Unit No. I

## CURRENT MANAGEMENT AND TREATMENT FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

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#### ABSTRACT

The incidence of chronic kidney disease (CKD) is rising in many parts of the world and primary care providers are poised to be the first point of contact for these patients. The optimal management of patients with CKD include early detection, cause identification, **CKD** progression retardation (including dietary support, blood pressure control, drug therapeutics), management of comorbid conditions, acute kidney injury prevention, and knowing when to refer for specialist care. In general, the concept of CKD progression retardation involves patient education on topics such as lifestyle modification measures, e.g., diet, to reduce burden on the kidneys and use of medications that can confer renoprotection while causing little if any side effects. The advent of SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and new potassium binders provides our patients with new hope to further lengthen the time to end-stage kidney failure. It is therefore necessary that stakeholders involved in the care of patients with CKD understand the latest evidence to optimise care and patient wellbeing.

Keywords: Chronic Kidney Disease, management, retardation

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## INTRODUCTION

Chronic kidney disease (CKD) with progression to end-stage kidney failure poses significant management challenges at all levels of public healthcare globally.<sup>1</sup> Primary care providers form the first line of defence in diagnosing patients with CKD, the diagnosis of which is important in view of its strong association with cardiovascular disease and mortality.<sup>2</sup>

Managing patients with CKD includes early detection, cause identification, CKD progression retardation, management of comorbid conditions, prevention of acute kidney injury, and timely referral to specialist care.

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## EARLY DETECTION

Patients at increased risk of CKD should be screened early to reduce risk of progression to established late-stage CKD. These high-risk individuals include those with diabetes mellitus, hypertension, and cardiovascular disease. In addition, patients who are elderly, obese, have systemic illnesses such as systemic lupus erythematosus, have a family history of kidney diseases, have a prior history of acute kidney injury or pre-eclampsia, and use high-risk medications such as nonsteroidal anti-inflammatory drugs should be screened for CKD.

The detection of CKD should involve the measurement of estimated glomerular filtration rate (eGFR) through the calculation of eGFR from stable serum creatinine levels using the CKD-EPI equation<sup>3,4</sup> as well as testing of urine albumin creatinine ratio (UACR). These two tests allow appropriate staging and prognostication of a patient's CKD status as is seen in **Table 1** from the KDIGO 2012 CKD clinical practice guidelines.<sup>5</sup> Appropriate interval testing of these parameters provides an avenue for screening and monitoring of CKD progression. Each incremental stage in progression signifies an increased risk in morbidity and mortality. In patients with an unexpected, raised serum creatinine, a repeat test within one week would be necessary to exclude acute kidney injury.

## CAUSE IDENTIFICATION

In addition to measurement of UACR and serum creatinine calculation of eGFR, it is necessary to identify the cause of the kidney disease. A comprehensive history including symptomatology, chronic diseases such as diabetes mellitus or hypertension, chronic usage of nephrotoxic medications such as NSAIDs, family history of kidney disease, systemic manifestations of conditions such as systemic lupus erythematosus, and occupation should be obtained. This would complement further tests such as urine dipstick or urine microscopy for microscopic haematuria, full blood count, erythrocyte sedimentation rate, fasting blood glucose, and kidney ultrasound scans. The presence of microscopic haematuria would warrant further evaluation on whether this is glomerular or non-glomerular in nature. This would determine whether further evaluation of the urinary system for structural causes is required or a glomerular disease is suspected. Additional diagnostic tests may be guided by these initial evaluations such as autoantibodies, virology, and serum and urine protein electrophoresis.

