

ARE OUR TYPE 2 DIABETES PATIENTS SUFFICIENTLY PROTECTED FROM CARDIORENAL COMPLICATIONS?

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ABSTRACT

Cardiovascular and renal outcome trials categorically demonstrate the benefits of SGLT2 inhibitors (SGLT2i). Various pharmacotherapy algorithms recommend early use of SGLT2i, especially among those with existing cardiovascular disease, heart failure, or kidney disease. Despite a widening spectrum of patient eligibility, treatment gaps and clinical inertia still exist.

KEYWORDS: Cardiorenal, SGLT2 inhibitor.

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ARTICLE

The sociological concept of diffusion of innovation¹ can be applied in medicine. It is easy to draw parallels: innovators are the researchers, early adopters are the early implementers in clinical settings, and those who are a little slower off the blocks often argue that a robust evidence base must exist or else risk violating *Primum Non Nocere*.

Wherever we as individuals may fall in Everett Roger's continuum, we owe it to our patients to keep up with the literature and critically appraise studies as data emerges. As a clinical community, we should improve both early implementation of effective therapy as well as de-adoption of interventions that lack value.

TREATMENT GAP EXISTS

Contrary to a wealth of evidence from cardiovascular outcome trials (CVOTs), and despite updates to clinical guidelines that prioritise SGLT2 inhibitor usage, adoption and implementation in daily real-life clinical practice is lagging.² By contrast, other classes of oral agents remain more widely used despite a lack of evidence of cardio-renal benefits and similar or even higher pill costs. In a local diabetes registry³ of more than 120,000 patients across primary and specialist care, the utilisation of SGLT2

inhibitors was still under 20 percent in 2019 (from an initial 0.2 percent in 2014 when the drug class was introduced in Singapore). With 82 percent of the registry patients having eGFR >45ml/min/1.73m² (current on-label eGFR recommendation), one would nonetheless expect a substantially higher prescribing rate.

Similar sentiments of clinical inertia echo across the globe,⁴ calling for a concerted shift from linear treatment algorithms based on a HbA1c target setting to parallel, independent considerations of atherosclerotic cardiovascular disease, heart failure, and renal risks.

ACCELERATE TRANSLATION FROM TRIALS TO CLINICAL PRACTICE

CVOTs with SGLT2 inhibitors showed a consistent risk reduction of approximately 30 percent for hospitalisation for heart failure (HF), and SGLT2 inhibitors had a great potential to be effective for prevention of HF in a wide variety of type 2 diabetes (T2D) patients independent of their history of HF or cardiovascular disease (CVD).

Restricted inclusion criteria in the initial CVOTs may limit generalisability to real-world people with T2D, especially those at the low end of the CV and renal risk spectrum. In most countries, SGLT2 inhibitors are not currently prescribed in patients with eGFR <45 mL/min/1.73 m², limiting the possibility of extending these observations to a T2D population at higher renal risk. Locally, on-label prescribing at the time of press is as follows:

	Dapagliflozin	Empagliflozin	Canagliflozin
	eGFR limit for indication (ml/min/1.73m ²)		
Type 2 diabetes	>45	>45	>45
Heart failure with reduced ejection fraction (HFrEF)	>30	Not HSA approved	Not HSA approved
Diabetes kidney disease	Pending HSA review (>25)	Not HSA approved	>30

The CREDENCE trial,⁵ released in 2019, involved patients with DKD, eGFR 30 to 90 ml/min/1.73 m², and urine albumin-to-creatinine ratio (UACR) ≥300 mg/g. Canagliflozin reduced the risk of the primary composite endpoint by 30 percent, defined by doubling of creatinine, renal replacement therapy, and renal or CV death. Importantly, the risk of end-stage kidney disease (ESKD)

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was reduced by 32 percent, and risks of major adverse CV events and hospitalisation for heart failure (HHF) were also reduced.

