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Framework of Guidelines for Management of CKD in Asia

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INTRODUCTION

Approximately 850 million individuals live with kidney disorders globally.[1] Chronic kidney disease (CKD) is an emerging public health concern with a global prevalence of 13.4%.[2] The overall prevalence of CKD in Asia is estimated to be 434.3 million (95% confidence interval [CI]: 350.2 to 519.7) including 65.6 million (95% CI: 42.2 to 94.9) with advanced disease.[3] However, there is substantial variation in CKD prevalence across the Asia-Pacific region (4.7%–17.4%) with the highest disease burden observed in China and India.[3] The high prevalence in Asia (approximately 34%) is attributable to exponential rise in the risk factors for CKD, including diabetes, hypertension, obesity, and cardiovascular disease (CVD).[3,4] Between 1990 and 2019, most Asian countries documented an increase of more than 100% in the absolute count of CKD incident cases, deaths, prevalent cases, and disability-adjusted life years.[5] CKD is associated with increased hospitalization, productivity loss, and substantial economic burden on patients, payers, and healthcare infrastructure.[6,7]

Appropriate screening, diagnosis, and optimum management of CKD and its comorbidities are imperative to delay the progression to kidney failure and premature mortality in this patient population. Although Kidney Disease Improving Global Outcomes (KDIGO) has developed evidence-based practice guidelines to optimize the management of patients with CKD, these guidelines have witnessed limited uptake especially in resource-limited countries. Adoption of KDIGO guidelines with the local perspective are likely to be instrumental in improving the accessibility of CKD care, outreach and patient compliance. This paper outlines a framework of guidelines for screening and diagnosis, treatment goals, management of various comorbidities and/or complications, and referral of patients to nephrologists in the Asian region. The overall objective is to utilize the existing international and national guidelines as a foundation to create more appropriate regional guidelines for management of CKD in Asian countries. Application of these evidence-based clinical practice guidelines (CPGs) in low- and middle-income countries (LMICs) is anticipated to improve the management of CKD and patient outcomes. In addition, strategies to ensure successful implementation of these regionally-adapted guidelines in clinical practice in LMICs are discussed.

Methods

For developing a recommendations framework for CKD in Asia, a 3-step process was implemented. A meeting was conducted where key recommendations from several international and local guidelines were discussed. The specialists provided insights based on their clinical experience regarding common practices and challenges in screening, diagnosis, and management of CKD in Asia. An evidence-based literature search that included a review of relevant international and regional guidelines was

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conducted in September 2022. The strength of evidence recommendations presented in these guidelines are indicated as Level 1 or Level 2 along with a rationale. The quality of the supporting evidence is categorized as high (Grade A) for evidence based on properly conducted randomized clinical studies; moderate (Grade B) for well-designed controlled trials without randomization; low (Grade C) for evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 center or group; or very low (Grade D), if there is low level of evidence (LOE) for the recommendation (Supplementary Table S1). A section on implications and outlook for Asian countries has been included. Practice points based on current regional practices for CKD management are also provided.

The framework of recommendations is designed for ease of adopting the international CKD guidelines across Asian countries.

FRAMEWORK FOR DIAGNOSIS OF CKD AND SCREENING FOR CKD

Recommendation Summary

- Target populations for screening to include:
  - diabetes mellitus
  - hypertension
  - obesity
  - CVD
  - family history of CKD
  - use of nephrotoxic drugs
  - use of herbs or exposure to nephrotoxins, and
  - history of acute kidney injury
- CKD screening tests in target population to include urinalysis, serum creatinine-based estimated glomerular filtration rate (eGFR), urine dipstick, and blood pressure (BP) measurement.
- Screening for CKD should be performed at the time of diagnosis of type 2 diabetes (T2D) followed by annual screening; and annually for individuals with type 1 diabetes mellitus 5 years after diagnosis.
- Urine albumin-to-creatinine ratio and eGFR should be used for the screening of CKD in adults with T2D, hypertension; and in all other high-risk groups population
- CKD screening and treatment requires multistakeholder implementation strategies to overcome barriers to high-quality CKD care.

Early diagnosis and appropriate management of CKD can prevent and delay the progression of the disease to end-stage kidney failure.[8–12] This section provides the framework for recommendations for screening and diagnosis of CKD.

Rationale

The most widely accepted diagnostic criteria for CKD are derived from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative of 2002, and the international guideline group of KDIGO of 2012.[13] CKD is defined as:

- Abnormalities of kidney structure or function, present for >3 months, with implications for health
- Either of the following must be present for >3 months:
  - Markers of kidney damage (1 or more)
  - Glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2

The KDIGO guidelines provide clinical recommendations on the screening, monitoring, and treatment of adults with stage 1 to 3 CKD (Table 1).[13,15-31] The recommendations from the Asian forum for CKD initiatives on screening identified the target populations for screening (age above 65 years; T2D; hypertension; obesity; family history of CKD; use of nephrotoxic drugs, herbs, or nephrotoxins; and history of acute kidney injury) and recommended the use of a spot urine sample for estimating protein and red blood cells and estimation of GFR (eGFR) based on serum creatinine concentration.[32] Screening should also include BP measurement. When screening a high-risk group (older age, high BP, diabetes, CVD, family history of kidney disease, history of acute kidney injury, or other medical conditions that impact kidney function), even if CKD is not confirmed, education of the patient can help in prevention. Therefore, it is necessary to conduct CKD screening in high-risk groups among the general population. In particular, for patients with T2D and hypertension, screening for CKD through GFR and proteinuria is cost-effective.[33–36] The frequency of screening for CKD should be performed yearly in patients with a high risk of CKD.

The KDIGO held a conference entitled "Early Identification and Intervention in CKD" in 2019 with a global multidisciplinary panel of clinicians and scientists. The panel reached a consensus with a comprehensive and proactive plan for CKD screening, risk stratification, and treatment with the goal of reducing the global burden of kidney disease (Table 1).[37] The KDIGO heat map is a useful tool in assessing the risk of kidney disease in individuals by risk stratification. It aids in monitoring progress and is critical in guiding ongoing treatment for individuals with risk factors. It uses the eGFR and albuminuria (measured by albumin-to-creatinine ratio) obtained from screening to evaluate the risk of kidney disease progression and end-stage kidney disease (Figure 1).[38]

Table 1. Recommendations of early identification and intervention in CKD: Asia perspectives[13,15-31]