				Persistent albuminuria categories		
CKD is defined as abnormalities of kidney structure or			A1	A2	A3	
function, present for >3 months Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g or <3 mg/mmol	30-300 mg/g or 3-30 mg/mmol	>300 mg/g or >30 mg/mmol
GFR categories (ml/min per 1.73m²)	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

#### Table I. KDIGO CKD Nomenclature

Green = low risk (if no other markers of kidney disease, no CKD)

Yellow = moderately increased risk

Orange = high risk

Red = very high risk

(Adapted from KDIGO 2012 CKD Clinical Practice Guideline)<sup>5</sup>

## **CKD PROGRESSION RETARDATION**

## 1. Lifestyle Measures

To retard progression of CKD, lifestyle modification forms an essential part of the holistic approach in managing patients with CKD. A concerted effort with practical advice enhances the ability of patients to adhere to any such regimen. Appropriate advice should include management of weight for an obese patient in view of obesity playing a role in hyperfiltration injury causing FSGS as well as worsening albuminuria in a patient who has other pre-existing risk factors. Regular exercise in particular has been shown to improve cardiovascular health in healthy individuals and in patients with CKD, potentially improve GFR, and reduce blood pressure.<sup>6</sup> In addition, heavy smoking is an important risk factor for the development of CKD and this is highly associated with the diagnoses of hypertensive nephropathy and diabetic nephropathy.7 In the Singapore Chinese Health Study, a strong dose-dependent association was seen between numbers of years of smoking and kidney failure, with risk reducing when smoking had ceased for more than 10 years.8

## 2. Diet

An individualised dietary plan should form part of the self-care advice of patients with CKD. Essentially, there are a couple of factors in which dietary adjustment plays a role. A kidney-friendly diet helps in managing risk factors associated with CKD such as diabetes mellitus and hypertension, reducing the speed in decline in GFR as well as managing uraemic complications in the later stages of CKD. In general, the two main key dietary foci are that of low sodium intake as well as protein restriction. Specific dietary potassium and phosphate restriction in general may become necessary in the later stages of CKD.

A diet high in sodium increases blood pressure and proteinuria, induces glomerular hyperfiltration, and blunts response to RAAS blockade. The KDOQI 2019 Nutrition in CKD clinical practice guideline recommends target intake for sodium in CKD of <100 mmol or <2.3 g per day, which is equivalent to ~6 g of salt daily.<sup>9</sup> This amount is equivalent to slightly more than one teaspoon. Some tips to limit dietary salt intake would include not adding salt to food when being cooked (using soya sauce as a replacement condiment<sup>10</sup>), and avoiding processed foods and usage of herbs and spices to enhance flavour. Salt substitutes such as Pansalt<sup>®</sup>, which contains higher amounts of potassium, should be avoided in patients with high serum potassium levels and in the later stages CKD in view of lower potassium clearance.

The other essential aspect to self-care is the dietary protein and energy intake adjustments necessary to retard progression towards end-stage kidney failure or death<sup>11,12</sup> and improve quality of life while balancing the risk of protein energy wasting. The minimum recommended protein intake for an adult as recommended by WHO is 0.75 g/kg body weight per day.<sup>13</sup> Over the years, there have been multiple conflicting recommendations on protein intake requirements in patients with CKD stages G3-G5 non-dialysis. The KDOQI 2019 Nutrition in CKD clinical practice guidelines recommend a low protein diet providing 0.55 to 0.60 g dietary protein/kg ideal body weight per day for patients with CKD stages G3-G5 non-dialysis who are metabolically stable.<sup>9</sup> This is similar to the ESPEN 2006 guidelines on Enteral Nutrition, which recommends GFR 25-70 ml/min.<sup>14</sup>

In general, patients with CKD should be educated on ensuring that greater than half of the protein intake should be of high biological value<sup>15</sup> with a total energy intake of between 25 to 35 kcal/kg lean body mass per day. Proteins in meats, poultry, fish, dairy products, soy protein, and eggs are of high biological value. These high biological value proteins contain essential amino acids (amino acids not able to be produced by the body). The usual recommended protein intake of an adult Singapore resident is 1.07 g/kg body weight per day, which is based on a 70 percent net protein utilisation of a mixed diet in Singapore.<sup>16</sup> Based on the Singapore National Nutrition Survey 2010, the majority of Singaporean residents' intake of protein is more than this recommendation and thus it is likely that patients with CKD require adjustment towards a lower protein diet to retard CKD progression.