In the DAPA-CKD¹⁰ trial, dapagliflozin reduced the primary endpoint by 39 percent, resulting in a number needed to treat of 19, and benefits were independent of glycaemic status. The risks of ≥ 50 percent eGFR decline and ESKD were reduced by 47 percent and 36 percent, respectively. The composite of CV death or HHF was reduced by 29 percent, and overall mortality was reduced by 31 percent. There were no new safety signals reported in the DAPA-CKD¹⁰ trial – in particular, no imbalances related to fracture, amputation, diabetic ketoacidosis, or serious renal events.

It is heartening to note that the cardiorenal benefits seen with SGLT2 inhibitors are also reflected in real-world evidence studies, which encompass more diverse patient characteristics and a close approximation of routine clinical practice.

CVD-REAL2,⁶ a large observational study including patients from Singapore, suggested that compared to other glucose-lowering drugs, initiation of SGLT2 inhibitors was associated with a lower risk of death and HF in real-world patients with T2D regardless of pre-existing CVDs. In both EMPRISE⁷ and CVD-REAL, a majority of patients did not have established CVD or HF at baseline, suggesting that SGLT2 inhibitors provide cardiorenal protection very early on in the progression of CVD.

EMPEROR-Reduced⁸ and DAPA-HF⁹ provided further convincing evidence that SGLT2 inhibitors, independent of diabetes status and glycaemic effects, are highly effective and well-tolerated therapies that reduce cardiovascular death/hypertensive heart failure (HHF) and improve quality of life in HFrEF. The benefits of SGLT2 inhibitors on HFrEF were similar in patients with and without diabetes, and extended down to eGFR 20 ml/min/1.73m².

Topline results from the EMPEROR-Preserved Phase III trial were released in July 2021. These results showed that it met its primary endpoint or significant risk reduction with empagliflozin for the composite of cardiovascular death or hospitalisation for heart failure in patients with heart failure with preserved ejection fraction (HFpEF) – widening the base of evidence for SGLT2 inhibitors in the spectrum of heart failure.

In the DAPA-CKD trial,¹⁰ dapagliflozin reduced the primary composite endpoint by 39 percent. The risks of ≥ 50 percent eGFR decline and end-stage kidney disease (ESKD) were reduced by 47 percent and 36 percent, respectively. EMPA-Kidney (ClinicalTrials.gov Identifier: NCT03594110) will further fill a data gap around efficacy and safety in people with lower eGFR and lower UACR.

CURRENT CLINICAL INDICATIONS FOR SGLT2 INHIBITORS

1. Type 2 diabetes
2. Type 2 diabetes and albuminuric kidney disease (albuminuria of ≥ 200 mg/g of creatinine plus eGFR of 25-90 ml/min per 1.73 m²)
3. Nondiabetic albuminuric kidney disease (albuminuria ≥ 200 mg/d plus eGFR of 25-75 ml/min per 1.73 m²)
4. Type 2 diabetes with cardiovascular disease
5. Heart failure with reduced ejection fraction, with or without diabetes

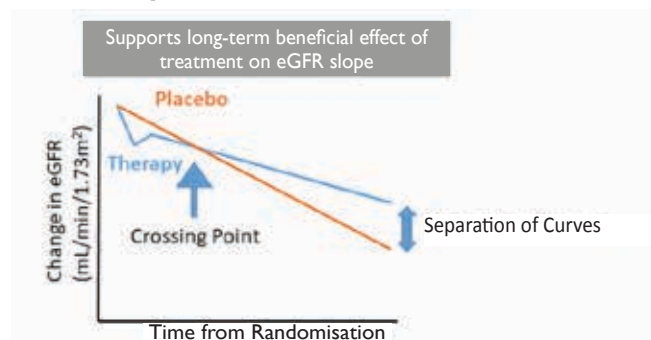
ADDRESSING BARRIERS

Cost and medication access are commonly cited barriers. Locally, this has been substantially ameliorated in the public sector with the entry of dapagliflozin and empagliflozin into the Medication Assistance Fund scheme (MAF) thanks to the onset of value-based pricing in 2017.