KDIGO consensus	Asia perspective	Asia recommendations and practice points
• Persons with hypertension, diabetes mellitus, or CVD should be screened for CKD. • CKD screening and treatment programs should also be implemented in other high-risk individuals and populations based upon comorbidities, environmental exposures, or genetic factors. Recommendation: Annual screening for diabetic kidney disease be performed beginning 5 years after diagnosis of T1D and at diagnosis of T2D [2C] Practice points: • Initial efforts for early CKD screening should target high-risk patients, such as older age, high BP, diabetes, CVD, family history of kidney disease, history of acute kidney injury, and other medical conditions that impact kidney function (e.g., SLE, HIV, obesity, and genetic risk factors) and high-risk occupations and environmental exposure to nephrotoxins • Geographically distributed screening targeted for at-risk populations should also be considered, especially in the setting of low socioeconomic status or poor access to healthcare	• Malaysia and Singapore recommend annual screening for CKD with urinary albumin assessment and eGFR in patients with diabetes (5 years after diagnosis of T1D and at diagnosis in T2D) and hypertensive patients but provide limited further guidance on other risk factors • As per Academy of Medicine Singapore, individuals at increased risk of developing CKD should undergo screening for kidney disease annually.[14] Screening includes assessment of proteinuria, hematuria, and kidney function. • In Hong Kong screening for CKD is targeted and performed in individuals at increased risk, including those with diabetes, hypertension, and established CVD. The screening tools include history taking, BP recording, urine dipstick testing for protein and red cells, and measurement of serum creatinine. Urinary albumin in diabetic patients, or UACR in dipstick-positive individuals is further evaluated • In Vietnam, high-risk population include patients with diabetes, hypertension, and a family history of CKD, and these patients should be screened for CKD annually (guidance for diagnosis and treatment in some nephrology and urology diseases) (Ministry of Health, 2015) • Countries with a high prevalence of CKD of unknown origin such as India, Taiwan, Thailand etc. should adopt frequent screenings such as the CKDNET programme in Thailand	• Targeted screening strategies developed for LMICs considering the limited availability of primary care health services and often under-resourced healthcare settings must be implemented • Determine local risk factors specific to the population for screening. • Identifying the geographical variation in the prevalence of CKD of unknown origin can aid in frequent screening and surveillance programs and timely interventions Recommendations: Patients with the following risk factors should be screened for CKD. • Elderly patients • Hypertension • T1D and T2D • Family history of CKD • History of CVD • Polycystic kidney disease • Obesity • Kidney toxicity drug exposure • History of acute kidney injury (including infectious causes such as malaria, acute gastroenteritis, and dengue) • Urinary tract infection, urolithiasis, urinary tract obstruction, low birth weight, systemic infection, autoimmune disease • Single kidney or renal parenchymal decrease • Screening frequency for each risk factor is to be individualized (e.g., annual screening for diabetes mellitus, hypertension, and CVD).
• The initiation of CKD screening should be based on comorbidities and individualized risk assessment of patient rather than at a specific chronologic age. Assessing both kidney function by eGFR through serum creatinine and kidney damage by measuring albuminuria through UACR is critical both to detect and to risk stratify CKD • Accurate GFR estimation includes both creatinine and cystatin C measurement for initial diagnosis and staging. The inclusion of cystatin C in CKD diagnosis and treatment initiatives is consistent with the KDIGO 2012 Guidelines and is a critical component of accurate risk stratification, as cystatin C markedly strengthens the association between eGFR and cardiovascular events, kidney failure, and death Recommendation: UACR and eGFR should be used for the screening of diabetic kidney disease in adults with diabetes mellitus [1B]	• The cost of measuring creatinine, cystatin C, and UACR in LMICs may be prohibitive. Creatinine testing and dipstick screening for albuminuria is considered to be an acceptable first step in targeted population if followed by appropriate confirmatory testing	• The risk factors for CKD such as diabetes, hypertension, and obesity are known to develop at a young age (approximately 50 years) in Asian population. Thus, age limit for CKD screening should be individualized with respect to epidemiology of CKD in individual countries • Random UACR predicts 24-hour urinary albumin excretion well and can be utilized instead of the 24-hour urine collection for albumin • In resource-limited countries, screening for albuminuria may suffice as it is a well-recognized independent risk factor for the development of CKD and cardiovascular morbidities and mortality Recommendations: Diagnosis of CKD is based on objective test results and is made through relatively simple blood and urine tests. The examination items for CKD diagnosis are as follows: • BP measurement • Urinalysis (UACR, urine sediment, urine dipstick test) • Calculation of eGFR

BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; CKDNET, chronic kidney disease prevention in the Northeast Thailand; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; LMICs, low- and middle-income countries; SLE, systemic lupus erythematosus; UACR, urinary albumin-to-creatinine ratio; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus.

Asia Perspective

Asia, being the most populous continent in the world with a staggering disease burden of diabetes and hypertension, is expected to witness an exponential rise in the burden of CKD.[39] This is also compounded by the fact that there is a general lack of disease awareness and access to treatment in Asian countries. The volume of undiagnosed diabetes mellitus, hypertension, and CKD in many areas of Asia with limited economic healthcare resources mandates CKD screening to be an integral part of the current healthcare strategies in Asia.[32] CKD screening and targeted early identification while asymptomatic or in an early clinical stage can enable effective interventions that delay disease progression and reduce the incidence of associated complications such as cardiovascular (CV) risk, hyperlipidemia, anemia, and mineral and bone disease (MBD).[1,40]

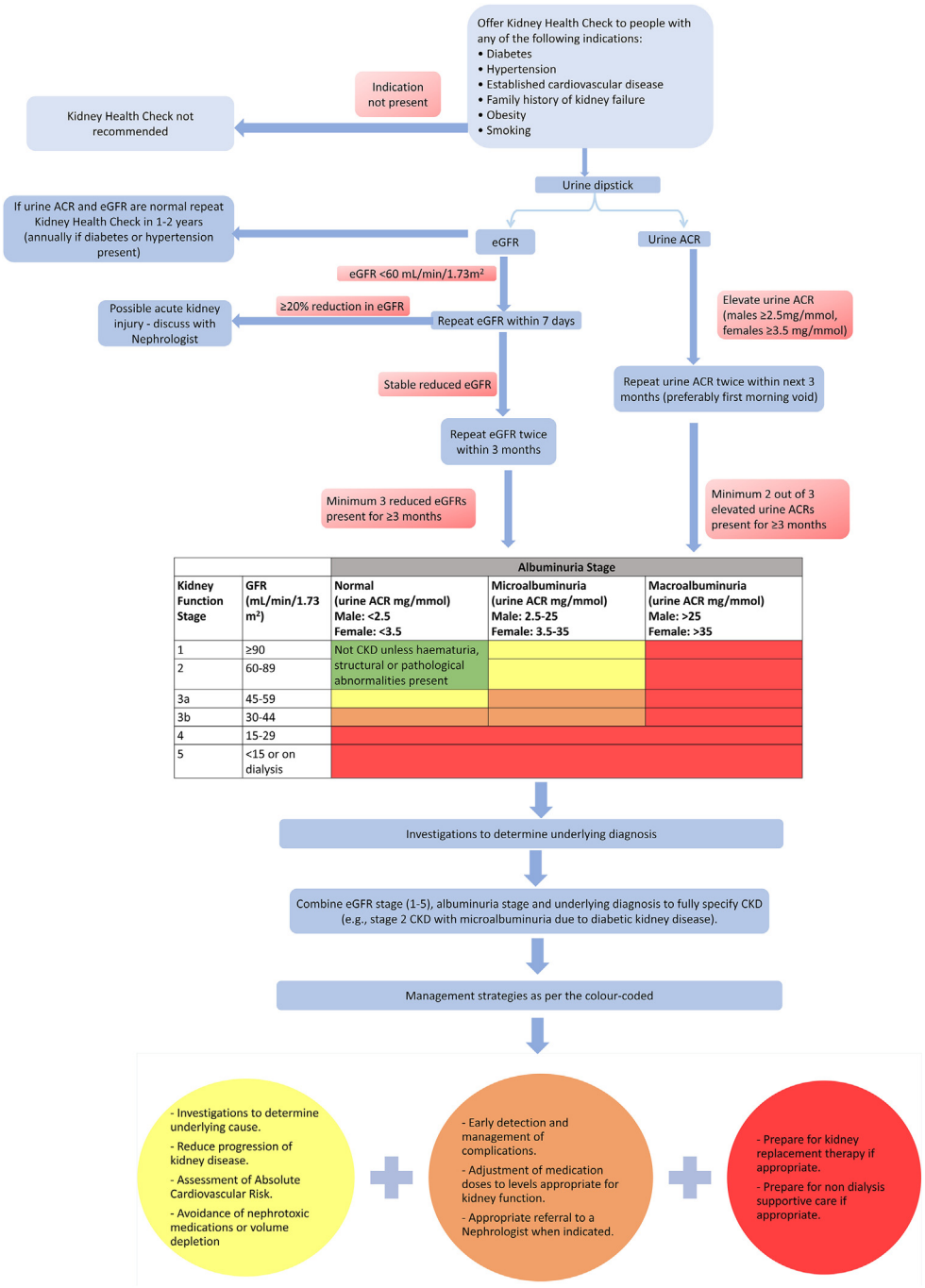

Figure 1. Conceptual framework of CKD screening, risk stratification, and treatment program.[38] The difference in the ACR thresholds may be due to lesser muscle mass and lower urinary creatinine excretion in females compared to males. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

However, numerous barriers attributable to patient-related factors or the health systems exist in Asian countries that affect the implementation of screening programs. Social risk factors such as limited financial resources and low health literacy are significant patient-level barriers. The absence of key strategies for CKD screening programs, lack of systems among primary care clinicians to detect early CKD, sparse educational initiatives for healthcare providers, lack of adequate patient follow-up routines, and lack of multidisciplinary care can be attributed to the health system.