Patients who are highly motivated and keen for an especially low protein diet providing 0.28 to 0.43 g dietary protein/kg ideal body weight per day with additional keto acid or amino acid analogues to meet protein requirements (0.55 to 0.60 g/kg body weight/day)<sup>9</sup> will require careful supervision by a dietitian to ensure nutritional status and energy intake is not compromised resulting in undernutrition. Dietitian support may also be necessary in patients with CKD stages G4/G5 entering dialysis as they may have poor oral intake due to uraemia, medications, or other comorbid conditions. Patients who start dialysis in a malnourished state are at greater risk of morbidity and mortality while on maintenance dialysis.<sup>17</sup>

Potassium levels may be high in patients with CKD due to excessive intake of foods high in potassium, use of angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEi) or mineralocorticoid receptor antagonists (MRA), acidosis, or constipation on a background of reducing kidney function. In most cases, hyperkalaemia occurs due to a combination of these factors. Dietary intake of potassium may need to be below 2 g per day in patients with persistent hyperkalaemia. In addition, to avoid the need for ARB or ACEi dose reduction being prescribed for kidney protection, diuretics (furosemide, hydrochlorothiazide, or indapamide) and potassium binders (sodium polystyrene sulfonate, sodium zirconium cyclosilicate, or patiromer) can be used to control chronic hyperkalaemia.

Serum phosphate levels typically rise at the later CKD stages of G3B onwards in view of reducing kidney function. Dietary phosphorus intake is important in phosphate control, and in managing mineral bone disease. Phosphorus

is found in food additives and is more readily absorbed than other dietary forms. Phosphorus intake should not be higher than 800-1,000 mg per day for patients with kidney disease; for patients without kidney disease, intake is usually 1,000-1,500 mg per day.

## 3. Blood Pressure Management

Blood pressure (BP) is commonly raised in patients with CKD and frequently require medication for control in addition to lifestyle modification. Often, routine office BP measurements are higher compared to standardised office BP measurement<sup>18,19</sup> (preferably measured by an automated office BP device) (refer to Table 2). Standardised office BP measurement should ideally be performed to ensure that the risk of overtreatment with BP medications resulting in morbidity is reduced.<sup>20</sup> This together with out-of-office BP measurements with ambulatory BP monitoring or home BP monitoring (HBPM) should be part of the monitoring process and therapeutic conversation when discussing about BP targets with patients with CKD and hypertension. It is recommended that patients with CKD and hypertension aim for a systolic BP target of less than 120 mmHg measured via the standardised office BP measurement. Patients should ideally have HBPM for comparison and especially if they seem intolerant to a target set based on shared decision making in the clinic.

The latest guideline-based target of systolic BP <120 mmHg is mainly driven by the pre-specified subgroup analyses of outcomes of baseline CKD patients within the Systolic Blood Pressure Intervention Trial (SPRINT).<sup>21</sup> The trial showed that patients with CKD and hypertension who are nondiabetic when targeting BP of less than 120 mmHg compared to <140 mmHg had reduced rates of major cardiovascular events and all-cause mortality. It is however noteworthy that despite reductions in cardiovascular events, there was no effect on the incidence of >50 percent decline in eGFR or end-stage kidney disease (ESKD) between the intensive and standard treatment group despite the intensive treatment group having lower levels of albuminuria throughout the follow-up period compared to baseline. The patients with CKD in the SPRINT cohort were generally thought to have mild CKD.

