliflozin, empagliflozin, canagliflozin and ertugliflozin) significantly reduce HbA1c, fasting plasma glucose, 2-h post prandial glucose, body weight, systolic and diastolic blood pressure compared to placebo, both when used as monotherapy and as add-on therapy to insulin or other diabetes drugs including metformin, SU, DPP4is and glucagon-like peptide 1 receptor agonists (GLP1-RAs) [26–51].

SGLT2is have also demonstrated reductions in overall morbidity and mortality in people with T2DM, by reducing CV and renal complications. Several clinical trials have assessed the impact of SGLT2is on CV outcomes: EMPA-REG OUTCOMES [52], CANVAS [53], VERTIS CV [54], and DECLARE TIMI 58 [55]. These studies have brought to light the cardioprotective benefits of this class of drugs in terms of reduction vs. placebo in hospitalisations for heart failure (HHF) (HRs between 0.65 and 0.73), composite of death from CV causes, nonfatal myocardial infarction and non-fatal stroke (HRs between 0.86 and 0.97), and any cause mortality (HRs between 0.68 and 0.93) [52–56].

DECLARE-TIMI 58 is the broadest, largest, and longest SGLT2i cardiovascular outcome trial (CVOT) to date. Participants in the trial were more representative of the general T2DM population compared to previous trials, including people with either multiple known risk factors for CVD or established atherosclerotic CVD. In this population, dapagliflozin was found to be both cardio- and renoprotective. Indeed, dapagliflozin was shown to prevent HHF vs. placebo consistently across a broad range of people with T2DM, regardless of history of established CVD or HF. A significantly lower risk for HHF vs. placebo was observed both in people with established CVD (HR 0.78, 95% CI 0.63–0.97) and in people with multiple

risk factors for CVD (HR 0.64, 95% CI 0.46–0.88). A lower risk for HHF was also observed in those with prior HF (HR 0.73, 95% CI 0.55–0.96) or no history of HF (HR 0.73, 95% CI 0.58–0.92). Of note, dapagliflozin was also associated with a significantly lower risk vs. placebo, of the cardiorenal composite of at least a 40% decrease in eGFR to less than 60 mL/min/ 1.73 m^2, end-stage kidney disease (ESKD), or death from renal or CV cause (HR 0.76, 95% CI 0.67–0.87) and of the renal specific composite of at least a 40% decrease in eGFR to less than 60 mL/min/1.73 m^2, ESKD, or death from renal cause (HR 0.53, 95% CI 0.43–0.66).

A systematic review and meta-analysis of EMPA-REG OUTCOMES [52], CANVAS [53] and DECLARE TIMI 58 [55] conducted in 34,322 people with T2DM (60.2% with established atherosclerotic CVD), demonstrated that SGLT2is reduced the risk for CV death or HHF by 23% (HR 0.77, 95% CI 0.71–0.84) [57, 58]. Reduction in HHF was observed in all CVOTs analysed in the study, regardless of atherosclerotic CVD or history of HF [57, 58]. The VERTIS CV [54] trial, which investigated the impact of ertugliflozin on CV outcomes, did not show a significant difference vs. placebo in the composite of death from CV causes, non-fatal myocardial infarction and non-fatal stroke; however, results demonstrated a decreased risk of death from CV causes or HHF in people receiving ertugliflozin. SGLT2is were also shown to reduce MACE incidence in older patients with T2DM. A recent systematic review and meta-analysis which evaluated both GLP1-RAs and SGLT2is showed that SGLT2is reduce MACE outcomes in older adults (over 65 years of age) by 16% (OR 0.831, 95% CI 0.699–0.989) [59]. The study included the main SGLT2i CVOTs (EMPA-REG OUTCOMES [52], CANVAS [53], DECLARE TIMI 58 [55] and CREDENCE [60]).

Furthermore, although designed to primarily assess CV outcomes, many CVOTs have shown that SGLT2is exert renal protective effects. The EMPA-REG OUTCOMES [52], CANVAS [53], VERTIS CV [54], and DECLARE TIMI 58 [55] trials assessed CV and renal outcomes in people with diabetes receiving empagliflozin, canagliflozin, ertugliflozin and dapagliflozin, respectively, in addition to standard of care. Results

from these trials showed significant benefits over placebo in terms of composite renal outcome of doubling serum creatinine/sustained decrease of 40% or more in eGFR, ESKD or death from renal or CV cause (HRs between 0.54 and 0.76) [53–55, 61]. A recent meta-analysis of CVOTs indicated that SGLT2is reduced the risk of progression of renal disease by 45% (HR 0.55, 95% CI 0.48–0.64), with a similar benefit in people with and without atherosclerotic CVD [57]. Overall, both the renal and CV endpoint data (Table 1) strongly indicate that SGLT2is are an effective tool to manage T2DM across the cardiorenal continuum.