Although there is consensus on the benefits of targeted screening programs directed at high-risk groups, there are conflicting views on population-wide CKD screening programs and policy.[41,42]

FRAMEWORK FOR TREATMENT GOALS OF CKD

Recommendation Summary

- Individuals with CKD should maintain a healthy weight (body mass index [BMI]: 18 to 23 kg/m^2).
- Individuals with CKD are suggested to undergo moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week or 75 minutes per week of vigorous-intensity physical activity
- Individuals with salt wasting nephropathy are not recommended low sodium intake if they are not hypertensive.
- Smoking cessation, vaping cessation, and limiting alcohol intake are recommended
- Renin-angiotensin-aldosterone system (RAAS) inhibitors are recommended to be initiated for proteinuric CKD unless contraindicated (such as in patients with hypotension or hypokalemia). Regular monitoring of BP, eGFR, and potassium levels is warranted after initiating RAAS inhibitors. In the case of hypotension, dose modulation may be necessary.
- Hemoglobin A1c (HbA1c) should be routinely monitored in individuals with T2D and CKD along with an individualized HbA1c target ranging from 6.5% to <8.0%.
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors are strongly recommended for individuals with or without T2D and in individuals with proteinuria without T2D considering their cardiorenoprotective effect and considered in individuals with proteinuria and without T2D.
- Physicians should consider prescribing finerenone for individuals with T2D for kidney and CV benefit.
- Structured self-management educational programs focusing on risk evaluation and patient empowerment in individuals with T2D and CKD to be implemented.

A key focus of the management of CKD is to maintain kidney function, thus delaying the progression to kidney failure. Treatment of CKD alone may not be possible because CKD usually manifests along with a plethora of other comorbidities, including CV and metabolic conditions. Treatment goals for CKD involve lifestyle modifications for disease management, management of hypertension, initiation of (RAAS) inhibitors for renal protection and management of other comorbidities of CKD, including CVD, anemia, electrolyte imbalance and acidosis, bone and mineral disease. This section focuses on the primary and secondary treatment of CKD. Management of comorbidities is elaborated in respective sections.

Lifestyle Modifications

Lifestyle modification, which involves dietary and weight management, physical activity, cessation of tobacco, and restricting alcohol intake has been recommended across all prevalent international CKD guidelines, including the KDIGO 2012 CPG for the Evaluation and Management of CKD,[13] the KDIGO 2020 and 2022 Guidelines for Diabetes Management in CKD,[43,44] KDIGO 2021 CPG for the Management of BP in CKD,[45] the American College of Cardiology/American Heart Association Guidelines on the Primary Prevention of CVD,[46] and National Institute for Health and Care Education CKD: Assessment and Management guidelines.[47] The recommendations for lifestyle modifications for individuals with CKD are detailed in Table 2.[13,43,45,46,48,49]

Rationale

Lifestyle changes primarily include weight management and a change in dietary patterns. Obesity is a known independent risk factor for CKD and accounts for 20% to 25% of individuals with CKD.[50] Obesity is also associated with an increase in all-cause mortality in individuals with CKD.[51] With the increasing prevalence of obesity globally, management of obesity is important in patients with CKD. Considering the association of obesity with metabolic syndrome and T2D, holistic management of obesity is important in individuals with CKD.[52] Restriction of processed and refined food and sweetened beverages is important for individuals with CKD, especially with comorbid diabetes mellitus.[53] KDIGO guidelines encourage following a plant-based diet with restricted protein intake. Lower dietary protein (0.8

Table 2. Recommendations for lifestyle modifications[13,43,45,46,48,49]

International guidelines	Recommendations for Asia
Diet	
Individuals should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages Lower dietary protein (0.8 g/kg/day in individuals with diabetes [2C] or without diabetes [2B] and GFR <30 ml/min per 1.73 m^2 and 1.3 g/kg/day in individuals with CKD at risk of progression [2C]) Sodium restriction (sodium intake <2 g of sodium per day or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in individuals with high BP and CKD with or without diabetes has also been recommended [2C]. We suggest maintaining a protein intake of 0.8 g protein/kg (weight)/day for those with diabetes and CKD not treated with dialysis [2C].	Recommendations: We suggest that people with CKD and GFR <30 ml/min per 1.73 m^2 receive a protein intake of not more than 0.8 g/kg/day and those with risk of progression receive a protein intake of not more than 1.3 g/kg/day [2C] Sodium restriction (sodium intake <2 g of sodium per day or <90 mmol of sodium per day, or <5 of sodium chloride per day) in individuals with high BP and CKD with or without diabetes has also been recommended [2C] Practice points: An individualized dietary plan with a diet rich in plant-based proteins should be considered. Processed meats that are high in salt and phosphate content and sweetened beverages should be avoided. Individuals should be encouraged to introduce a healthy diet gradually and steadily in their routine life. Individualized diet plan to be formulated with a consideration of low potassium diet individuals with hyperkalemia and low phosphorus diets for patients with hyperphosphatemia.
Physical activity	
Individuals should undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or 75 minutes per week of vigorous-intensity physical activity or to a level compatible with their CV and physical tolerance [1D].	Recommendation: Individuals should undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week [1C] Practice points: Individuals should be encouraged to gradually increase exercise duration and intensity. Individuals should be encouraged to perform exercise levels compatible with their CV and physical tolerance 65%-75% heart rate reserve (from ESC/ESH HTN guidelines)
Weight management	
Individuals should be encouraged to achieve a healthy weight (BMI 20–25 kg/m^2, according to country-specific demographics) [1D] Physicians should consider advising/encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with eGFR <30 ml/min per 1.73 m^2	Recommendation: Individuals should be encouraged to achieve a normal body weight (BMI 18–23 kg/m^2) [1D] Practice points: Holistic management of obesity should be considered in obese individuals with CKD. Physicians should consider advising/encouraging individuals with obesity, diabetes, and CKD to lose weight, particularly individuals with eGFR <30 ml/min per 1.73 m^2 with individualized lifestyle changes (ideal body weight is the best goal but ≥ 1 kg reduction in body weight for most adults who are overweight). Physicians should consider the use of glucose-lowering agents with weight reduction benefits such as metformin, SGLT2 inhibitors or GLP-1 receptor agonists
Tobacco use	
People who use tobacco should be advised to quit using tobacco products [1D] For individuals with hypertension and who drink alcohol, reduce daily alcohol intake to two or fewer drinks for men, and one or fewer drinks for women	Recommendation: It is recommended to quit smoking and use of oral tobacco products [1D] Practice point: Physicians should counsel individuals on smoking and vaping cessation and be provided with appropriate interventions

BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESH, European Society of Hypertension; GLP-1, glucagon-like peptide 1; HTN, hypertension; SGLT2, sodium-glucose cotransporter-2.

g/kg/d in individuals with diabetes [2C] or without diabetes [2B] and GFR <30 ml/min per 1.73 m^2 and 1.3 g/kg/d in individuals with CKD at risk of progression [2C]) is recommended by several guidelines to limit glomerular hyperfiltration.[54] However, the long-term effects of this diet have not yet been evaluated in individuals with CKD.[55] Protein restriction in patients with CKD may result in malnutrition, loss of muscle mass, and multisystem impairment associated with increased vulnerability to stressors. Thus, low protein diet should be prescribed with continuous close monitoring of nutritional status.[55] Sodium restriction (sodium intake <2 g/d or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in individuals with high BP and CKD with or without diabetes has also been recommended [2C].[45] Sodium restriction is associated with benefits in both BP and CVD risk reduction in a meta-analysis[56] and Cochrane systematic reviews.[57,58]

In addition, the guidelines caution that malnutrition may result from a very low protein intake, leading to a deleterious effect on prognosis in patients with CKD. Maintaining a healthy weight (normal BMI) and regular physical exercise (at least 150 minutes per week, or to a level compatible with their CV and physical tolerance) (both 1D) are recommended in KDIGO 2022 guidelines for diabetes management in CKD. A multitargeted approach should be applied for management of obesity in individuals with CKD.

