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COMPLICATIONS OF CHRONIC KIDNEY DISEASE: THERAPEUTIC APPROACHES AND WHAT CAN BE DONE TO HALT DISEASE PROGRESSION?

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ABSTRACT

Singapore is one of the most rapidly ageing societies in the world. Currently, Singapore ranks first in the world for the incidence of diabetes-induced end-stage renal disease (ESRD) and seventh for the incidence of kidney failures per million population. It is estimated that nearly one-quarter of Singapore's population will have chronic kidney disease (CKD) by 2035. Disease management of CKD has been identified as a critical issue due to the rapid increase in cases among the elderly in recent years. Chronic kidney disease is associated with adverse clinical outcomes, and metabolic complications such as anaemia, cardiovascular events, and CKD-associated metabolic bone diseases present treatment management complexities to healthcare professionals. Early detection and management of CKD can avert complications before symptoms occur and prevent the progressive loss of kidney function over time. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) are recommended for hypertension and proteinuria management in CKD patients with and without diabetes. However, neither of these agents alone reduces the risk of all-cause mortality; furthermore, combinational therapy of ACEI plus ARB is associated with renal dysfunction, stroke, and/or hyperkalaemia. Recently, the use of sodium–glucose cotransporter 2 inhibitors (SGLT2i) has been shown to provide favourable effects on the kidney and cardiovascular outcomes in patients with or without type 2 diabetes mellitus. Studies have shown that early initiation of SGLT2i may slow or halt the progression of CKD in patients with the risk of CKD and ESRD. This review discusses the mechanisms underlying the progression of CKD, its associated risk factors and summarises the management strategies as per Kidney Disease Outcomes Quality Initiative clinical practice guideline recommendations. This article also summarises the evidence regarding the use of SGLT2i in slowing the progression of CKD and improvement of health-related quality of life.

Keywords: CKD, Complications, Hyperkalaemia, Anaemia of CKD, CKD metabolic bone diseases, SGLT2i

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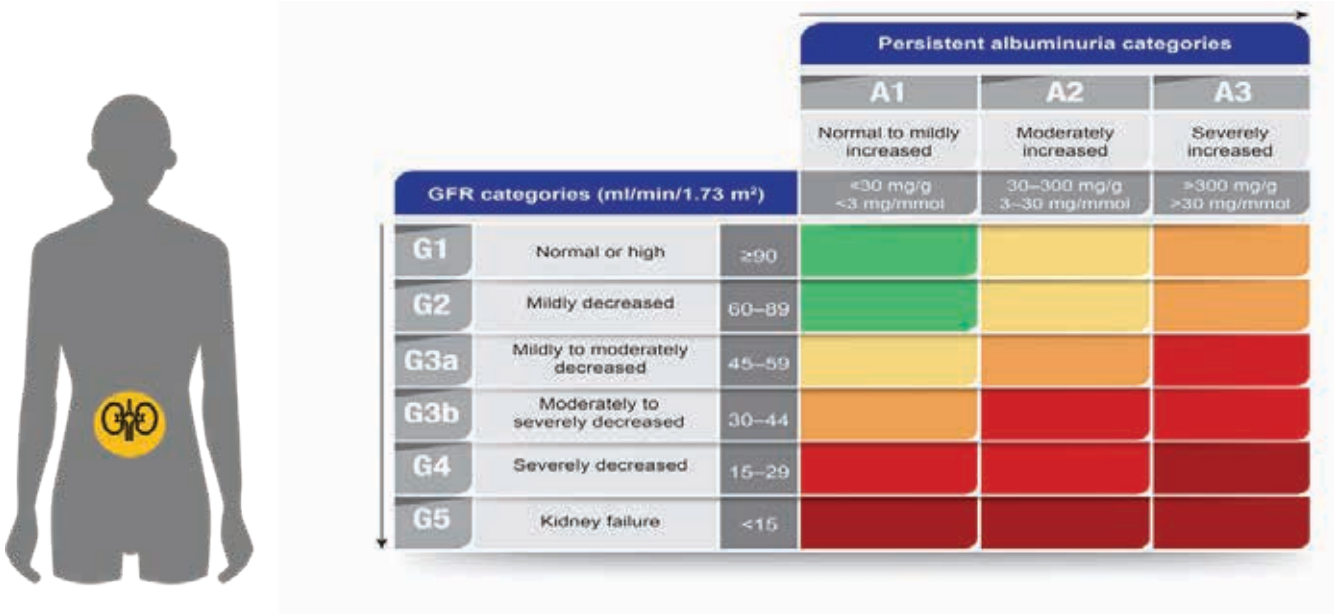
INTRODUCTION