The situation is less clear in patients with CKD and diabetes with intensive systolic BP (SBP) control to <120 mmHg. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive SBP <120 mmHg compared to standard SBP <140 mmHg did not show reduction in risk of a prespecified primary endpoint of composite cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) between the two trial groups.<sup>22</sup> Patients with a serum creatinine of >132.6 µmol/ liter were excluded. The trial however did show a reduction in prespecified secondary endpoint of stroke risk (HR: 0.59; 95 percent CI: 0.39-0.89) comparing intensive SBP to standard SBP. A higher serious adverse event rate was noted in the intensive SBP group attributed to antihypertensive therapy compared to the standard SBP group.

# Table 2. Summary of standardised office BP measurement<sup>18</sup>

Patient preparation	Avoid caffeine, exercise, and smoking (>30 minutes prior to BP measurement)		
	Empty bladder before BP measurement		
	Patient should be seated in a chair with back support and feet placed on the floor, relax for >5 minutes		
	Patient or observer should refrain from talking during the resting and measurement period		
	All clothing covering the cuffing location should be removed		
Choosing the BP measurement for	Measure BP from both arms during the first visit		
diagnosis and treatment	Choose the arm with the higher BP for the following measurements		
BP measuring technique	Use a validated BP measuring device (regularly calibrated)		
	Arm should be supported, with the cuff positioned on the upper arm		
	Use proper-sized cuff (bladder size should be 80 percent of the arm circumference)		
Documentation of BP measurement	≥2 BP measurements with 1-2 minutes interval should be taken		
	Document the average of these BP measurements		
	Record both SBP, DBP, and the time of most recent BP medication intake prior to BP measurement		

BP = blood pressure

SBP = systolic blood pressure DBP = diastolic blood pressure

(Adapted from Lee JY and Han SH)<sup>18</sup>

## 4. Medications

In addition to appropriate setting of BP targets through a shared decision-making process, the choice of medication that confers renoprotection benefits is necessary to retard progression of CKD. Since the 1990s, ACEi and ARB a decade later have been the backbone of drug therapy for patients with CKD. This has in recent years been followed by landmark trials of SGLT2is in patients with both diabetic and nondiabetic CKD providing multiorgan protection beyond their initial role of glucose control and, even more recently, the beneficial effects of nonsteroidal mineralocorticoid receptors antagonists in patients with diabetic CKD.

## a. Renin-Angiotensin-Aldosterone System (RAAS) blockade

The two main angiotensin receptor blockers trials of importance that studied primary composite renal endpoints were the RENAAL (The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study) and IDNT (Irbesartan Diabetic Nephropathy Trial). In the RENAAL study, losartan compared to placebo resulted in a 16 percent (RR: 0.84; 95 percent CI: 0.72-0.98) risk reduction of the primary composite endpoint of doubling of serum creatinine, dialysis, or death.<sup>23</sup> Furthermore, the losartan group had a 35 percent reduction of albuminuria levels whereas placebo had increased in albuminuria by 4 percent. In the IDNT study, irbesartan compared to amlodipine resulted in a 23 percent (RR: 0.77; 95 percent CI: 0.63-0.93) risk reduction of the primary composite endpoint of doubling of serum creatinine, ESKD, or death from any cause, compared to placebo having a 20 percent (RR: 0.80; 95 percent CI: 0.66-0.97) risk reduction.<sup>24</sup>

## b. Real-world observations of RAAS inhibitors (RAASi)

One major point of note in the use of ARB and ACEi is that they should be administered at the highest tolerated approved doses in order to provide patients with the maximum renoprotection as is seen in positive clinical trials.<sup>20</sup> This practice however is contrary to what is observed in multiple real-world retrospective association studies of RAASi exposure dosage and the consequently poor cardio renal outcomes in view of inadequacies in following evidence-based maximally approved dosages. In a large US population-based electronic health records database review of patients with CKD, heart failure, or diabetes, only 19-26 percent of patients were noted to have been prescribed maximum doses of RAASi at various combinations of these comorbidities.<sup>25</sup> RAASi dosages in the maximum dose group were reduced in 16-21 percent of patients, and discontinued in 22-27 percent of patients, after hyperkalaemia occurrences. 54.4 percent of patients with CKD stages G3 to G4 who discontinued RAASi had an adverse outcome or death compared to 47.7 percent of patients in the submaximal group and 42.6 percent of patients in the maximum dose group (p<0.05). Adverse outcomes were defined by CKD progression and development of ESKD, stroke and acute myocardial infarction, coronary artery bypass graft, and percutaneous coronary intervention or all-cause mortality.<sup>25</sup>