Smoking is a key risk factor for several chronic diseases, including CKD and a leading cause of death in individuals globally.[59,60] Observational and cohort studies have evaluated the effect of smoking on the progression of CKD. In a prospective cohort study, a higher risk of CVD was reported in individuals with diabetes and CKD who smoked than in non-smokers.[61] Thus, along with other lifestyle changes, KDIGO guidelines recommend smoking cessation in individuals with CKD [1D].

Asia Perspective

The Asia-Pacific Society of Nephrology CPG on Diabetic Kidney Disease (DKD) recommends maintaining normal body weight [1C], restricting protein intake [2C], and smoking cessation [1C].[27] In other guidelines, like Malaysia, no recommendations for lifestyle modification have been presented currently.[17]

The effect of lifestyle modification on CKD progression in Asia has been evaluated in several studies. However, most of the studies are of a lower LOE. There is very high prevalence of obesity in Asian countries with 2 in 5 persons being overweight or obese, resulting in an increased incidence of metabolic comorbidities.[62-64] The prevalence of metabolic disorders is greater in Asians than in Caucasians at a given BMI. Therefore, it is generally accepted that the BMI cut-off points for defining overweight and obesity should be lower for Asians.[65] However, considering the multiethnic population in Asian countries, in 2004, the World Health Organization revised the criteria for the classification of overweight and obesity in the Asian population into roughly even-spaced multiple categories.[66] As per the new criteria, a BMI of 18.0 to 23.0 kg/m^2 has been accepted as normal.[66] Despite this, large randomized controlled trials have not evaluated the effect of reversion to or maintenance of a normal BMI[67-69] and physical activity[70,71] on the progression and prognosis of CKD. Therefore, we propose a grading of 1D for the recommendations based on the available literature and the prevalence of metabolic comorbidities in the general population in Asian countries; however, we have added the Asia-specific BMI categories in our recommendation.[67,69] Glucose-lowering agents such as metformin, SGLT2 inhibitors, or glucagon-like peptide-1 receptor agonists reported to have weight reduction benefits in patients with T2D.[72-75] However, metformin use was found to be associated with increased risk of lactic acidosis in patients with T2D and CKD stage G4–G5.[76,77] Physicians should be aware of the risk of developing lactic acidosis, especially in patients with T2D and CKD stage G4–G5. KDIGO guidelines recommended that metformin should be discontinued when eGFR falls <30 ml/min per 1.73 m^2 to reduce risk of lactic acidosis.[44]

Considering the controversial evidence for daily protein intake, the recommendation for restricting protein intake has been graded 2B in individuals without diabetes and grade 4 to 5 CKD and 2C in individuals at risk of CKD progression, thus reflecting the KDIGO guidelines.[78-80] Considering the benefit of a low-sodium diet, especially in individuals with high BP and CVD, the recommendation for a low-sodium diet has been retained [2C]. This recommendation excludes individuals with salt wasting nephropathy because they are usually not hypertensive, thus need not be recommended with low sodium intake.

Several cohort studies have evaluated the effect of smoking on CKD progression and mortality.[81-85] Recently, with increased public awareness about adverse effects of conventional cigarettes, consumption of e-cigarettes or vaping has been on a steady increase. However, in recent studies, vaping was also associated with increased albuminuria, serum uric acid level, and hyperuricemia in healthy individuals.[86,87] Therefore, individuals with CKD should be consulted for vaping cessation along with smoking cessation. Considering the LOE, we propose the grading recommendation for smoking cessation be 1D, again mirroring the KDIGO guidelines.

BP Control

Hypertension is a major risk factor for CKD, CVD, and the progression of CKD to renal failure.[88,89] Though a modifiable risk, there is a high prevalence of uncontrolled hypertension in individuals with CKD as reported by the National Health and Nutrition Examination Survey.[48] The panel's recommendations for BP control, and interventions for BP control and target BP are presented in Table 3.[43,45,46,49]

Rationale

Several studies have established that controlling BP is associated with a decrease in the risk of CVD and all-cause mortality in individuals with CKD.[90-95] There is varying evidence on the target systolic BP (SBP) in individuals with CKD. As per KDIGO 2021 guidelines, a target SBP of <120 mm Hg is recommended in individuals with hypertension and CKD [2B]. However, this recommendation is based on a single high level evidence study (and importantly, all patients who participated in the SPRINT study had their BP measured by standardized office BP measurement, which requires more time for patients and healthcare professionals and may not be performed in routine medical practice).[90] The SPRINT study included a subgroup of individuals with CKD. The individuals with CKD did not have a statistically significant difference in CV risk in individuals with SBP <120 mm Hg compared to SBP <140 mm Hg. The 2017 American Heart Association/American College of Cardiology[46] guidelines recommend an SBP and a diastolic BP of <130 and <80 mm Hg, respectively for individuals with CKD; whereas the European Society of Cardiology/European Society of Hypertension[96]

Table 3. Recommendations for BP control and RAAS inhibitors[43,45,46,49]

International guidelines	Recommendations for Asia
BP Target	
KDIGO: We suggest that adults with high BP and CKD be treated with a target SBP of <120 mm Hg when tolerated, using standardized office BP measurement [2B]. NICE: In adults with CKD and an ACR under 70 mg/mmol Cr, aim for a clinic SBP below 140 mm Hg (target range 120 to 139 mm Hg) and a clinic DBP below 90 mmHg In adults with CKD and an ACR of 70 mg/mmol Cr or more, aim for a clinic SBP below 130 mmHg (target range 120 to 129 mm Hg) and a clinic DBP below 80 mm Hg AHA: Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg [Category 1].	Recommendation: Adults with high BP and CKD with or without diabetes should be treated with a target SBP of <120 mm Hg when tolerated, using standardized office BP measurement [2B] Practice Points: Physicians should aim at an individualized BP target for individuals with other comorbidities, geriatric individuals, or individuals at risk of side effects like frailty and with a history of falls
Initiating RAAS inhibitors	
KDIGO: We recommend initiating RAAS inhibitors (ACEi or ARB) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes [1B]. We suggest starting RAAS inhibitors (ACEi or ARB) for people with high BP, CKD, or moderately increased albuminuria (G1–G4, A2) without diabetes [2C]. We recommend starting RAAS inhibitors (ACEi or ARB) for people with high BP, CKD, or moderately-to-severely increased albuminuria (G1–G4, A2, and A3) with diabetes [1B]. AHA: In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g UACR or the equivalent in the first-morning void]), treatment with an ACEi is reasonable to slow kidney disease progression. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/g, or ≥300 mg/g UACR in the first-morning void]) ARB may be reasonable if an ACEi is not tolerated NICE: ACEi/ARB should be used as a first-line agent in • DKD with albuminuria • non-DKD when urinary protein excretion ≥1.0 g/day • non-DKD with hypertension when urinary protein excretion ≥0.5 g/d The renal profile should be carefully monitored following initiation or dose escalation of ACEi/ARB	Recommendations: RAAS inhibitors should be initiated in all patients with high BP and albuminuria with or without diabetes [1B] Practice Points: Individuals should be regularly assessed for hypotension, hyperkalemia, and increased serum creatinine Lifestyle as well as pharmacotherapeutic intervention should be offered to reduce hyperkalemia associated with use of RAAS inhibitors rather than decreasing the dose or stopping RAAS inhibitors. Consider reducing the dose or discontinuing ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure
Initiating MRAs	
KDIGO 2022 recommends a nonsteroidal MRA with proven kidney or CV benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria despite maximum tolerated dose of RAAS inhibitor [2A]	The addition of nonsteroidal MRA, finerenone, should be recommended in patients with residual albuminuria along with RAAS inhibitors [2A]
Dual Therapy with RAAS Inhibitors	
KDIGO: We recommend avoiding any combination of ACEi, ARB, and DRI therapy in patients with CKD, with or without diabetes [1B] NICE: Dual renin-angiotensin system blockade should only be used in carefully selected non-DKD patients with proteinuria under close supervision by nephrologists	Recommendation: Any combination of ACEi, ARB, and DRI therapy in individuals with CKD, with or without diabetes should be avoided [1B] Practice Points: In case of uncontrolled BP, consider adding MRA, calcium channel blocker or beta-blockers