Chronic kidney disease (CKD) is a serious, under-recognised public health problem, affecting more than 850 million people globally.[1] The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI) published the first set of guidelines in 2002, which defined CKD as either kidney damage (albuminuria, kidney biopsy findings, or imaging abnormalities) or an estimated glomerular filtration rate of <90 mL/min/1.73 m^2 (CKD stage 2-5) for three or more months, independent of the cause.[2] The current definition of CKD has been revised to include albuminuria and is based on the following criteria (refer to **Figure 1**): (i) estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 (G2-G5); or (ii) markers of kidney damage (one or more): albuminuria (urine albumin excretion rate ≥30 mg/24 h; urine albumin-to-creatinine ratio (UACR ≥30 mg/g [≥3 mg/mmol]) or history of kidney transplantation for more than three months.[3,4] Studies have shown that CKD has a powerful impact on global morbidity and mortality by increasing the risk of cardiovascular diseases (CVD), diabetes, hypertension, and systemic immune disorders.[5-8]

According to the International ESRD Comparisons Report (2020) by the United States Renal Data System (USRDS), Singapore ranks first in the world for diabetes-induced ESRD and seventh for the incidence of kidney failures per million population (pmp).[9] In Singapore, the number of patients initiated on dialysis due to diabetic kidney disease (DKD) has increased by 74 percent from 2009 to 2018.[10] As per Singapore's Renal Registry Annual Report (2020), the crude incidence rate of CKD stage 5 (G5, A1-A3) has increased significantly from 418.6 pmp in 2011 to 516.4 pmp in 2019.[11] Though the age-standardised incidence rate (ASIR) of CKD stage 5 has remained relatively stable between 2011 and 2019 (266.7 pmp and 295.3 pmp respectively), the ASIR of definitive dialysis has increased significantly from 169.6 pmp in 2011 to 187.3 pmp in 2020.[11] In addition, the age-standardised prevalence rate (ASPR) of definitive dialysis has also increased significantly from 919.2 pmp in 2011 to 1,132.0 pmp in 2020. The report pointed out that diabetic nephropathy was the main cause of CKD stage 5 among dialysis patients in 2020 (new patients: 67.8 percent and prevalent patients: 56.0 percent) and cardiac events were the predominant cause of death among prevalent dialysis patients.[11]

A study by Wong et al projected that nearly one-quarter of the population of Singapore aged 21 years and above is expected to have CKD by 2035.[6] The study also highlighted that CKD stages 1 and 2 were predicted to constitute the largest fraction of CKD patients, followed by stages 3, 4, and 5.[6] Additionally, by 2030, approximately 20.5 percent

Figure 1: Classification of chronic kidney disease and its progression. Adapted from: Vassalotti et al 2016[3] and Inker et al 2014.[4] Chronic kidney disease progression is defined as (i) a decrease in the GFR category; or (ii) a decrease in the GFR category combined with a ≥25 percent reduction in eGFR from baseline.[8] The CKD progression is considered "rapid" if a sustained decline in eGFR of >5 mL/min/1.73 m²/year is noted.[8]



GFR: Glomerular filtration rate
eGFR: Estimated glomerular filtration rate
CKD: Chronic kidney disease
KDIGO: Kidney Disease Improving Global Outcomes
ACR: Albumin-to-creatinine ratio

Note: (i) Green colour indicates CKD with normal eGFR and ACR in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with annual follow-up measurements; (ii) yellow colour indicates caution and follow-ups at least once/year; (iii) orange colour indicates the requirement of follow-up measurements twice/year; (iv) red colour indicates the requirement for measurements thrice/year; and (v) deep red indicates very high-risk category requiring follow-ups four times/year.

of Singapore's population is estimated to be elderly over 65 years, which is postulated to further increase CKD cases in the nation.[6] Early detection of CKD and management of its metabolic complications (anaemia, hyperkalaemia, metabolic acidosis, metabolic bone disease) is imperative for delaying disease progression and the prevention of CKD-associated CVD and mineral bone disease. This review discusses the mechanisms underlying the progression of CKD, CKD-associated complications, and therapeutic approaches for managing CKD as per Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline recommendations. This article also summarises the benefits of SGLT2i, in addition to that of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), in slowing the progression of CKD, management of CKD complications, and improving quality of life (QoL).

PROGRESSION OF CHRONIC KIDNEY DISEASE AND MANAGEMENT STRATEGIES AS PER GUIDELINE RECOMMENDATIONS

Risk Factors and Complications of CKD

The potential underlying mechanisms that augment the risk for CKD and progression to ESRD include obesity-mediated hypertension, inflammation, glomerular hyperfiltration, activation of the renin-angiotensin-aldosterone system, insulin resistance, hyperglycaemia, dysregulation of adipocytokines, and consequences of extra- and intrarenal ectopic fat depositions described in fatty kidney disease.[8,12] Chronic kidney disease stages 3-5, proteinuria, diabetes, and hypertension are strongly associated risk factors for CKD progression.[13] Other cited risk factors associated with CKD progression include low birth weight, high uric acid levels, hyperlipidaemia, metabolic acidosis, and disorders of metabolic bone disease.[13]