These results were similar to a more recent study conducted in UK based on primary healthcare electronic health records.<sup>26</sup> This retrospective real-world association study, which included 100,572 new onset CKD patients and 13,113 heart failure patients, was studied for total RAASi exposure and association between hyperkalaemia and RAASi

Outcome	RAASi Dose (of ESC Guideline-Recommended)	Rate per 1,000 Patient-Years (95% CI)	Adjusted IRR (95% CI)
Mortality	<50%	57.73 (56.63-58.85)	5.59 (5.28-5.92)
	≥50%	7.17 (6.80-7.56)	Reference
MACE	<50%	130.38 (128.72-132.05)	1.61 (1.56-1.66)
	≥50%	72.95 (71.75-74.17)	Reference

Table 3. Incidence of Mortality and MACE in the CKD cohort stratified by RAASi Dose

CKD = chronic kidney disease

ESC = European Society of Cardiology

IRR = incident rate ratio

MACE = major adverse cardiac event

RAASi = renin-angiotensin-aldosterone system inhibitor

(Adapted from Linde et al)<sup>26</sup>

down titration, as well as major adverse cardiovascular events (MACE) and mortality. In the CKD cohort, 63.7 percent of patients were prescribed ACEi doses of >50 percent of guideline recommended doses compared with only 39.8 percent prescribed with ARB (refer to **Table 3**). There was also a linear correlation between severity of hyperkalaemia resulting in either down titration or discontinuation of RAASi. The incidence of MACE and mortality was consistently lower in patients being treated with >50 percent of guideline recommended dose within the 10-year period.<sup>26</sup>

These observations despite them being retrospective does cast a shadow on suboptimal use of RAASi in patients with CKD. The cause of RAASi discontinuation or down titration may be due to patient intolerance, AKI events, or hyperkalaemia. In patients with stable GFR and have chronic hyperkalaemia, after excluding pseudohyperkalaemia, it is advisable for serum potassium optimisation through dietary measures, use of potassium losing diuretics, and or use of newer generation potassium binders such as sodium zirconium cyclosilicate or patiromer. These new potassium binders have better tolerability and safety profile (5-8) to allow for concomitant use with maximal tolerated doses of RAASi to reduce risk of poor cardio renal and mortality outcomes.

#### c. Sodium-Glucose Cotransport-2 inhibitors (SGLT2i)

There has been great excitement around the use of SGLT2i not only as a glucose-lowering agent but more widely for cardiovascular and multi-organ protection in view of its benefits in improving the metabolic profile of patients. The concept of multi-organ protection arose from the multiple mechanisms by which SGLT2i influences. Besides glucose lowering in diabetic patients, these metabolic effects include tubuloglomerular feedback resulting in reduced glomerular hyperfiltration for renoprotection, osmotic diuresis for cardiac protection, and improvement in fatty acid utilisation for liver protection, and improvement in insulin sensitivity from preserving beta cell function.<sup>31,32</sup>

In patients with type 2 diabetes mellitus, it is clear that SGLT2i improves kidney and cardiovascular outcomes. The CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial, which was stopped early because of overwhelming benefit, recruited patients with eGFR of 30 to 90 mL/min/1.73 m<sup>2</sup> body surface area (BSA) and a UACR of 300 to 5,000 mg/g on RAS blockade.<sup>33</sup> Canagliflozin reduced the relative risk of a composite primary outcome of ESKD, doubling of the serum creatinine and death from renal or cardiovascular causes by 30 percent (HR: 0.70; 95 percent CI: 0.59-0.82), resulting in a number needed to treat of 22 for 2.5 years. These benefits were present irrespective of Hba1c levels.