ACEi, angiotensin-converting-enzyme inhibitors; ACR, albumin-to-creatinine ratio; AHA, American Heart Association; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; Cr, creatinine; CV, cardiovascular; DBP, diastolic blood pressure; DKD, diabetic kidney disease; DRI, direct renin inhibitor; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; NICE, National Institute for Health and Care Excellence; KDIGO, Kidney Disease: Improving Global Outcomes; RAAS, renin-angiotensin aldosterone system; SBP: systolic blood pressure; T2D, type 2 diabetes mellitus; UACR: urinary albumin-to-creatinine ratio.

guidelines recommend SBP between 130 and 139 mm Hg; and the National Institute for Health and Care Excellence[49] guidelines recommend SBP and diastolic BP of <140 and <90 mm Hg, respectively in adults with albuminuria of <70 mg/mmol, and <130 and <80 mm Hg, respectively in individuals with albuminuria ≥70 mg/mmol.

Asia Perspective

Most Asian countries have guidelines for the assessment and management of hypertension in the general population. Several Asian countries recommend a target BP of <140/90 mm Hg in the general population (except Indonesia [SBP of <130 mm Hg], Japan, Philippines, and Vietnam [<130/80 mm Hg], and Thailand [120–130/70–79 mm Hg]) and <130/80 mm Hg in individuals with CKD.[97] The Asian-Pacific Society also recommends a target BP of 130/80 mm Hg for stroke and CV protection and slowing of kidney disease progression in individuals with CKD and T2D [2C]. Our recommendation on target BP follows the KDIGO 2021 recommendations grade of evidence, considering the high prevalence of hypertension and comorbidities in Asian countries.

Initiation of RAAS Inhibitors for Renoprotection

The recommendations for initiating RAAS inhibitors in Asian countries are presented in Table 3.[43,45,46,49]

Rationale

RAAS inhibitors include an angiotensin-converting-enzyme inhibitor (ACEi), or an angiotensin receptor blocker (ARB), which are known to prevent or decrease the rate of progression of CKD.

A meta-analysis of 119 randomized controlled trials evaluated the effect of ACEi and ARBs on renal and CV outcomes in individuals with CKD; ACEi reduced the risk of kidney failure by 39% and 35% and ARBs by 30% and 25% compared to placebo and active comparators, respectively; and the risk of CV events was reduced by 18% and 24% by ACEi and ARBs,

respectively.[98] In individuals with T2D, RAAS inhibitors have shown modest benefit in slowing the decline of eGFR rate in several studies, including REIN-STRATUM-I,[99] REIN-STRATUM-II,[100] AIPRI,[101] and meta-analysis of these studies.[102-104] In one meta-analysis, a significant reduction in renal risk by 43% was reported with ACEi and ARBs.[45] Benazepril therapy was associated with a 52% reduction in the level of proteinuria and a reduction of 23% in the rate of decline in renal function.[104] In another meta-analysis, ACEi reduced the risk of renal disease by 33%.[103] In individuals with moderately increased albuminuria, ACEi reduced the risk of all-cause mortality by 20%, myocardial infarction (MI) by 26%, and stroke by 30%.[105] Among individuals with diabetes with or without elevated BP, RENAAL[106] and IDNT[107] studies evaluated the efficacy of ARBs in individuals with severe albuminuria. The risk of renal progression was reduced by 16% and 20% as reported by RENAAL and IDNT studies, respectively.[106,107] In the Micro-Heart Outcomes Prevention Evaluation (HOPE) study evaluating ramipril, approximately 29% of risk reduction in the composite of MI, stroke, and CV death was reported with a reduction in renal disease progression from moderate albuminuria to severe albuminuria.[108]

Initiation of ACEi or ARBs blockade is strongly recommended by the KDIGO 2020 Guidelines for Diabetes Management in CKD,[43] KDIGO 2021 CPG for the Management of BP in CKD[45], NICE[49] guidelines and UMHS CKD Guideline, July 2019[109] in individuals with severely increased albuminuria and high BP with or without diabetes [1B], and in individuals with moderately increased albuminuria and high BP [2C].

However, there is no evidence of the benefit of dual agents or combination therapy of ARB and ACEi in CKD in individuals with or without diabetes.[98] Dual therapy with ARB and/or ACEi is associated with an increased risk of acute kidney injury (40% increase) and all-cause mortality (9% increase).[45] Thus KDIGO 2021, KDIGO 2020 and UMHS CKD Guideline, July 2019[109] guidelines strongly recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor therapy in individuals with CKD, with or without diabetes [1B].[43,45]

ACEi or ARBs should be titrated to the highest tolerable dose with consideration of hyperkalemia, transient increase in serum creatinine and hypotension as major adverse events.[45] Transient hyperkalemia with RAAS inhibitors should be ruled out and strategies, including dietary restriction, discontinuation of potassium supplements, certain salt substitutes, and hyperkalemic drugs; adding potassium-wasting diuretics, and oral potassium binders should be implemented. Oral potassium binders can also be recommended to continue RAAS inhibitors at recommended dose. However, the dose of RAAS inhibitors should be reduced or discontinued in patients with hyperkalemia after other measures have failed to achieve a normal serum potassium level. Calcium channel blockers also showed an inverse relationship with overall mortality in the DOPPS survey on antihypertensives.[110] KDIGO's 2021 guidelines recommend calcium channel blockers along with RAAS inhibitors and thiazide diuretics for CVD prevention in primary hypertension.[45]

For individuals with uncontrolled hypertension, KDIGO suggests adding steroidal mineralocorticoid receptor antagonists (MRAs). However, hyperkalemia and decline in renal function with MRAs should be considered while initiating therapy. Along with ACEi and ARBs, a nonsteroidal MRA, finerenone, has shown efficacy in reducing urinary albumin-to-creatinine ratio when treated with RAAS inhibitor with a lower risk of hyperkalemia.[111] Recently, finerenone has shown promising efficacy in reducing CV outcomes in individuals with CKD and T2D in the Finerenone in Reducing Kidney Failure and Disease Progression in DKD study and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in DKD study. Based on these results, KDIGO's 2022 guidelines for diabetes management in CKD suggest a nonsteroidal MRA with proven kidney or CV benefit for patients with T2D, an eGFR $\geq$25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria despite maximum tolerated dose of RAAS inhibitor.[44] In order to mitigate risk of hyperkalemia, individuals should be monitored for serum potassium regularly after initiation of a nonsteroidal MRA.

Asia Perspective

In Asian countries, the availability of resources and drugs is a concern and often guides the treatment patterns. The Asia BP@Home study evaluated the treatment patterns for hypertension in 12 Asian countries.[112] In most countries, calcium channel blockers and beta-blockers were the treatment of choice and also recommended by local guidelines, except in Malaysia and Indonesia, where ACEi or ARB were recommended and prescribed.[113-121] However, the study also noted an upcoming change in treatment patterns with increased prescription of ACEi and ARBs inhibitors in these countries. There is a lack of formal guidelines for the control of hypertension in individuals with CKD. The Asia-Pacific Society guidelines for the management of DKD has adopted the KDIGO guidelines (with the same grades for recommendations) for hypertension management in individuals with diabetes and CKD and recommends the use of ACEi or ARBs as first-line therapies followed by the addition of other

antihypertensive drugs (calcium channel blockers, diuretics, MRA, or beta-blockers)[122] in the case of uncontrolled BP, heart failure, or as otherwise indicated for comorbid conditions.[27]

Framework for Treatment of T2D in CKD

T2D is a common cause of kidney failure worldwide.[123] With almost 537 million people with T2D,[124] and 26% to 48% prevalence of CKD[125,126] in people with T2D, DKD is a major concern. People with DKD are at an increased risk of CVD, heart failure, and death.[127] Therefore, it is critical to set goals for the management of diabetes in individuals with CKD. KDIGO presented its first guideline for the management of diabetes in individuals with CKD in 2020, the CPG for Diabetes Management in CKD (and updated in 2022).[43,44] This guideline has been endorsed by the National Kidney Foundation as well as America Diabetes Association.[128,129] In Asia, the Asia-Pacific Society for Nephrology (APSN) provides extensive guidelines for the management of DKD.[27]

The guidelines for management focus on lifestyle modification, initiation of RAAS inhibitors, and management of hyperglycemia with renoprotective drugs. The details on lifestyle modification and RAAS inhibitors have been elaborated on in respective sections. In this section, we will focus on the glycemic targets in individuals with CKD and T2D and the management of hyperglycemia.