Anaemia is a common complication in CKD and a predictor of mortality, CVD-related hospitalisations, and ESRD.[14,15] The primary cause of anaemia in CKD is the inadequate production of erythropoietin by the kidneys to support erythropoiesis, which results in decreased red blood cell production.[14,15] Untreated anaemia can also accelerate the decline in renal function and affect QoL.[14-16] According to a retrospective, case-control study by Lau et al, the most reported risk factors or co-morbidities associated with CKD progression in Singapore were dyslipidaemia (92.8 percent), followed by hypertension (89.3 percent) and diabetes (64.6 percent).[16] Multivariate analysis showed that the odds of developing anaemia were significantly greater in individuals with: (i) stage 5 CKD; (ii) haematological disorders; and (iii) respiratory disorders.[16] In addition, the study highlighted that the probability of developing anaemia was reduced in patients who received iron supplements.[16]

Metabolic acidosis or acid-base imbalance is also commonly found in CKD patients due to impaired ammonia excretion, decreased tubular reabsorption of bicarbonate, and inadequate renal bicarbonate production in relation to acids produced in the body and ingested with food. Increased metabolic acidosis is linked to the shift of potassium from the intracellular to the extracellular space leading to hyperkalaemia (serum potassium >5.0 mmol/L), which is associated with significant mortality. Hyperkalaemia is observed in patients with CKD, heart failure (HF), and diabetes mellitus[17-19] due to either kidney-associated pathophysiological mechanisms mentioned above or due to the common classes of medications used in the treatment of these disorders, such as ACEIs or ARBs.[20] A substantial proportion of patients receiving renin-angiotensin-aldosterone system inhibitor (RAASi) therapy (ACEIs or ARBs) have their therapy down titrated or discontinued after a single episode of moderate-to-severe hyperkalaemia.[20] Studies have demonstrated that sub-maximal RAASi dosing or RAASi discontinuation are associated with worse cardio-renal outcomes and an increased risk of hospitalisation and mortality than patients on maximum doses.[20-22] It is important to restrict dietary potassium for the management of hyperkalaemia. However, it is important to note that highly restrictive dietary prescriptions may reduce the total calorie and protein intake, and lead to malnutrition.[4] Fluid overload often manifests in patients with moderate-to-late stages of CKD and has been associated with other co-morbidities or complications, such as anaemia, hypertension, congestive HF, left ventricular hypertrophy, and arterial stiffness.[23]

Sustained fluid overload is considered a major aetiological risk factor for hypertension, HF, hospitalisations, and mortality in patients on haemodialysis. Hypertension is both a cause and consequence of CKD and its prevalence ranges between 60-90 percent among patients with CKD.[8] Disturbances in mineral and bone metabolism affect phosphorus, calcium, and intact parathyroid hormone (IPTH) serum levels, which result in metabolic bone disease, fractures, cardiovascular complications, vascular calcification, and death among patients receiving dialysis.[24-26] A single-centre, retrospective cohort study by Chuang et al evaluated the prevalence of metabolic bone disease in CKD patients and examined the impact of achieving target parameters (serum calcium, phosphorus, and IPTH concentrations) on morbidity and mortality one year after peritoneal dialysis (PD) initiation in Singapore.[27] At baseline, 84.9 percent and 41.9 percent of the patients were prescribed phosphate binders and vitamin D supplements, respectively, for the management of metabolic bone disease.[27] The study found that the prevalence of CKD-associated metabolic bone disease in 86 patients was 67.4 percent at baseline and 86.0 percent at 4-6 months after PD initiation.[27] **Table 1** summarises the potential risk factors linked to CKD progression (A) and consequences versus benefits of early risk assessment (B).[3,4,11,28-31]

Table 1: (A) Risk factors for progression of CKD and (B) consequences of CKD prognosis versus benefits of early risk assessment and prognosis in Singapore. Adapted from: Vassalotti et al,[3] Inker et al 2014,[4] Singapore Renal Registry Annual Report 2020,[11] KDIGO 2012 clinical practice guideline for the evaluation and management of CKD,[28] Bello et al 2017,[29] Watanabe et al 2020,[30] and Hannedouche et al 2018.[31]

A) Risk factors for progression of CKD
• Diabetes • Low birth weight • Neoplasia • Hypertension • Urinary stones • Smoking • Obesity • Urinary tract infections and lower urinary tract obstruction • Autoimmune diseases • History of cardiovascular disease • Old age • Reduction in kidney mass • Systemic infections • Family history of chronic kidney diseases • Recovery from AKI

B) Consequences of CKD progression versus benefits of early risk assessment in Singapore
Consequences of CKD progression
• Anaemia • Metabolic acidosis and electrolyte abnormalities, including hyperkalaemia • Fluid overload and severe hypertension • Increased CVD risk (angina, left ventricular hypertrophy, and worsening HF) • Metabolic bone disease • Higher hospitalisation rate • Higher 1-year mortality rate • Psychosocial implications and worsening of QoL