Economic Value of SGLT2is in T2DM

Besides showing significant clinical benefits, SGLT2is have also demonstrated economic value for the treatment of T2DM. In a UK study assessing the economic implications of dapagliflozin in T2DM, based on DECLARE TIMI data, use of dapagliflozin over 4 years resulted in 1.5 fewer ESKD events and 8.9 fewer HHF events per 1000 patients, with an estimated 27% reduction in total HHF-related length of stay (LOS), compared to placebo. Avoidance of these events translated into a reduction of £141,209 per 1000 patients over 4 years (£142 per person); and £2.7 million over a lifetime (40-year projections) [62].

A systematic review that included SGLT2i cost-effectiveness studies available up to 2018 (15 dapagliflozin, 10 canagliflozin and 12 empagliflozin studies) concluded that SGLT2is were the most cost-effective treatment, compared to other oral antidiabetes therapies and insulin, in uncontrolled T2DM [63]. For example, in the economic studies conducted in the UK setting, dapagliflozin (as monotherapy or combination therapy) yielded incremental cost-effectiveness ratios (ICERs) ranging between £1847 and £30,795/quality-adjusted life year (QALY) gained [63]. These conclusions, however, were mostly based on the antihyperglycaemic effects of SGLT2is and so did not capture the full economic value of these drugs, such as the burden associated with CV and renal complications. In a modelling study analysing the

Table 1 Summary of CV and renal outcomes from SGLT2i CVOTs

Trial	Year	SGLT2 inhibitor	Number of participants	Median follow-up (years)	T2DM (%)	Main outcomes	HR/mean (95% CI)	p value
EMPA-REG [52]	2016	Empagliflozin	7020	3.1	100	*Renal composite* ESKD, doubling of creatinine, death from renal causes	0.54 (0.40–0.75)	< 0.001
						CV composite Death from CV causes, nonfatal myocardial infarction, or nonfatal stroke	0.86 (0.74–0.99)	< 0.001 for noninferiority and $p = 0.04$ for superiority
CANVAS [53]	2017	Canagliflozin	10,142	2.4	100	*Renal composite* Sustained 40% reduction in eGFR, need for RRT or death from renal causes	0.60 (0.47–0.77)	< 0.01
						CV composite Death from CV causes, nonfatal myocardial infarction, or nonfatal stroke	0.86 (0.75–0.97)	< 0.001 for noninferiority and $p = 0.02$ for superiority
DECLARE-TIMI 58 [55]	2019	Dapagliflozin	17,160	4.2	100	*Renal composite* eGFR decline of $\geq$ 40% to < 60 mL/min/1.73 m^2, ESKD, or death from renal causes	0.53 (0.43–0.66)	< 0.0001
						CV composite CV death or HHF	0.83 (0.73–0.95)	0.005
DAPA-HF [4]	2019	Dapagliflozin	4644	1.5	45	*Renal composite* Worsening renal function (eGFR decline of $\geq$ 50%, end-stage kidney disease, or renal death)	0.71 (0.44–1.16)	Not reported
						CV composite Worsening HF (unplanned hospitalisation or an urgent visit resulting in intravenous therapy for HF) or death from CV causes	0.74 (0.65–0.85)	< 0.001
CREDENCE [60]	2019	Canagliflozin	4401	2.6	100	*Renal composite* ESKD, doubling of creatinine, death from renal causes	0.66 (0.53–0.81)	< 0.001
						CV composite CV death, myocardial infarction, stroke, or HHF or unstable angina	0.74 (0.63–0.86)	Not reported
VERTIS CV [54]	2020	Ertugliflozin	8246	3.5	100	*Renal composite* ESKD, doubling of creatinine, death from renal causes	0.81 (0.63–1.04)	Not reported
						CV composite Death from CV causes, nonfatal myocardial infarction, or nonfatal stroke	0.97 (0.85–1.11)	< 0.001

Table 1 continued

Trial	Year	SGLT2 inhibitor	Number of participants	Median follow-up (years)	T2DM (%)	Main outcomes	HR/mean (95% CI)	p value
EMPEROR-REDUCED [5]	2020	Empagliflozin	3730	1.3	50	Renal composite RRT, transplant, sustained eGFR reduction of 40% or more, eGFR < 15 mL/min/1.73 m²	0.50 (0.32–0.77)	Not reported
						CV composite CV death or HHF	0.75 (0.65–0.86)	< 0.001
DAPA-CKD [6]	2020	Dapagliflozin	4304	2.4	67.5	Renal composite eGFR decline of ≥ 50%, ESKD or death from renal causes	0.56 (0.45–0.68)	< 0.001
						CV composite HHF or death from CV causes	0.71 (0.55–0.92)	0.009
SCORED [70]	2021	Sotagliflozin	10,584	1.3	100	Renal composite ≥ 50% decrease in eGFR, RRT, renal transplantation, sustained eGFR of < 15 mL/min/1.73 m² for ≥ 30 days	0.71 (0.46–1.08)	Not reported
						CV composite Death from CV causes, HHF, urgent visits for HF	0.74 (0.63–0.88)	< 0.001
SOLOIST-WHF [69]	2021	Sotagliflozin	1222	0.75	100	Renal outcome Change in eGFR	− 0.16 (− 1.30 to 0.98)	Not reported
						CV composite Deaths from CV causes and hospitalisations and urgent visits for HF	0.67 (0.52–0.85)	< 0.001
EMPEROR-Preserved [72]	2021	Empagliflozin	5988	2.1	49	Renal outcome Decline in eGFR	1.36 (1.06–1.66)	< 0.001
						CV composite CV death or HHF	0.79 (0.69–0.90)	< 0.001