The recommendations from KDIGO 2020 guidelines (KDIGO 2022) and APSN for glycemic targets and management are detailed in Table 4.[43,44,129-131]

Rationale

Glycemic Targets

For long-term glycemic control, measurement of HbA1c has been considered a gold standard. Several studies have established reduced risk of CVD, diabetic complications, and mortality in individuals with lower HbA1c values.[132-134] Although no high LOE studies are available for the correlation of HbA1c with mean blood glucose, systematic literature reviews have correlated HbA1c with fasting blood glucose in the non-CKD population.[43] Other biomarkers such as fructosamine and glycated albumin have been evaluated for their correlation with blood glucose. However, due to their short half-life, they are ineffective for the measurement of long-term glycemic control in patients with DKD.[135] In patients with DKD, the LOE for evaluating HbA1c for monitoring glycemic control is 1C because HbA1c levels may be shortened by erythrocyte survival and anemia.[136,137] Correlation of HbA1c with blood glucose declines in advanced-stage CKD.[135,138-140] Thus, KDIGO recommends continuous glucose monitoring in individuals whose HbA1c levels are not concordant with blood glucose. Continuous glucose monitoring with self-monitoring of blood glucose is also helpful in individuals who have initiated antihyperglycemic agents to prevent hypoglycemia.

In individuals with T2D and CKD, lower glycemic targets are also associated with increased mortality due to hypoglycemia and consequent CV events.[141] In a Cochrane systematic review, HbA1c of <7.0% was associated with decreased incidence of MI and progression of albuminuria and <6.5% decreased incidence of moderately increased albuminuria and renal failure.[142] However, in 2 observational studies, <6.0% HbA1c target was associated with increased all-cause mortality, thereby signifying the U-shaped correlation of HbA1c with CV risks.[141,143]

Management of Glycemia

Metformin is associated with a reduction in HbA1c in individuals with T2D.[72,73] In the United Kingdom Prospective Diabetes Study, metformin monotherapy reduced HbA1c and blood glucose in obese individuals with a lower risk of hypoglycemia along with a decrease in body weight.[144] Compared to sulphonylureas, thiazolidinediones, and DPP-4 inhibitors, metformin was associated with a greater decrease in body weight.[72,73] Metformin also decreased microvascular complications, CV mortality, and all-cause mortality compared to sulphonylureas.[72] In the TREAT study, metformin treatment was independently associated with a reduced risk of all-cause mortality, CV death, CV composite, and kidney disease composite.[145] Although all studies evaluating metformin for CV and renal outcomes are *post hoc* or exploratory analysis, considering the strength of evidence, KDIGO[44] and America Diabetes Association[129] guidelines place a higher value on the weight reduction and CV protective effect of metformin.

Recently, SGLT2 inhibitors have been strongly recommended in individuals with established CVD or with risk factors for CVD with eGFR ≥20 ml/min per 1.73 m^2 [1A].[44,129] This recommendation is based on several CV protective trials of SGLT2 inhibitors.[74,86,146-149] The recommendation for glucagon-like peptide-1 receptor agonists [1B] is also supported by several clinical studies.[75,150-153] All trials and meta-analyses of the trials showed improvement in the composite renal outcomes (new-onset severely increased albuminuria, doubling of serum creatinine, kidney failure, or death from kidney disease) in individuals with CKD.[154] A summary of studies with these agents is presented in Supplementary Tables S2, S3, and S4. These agents should be considered in individuals with or without established CVD for cardiorenal protection.

Table 4. Recommendations for T2D management in individuals with CKD[43,441]

International guidelines	Recommendations for Asia
Glycemic targets	
KDIGO: We recommend using HbA1c to monitor glycemic control in patients with diabetes and CKD [1C] We recommend an individualized HbA1c target ranging from 6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis [1C] APSN: We recommend that HbA1c and SMBG be used to assess glycemic control in adults with DKD [1C] We suggest that HbA1c be targeted toward and not lower than 7.0% in adults with DKD, balancing the risks of micro- and macrovascular complications and the development of hypoglycemia [2C]	Recommendations: We recommend using HbA1c to monitor glycemic control in individuals with diabetes and CKD [1C] We recommend an individualized HbA1c target ranging from 6.5% to <8.0% in individuals with diabetes and CKD not treated with dialysis [1C] Practice Points: SMBG should be utilized along with routine HbA1c for regular glycemic control
Glucose-lowering therapies in individuals with T2D and CKD	
We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with metformin [1B]	Recommendation: Individuals with eGFR ≥30 ml/min per 1.73 m^2 should be initiated on metformin [1B] Practice Point: Decline in eGFR should be monitored when individuals are prescribed metformin. Increased monitoring is required when eGFR is <60 ml/min per 1.73 m^2
KDIGO 2022: We recommend treating patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i [1A] APSN: We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with an SGLT2i [1A]	Recommendation: Individuals with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 should be initiated on SGLT2i [1A] Practice Point: Consider adding SGLT2i for kidney and CV protection, even for those without T2D (especially in patients with albuminuria > 300 mg/g) If individuals with T2D are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 mL/min/1.73 m^2, unless it is not tolerated, or kidney replacement therapy is initiated For individuals without T2D, there is no evidence in conditions that were excluded from SGLT2i trials – polycystic kidney disease, lupus nephritis, ANCA vasculitis, T1D
In patients with T2D and CKD who have not achieved individualized glycemic targets despite the use of metformin and SGLT2i, or who are unable to use those medications, we recommend a long-acting GLP-1 RA [1B] [2C as per APSN]	Recommendation: GLP-1RA is recommended to be initiated in individuals with inadequate response to metformin and SGLT2i (other suitable patients are obese with established or high risk for atherosclerotic CVD) Practice Points: Physicians to regulate the dose of other glucose-lowering agents, especially sulphonylureas and insulin to reduce the risk of hypoglycemia Physicians to consider prescribing finerenone in individuals with T2D for kidney and CV benefit
Management of patients	
We recommend that a structured self-management educational program be implemented for the care of people with diabetes and CKD [1C]	We recommend that a structured self-management educational program be implemented for the care of people with diabetes and CKD [1C]
We suggest that policymakers and institutional decision-makers implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care to patients with diabetes and CKD [2B]	We suggest that policymakers and institutional decision-makers implement multidisciplinary team-based, integrated care targeting multiple-risk evaluation and patient empowerment to provide comprehensive care to individuals with diabetes and CKD [2B]

ADA, American Diabetes Association; ANCA, antineutrophil cytoplasmic autoantibody; APSN, Asia-Pacific Society for Nephrology; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus.