Benefits of early CKD (stages 1-3) prognosis

- Better management of CVD and CKD complications (anaemia, metabolic bone disease, and metabolic acidosis)
- Reduced need for urgent dialysis initiation due to undiagnosed late-stage CKD
- Delay in the progression of CKD and the need to initiate renal replacement therapy (such as dialysis or transplantation)
- Reduced hospital length of stay and healthcare costs
- Improved nutritional status and QoL

CKD: Chronic kidney disease
CVD: Cardiovascular disease
RRT: Renal replacement therapy
ESRD: End-stage renal disease
AKI: Acute kidney injury
QoL: Quality of life
HF: Heart failure

MANAGEMENT OF CHRONIC KIDNEY DISEASE AS PER KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE CLINICAL PRACTICE GUIDELINE RECOMMENDATIONS

The primary goal of CKD management is to prevent disease progression, manage risk factors, reduce the risk of complications, and improve QoL. **Table 2** lists the KDOQI clinical practice guideline recommendations for the management of CKD and its complications. The KDOQI guideline recommends early identification and broad-based reporting of eGFR by clinical laboratories to maximise the prognosis of occult CKD. The KDOQI lists interventions that delay CKD progression, which include: (i) management of anaemia in CKD; (ii) ACEI/ARB for hypertension and albuminuria; (iii) control of diabetes; (iv) lipid management; and (v) correction of metabolic acidosis, hyperkalaemia, and metabolic bone disease.[3,4,32,33]

Table 2: A) KDOQI clinical practice guidelines for the management of CKD and complications. B) Criteria for referral to nephrologists. Adapted content from: Vassalotti et al 2016,[3] Inker et al 2014,[4] Kliger et al 2013,[32] and Sarnak et al 2015.[33]

A) KDOQI clinical practice guidelines for the management of CKD and complications	

Anaemia in CKD	• Diagnose anaemia in adults and adolescents (>15 years) with CKD when the Hb is <13.0 g/dL in males and <12.0 g/dL in females
	• Evaluate anaemia in patients with CKD at least once annually beginning with CKD stage G3a
	• Iron therapy has the potential to increase Hb concentrations or decrease ESA dose when TSAT is ≤30 percent and should be considered
	• A decision to administer iron in the setting of high ferritin would require assessing risks vs. benefits of persistent anaemia, ESA dosage, prevalent medical conditions, and QoL
	• Hb response to iron therapy, TSAT, and ferritin should be monitored closely, and further iron therapy should be titrated appropriately
	• Refer to nephrology for initiation of ESA therapy when Hb concentration is between 9.0 g/dL and 10.5 g/dL
	• Iron therapy for paediatric CKD cases with anaemia:
	  ◦ Initial route: oral iron (3-6 mg of elemental iron per kilogram of target dry weight once daily for 3 months)
	  ◦ Consideration of IV iron preparations for patients receiving maintenance haemodialysis
	• Overly restrictive dietary prescriptions should be avoided as a reduction in total caloric and protein intake may result in malnutrition

Metabolic acidosis	• Use of oral bicarbonate supplements is advised in CKD patients with serum bicarbonate levels <22 mmol/L, unless contraindicated • If this does not result in a serum bicarbonate level of at least 22 mmol/L, a nephrology referral is indicated
Mineral bone disorders	• It is important to measure serum levels of calcium, phosphate, PTH, alkaline phosphatase activity, and a total 25-hydroxy vitamin D at least once in adults with GFR <45 mL/min/1.73 m^2 (GFR categories G3b-G5) to determine baseline values • Suggest not to prescribe bisphosphonates in patients with GFR <30 mL/min/1.73 m^2. If hyperphosphataemia or significant IPTH elevation is noted, refer to nephrology • Prescribe vitamin D supplementation only if there is evidence of documented deficiency • Limit daily calcium intake from phosphate binders to 1,500 mg/day for elemental calcium and 2,000 mg/day for a total intake of elemental calcium including dietary calcium irrespective of the presence of calcification. If the serum calcium level is low, vitamin D sterols can be advised. If the serum calcium level is high, a calcimimetic can be advised