Clinical inertia is next. Jeong et al¹¹ documented that SGLT2 inhibitors are underutilised for eligible patients (eGFR of at least 45 mL/min/1.73 m² and UACR of at least 30 mg/g): only 32.9 percent of patients were receiving the drug treatment. The authors also observed that primary care doctors in South Korea were deferring the decision to endocrinologists, adding to treatment delay. Globally, cardiologists and nephrologists are now reframing their therapy focus, viewing SGLT2 inhibitors as agents with robust evidence for cardiovascular and renal benefits, rather than waiting for primary care or endocrinology to initiate a glucose-lowering agent.

Fear of acute kidney injury also hinders drug initiation. In reality, the initial decline in eGFR of up to 30 percent after SGLT2 inhibitor initiation is likely due to a reduction in intraglomerular pressure and actually reflects the desired drug action. In the absence of hemodynamic instability, SGLT2 inhibitors do not increase the risk of acute kidney injury (AKI). In fact, an overall reduction in AKI has been observed with SGLT2 inhibitor use.¹² It is also consistently demonstrated that eGFR curves cross at 12-14 months, with continued separation, emphasising the sustained benefits of staying on therapy.

Figure 1: The acute reversible reduction in eGFR with subsequent sustained benefits¹³



SGLT2 inhibitors do not increase the risk of hypoglycaemia even when co-administered with insulin, but a decrease in the dose of sulphonylureas may be needed. It is worth noting that SGLT2 inhibitors have not been shown to cause hypoglycaemia in patients *without* diabetes.

Effective and sensible risk mitigation strategies should always be deployed in patient selection. For those with a history of euglycaemic diabetic ketoacidosis, mycotic genital infections, or volume depletion, particularly if recent or recurrent, careful consideration should be given to the balance of benefits and harms of SGLT2 inhibitors. Inclusion of patients in shared decision-making and counselling regarding use of an SGLT2 inhibitor aids in facilitating safe implementation.

In a discrete choice experiment, adult patients with T2D in Singapore who were currently on metformin and/or sulphonylurea (first-line treatments) were asked to choose between two hypothetical medications defined by six attributes: years of medication effectiveness in controlling blood glucose; weight reduction; urinary and genital tract infection (UGTI) risk; risk of hospitalisation from heart failure; all-cause mortality risk; and out-of-pocket medication cost.¹⁴ On average, patients were willing to trade a higher UGTI risk for a more effective medication, and 88 percent selected SGLT2 inhibitors as their preferred choice. Physicians should not assume that all patients are unwilling to accept higher UGTI risk because there is notable heterogeneity in how patients trade benefits and risks.

CALL TO ACTION

Are our patients sufficiently protected from cardiorenal complications? No.

Can and should we do more? Yes.

We should no longer need to debate or hesitate over considering SGLT2 inhibitors for every eligible person with T2D, HFREF, or chronic kidney disease (CKD). The CKD and CVD risk reductions in the clinical trials of these agents occurred irrespective of glycaemic control or use of other glucose-lowering agents. It is also timely to update our local Appropriate Care Guidance on oral agents for type 2 diabetes with the abundance of evidence for cardio-renal outcomes and SGLT2 inhibitors.

In terms of therapy initiation, the narrative has already moved into (a) treating beyond glucose, and (b) beyond outpatient care: whether in-hospital initiation is safe and effective – a question that was studied in the SOLOIST-WHF trial¹⁵ for heart failure.

The evidence is clear, and growing, that SGLT2 inhibitors offer cardiorenal protection for patients both with and without T2D. Let us not be the ones to deny potentially beneficial and life-extending therapies to our patients who need it the most.

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LEARNING POINTS

- **In heart failure trials for SGLT2 inhibitors, there is consistently demonstrated reduction in cardiovascular death and hospitalisation for heart failure.**
 - **In renal outcome trials for SGLT2 inhibitors, there is consistently demonstrated reduction in clinically important hard renal endpoints.**
 - **Tackling clinical inertia requires a multifactorial approach including timely updates of guidelines, early adoption of effective therapies by clinicians, and shared decision-making with patients.**
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