CV cardiovascular, eGFR estimated glomerular filtration rate, ESKD end-stage kidney disease, HF heart failure, HHF hospitalisation for heart failure, HR hazard ratio, RRT renal replacement therapy, T2DM type 2 diabetes mellitus

cost-effectiveness of dapagliflozin in high-risk T2DM, capturing long-term CV and renal outcomes, dapagliflozin was deemed dominant compared to placebo, providing 0.06 QALY gains and £2552 savings per person [64]. Similar results were observed in all subgroups analysed, with the greatest benefit observed in individuals with prior HF (+ 0.11 QALYs and £4150 saved) and in those with established CVD (+ 0.09 QALYs and £2831 saved) [64]. Of note, this study adopted a conservative approach by assuming that dapagliflozin would be discontinued when eGFR reached values below 45 mL/min/1.73 m^2. However, more recently, the DAPA-CKD study has shown that dapagliflozin benefits can persist beyond this threshold; thus, the actual savings may be greater than the ones estimated in the study [6].

Recently, a multinational economic analysis was conducted to assess the cost-effectiveness of the SGLT2is as a class, versus standard of care in people with T2DM with and without established CV disease [65]. The analysis took into consideration evidence from both CVOTs and real-world studies and demonstrated that SGLT2is were cost-saving or cost-effective at relevant willingness to pay (WTP) thresholds in the UK, USA and China. The study highlighted that although associated with increased treatment costs, SGLT2is reduced costs associated with CV and microvascular complications, while also extending life expectancy [65]. Subgroup analysis in people with established CVD, MRF, previous history of HF and no prior HF confirmed the cost-effectiveness of SGLT2is. In the UK setting, SGLT2is were deemed dominant across all subgroups, yielding a net monetary benefit (NMB) over lifetime of £15,345/person and with the highest benefits observed in people with established CVD and prior HF (NMB £17,834 and £17,440) [65].

These conclusions together with the clinical evidence indicate that for all patients across the continuum of T2DM (T2DM ± HF ± CKD), SGLT2is inhibitors represent good clinical and economic value. Indeed, this drug class serves the objective of reducing the overall burden of disease well, helping to address T2DM from a holistic viewpoint, rather than according to the traditional approach of controlling each risk factor or comorbidity as a separate entity. In clinical practice thinking needs to be directed towards the patient and why they are not being considered for an SGLT2i.

SGLT2IS IN HF

Clinical Value of SGLT2is in HF

It is estimated that there are approximately 23 million individuals with HF worldwide, and approximately 50% of these cases are attributed to HF with reduced ejection fraction (HFrEF) [56]. Current treatment options for HFrEF include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (MRA), and angiotensin receptor neprilysin inhibitors (ARNI), in combination with diuretic therapy. However, substantial mortality and morbidity is still observed in this population, indicating a need for more effective treatments [56]. Recently, SGLT2is have emerged as a novel strategy to reduce the clinical burden of HFrEF.

Previous CVOTs have shown that SGLT2is reduce the risk of new-onset HF in people with T2DM, as demonstrated by a reduction in CV events and HHF [52–55]. Data from the DAPA-HF study [4] demonstrated that dapagliflozin improved outcomes in individuals with established HF. The trial included 4744 people with NYHA class II to IV HFrEF (less than 40%) receiving standard of care, and the results demonstrated that dapagliflozin in addition to standard of care reduced the primary outcome of risk of worsening of HF and CV death by 26% (HR 0.76, 95% CI 0.65–0.85). Of note, 55% of DAPA-HF trial participants did not have T2DM [4], and the results were similar irrespective of the presence of diabetes, with HR 0.73 (95% CI 0.60–0.88) and HR 0.75 (95% CI 0.63–0.90) in people with and without diabetes, respectively. Dapagliflozin significantly reduced death from CV causes (HR 0.82, 95% CI 0.69–0.98) and death from any cause (HR 0.83, 95% CI 0.71–0.97). In addition, dapagliflozin was associated with clinically meaningful improvement in symptoms as demonstrated by a 5-point or

more change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) (odds ratio 1.13, 95% CI 1.07–1.21). A trend towards a better preservation of renal function was also observed in the dapagliflozin group as indicated by the composite of reduction of 50% or more in the eGFR sustained for at least 28 days, ESKD, or death from renal causes (HR 0.71, 95% CI 0.44–1.16). Dapagliflozin benefits were also consistent independent of age [66].