Glycaemic control	• It is important to target an HbA1c of ~7.0 percent to prevent or delay the progression of microvascular complications of diabetes in CKD patients • A higher target above 7.0 percent is suggested in individuals with: (i) comorbidities; (ii) increased risk of hypoglycaemia; and (iii) reduced life expectancy • Consider a reduced dose of insulin when GFR <30 mL/min/1.73 m^2 • Metformin is probably safe when GFR ≥45 mL/min/1.73 m^2. Avoid in individuals with GFR <30 mL/min/1.73 m^2; however, assess its use if GFR is stable
Blood pressure management	• The recommended target blood pressure for patients with CKD without albuminuria is ≤140/90 mmHg, whereas it is ≤130/80 mmHg for patients with albumin excretion ≥30 mg/24 h • ACEI or ARB to be advised in CKD patients with and without diabetes and urine albumin excretion >300 mg/24 h. ACEI or ARB to be used in patients with diabetes and CKD with urine albumin excretion 30-300 mg/24 h. A combination of ACEI+ARB is not advised due to increased risks of hyperkalaemia and AKI • Lower salt intake to <2 g per day of sodium (or ~5 g of sodium chloride) in adults • Use ARBs/ACEIs with caution in individuals with functional renal artery stenosis
Hyperkalaemia	• A combination of ACEI+ARB is not advised due to increased risks of hyperkalaemia and AKI. • Begin ACEI or ARB at a lower dose in people with GFR<45 mL/min/1.73 m^2. Do not routinely discontinue in individuals with GFR<30 mL/min/1.73 m^2 as they remain nephroprotective. It is important to assess GFR and measure serum potassium within 2-4 weeks of starting or following any dose escalation For the management of hyperkalaemia, it is important to (i) identify and restrict dietary potassium; (ii) manage metabolic acidosis; (iii) consider thiazide (G1-G3b CKD) or loop diuretic therapy (G4 CKD) to increase potassium excretion; and (iv) treat with a potassium-binding exchange resin for short-term usage or novel potassium binders for long-term usage
CVD complications	• Adults with CKD at risk for atherosclerotic events can be advised treatment with low-dose aspirin (acetylsalicylic acid) for secondary prevention of CVD, unless contraindicated • Treatment with lipid-lowering therapy is advised in adults younger than 50 years with (i) MI or coronary revascularisation; (ii) diabetes mellitus; (iii) history of ischemic stroke; or (iv) estimated 10-year risk of coronary mortality or nonfatal MI >10 percent • Lipid-lowering therapy in elderly individuals (aged ≥50 years) should be based on the assessment of CVD risk instead of elevated LDL-C levels

(B) Criteria for referral to nephrologists	
• AKI or abrupt sustained fall in GFR	• Hypertension refractory to treatment with 4 or more antihypertensive agents
• GFR <60 mL/min/1.73 m^2 (G3a-G5)	• Persistent abnormalities of serum potassium
• ACR >300 mg/g	• Recurrent or extensive nephrolithiasis
• Progression of CKD with a sustained decline in eGFR of >5 mL/min/1.73 m^2/year	• Hereditary kidney disease
• Patients with side-effects or contraindications to ACEI/ ARB therapy, but albuminuria >300 mg/g or nephrotic range albuminuria or proteinuria	• Persistent unexplained haematuria
• Difficulty in decreasing level of albuminuria despite the use of ACE-inhibitor or ARB therapy	• Secondary hyperparathyroidism or persistent metabolic acidosis
• Hyperkalaemia	• Concerns regarding the aetiology of albuminuria

KDOQI: Kidney Disease Outcomes Quality Initiative
CKD: Chronic kidney disease
CVD: Cardiovascular disease
Hb: Haemoglobin
GFR: Glomerular filtration rate
eGFR: Estimated glomerular filtration rate
ACR: Albumin-to–creatinine ratio
ACEI: Angiotensin-converting enzyme inhibitor
ARB: Angiotensin receptor blockers
TSAT: Serum transferrin saturation
ESA: Erythropoiesis stimulating agents
QoL: Quality of life
HbA1c: Glycated haemoglobin
IPTH: Intact parathyroid hormone
MI: Myocardial infarction
LDL: Low-density lipoprotein
IV: Intravenous

A meta-analysis by Sharma et al studied the impact of ACEI and ARB on all-cause mortality in non-diabetic patients with early-stage (stages 1-3) CKD and concluded that the evidence was inadequate in determining whether ACEI/ARB was beneficial in this subgroup of the patient population.[34] Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) monotherapy is associated with an acute reversible decline in GFR at the start of therapy (10-20 percent) depending on the baseline GFR.[35] In addition, ACEI and ARBs induce adverse effects linked to renin-angiotensin-aldosterone system inhibition, particularly hyperkalaemia noted in nearly 30 percent of patients with advanced CKD (stages 4-5).[35] These are some of the concerns with the historical usage of ACEI and ARBs in CKD, hypertension, diabetes mellitus, and CVD management. Currently, the KDOQI guidelines recommend ACEI or ARB therapy in (i) diabetic and non-diabetic adults with CKD and urine albumin excretion >300 mg/24 hours; and (ii) diabetic patients with CKD with urine albumin excretion of 30-300 mg/24 hours.[4]