These findings were again shown in the DAPA-CKD (Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease) trial, which was also stopped early because of overwhelming efficacy. The DAPA-CKD trial recruited patients with or without type 2 diabetes mellitus with eGFR of 25 to 75 ml/min/1.73 m<sup>2</sup> BSA and a UACR of  $\geq$ 200 mg/g on stable maximally tolerated dose of ACEi or ARB. Dapagliflozin reduced the relative risk of a composite primary outcome of a sustained decline in the eGFR of at least 50 percent, ESKD, or death from renal or cardiovascular causes by 39 percent (HR: 0.61; 95 percent CI: 0.51 to 0.72), resulting in a number needed to treat of 19 for 2.4 years.<sup>34</sup> This effect was similar in patients with and without type 2 diabetes. In addition, the risk of the primary endpoint was maintained in patients with or without a history of known cardiovascular disease at baseline.

What was especially noteworthy in the DAPA-CKD trial was the benefit in patients with nondiabetic CKD (ischaemic/ hypertensive nephropathy, IgA nephropathy, and focal segmental glomerulosclerosis (FSGS)) as well. Furthermore, no safety signals related to severe hypoglycaemia, fractures, amputation, diabetic ketoacidosis (DKA), or serious renal events were seen in the dapagliflozin group. Is dapagliflozin ready for prime-time use in patients with nondiabetic CKD? Based on the mechanism of action of SGLT2i, the kidney and heart protection is likely due to a reduction in intraglomerular pressure as a result of glycosuria and natriuresis and tubuloglomerular feedback reducing single nephron GFR, thereby protecting proximal tubules by reducing workload already compromised by decreased oxygenation.<sup>35</sup> This mechanism of reducing glomerular filtration rate protects the surviving nephrons of patients with CKD.

In view of these effects, it is likely that the beneficial effects of SGLT2i can be seen in the chronic phase of patients with IgA nephropathy as well as in non-immune mediated glomerular diseases such as hypertensive nephropathy and secondary FSGS. The role of SGLT2i in patients with active immune mediated glomerular diseases and polycystic kidney disease (deleterious in some animal studies) is currently unknown and subject to further investigation. The results of EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin, NCT03594110), which also included patients with or without type 2 diabetes mellitus and eGFR 20 to 90ml/min/1.73m<sup>2</sup> BSA, is currently awaited. This study has also been stopped early due to positive efficacy.

One of the issues with starting SGLT2i is related to the patient education necessary to prime patients of potential safety issues and ways to mitigate this. Patients on SGLT2i who are at risk of DKA include patients who have had prior history of DKA, patients who have late autoimmune diabetes in adults (LADA), patients with pancreatic failure, patients who have rapid progression to needing insulin at diabetes mellitus onset, and patients who are dependent and drink excessive alcohol. In addition, patients with very high HbA1c and have osmotic symptoms should not be started on SGLT2i at the outset. Patients should be provided "Sick Day" guidance to mitigate risks of adverse events related to SGLT2i use. This "Sick Day" advice should include holding off on taking SGLT2i in the event the patient is unwell and unable to keep up with fluid intake and at risk of dehydration. Patients on insulin and if unwell or temporarily stopped for serious illness or surgery should also have their SGLT2i withheld. This can however be restarted once the patient is better and is on stable doses of insulin.

In addition to "Sick Day" guidance, it would be necessary to forewarn patients of the risk of mycotic genital infections, which can be mitigated by advice on good genital hygiene. These patients should also be counselled on self-care with the use of anti-mycotic creams or powders. For patients who have excellent Hba1c levels and are on insulin or sulphonylureas, due consideration should be made to reduce these medications prior to starting SGLT2i in view of a potential small risk of hypoglycaemia.