The beneficial effects of SGLT2is were also confirmed by the EMPEROR-Reduced trial [5], which investigated the efficacy and safety of empagliflozin in 3730 people with class II to IV HFrEF (40%). In this study, the incidence of CV death or hospitalisation for HF was significantly lower with empagliflozin (25% reduction) compared with placebo. Similarly to the DAPA-HF trial, significant benefits were observed regardless of diabetes status [5]. EMPEROR-Reduced also highlighted the renal benefits of SGLT2is, as shown by the mean slope of change in eGFR per year (difference 1.73; $p < 0.001$) and the composite renal outcome of chronic dialysis or renal transplantation or a sustained reduction in the eGFR (HR 0.50, 95% CI 0.32–0.77) [5]. Benefits in terms of the primary composite of CV death or HHF and the composite renal outcomes were consistent across a broad range of baseline kidney function, including people with eGFR as low as 20 mL/min/1.73 m^2 [67].

A recent meta-analysis of the two trials confirmed the clinical benefits of SGLT2is in HFrEF, showing a significant reduction in all cause (13%) and CV mortality (14%) as well as in first HHF and the composites of first HHF or CV mortality, and all HHF or CV mortality [68]. Sotagliflozin, a dual SGLT2/1 inhibitor, has also been associated with a significant reduction in the composite endpoint of CV deaths, HHF and urgent HF visits in both people with acute decompensated HF (SOLOIST-WHF trial; 33% reduction) and people with T2DM and additional CV risk factors (SCORED trial; 26% reduction) [69, 70]. Additionally, in the SCORED trial, sotagliflozin was associated with a 23% decrease in the total number of deaths from CV causes, non-fatal myocardial infarctions, and non-fatal strokes. The benefits of

SGLT2is in HF are also supported by the DEFINE-HF trial, in which dapagliflozin led to improvement in HF symptoms, based on KCCQ, over 12 weeks in 263 people with NYHA II–III HFrEF (40% or less), irrespective of T2DM [71]. This body of evidence supports consistent clinical benefits of SGLT2is in HFrEF in terms of prevention of CV complications and preservation of renal function (low rate of eGFR decline and ESKD or transplantation) across all thresholds of eGFR [67].

Interestingly, the EMPEROR-Preserved trial has recently shown that empagliflozin reduces the risk of HHF or CV death in people with heart failure and preserved ejection fraction (HFpEF), regardless of the presence of diabetes (people with diabetes: HR 0.79, 95% CI 0.69–0.90; people without diabetes: 0.78, 95% CI 0.64–0.95), thus paving the way for the use of SGLT2 inhibition in HFpEF [72]. The role of SGLT2is in the management of HFpEF will be further explored in the DELIVER study [73].

Economic Value of SGLT2is in HF

Besides showing significant clinical benefits, SGLT2is have also demonstrated health economic value in the treatment of HF. In a modelling study conducted in the UK setting, introduction of dapagliflozin to the treatment algorithm for HFrEF was estimated to yield a cost-offset of £26.2 million over 5 years. Savings were mainly driven by reduction in HHF, urgent HF visits and CV deaths [74].

Dapagliflozin, added to standard therapy, has been shown to be cost-effective, compared to standard therapy alone in people with HFrEF, with or without diabetes, in various settings. Dapagliflozin was estimated to increase life-years and QALYs and reduce lifetime hospitalisation; this was associated with ICERs well below the accepted WTP threshold in the UK, Germany, and Spain (ICERs were £5822, €5379 and €9406/QALY, respectively) [75]. Dapagliflozin was particularly cost-effective in high-risk subgroups yielding ICERS of £5625/QALY with prior HHF (vs. £5968 with no prior HHF) and £5648/QALY in people with more than 2 years duration of HF (vs. £ 6114 of people with lower

duration) [75]. Conversely, the ICER was higher in people with T2DM than in people without diabetes (£6350 vs. £5419/QALY) [75]. The economic value of dapagliflozin was also investigated by two studies in the US setting, with both studies indicating that dapagliflozin provided incremental QALYs as compared to standard therapy alone [76, 77].

Whilst the economic value for dapagliflozin was assessed in people with HF with and without diabetes, data for empagliflozin are only available for people with HF and T2DM. In this population, empagliflozin has been found to be cost-effective when added to standard of care. In the UK setting, empagliflozin was associated with increased life years and QALYs, with an ICER of £2093/QALY gained [78].

Overall, the evidence presented indicates that SGLT2is provide good clinical and economic value for all individuals with HF, across the whole cardiorenal metabolic continuum (HF ± T2DM ± CKD).

In clinical practice, thinking needs to be directed toward the patient with cardiorenal metabolic disease and why they are not being considered for an SGLT2i.

SGLT2IS IN CKD

Clinical Value of SGLT2is in CKD

CKD affects approximately 13.4% of the global population [79], and is associated with high morbidity and mortality, which is mainly determined by a progressive deterioration of kidney function, ultimately leading to ESKD and increased risk of CV mortality; CV events are the leading cause of death in this population [80–83]. Diabetic kidney disease, ageing, hypertension and obesity are among the key drivers of CKD prevalence and mortality. As such, the cornerstones of CKD treatment include blockade of the renin–angiotensin–aldosterone system (RAAS) pathway, as well as optimisation of glucose and blood pressure control. However, despite available treatments, risk of CKD progression and CV mortality remain high and there is an unmet need for novel renoprotective therapies. Recently, data