The avoidance of ACEI plus ARB combination therapy is suggested due to severe adverse effects such as renal dysfunction, stroke, and hyperkalaemia.[4] In case of hyperkalaemia, it is important to consider stepwise dietary potassium (K+) restriction, consider thiazide (G1-G3b CKD) or loop diuretic therapy (G4 CKD) to increase potassium excretion, and treat with a potassium-binding exchange resin for short-term usage or novel potassium binders for long-term usage.[3,4,19,32,33,36] Non-sodium-containing cation exchange resins (calcium polystyrene sulphonate [CPS]) are used in patients with advanced CKD for the management of mild hyperkalaemia by entrapping potassium in the distal colon in exchange for calcium.[19] Recently, two novel potassium binders (sodium zirconium silicate [SZC] and patiromer sorbitex calcium) have shown clinical efficacy in reducing serum potassium with a favourable safety profile.[19] These agents open new possibilities for (i) extension RAASi therapy in patients with hyperkalaemia; (ii) normokalaemia in comorbid patients on RAASi therapy; and (iii) maintenance of cardio-renal protective effects in patients with CKD and CVD on RAASi therapy.[19] Furthermore, these novel agents have better safety profiles for long-term usage (up to one year based on current data), in comparison to the data supporting only short-term usage of the traditional potassium binders, where prolonged usage has been associated with serious complications and side effects.

CHRONIC KIDNEY DISEASE AND SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2I): A REVIEW OF THE EVOLVING TREATMENT LANDSCAPE

As the prevalence of DKD continues to rise in Singapore, so does the need for a novel therapeutic modality that can slow CKD progression and prolong the survival of patients with CKD. Sodium-glucose cotransporter 2 inhibitors (SGLT2i, dapagliflozin, canagliflozin, and empagliflozin) are promising new drug classes for renoprotection that has been shown to slow the progression of CKD with CVD benefits in clinical trials.[8] They block the reabsorption of glucose and sodium in the proximal tubule, reduce renal oxygen consumption, and promote diuresis due to glucosuria and natriuresis.[37,38] They also reduce diabetes-associated hyperfiltration, lower blood pressure, and reduce the risk of HF events.[37,38] In the past, cardiovascular outcome trials in **Table 3** have demonstrated the efficacy of SGLT2i (empagliflozin [EMPA-REG OUTCOME], canagliflozin [CANVAS], and dapagliflozin [DECLARE-TIMI 58]) in slowing CKD progression and reducing hyperglycaemia in patients with type 2 diabetes mellitus (T2DM).[39-48] However, these are largely secondary outcomes, and the mean eGFR inclusion criteria was >60 ml/min/1.73m^2. Recently, a meta-analysis study by Zhao evaluated the potential benefits of a combination of SGLT2i and ACEI/ARB over ACEI/ARB plus placebo in lowering cardiorenal events in patients with T2DM.[49] The study concluded that combination therapy would yield greater efficacy in terms of a sustained reduction in eGFR, doubling of serum creatinine, ESRD, initiation of renal replacement therapy (RRT), hospitalisation for HF, and lowering of renal or CV-related death, when compared to that of ACEI/ARB therapy alone.[49]

The key highlights of dedicated renal disease-focused outcome trials (CREDENCE and DAPA-CKD) are summarised in **Table 4A**[47,48,50-53] and **4B**.[8,10,54] These trials highlighted the benefits of canagliflozin and dapagliflozin in reducing ESRD risk, renal or CVD-related death, and hospitalisation for HF in DKD patients. DAPA-CKD was the first trial to include non-diabetic CKD patients and the first to show a reduction in risk of all-cause mortality by 31 percent in patients with CKD (eGFR: 25-75 mL/min/1.73 m^2; UACR: 200-5,000 mg/g) with or without T2DM.[8] In addition, dapagliflozin was shown to cause a 27 percent reduction in sustained decline in eGFR, ESRD, and renal or CV-related deaths. Dapagliflozin also showed reductions in renal, CV, and all-cause mortality endpoints of 29 percent, 17 percent, and 32 percent, respectively, in stage 4 CKD patients.[51] Furthermore, there were no reports of hypoglycaemia or diabetic ketoacidosis (DKA) with dapagliflozin in patients without T2DM in the DAPA-CKD study.[51]

Table 3: Key highlights of the SGLT2i cardiovascular outcomes trials (CVOTs). Adapted data from: Mahaffey et al 2019,[39] Wiviott et al 2019,[40] Roy et al 2020,[41] Zinman et al 2015,[42] Rangaswami et al 2020,[43] McMurray et al 2019,[44] Packer et al 2020,[45] Anker et al 2021,[46] Perkovic et al 2019,[47] Heerspink et al 2020.[48]

