

ACTING ON THE LATEST SGLT2I EVIDENCE TO TREAT CKD PATIENTS IN PRIMARY CARE

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DISCLOSURE

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ABSTRACT

The prevalence of Chronic Kidney Disease (CKD) in Singapore is increasing due to an ageing Singapore population and the increasing prevalence of risk factors such as hypertension and diabetes. Screening using serum creatinine and urine albumin to creatinine ratio (UACR) aids in the detection and classification of CKD. This allows interventions for the retardation of kidney function decline and the prevention of the complications of CKD, which includes end-stage kidney disease (ESKD), anaemia, mineral bone disorder, and mortality. Besides the optimal use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) in both diabetic and non-diabetic CKD, sodium-glucose cotransporter type 2 inhibitors (SGLT2i) have been identified to retard CKD, prevent ESKD, and mortality. More recent studies suggest that regardless of the degree of albuminuria or glycated haemoglobin, SGLT2i improves the outcomes of CKD patients. Moreover, SGLT2i can be initiated with an estimated glomerular filtration rate as low as 20 mL per minute per 1.73 m² body surface area. As nephron loss is irreversible, aggressive control of risk factors to target goals and using kidney-protective medications such as ACE-I, ARB, and SGLT2i are crucial in the remission of early CKD.

Keywords: Chronic Kidney Disease, Hypertension, Albuminuria, Asian Diabetes

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PREVALENCE OF CKD

The prevalence of Chronic Kidney Disease (CKD) in Singapore is increasing due to an ageing population and increasing prevalence of risk factors of hypertension and

diabetes. The prevalence of CKD in Singapore residents is estimated to increase from 12.2 percent in 2007 to 24.3 percent in 2035.¹ Patients with CKD stages G1 and G2 are predicted to constitute the largest proportion of CKD patients. In 2018, the National Disease Registry Office (NDRO) reported that more than 65 percent of incident end-stage kidney disease (ESKD) patients starting dialysis had diabetic kidney disease as the main cause.² Early detection of CKD and management of risk factors for progression is vital to reduce the burden of ESKD and its implication on healthcare costs and disability-free longevity.

To manage a quarter of the resident population having early stages of CKD, primary care doctors will have to bear the burden of screening and managing CKD stages G1 to G3. However, in a survey of primary care doctors, many expressed a lack of confidence in managing CKD. The methods of identifying CKD were varied and not in keeping with clinical practice guidelines.³

SCREENING FOR CKD

According to the Kidney Disease Improving Global Outcomes clinical practice guidelines, screening for CKD should be considered in patients with a history of urinary tract abnormalities such as infection or stones, chronic systemic diseases such as hypertension or diabetes, and a family history of CKD.⁴ Serum creatinine and urine albumin to creatinine ratio (UACR) are used to identify and stage CKD. Serum creatinine is used to estimate the glomerular filtration rate (eGFR in mL per minute per 1.73 m² body surface area (BSA)). Further clinical and biochemical tests will be performed according to the severity of CKD and treatment instituted for complications or preventing complications of CKD. These include blood pressure control, cardiovascular risk reduction (anti-platelet agents and cholesterol-lowering drugs), anaemia monitoring (iron supplements and erythropoiesis-stimulating agents), and mineral bone disorder management (phosphate binders and vitamin D supplementation).

In Singapore patients, up to 50 percent of patients who are receiving primary care for diabetes in polyclinics or a specialist outpatient clinic may have CKD as identified by elevated albuminuria of >30 mg/g or eGFR <60 mL/min per 1.73 m² BSA.⁵ It is thus beneficial to routinely perform serum creatinine and UACR to identify and stage CKD in order to institute CKD retardation treatments and prevent CKD complications.

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MANAGEMENT OF CKD

The key intervention in CKD retardation is office blood pressure control to a goal of <130/80 mmHg where tolerated or achievable without inducing other complications. Patients with CKD and albuminuria stage A2 or A3 have a compelling reason to be on an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin-receptor blocker (ARB); these agents are beneficial for CKD retardation beyond their blood pressure-lowering effects.