from the SGTL2i CVOTs (as described in the previous sections) have firmly established SGLT2is, in addition to standard of care, as an effective strategy to slow down the progression of CKD and reduce some of its associated complications in people with diabetes (EMPA-REG OUTCOMES [52], CANVAS [53], VERTIS CV [54], and DECLARE TIMI 58 [55]) and HF (DAPA-HF [4] and EMPEROR-Reduced [5]). Prompted by these results, recent randomised control trials (RCTs) were specifically designed to evaluate primary renal endpoints and confirmed that SGLT2is are an effective strategy to slow down the progression of renal disease in people with established CKD, regardless of diabetes. In the DAPA-CKD trial [6], which included 4304 individuals with an eGFR of 25–75 mL/min/1.73 m^2 and urine albumin to creatinine ratio (UACR) of at least 200 mg/g (22.6 mg/mmol) and at most 5000 mg/g (565 mg/mmol), dapagliflozin was associated with a significant decrease in the composite endpoint of sustained decline in the eGFR of at least 50%, ESKD, or death from renal or CV causes (HR 0.56, $p < 0.001$). Similar results were obtained for the composite kidney outcome of a sustained decline in the eGFR of at least 50%, ESKD, or death from renal causes (HR 0.56, 95% CI 0.45–0.68) and in the composite CV outcome of HHF or death from CV causes (HR 0.71, 95% CI 0.55–0.92). The results were consistent in both people with CKD with and without diabetes and across different eGFR thresholds.

The renoprotective effects of SGLT2is are also supported by data from the SCORED [70] and CREDENCE [60] studies. The former, indicated that sotagliflozin may slow progression of CKD in people with diabetes and CKD regardless of the presence of albuminuria. In this study, sotagliflozin showed a trend toward a reduction, over placebo, in the composite endpoint of first occurrence of a sustained decrease of 50% or more in the eGFR, from baseline for at least 30 days, long-term dialysis, renal transplantation, or sustained eGFR of less than 15 mL/min/1.73 m^2 for at least 30 days (HR 0.71, 95% CI 0.46–1.08). The CREDENCE study, which included people with T2DM and diabetic kidney disease as evidenced by UACR greater than

30 mg/mmol and eGFR greater than 30 mL/min/1.73 m^2 showed a significant reduction in the risk of renal composite of ESKD, doubling of creatinine levels or death from renal causes in people treated with canagliflozin (34% reduction; HR 0.66, 95% CI 0.53–0.81).

The benefits of SGLT2is, in terms of preventing renal outcomes, have been confirmed in the real-world setting. The CVD-REAL 3 study, a multinational, observational cohort study including data from 65,231 participants, showed that initiation of SGLT2is was associated with a 51% decrease in relative risk of the renal composite outcome of 50% decline in eGFR or ESKD, compared with other glucose-lowering drugs [7].

Economic Value of SGLT2is in CKD

Given the renal protective effects of SGLT2is and the substantial healthcare costs associated with CKD, several studies have sought to determine the heath economic value of SGLT2is in CKD.

In a study assessing the budget impact of dapagliflozin for the treatment of CKD in the UK setting, use of this treatment in the eligible population (based on CKD prevalence and DAPA-CKD criteria) led to a reduction in total 3-year costs associated with CKD management of approximately £3.3 million [84].

In a multinational study, based on data from DAPA-CKD, dapagliflozin was shown to improve clinical outcomes (i.e. rates of CKD progression and life expectancy) and quality of life in people with and without T2DM, at a cost well below the WTP thresholds in UK, Germany, and Spain (ICERs of £5940, €11,687 and €10,699, respectively) [85, 86]. Results were consistent across different subgroups (people with and without T2DM, eGFR at least and at most 45 mL/min/1.73 m^2, age less than and greater than 65, UACR 30–299 mg/g and UACR greater than 300 mg/g), with all ICERs falling below the accepted WTP threshold.

The economic value of SGLT2is is also supported by a cost-effectiveness analysis of the use of canagliflozin in people with diabetic kidney disease. The study, which was based on data

from the CREDENCE trial, demonstrated significant health gains (e.g. preservation of eGFR, reductions in the risks of dialysis, CV events, and mortality) and cost savings of £4706 per person over 10 years, in the UK setting [87]. Overall, the evidence presented indicates that SGLT2is provide good clinical and economic value for all individuals with CKD, across the whole cardiorenal metabolic continuum (CKD ± T2DM ± HF). As such, SGLT2is should no longer be considered solely as a glucose-lowering treatment and should be included as part of standard care for CKD management. In clinical practice thinking needs to be directed toward the patient with cardiorenal metabolic disease and why they are not being considered for an SGLT2i.

SGLT2IS IN CARDIORENAL METABOLIC DISEASE

Cardiorenal metabolic disease represents a significant burden in primary care. However, the evidence is compelling with respect to the outcome benefits associated with SGLT2is across the continuum of cardiorenal metabolic disease, highlighting the importance of these agents as key tools for primary care. Indeed, this drug class has been associated with significant reductions in HbA1c, blood pressure and body weight, thus substantially improving glycaemic and metabolic control in T2DM [26–51], as well as offering cardiac protection through its effects on reducing MACE, HHF and CV death [52–56, 59], and renal protection in terms of reductions in renal adverse outcomes, albuminuria, eGFR worsening and ESKD [6, 7, 52–56, 59, 60, 70] (Fig. 1).