## d. Mineralocorticoid receptor antagonist

Aldosterone typically regulates extracellular volume and maintains sodium and potassium homeostasis. However, aldosterone can also directly accelerate kidney damage by sustaining cell growth, causing inflammation and fibrosis.<sup>36</sup> Steroidal MRA such as spironolactone is

typically used in patients with early stage CKD to aid in reduction of proteinuria as well as control BP in patients with resistant hypertension.<sup>37</sup> Spironolactone is usually added on to patients already on maximum doses of ACEi or ARB who show evidence of aldosterone escape (nonmaximal suppression of proteinuria). Nevertheless, use of spironolactone is typically limited by hyperkalaemia and gynaecomastia.

Finerenone is a novel nonsteroidal MRA that binds to the mineralocorticoid receptor with higher affinity than steroidal MRAs and inhibits recruitment of transcriptional coactivators involved in expression of hypertrophic and profibrotic genes. The Fidelio DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) recruited patients with UACR of 30 to 300 mg/g, eGFR of 25 to less than 60 ml/minute/1.73 m<sup>2</sup> BSA and diabetic retinopathy, or patients with UACR 300 to 5,000 mg/g and eGFR of 25 to less than 75 ml/minute/1.73 m<sup>2</sup> BSA. All patients were on stable maximally tolerated RAS blockade before being randomised with a serum potassium level of ≤4.8 mmol/L. Finerenone reduced the primary composite outcome of kidney failure, sustained decrease of 40 percent in the eGFR from baseline, or death from renal causes compared to placebo by 18 percent (HR: 0.82; 95 percent CI 0.73-0.93).<sup>38</sup> Hyperkalaemia-related adverse events were noted to be 18.3 percent in the finerenone group and 9.0 percent in the placebo group. Hyperkalaemia led to discontinuation of trial drug in 2.3 percent of the finerenone group and 0.9 percent in the placebo group. The American Diabetes Association guideline update 2022 recommends that patients with diabetes mellitus and CKD at increased risk for cardiovascular events or CKD progression or are unable to use a SGLT2i be prescribed finerenone to reduce risk of CKD progression and cardiovascular events.<sup>39</sup> The role of finerenone in patients with nondiabetic CKD is currently still under investigation.

## MANAGEMENT OF OTHER COMORBIDITIES

In addition to lifestyle measures, blood pressure control, and use of appropriate drugs to retard progression of CKD, other comorbidities such as gout, dyslipidaemia, and diabetes mellitus need to be controlled as these are risk factors for cardiovascular disease and CKD progression.

## PREVENTION OF ACUTE KIDNEY INJURY

One of the risk factors for progressive CKD is repeated kidney insults. This can be from over-the-counter medications such as nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or long-term use of omeprazole leading to interstitial nephritis. Other potential insults include use of iodinated contrast agents for scans or cardiac interventions. The risk factors associated with poor outcomes from an episode of AKI causing progressive decline in kidney function include older age, delayed recovery from AKI, severe AKI episodes, presence of proteinuria, and the presence of comorbid conditions such as diabetes mellitus, hypertension, and heart failure. $^{40}$ 

## TIMELY REFERRAL TO SPECIALIST CARE

Referral of a patient to a nephrologist may be necessary under the following conditions (refer to **Table 4**). The typical reason would be if the cause of CKD is unclear beyond diabetic kidney disease or hypertensive nephropathy due to longstanding hypertension. Patients who have persistence of microscopic haematuria (>3 red blood cells per high power field) may require urological opinion especially if the patient is a smoker, male, and is aged more than 35 years of age. At times, both nephrological and urologic consult may be necessary. Patients who have concomitant proteinuria, haematuria, and high blood pressure may have a nephritic process that would warrant urgent referral to a nephrologist. Unexplainable acute kidney injury or fast progressors (>5 ml/min decline in eGFR per year) warrants early referral as well.