SODIUM-GLUCOSE COTRANSPORTER TYPE 2 INHIBITORS (SGLT2I)

More recently, two primary kidney outcome studies have confirmed the CKD retardation properties of Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) on top of optimal use of ACE-I or ARB.^{6,7} The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial was stopped early after an interim analysis on the recommendation of the safety monitoring committee.⁷ The trial recruited patients with type 2 diabetes and diabetic kidney disease (eGFR 30 to <90 mL/min per 1.73 m² BSA) and albuminuria (UACR, >300 to 5000 mg/g). At least 60 percent of patients had an eGFR of 30 to <60 mL per minute per 1.73 m². At the cessation of the trial, 4,401 patients were randomised, with a median follow-up of 2.62 years. The relative risk of the primary outcome (a composite of ESKD, doubling of the serum creatinine level from baseline, or death from renal or cardiovascular disease) was 30 percent lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; P=0.00001). The relative risk of the renal-specific composite of ESKD, a doubling of the creatinine level, or death from renal causes was 34 percent lower (hazard ratio, 0.66; P<0.001), and the relative risk of ESKD was 32 percent lower (hazard ratio, 0.68; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; P=0.01) and hospitalisation for heart failure (hazard ratio, 0.61; P<0.001).

SGLT2I USE IN NON-DIABETIC CKD

The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trial recruited both diabetic and non-diabetic CKD patients with an eGFR of 25 to 75 mL/min per 1.73 m² BSA, and an UACR of 200 to 5000 mg/g.⁷ The data monitoring committee recommended stopping the trial due to efficacy. A time-to-event analysis of reaching the primary composite outcome was assessed. The primary composite outcome was the first occurrence of any of the following: a decline of at least 50 percent in the eGFR, the onset of ESKD, or death from renal or cardiovascular causes. Over a median of 2.4 years, a primary outcome event occurred in 9.2 percent (197/2,152) of participants in the dapagliflozin group versus 14.5 percent (312/2,152) of participants in the placebo group (hazard ratio, 0.61; P<0.001). The hazard

ratio for the composite of a sustained decline in the eGFR of at least 50 percent, ESKD, or death from renal causes was 0.56 (P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalisation for heart failure was 0.71 (P=0.009). Death occurred in 4.7 percent (101/2,152) of participants in the dapagliflozin group and 8.6 percent (146/2,152) of participants in the placebo group (hazard ratio, 0.69; P=0.004). The effects of dapagliflozin were similar in all participants regardless of the presence of diabetes. The number of patients to treat in order to prevent one primary outcome event was low at 19. The participants without diabetes had a wide variety of causes of CKD, with the majority having hypertensive glomerulosclerosis or ischemic nephropathy, IgA nephropathy, and focal and segmental glomerulosclerosis.⁸

EFFECTS OF SGLT2I FROM CARDIOVASCULAR OUTCOME TRIALS

The effects of SGLT2i use in non-renal outcome trials on kidney-specific outcomes were also consistent in reducing the rate of eGFR decline, ESKD events, or death (see Table 1).⁹ In these studies of patients with congestive heart failure, both diabetic and non-diabetic patients with CKD (by eGFR criteria) were tested. All reported beneficial effects on kidney-specific outcomes regardless of the degree of albuminuria (A1 to A3).

The appearance of albuminuria A2 and A3 grades, and reduction of eGFR below 60 mL/min per minute, represent clear CKD, and may in fact be considered late presentations. Diabetic kidney disease and the kidney in metabolic syndrome often present with hyperfiltration, which is likely a process that in the long run contributes to nephron loss and irreversible loss of kidney function.¹⁰ Thus, early initiation of SGLT2i in diabetic and non-diabetic patients with glomerular hyperfiltration may be kidney-protective.