These outcome benefits of SGLT2 inhibitors have been consistent across many patient subgroups, including those with and without T2DM, at different stages of CKD, with and without established atherosclerotic disease and with and without a previous history of HF [6, 7, 26–56, 59, 60, 70]. As such, SGLT2is should be considered as cornerstones of integrated care strategies in primary care in order to address the burden of cardiorenal metabolic disease, rather than being considered as discrete

Table 2 Summary of SGLT2i licensed indications

	Ertugliflozin	Canagliflozin	Empagliflozin	Dapagliflozin
Licensed indications	T2DM	T2DM	T2DM HFrEF	T2DM HFrEF CKD
Doses	5 mg once daily (recommended starting dose) Can be increased to 15 mg once daily if additional glycaemic control is needed and 5 mg once daily is tolerated	100 mg once daily (recommended starting dose) Can be increased to 300 mg dose if additional glycaemic control is needed and 100 mg once daily is tolerated	10 mg once daily (recommended starting dose) Can be increased to 25 mg dose if additional glycaemic control is needed and 10 mg once daily is tolerated	10 mg once daily
EGFR	≥ 60 mL/min/1.73 m^2 Initiation: 5 mg once daily Continuation: no dose adjustment needed ≥ 45 to < 60 mL/min/1.73 m^2 Initiation: not recommended Continuation: maintain dose < 45 mL/min/1.73 m^2 Initiation: not recommended Continuation: discontinue	≥ 60 mL/min/1.73 m^2 Initiation: 100 mg once daily Continuation: no dose adjustment needed ≥ 30 to < 60 mL/min/1.73 m^2 Initiation: 100 mg once daily Continuation: 100 mg once daily If further glycaemic control is needed, the addition of other antihyperglycaemic agents should be considered < 30 mL/min/1.73 m^2 Initiation: should not be initiated Continuation: 100 mg once daily if eGFR falls below 30 mL/min/1.73 m^2 (provided ACR > 30 mg/mmol). Canagliflozin may be continued for cardiorenal protection until commenced on renal replacement therapy	≥ 60 mL/min/1.73 m^2 Initiation: 10 mg once daily Continuation: no dose adjustment needed ≥ 30 to < 60 mL/min/1.73 m^2 Patients with T2DM and established CVD Initiation: 10 mg once daily Continuation: no dose adjustment needed < 30 mL/min/1.73 m^2 Initiation: not recommended Continuation: discontinue *Treatment of HFrEF* Empagliflozin can be initiated at a baseline eGFR ≥ 20 mL/min/1.73 m^2. No dose adjustment is needed. If baseline eGFR < 20 mL/min/1.73 m^2 empagliflozin is not recommended	≥ 45 mL/min/1.73 m^2 Initiation: 10 mg once daily Continuation: no dose adjustment needed ≥ 15 to < 45 mL/min/1.73 m^2 Initiation: 10 mg once a day Continuation: no dose adjustment needed Additional glucose-lowering treatment should be considered if further glycaemic control is needed *Treatment of HFrEF* Dapagliflozin can be initiated at a baseline eGFR ≥ 15 mL/min/1.73 m^2. No dose adjustment is needed. If baseline eGFR < 15 mL/min/1.73 m^2 dapagliflozin is not recommended *Treatment of CKD* Dapagliflozin can be initiated at a baseline eGFR ≥ 15 mL/min/1.73 m^2. No dose adjustment is needed. If baseline eGFR < 15 mL/min/1.73 m^2 dapagliflozin is not recommended

Table 2 continued

	Ertugliflozin	Canagliflozin	Empagliflozin	Dapagliflozin
Drug interactions	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulfonylureas, may be enhanced	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulfonylureas, may be enhanced. Co-medication with known enzyme inducers such as rifampicin and phenytoin may lead to decreased efficacy. Plasma digoxin concentrations may increase. No dose adjustment of digoxin is recommended but patients at risk should be monitored for digoxin toxicity	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulfonylureas, may be enhanced. Co-medication with known enzyme inducers such as rifampicin and phenytoin may lead to decreased efficacy	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulfonylureas, may be enhanced

ACR albumin/creatinine ratio, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *T2DM* type 2 diabetes mellitus

therapy options within individual disease states. The use of SGLT2is to manage cardiorenal patients from a holistic perspective offers an opportunity to reduce the disease burden and is likely to result in a substantial reduction in the number of hospitalisations, disease prevalence and associated costs over the next decade [88].

Despite the obvious outcomes benefits there is still an element of confusion around implementation of these agents in clinical practice, which is driven by variety of factors including confusion around label indications and dosing strategies, and misconceptions and concerns around adverse event profiles. With these issues in mind, understanding the practical considerations around SGLT2i use in the context of cardiorenal metabolic disease is essential in order to ensure optimal and appropriate use of these agents in primary care.