Along with the therapeutic agents, KDIGO 2020 guidelines focus on a self-management education program for individuals with CKD and T2D [1C]. The objectives of the self-management program are detailed in Figure 2.[155] The benefit of self-management education programs has been reported in a systematic review.[43] In addition, the KDIGO 2020 and KDIGO 2022 guidelines recommend team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care to individuals with diabetes and CKD [2B]. This recommendation is based on systematic reviews and meta-analyses, where integrated care with patients and care providers resulted in reduced cardiometabolic risk factors in T2D.[155-157]

Asia Perspective

The APSN released the guidelines for the management of DKD in 2020.[27] It adopted all the recommendations from KDIGO 2020 guidelines with the same grades. However, considering the recent data on SGLT2 inhibitors, and KDIGO 2022 guidelines, updated Asian guidelines are awaited. Though HbA1c is recognized as a gold standard in Asian countries for evaluating glycemic control, APSN also recommends adding continuous glucose monitoring and self-monitoring of blood glucose as tools for evaluating glycemic control for individualized treatment. The APSN recommends that the HbA1c target should not be lower than 7.0% because this may result in hypoglycemia in individuals with advanced CKD.[27] This guideline takes into consideration that most individuals with CKD are diagnosed at an advanced stage in LMICs. In addition, routine HbA1c measurement may not be possible in LMICs due to limited resources; thus, the range of ≥7.0% to ≤8.0% is recommended. Huang *et al.*[158] showed a decreased risk of all-cause mortality with HbA1c level of 6.0% to 6.9% compared to <6.0%, whereas another cohort-study from UK General

Figure 2. Key objectives of glucose-lowering medications.[155]

Practice Research Database reported lowest hazard ratio for all-cause mortality at an HbA1c of 7.5%,[159] revealing the U-shaped relationship with HbA1c levels. KDIGO work group however proposed that medications with lower risk of hypoglycemia should be considered whenever feasible over choosing a higher HBA1c target because higher HbA1c targets may lead to insufficient diabetes control.[44] Other factors, such as cost of therapy and availability of resources may modify the approach and regional therapeutic practices. Thus, taking a conservative approach, in individuals with T2D and CKD the individualized HbA1c target of 6.5% to <8.0% is recommended.

All the guidelines strongly recommend that individuals with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 should be initiated on SGLT2 inhibitors [1A] because of the kidney and heart protective effects of this class of drugs and a lower value on the costs and adverse effects of this class of drug. However, considering the adverse effects, physicians should counsel individuals on the importance of adequate water intake, genitourinary hygiene, and risk factors for euglycemic diabetic ketoacidosis. Sick day protocol should also be developed on consultation with physicians after considering the country-level practices and regulations.[160]

Secondary Prevention Strategies

Avoiding Nephrotoxins

Drug-induced kidney damage, both acute as well as chronic, is a known risk in the general population. This risk increases in individuals with CKD and may result in an accelerated decline in kidney function. In most cases, drug-induced nephrotoxicity is reversible if treated early. Although no specific recommendations are available for the prescription of concomitant medications in CKD, several drugs have been known to result in nephrotoxicity and should be avoided in individuals with CKD.[109] Table 5 presents strategies, risk factors, and drugs associated with nephrotoxicity.[109]

In addition, in LMICs, alternative and or herbal medications are widely prescribed.[161-163] They increase the risk of hyperkalemia, and some may result in kidney injury or damage due to acute or chronic interstitial nephritis or renal tubular cell toxicity (Table 5).[109] In LMICs, there is a concern about fake and counterfeit medications (as much as 10%–60%), which may be a significant cause of CKD.[164,165] Physicians should note a detailed history of previous and current medications, including herbal medicines.[166] Individuals should be counseled to avoid alternative medicines, especially those with a known risk of renal damage or with known drug interactions.

Vaccination

Individuals with CKD have impaired immune systems and are thus at increased risk for infections. Vaccination in CKD is thus an important secondary preventive measure that needs to be incorporated into the holistic management of CKD.[167] The Center for Disease Control and Prevention guidelines for vaccination in CKD recommend the following vaccines for all individuals: the annual inactivated influenza vaccine, the measles/mumps/rubella vaccine, and the varicella vaccine if not contraindicated.[168] Although further research is required for evaluating the efficacy of the COVID-19 vaccine in individuals with CKD, it has been deemed to be safe and is highly recommended for patients with CKD who are at a much-increased risk of adverse outcomes.[169] Therefore, individuals with CKD are prioritized to receive the COVID-19 vaccine given their vulnerability to the disease.[170,171] Although significant association between mRNA-based COVID-19 vaccine and increased incidence of glomerulonephritis was not found, most of the new-onset glomerulonephritis cases were reported shortly after COVID-19 vaccination.[172] A population-based study also reported an increased relative risk of relapses of glomerular disease after second or third dose of COVID-19 vaccination.[173] These results indicate that patients with glomerular disease need to be closely monitored after COVID-19 vaccination. In CKD and dialysis, the hepatitis B vaccine and pneumococcal vaccine are also recommended. Quadrivalent meningococcal vaccine is also recommended in individuals with CKD, especially in patients receiving complement inhibitors.[174] KDIGO recommends annual

Table 5. Drug-induced and selected herbs that induce nephrotoxicity: prevention strategies, patient risk factors, and associated drugs[109]

General strategies to prevent drug-induced nephrotoxicity	
Assess baseline renal function before initiating potentially nephrotoxic drugs	
Adjust medication dosages based on renal function as needed	
Avoid nephrotoxic drug combinations	
Use non-nephrotoxic alternatives whenever possible	
Correct risk factors for nephrotoxicity before initiating drug therapy whenever possible	
Ensure adequate hydration before and during therapy with potential nephrotoxic drugs	
Limit dose and duration of therapy when possible	
Key risk factors predisposing patients to drug-induced nephrotoxicity	
Age greater than 60 years	History of kidney transplant
Diabetes mellitus	Multiple myeloma
Drug-drug interactions resulting in synergistic nephrotoxic effects	Sepsis
Exposure to multiple or high doses of nephrotoxins	Underlying kidney dysfunction (eGFR $<$60 mL/min/1.73 m^2; renal artery stenosis)
Heart failure	Vascular disease
	Volume depletion
Select drugs associated with nephrotoxicity	
Allopurinol	Lithium
Aldosterone inhibitors	Methamphetamines
Aminoglycosides	Methotrexate
Calcium channel blockers	Nonsteroidal antiinflammatory drugs
Cephalosporins	Oral sodium phosphate solution
Combined phenacetin, aspirin, and caffeine analgesics	Pamidronate
Cyclooxygenase-2 inhibitors	Penicillamine
Cyclosporine	Penicillins
Direct renin inhibitors	Propylthiouracil
Fluoroquinolones	Proton pump inhibitors
Foscarnet	Iodinated contrast agents
Gold	Rifampin
Hydralazine	Sulfonamides
	Tacrolimus
	Vancomycin
Select herbs that may be harmful to patients with CKD	
Alfalfa	Horse chestnut (Inedible)
Aloe	Horsetail
Aristolochic acid	Licorice
Artemisia absinthium (wormwood plant)	Lobelia
Autumn crocus	Mandrake
Bayberry	Mate
Blue cohosh	Nettle
Broom	Noni juice
Buckthorn	Panax
Capsicum	Pennyroyal
Cascara	Periwinkle
Chaparral	Pokeroot
Chuifong tuokuwan (Black Pearl)	Sassafras
Coltsfoot	Senna
Comfrey	St. John's wort
Dandelion	Tung shueh
Ephedra (Ma Huang)	Vandelia cordifolia
Gingko	Vervain
Ginseng	Yohimbe

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

influenza vaccination in adults with CKD unless contraindicated, and polyvalent pneumococcus vaccine every 5 years unless contraindicated.[13] However, currently there are no formal guidelines on the same in LMICs. In addition, in LMICs, availability and awareness about vaccination is of concern.

CKD of Unknown Origin (CKDu)

CKDu has been documented in Southeast Asia, Central America, and some African countries. Common causes for CKDu include excessive heat exposure and dehydration and exposure to nephrotoxins, including nonsteroidal antiinflammatory drugs and other painkillers, and pesticides. There is limited evidence about exposure to heavy metals (e.g., arsenic) and infections resulting in CKDu. Physicians should consider the patient's sociodemographic and family history while investigating CKD to rule out CKDu and should incorporate preventive and management strategies accordingly.[175]

Therefore, a customized approach needs to be undertaken for the prevention and management of CKD complications in this population facing a dual challenge of a high prevalence of risk factors for CKD as well as comorbid conditions which can lead to serious complications.