MECHANISM OF SGLT2I

SGLT2i work by blocking the sodium-glucose cotransporter type 2 in the nephron, resulting in an increase in urinary excretion of sodium and glucose. Clinically, patients may experience a slight drop in body weight, blood pressure, and an increase in urination. The degree of effects is proportional to the eGFR and control of blood glucose in patients with diabetes. The exact mechanism of kidney protection is unclear but may be related to reducing the work of the nephron, since less sodium and glucose is reabsorbed, leading to reduced nephron ischaemia. Another postulation is the restoration of the tubuloglomerular feedback mechanism. In advanced CKD with eGFR <30 mL/min per 1.73 m², the clinical effects are considerably less, and it is ineffective for the original indication of diabetes as the amount of glucose loss is too little to affect diabetes control. However, the kidney- and heart-protective effects remain and may be related to restoring or maintaining function in the remaining nephrons.

Table 1. Summary of SGLT2i trials on kidney outcomes

Kidney-outcome SGLT2i trials	eGFR (mL/min per 1.73 m ² BSA)	Albuminuria (mg/g)	Diabetic CKD or non-diabetic CKD	Kidney outcomes*
CREDESCENCE ⁶	30 to 90	>300 to 5000	Diabetic	Improved
DAPA-CKD ⁸	25 to 75	>200	Both	Improved
Cardiovascular-outcome SGLT2i trials	eGFR (mL/min per 1.73 m ² BSA)	Albuminuria (mg/g)	Diabetic CKD or non-diabetic CKD	Kidney outcomes*
EMPA-REG ¹⁴	>30	No restriction	Diabetic	Improved ¹⁵
CANVAS ¹⁶	>30	No restriction	Diabetic	Improved
DAPA-HF ¹⁷	>30	No restriction	Both	Improved ¹⁸
EMPEROR-reduced ¹⁹	>20	No restriction	Both	Improved

* Composite outcomes of decline in eGFR, ESKD, or death. Refer to the studies for details. Cardiovascular outcome trials had secondary analyses or a post-hoc analysis for kidney outcomes individually or in composite. This is not an exhaustive summary of all SGLT2i trials.

PRACTICAL POINTS IN USING SGLT2I

SGLT2i may be commenced in patients with diabetic or non-diabetic CKD down to an eGFR of 20 mL/min per 1.73 m². There may be a slightly increased risk of genitourinary infections and reduced blood pressure. SGLT2i were mostly well tolerated with few side effects. Personal hygiene, drinking enough water, and holding SGLT2i during a period of intercurrent illness should be advised. Some patients may need to reduce other anti-hypertensives, and occasionally some patients are symptomatic and unable to tolerate SGLT2i despite medication adjustments. In patients with poorly controlled diabetes, intercurrent illness, and relatively preserved kidney function, SGLT2i may cause diabetic ketoacidosis. To safely use SGLT2i, diabetic patients need to have adequate insulin and glucose control. In the trials, slopes of eGFR initially declined more in patients on SGLT2i when compared to placebo. However, the trajectory of the slope and gradient became less steep after about 12 months. Therefore, it is important to persist with SGLT2i treatment even if the eGFR declines initially.

SGLT2I: KIDNEY FUNCTION AND RECOMMENDATIONS

From the clinical trials, SGLT2i were initiated down to eGFR of 20 mL/min per 1.73 m². In numerous studies, SGLT2i were continued until death or ESKD. Various professional societies and organisations have included early initiation of SGLT2i from various perspectives including diabetes, congestive heart failure, and diabetic and non-diabetic kidney disease.¹¹⁻¹³ In patients with risk of CKD and ESKD, early initiation of SGLT2i may prevent the complications of CKD.

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LEARNING POINTS

- **Both diabetic and non-diabetic CKD require early detection via screening of at-risk patients in primary care and aggressive risk factor management to retard CKD, prevent ESKD, and reduce all-cause mortality.**
 - **The management of CKD includes reduction of office blood pressure to <130/80 mmHg using (in particular, ACE-I or ARBs where feasible), cholesterol-lowering medications, anaemia, and mineral bone disorder management.**
 - **SGLT2i are indicated for both diabetic and non-diabetic CKD patients with GFR >25 mL/min per 1.73 m² BSA, or albuminuria stage A2 or A3 patients in preventing ESKD and death.**
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