PRACTICAL CONSIDERATIONS

While the outcome benefits and clinical and economic value for SGLT2is are clear to appreciate from the wealth of evidence, timely and appropriate prescription of these agents, particularly in primary care, requires some consideration to optimise the risk–benefit profile.

Recent clinical trials have included individuals with eGFRs as low as 25 mL/min/1.73 m^2, thereby providing reassurance that eGFR itself is not a contraindication; however, different SGLT2is have differing licences based on their respective pivotal studies (Table 2). Thus, clinicians ought to refer to the respective licence when initiating a SGLT2i. A modest decline in eGFR (approx. 3 to 4 mL/min/1.73 m^2) is expected after initiation and should not automatically lead to drug discontinuation. For this reason, although periodic monitoring is recommended in people with CKD, guidelines do not recommend routine additional assessment of renal function following prescription of SGLT2is [11, 89–94]. Specific considerations regarding SGLT2i initiation and eGFR in people with T2DM, HF and CKD have been summarised elsewhere [11, 95–97].

The SGLT2i CVOTs have demonstrated that SGLT2is are well tolerated with a low risk of

serious adverse effects. A recent meta-analysis has sought to evaluate the overall safety of SGLT2is (ertugliflozin, empagliflozin, canagliflozin and dapagliflozin) in T2DM, HF and CKD using data from the SGLT2i CVOTs VERTIS-CV, EMPA-REG OUTCOME, EMPEROR-Reduced, CANVAS, CREDENCE, DECLARE–TIMI 58, DAPA-HF, and DAPA-CKD. Results are in line with previous reports from the literature, indicating that most of the adverse events associated with SGLT2is are consistent with the glycosuria mechanism of action of this drug class and include minor complications such as genital mycotic infections and volume depletion that should not overshadow the significant cardioprotective benefits [98] (Table 3).

The most common adverse event related to SGLT2is is genital fungal infections, which has been reported to occur in up to 11% of those receiving SGLT2i treatment [89–91, 99–101]. However, most SGLT2i-related genital mycotic infections are easily managed with topical antifungal agents, and do not require treatment discontinuation, except in cases of recurrent or persistent candidiasis [100]. Urinary infections may also occur; nevertheless, these infections are usually rare and can be addressed with standard antibiotics [102–104]. Individuals prescribed an SGLT2i should be informed about the possibility of urogenital infections and encouraged to maintain basic genital hygiene and seek medical attention if symptoms of urogenital infection develop [99, 100].

As a result of the osmotic diuretic effects associated with SGLT2is, mild volume depletion, orthostatic hypotension and dizziness may be observed in those receiving this treatment [2, 19]. Prior to initiation, blood pressure and volume status should be assessed and SGLT2is should not be initiated in hypotensive/hypovolaemic individuals [99]. This is of particular importance in those with either HFrEF or CKD. If a person with CKD develops hypotension, physicians should aim to maintain stable doses of RAAS inhibitor which have been demonstrated to confer prognostic benefit. Other antihypertensives may be reduced, particularly diuretic dosing which would address volume depletion [97]. If volume depletion occurs, SGLT2i treatment should be suspended until

this is corrected [99]. Patient education around the importance of maintaining adequate hydration is essential to minimize the incidence of these complications [100].

Although rare (0.1–0.5% in RCTs), diabetic ketoacidosis (DKA), a serious life-threatening complication, can occur in people treated with SGLT2is [99, 105]. As a result of their insulin-independent effect on glycaemia, over a third of DKA cases associated with SGLT2is present in the absence of hyperglycaemia or with mildly elevated glucose levels (euglycaemic DKA), which can be difficult to diagnose [106–108]. Thus, people prescribed SGLT2is should be advised to seek immediate medical attention if experiencing DKA symptoms (nausea, vomiting, abdominal pain) and should be evaluated for DKA and, if confirmed, SGLT2i therapy should be stopped [106, 109]. SGLT2is should not be restarted in individuals who have experienced DKA [110]. In addition, individuals prescribed SGLT2is should be educated around sick day rules in case of acute illness or in preoperative settings which should include information regarding the frequency of monitoring of blood glucose and ketone levels and the identification of symptoms of DKA.

Although SGLT2is present a low risk of hypoglycaemia, this may occur when SGLT2is are combined with other antihyperglycaemic agents, such as insulin, sulfonylureas or glinides [99, 100, 111, 112]. Thus, dose adjustments for background antidiabetes therapies should be considered in people with optimal glucose control or that have already experienced hypoglycaemia [99, 100]. Individuals should be familiar with hypoglycaemia symptoms and be advised to regularly monitor their blood glucose when starting an SGLT2i if they are on any medications that are known to precipitate hypoglycaemia [99, 100].