		Outcomes	Canagliflozin	Dapagliflozin	Empagliflozin
T2DM	Risk factors of ASCVD		CANVAS[39]	DECLARE TIMI-58[40,41]	EMPA REG[42,43]
		HF hospitalisation	✓ 30% RRR (CI 0.39–0.86), NR	✓ 36% RRR (CI 0.46–0.88), NR	Not studied
		Renal outcome	✓ 31% RRR (CI 0.54–0.88), NR	✓ 49% RRR (CI 0.37–0.69), NR	
	With ASCVD	HF hospitalisation	✓ 39% RRR (CI 0.44–0.85), NR	✓ 22% RRR (CI 0.63–0.97), NR	✓ 35% RRR (CI 0.50–0.65), p<0.002
		Renal outcome	✓ 30% RRR (CI 0.56–0.88), NR	✓ 45% RRR (CI 0.41–0.75), NR	✓ 46% RRR (CI 0.40–0.73), p<0.001
HFrEF			NA	DAPA-HF[44]	EMPEROR-REDUCED[45]
		Primary outcome for HF outcome	Not studied	✓ 26% RRR (CI 0.65–0.85), p<0.001	✓ 25% RRR (CI 0.65–0.86), p<0.001
		CV death		✓ 18% RRR (CI 0.69–0.95), NR	✗ 18% RRR (CI 0.75–1.12), NR
		All-cause death		✓ 17% RRR (CI 0.71–0.97), NR	✗ 15% RRR (CI 0.77–1.10), NR
HFpEF			NA	NA	EMPEROR-PRESERVED[46]
		Primary outcome for HF outcome	Not studied	Not completed	✓ 21% RRR (CI 0.03–0.93), p<0.001
		Renal outcome			✗ 5% RRR (CI 0.89–1.24), NR
CKD			CREDENCE[47]	DAPA-CKD[48]	NA
	Diabetes	Primary outcome for CKD progression	✓ 30% RRR (CI 0.59–0.82), p<0.001	✓ 48% RRR (CI 0.62–0.70), NR	Not completed
		All-cause death	✗ 17% RRR (CI 0.68–1.02), NR	✓ 29% RRR (CI 0.56–0.90), p=0.004	
	Non-diabetes	Primary outcome for CKD progression	Not studied	✓ 50% RRR (CI 0.35–0.72), NR	
		All-cause death		✓ 46% RRR (CI 0.29–0.93), NR	

ASCVD: Atherosclerotic cardiovascular disease
HF: Heart failure
CV: Cardiovascular
RRR: Relative risk reduction
CI: Confidence interval
NR: Not reported
NA: Not applicable
CKD: Chronic kidney disease
HRrEF: Heart failure with reduced ejection fraction
HFpEF: Heart failure with preserved ejection fraction
CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
DAPA-CKD: Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
EMPEROR-preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction
EMPEROR-reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reserved Ejection Fraction
DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DECLARE-TIMI 58: Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58
EMPA-REG: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose

Table 4: A) Key highlights of CREDENCE and DAPA-CKD trials. B) Summary of recommendations on the use of SGLT2i for the management of patients with CKD. Adapted content from: Perkovic et al 2019,[47] Heerspink et al 2020,[48] HSA approval for Canagliflozin,[50] Chertow et al 2021,[51] Jafar et al 2021,[52] HSA approval for Dapagliflozin,[53] Mende et al 2022,[8] Fong et al 2020,[10] Wang et al 2020.[54]

A) CREDENCE and DAPA-CKD trial: Key highlights			
	Study design	**Outcomes relative to placebo**	**HSA approval status (year)**
CREDENCE trial[47] Canagliflozin 100 mg daily versus placebo	4,401 patients with T2DM and CKD (eGFR: 30-<90 mL/min/1.73 m^2; UACR ≥300-5,000 mg/g)	• Reduction in the risk of ESRD by 32 percent (p=0.002) and of the composite endpoint of ESRD, doubling of serum creatinine, or renal-associated death by 34 percent (p<0.001). Reduced risk of CV-associated death, MI, stroke (p=0.01), and hospitalisation from HF (p<0.001)	CKD patients with T2DM, and albuminuria >300 mg/day to reduce the risk of ESRD, doubling of serum creatinine, and CV death (2020)[50]
DAPA-CKD trial[48,51,52] Dapagliflozin 10 mg once daily versus placebo	4,304 patients with T2DM (N=2,906) and non-diabetic (N=1,398) with CKD (eGFR: 25-75 mL/min/1.73 m^2; UACR: 200-5,000 mg/g)	• Dapagliflozin resulted in a sustained (at least 50 percent) reduction in eGFR, ESRD, and renal or CV-associated death by 39 percent (p<0.001). Reduction in all-cause mortality by 31 percent • In 293 patients with stage 4 CKD, dapagliflozin resulted in a 27 percent reduction in sustained (at least 50 percent) decline in eGFR, ESRD, and renal or CV-associated death. Reductions in renal, CV, and all-cause mortality endpoints by 29 percent, 17 percent, and 32 percent, respectively, were also shown	CKD patients with or without T2DM at risk of CKD progression, to reduce the risk of sustained eGFR decline, end-stage kidney disease, and cardiovascular death (2021)[53]