Beyond these acute reasons for referral, patients with CKD stage G4 or G5 should be referred to a multidisciplinary CKD care (nephrologists, advanced practice nurses, renal coordinators, dietitians, pharmacists, medical social workers) programme. These patients usually require patient education, more intensive nutrition support counselling, and pre-dialysis counselling to improve cardiovascular mortality, slow progression of CKD, and improve transition of care to dialysis therapies or transplantation.<sup>40</sup> In addition, patients with CKD stage G5, who are frail with multiple comorbidities and opt for comprehensive conservative management through a planned shared decision-making process taking into account their values, goals, priorities, and prognosis, can be holistically supported.

#### Table 4. Referral criteria to a nephrologist

CKD stages G4 and G5 (with or without diabetes)

>5 ml/min reduction in GFR in 1 year

Suspicion of glomerulonephritis or renal vasculitis

Unexplainable AKI (e.g., sustained >30% reduction in serum creatinine from baseline after starting ACEi/ARB)

Possible systemic illness (e.g., SLE or Myeloma)

Poorly controlled BP despite four BP medications

Suspected genetic cause of CKD

#### CONCLUSION

In recent years, there have been new groundbreaking therapeutics, notably the SGLT2i, that have changed the paradigm for treatment of patients with CKD. The concept of multi-organ protection and reduction in cardiovascular disease risk through correction of metabolic dysfunction by these medications afford patients with established CKD a longer runway towards end-stage kidney failure. Notwithstanding, traditional interventions such as dietary modifications, control of blood pressure, and comorbid conditions as well as the prevention of AKI still play an important part in the management of CKD. It is necessary that CKD management be inclusive of a holistic approach driven by patient-centred care and shared decision-making processes.

## **DECLARATION OF CONFLICT OF INTEREST**

Dr Choo Chon Jun Jason reports serving as Consultant and Advisory board member for Novartis, Bayer, AstraZeneca, Nitto Denko Asia Technical Centre, and GlaxoSmithkline; Steering Committee member for AstraZeneca and Boehringer Ingelheim; Speaker for Abbott, Bayer, and AstraZeneca; Scientific grant funding from Nitto Denko Asia Technical Centre, NMRC Singapore, and SingHealth.

#### REFERENCES

- Shlipak MG, Tummalapalli SL, Boulware LE, Grams ME, Ix JH, Jha V, et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2021;99(1):34-47.
- Ryu H, Kim J, Kang E, Hong Y, Chae D-W, Choi KH, et al. Incidence of cardiovascular events and mortality in Korean patients with chronic kidney disease. Scientific Reports. 2021;11(1).
- Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. Annals of Internal Medicine. 2009;150(9):604.
- Teo BW, Xu H, Koh YY, Li J, Sinha AK, Shuter B, et al. Estimating Kidney Function in a Multiethnic Asian Population With Multiple Filtration Markers. American Journal of Kidney Diseases. 2012;60(3):500-2.
- Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease. JAMA : the journal of the American Medical Association. 2015;314(2):151.
- Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, et al. Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia. JAMA : the journal of the American Medical Association. 2014;312(21):2223.
- Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, et al. Sodium Zirconium Cyclosilicate in Hyperkalemia. New England Journal of Medicine. 2015;372(3):222-31.
- Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors. New England Journal of Medicine. 2015;372(3):211-21.

#### LEARNING POINTS

- Lifestyle measures, especially dietary modification with adherence to a low-protein diet and sodium restriction, forms an important part of the self-care of a patient to retard progression of CKD.
- Real-world observation on the use of renin angiotensin system blockers suggests that there needs to be more effort in ensuring that patients with CKD be prescribed maximally tolerated doses to improve cardio renal outcomes. Hyperkalaemia events triggering down titration of RAS blockers can be mitigated with the use of newer potassium binders.
- There is emerging evidence that SGLT2 inhibitors can be prescribed to patients with nondiabetic CKD EXCEPT for active immune mediated glomerular diseases and polycystic kidney disease (where evidence is currently lacking).