An increased overall risk of fractures has been described for canagliflozin, in the CANVAS trial; however, these findings were not confirmed in subsequent studies. Volume depletion and related increased risk of falls may be a possible explanation for this observation, particularly given that most of the events occurred in the first 6 months of the trial [112, 113]. A significant increase in lower limb amputation

Table 3 Reported adverse event rates associated with SGLT2is

Event	All		TD2M		HF		CKD	
	SGLT2i	Placebo	SGLT2i	Placebo	SGLT2i	Placebo	SGLT2i	Placebo
Fracture	1357/33,124	1021/26,568	1178/26,744	860/20,188	94/4231	92/4231	85/2149	69/2149
	4.0%	3.8%	4.4%	4.2%	2.2%	2.1%	3.9%	3.2%
Ketoacidosis	75/33,124	22/26,568	72/26,744	20/20,188	03/4231	0/4231	0/2149	2/2149
	0.2%	0.1%	0.3%	1.0%	1.0%	0%	0%	1.0%
Amputation	593/33,124	372/26,568	532/26,744	311/20,188	26/4231	22/4231	35/2149	39/2149
	1.7%	1.3%	2.0%	1.5%	0.6%	0.5%	1.6%	1.8%
Urinary infection	2223/33,124	1322/26,568	2101/26,744	1207/20,188	102/4231	100/4231	20/2149	15/2149
	6.7%	5.0%	7.5%	6.0%	2.4%	2.3%	0.9%	0.7%
Genital infection	1249/33,124	216/26,568	1216/26,744	201/20,188	32/4231	15/4231	1/2149	0/2149
	3.7%	0.8%	4.5%	1.0%	0.8%	0.4%	0.04%	0.0%
Acute kidney injury	449/31,261	496/24,705	387/26,744	398/20,188	23/2368	46/2368	39/2149	52/2149
	1.4%	2.0%	1.4%	2.0%	1.0%	1.9%	1.8%	2.4%
Severe hypoglycaemia	476/33,124	348/26,572	452/26,744	309/20,188	10/4231	11/4235	14/2149	28/2149
	1.4%	1.3%	1.7%	1.5%	0.2%	0.3%	0.7%	1.3%
Volume depletion	1476/33,124	1053/26,568	974/26,744	617/20,188	375/4231	346/4231	127/2149	90/2149
	4.5%	4.0%	3.6%	3.1%	8.9%	8.2%	5.9%	4.18%

Data is from a meta-analysis assessing the safety of SGLT2is (ertugliflozin, empagliflozin, canagliflozin and dapagliflozin) in T2DM, HF and CKD [98]. The meta-analysis included the SGLT2i CVOTs VERTIS-CV, EMPA-REG OUTCOME, EMPEROR-Reduced, CANVAS, CREDENCE, DECLARE-TIMI 58, DAPA-HF, and DAPA-CKD

CKD chronic kidney disease, *HF* heart failure, *RR* risk ratio, *T2DM* type 2 diabetes mellitus

risk has been observed with canagliflozin, in comparison to placebo (HR 1.97, 95% CI 1.41–2.75) [109]; however, this was not observed in following studies such as the CREDENCE trial [60]. When considering initiation of SGLT2is in individuals at high risk of amputation the importance of routine preventative foot care and ongoing monitoring should be stressed [11, 109, 112].

As a result of the presence of several comorbidities in people with cardiorenal metabolic conditions, polypharmacy may also raise certain concerns among physicians, when initiating SGLT2i treatment. Nevertheless, in all RCTs supporting the multiple indications of SGLT2is, these agents were administered on top of current standard of care and demonstrated a positive safety and tolerability profile [89–91, 114].

In addition, a recent meta-analysis [115] assessed the impact on cardiorenal outcomes of SGLT2is in combination with RAAS inhibitors vs. SGLT2is alone in people with T2DM. This study suggested that the combination with RAAS inhibitors may show additive benefit compared to SGLT2is alone, while no significant differences in terms of safety were found between people receiving SGLT2 alone or in combination with RAAS inhibitors.

Taking into account the considerations discussed above, both healthcare professional and patient education are important to maximise the risk–benefit ratio of SGLT2is. Patient education should be structured and include information on topics such as how SGLT2is work, benefits and potential side effects, as well as when to stop or resume SGLT2i therapy, and

sick day rules [116, 117]. In addition, specific education of healthcare professionals on the best use of SGLT2is in clinical practice is essential, particularly to ensure that all are aware of the benefits of these agents across the cardiorenal metabolic continuum [95, 118].

SUMMARY

SGLT2is have changed the therapeutic landscape of cardiorenal metabolic disease management and its related complications, providing good clinical and economic value across the cardiorenal metabolic continuum.

Considering the benefits of SGLT2is in terms of CV, renal and metabolic outcomes, it is now time to start think differently around the paradigm of SGLT2is in clinical practice. Indeed, use of this class of drugs should not be solely focussed on a glucose-centric therapeutic approach, but rather a holistic person-centred one. Such an approach should be aimed at mitigating morbidity and mortality over the patient lifetime by maximising outcome benefits across the cardiorenal metabolic continuum, rather than defining the treatment plan based on individual indications. With this in mind, and in line with the recently updated NICE T2DM clinical guideline which recommends wider use of SGLT2 inhibitors, alongside metformin, in the first-line treatment of T2DM [93], we encourage those involved in primary care to recognise the remarkable benefits of SGLT2is and when managing patients with cardiorenal metabolic disease to think about their patient and why they have not been prescribed an SGLT2i.

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