B) Summary of recommendations on the use of SGLT2i in CKD Management[8,10,54]

- In patients with the risk of ESRD, early initiation of SGLT2i may slow the complications of CKD in patients with or without T2DM
- SGLT2i may cause DKA in patients with poorly controlled diabetes, patients with T1DM, and hospitalised patients at high risk of DKA (surgery, infection, volume depletion, or decreased oral intake)
- With SGLT2i, it is important to start low-dose and titrate upwards. In patients with well-controlled diabetes who are on insulin therapy, it may be necessary to reduce the insulin dose to avoid the risk of hypoglycaemia. It is better to avoid excessive reductions in insulin dosage as it can increase the risk of euglycaemic DKA, which must be avoided
- As SGLT2i exhibit a diuretic effect, consider decreasing the dose of diuretic therapy and reassessing fluid status, especially in clinically euvolaemic or elderly patients

CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
UACR: Urinary albumin-to-creatinine ratio
DAPA-CKD: Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
T1DM: Type 1 diabetes mellitus
T2DM: Type 2 diabetes mellitus
SGLT2i: Sodium-glucose cotransporter 2 inhibitors
CV: Cardiovascular
CKD: Chronic kidney disease
ESRD: End-stage renal disease
eGFR: estimated glomerular filtration rate
MI: Myocardial infarction
HF: Heart failure
HSA: Health Sciences Authority

SGLT-2 inhibitors are beneficial, particularly in patients with persistent albuminuria, but have been avoided previously if eGFR is <30 mL/min/1.73 m^2. As the latest evidence shows that SGLT2i halt CKD progression, primary care physicians and nephrologists can make significant strides towards improving the outcomes of CKD patients. **Table 5** shows the HSA-approved indications and eGFR cut-offs of SGLT2i for diabetic and non-diabetic CKD patients with eGFR >25 mL/min per 1.73 m^2.[55-57]

Table 5: Health Sciences Authority (HSA)-approved indications for SGLT2i in Singapore. Adapted content from: Dapagliflozin 5 mg and 10 mg: Singapore Prescribing Information,[55] Jardiance film-coated tablets 10 mg and 25 mg: Singapore Prescribing Information,[56] Invokana (canagliflozin) film-coated tablets: Singapore Prescribing information.[57]

	Dapagliflozin 10 mg[55]	Empagliflozin 10 mg, 25 mg[56]	Canagliflozin 100 mg, 300 mg[57]
	eGFR cut-off (mL/min/1.73 m^2)		
Diabetes treatment	≥25* **continue until dialysis** (10 mg) *If eGFR falls below 45 mL/min/1.73 m^2, additional glucose-lowering treatment should be considered in patients with diabetes mellitus.	≥45 (10 mg, 25 mg)	≥45 (100 mg, 300 mg)
HFrEF treatment		≥20 (10 mg)	Not HSA approved
CKD treatment (patients with T2DM)		Not HSA approved	≥30 **continue until dialysis** (100 mg)
CKD treatment (patients without T2DM)		Not HSA approved	Not HSA approved

T2DM: Type 2 diabetes mellitus
CKD: Chronic kidney disease
eGFR: estimated glomerular filtration rate
HSA: Health Sciences Authority
HFrEF: Heart failure with reduced ejection fraction

CONCLUSION

Chronic kidney disease is associated with adverse clinical outcomes and presents numerous treatment management complexities to healthcare professionals such as anaemia, CV events, hypertension with fluid management, electrolyte abnormalities, and metabolic bone disease. The latest KDOQI guidelines recommend various treatments for the complications associated with various stages of CKD and the related co-morbidities, some of which have been detailed in this article. Early identification, broad-based reporting of eGFR by clinical laboratories, and targeted screening of at-risk patients are important to maximise the early diagnosis of occult CKD, improve clinical outcome measures, enhance QoL, and reduce all-cause mortality.

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LEARNING POINTS

- **The KDOQI guideline recommends ACEI or ARB therapy for (i) CKD patients with or without diabetes and urine albumin excretion >300 mg/24 hours; and (ii) CKD patients with diabetes and urine albumin excretion of 30-300 mg/24 hours.**
- **Hyperkalaemia has been regarded as a major reason for RAASi (ACEI or ARB) non-prescription, down titration, or discontinuation in CKD patients. Mortality rates are higher due to suboptimal ACEI or ARB dosing among patients with CKD, diabetes, or HF as compared to full dosing. The use of novel potassium binders (SZC and patiromer sorbitex calcium) can help clinicians extend RAASi therapy in patients with hyperkalaemia.**
- **In patients with the risk of ESRD, early initiation of SGLT2i, particularly those with primary evidence for retardation of CKD progression such as dapagliflozin, may slow the complications of CKD in patients with or without T2DM. As the latest evidence shows that SGLT2i halt CKD progression, primary care physicians and nephrologists can make significant strides towards improving the overall prognosis of CKD in patients.**