FRAMEWORK FOR REFERRAL OF PATIENTS TO NEPHROLOGISTS

Recommendation Summary

- Early referral to nephrology services and timely preparation for kidney replacement therapy (KRT) should be advised for individuals progressing rapidly despite intervention and regular monitoring.
- Individuals should be referred to nephrologists in case of persistent and severe albuminuria (stage A3 or urine albumin-to-creatinine ratio ≥1000 mg/g) or eGFR <30 ml/min per 1.73 m^2 (GFR categories G4–G5) is reported (stage A3: urine albumin-to-creatinine ratio >300 mg/g).
- A robust methodology to collect data and also monitor the current and future nephrology workforce should be developed.
- The participation of allied health professionals in CKD care to increase efficiency and share the load with nephrologists should be considered.
- In regions with a shortage of nephrologists, protocol-driven management of individuals with CKD and shared care with primary care physicians (PCPs) with nephrology oversight could be considered to mitigate the high workload.
- Build cost-effective technology to increase access to specialist care along with defining the scope of PCPs and other allied health professionals in managing and improving outcomes of kidney patients.

PCPs play a vital role in the management and referral of patients with CKD to nephrologists. Optimum timing of referral to nephrologists positively affects the initiation of long-term dialysis in patients with kidney failure and the creation of dialysis access. It allows nephrologists sufficient time to implement integrated pre-kidney failure care and thus improves the prognosis of patients with advanced kidney disease. In addition, early access creation can significantly reduce sepsis and death associated with the use of temporary double-lumen catheters. It is generally believed that early angiogenesis can allow a longer time for blood vessels to mature. Late referral (1–6 months before long-term dialysis) is reported to be associated with increased mortality and hospitalization rates after the initiation of long-term dialysis and increased healthcare expenditure due to poorly controlled CKD complications such as hypertension, anemia, bone and mineral imbalances, and acidosis, or lack of timely preparation for dialysis.[13,155–159]

The goals of early referral include the provision of specific therapies based on the diagnosis, slowing or arresting CKD progression; evaluation and management of comorbid conditions; prevention and management of CV disease; identification, prevention, and management of CKD-specific complications, including malnutrition, anemia, bone disease and acidosis; planning and preparation for KRT; and psychosocial support and provision of conservative care and supportive care options, where required.

The literature concerning late referral has identified a number of adverse consequences of late referral and related benefits of early referral (Figure 3).[176] A meta-analysis by Chan *et al.*[177] has shown a significant increase in mortality rate with late referral versus early referral. A span of 3 months or less before initiation of KRT is usually termed as a late referral. Patients who are aged ≥75 years, female, non-Caucasian, uninsured, of lower socioeconomic or educational status, or have multiple comorbidities are most at risk of late referral for CKD care.[13,155,161]

Several CPGs vary on the optimal referral criteria for patients with CKD. The KDIGO 2012[13] and the British guideline from the NICE 2014[47] guideline recommend referral to nephrologists from stage 4 CKD (GFR <30 mg/ml); or GFR of 30–59 ml/min and additional risk factors. The NICE 2021 guidelines recommend using the kidney failure risk equation with a 5% threshold for referral to estimate the 5-year risk of requiring KRT.[47] In this section, we review the international guidelines and provide a framework of guidelines for the referral of patients to nephrology services in Asia.

Rationale

The aim of referral to a nephrologist is to ensure timely and adequate access to nephrology services for patients at risk of complications or progression to renal failure and patients requiring specific treatment (Figure 4).[13] The recommendations from international guidelines are presented in Table 6.[13,130,178–180] In patients with an increased risk of kidney failure within 1 year, as determined by validated risk prediction tools, it is recommended that a timely referral is made for the planning of KRT.[13,109,160] All clinical guidelines for CKD recommend that all patients with GFR <30 ml/min per 1.73 m^2 (stage 4 and 5 CKD), with uncontrolled hypertension, severe and persistent albuminuria irrespective of diabetes should be referred to a nephrologist.

Based on retrospective studies and systematic analysis of referrals in various countries, current evidence strongly supports the early referral (>12 months prior to initiation of KRT) of patients with CKD to nephrologists and multidisciplinary care programs.[176,181] Referral to nephrology is also important for planning KRT and transplant evaluation. The trajectories of GFR decline are highly variable and depend on albuminuria, age, types of kidney disease, comorbidity, and effective risk factor control. There was a 38% increase in total

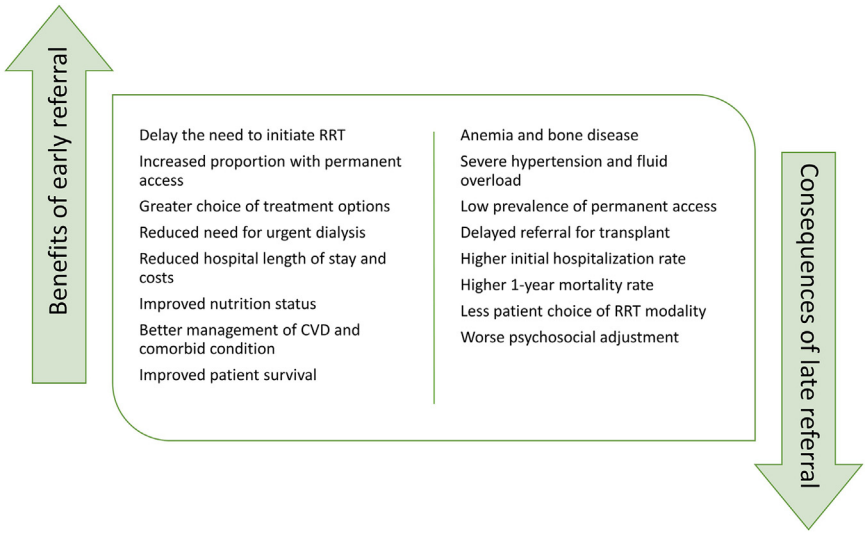

Figure 3. Benefits of early referral and consequences of late referral.[176] CVD, cardiovascular disease; RRT, renal replacement therapy.

nephrology patient volume and a 67% increase in new referrals upon the implementation of KDIGO referral criteria in a primary care population.[182]

Considering the efficacy of SGLT2 inhibitors in improving the prognosis of individuals with early CKD, use of SGLT2 inhibitors early-on in individuals with CKD would be beneficial.[183,184] Thus, initiation of SGLT2 inhibitors should occur in primary care with physicians being appropriately educated on the benefits of early intervention.

Asia Perspective

PCPs need to identify patients with CKD at an early stage of the disease for appropriate referral. A challenge for early referral in Asia is a late diagnosis of CKD. Particularly in LMICs, a majority of patients with CKD are diagnosed at a late stage where the eGFR at diagnosis is <30 ml/min per 1.73 m^2, leading to late referrals in most of the cases. The barriers and solutions to nephrology referral are presented in Table 7.[18] Several Taiwanese cohort studies have indicated that referral and care from the nephrologist before dialysis was associated with a reduction in postdialysis mortality, and referral of patients with stage 4 and 5 CKD to a nephrologist had substantial benefits. However, whether stage 3 and earlier stages of CKD should be referred to specialist nephrology care is still inconclusive.[185-187]

Although early initiation of SGLT2 inhibitors in individuals with or without diabetes with CKD has shown improved prognosis, in majority of Asian countries, the costs of SGLT2 inhibitors are not covered or reimbursed through insurance. In addition, the

GFR categories (ml/min/1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60-89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45-59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30-44	Monitor	Monitor	Refer
	G4	Severely decreased	15-29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Figure 4. Referral decision-making by GFR and albuminuria.[13] <*Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring. GFR, glomerular filtration rate.

Table 6. Computable criteria for indications for nephrology referral and recommendations[13,1309]

International recommendations	Recommendations for Asia
• CKD of uncertain cause or etiology • Persistent and severe albuminuria (stage A3; UACR) ≥300 mg/g • AKI or abrupt sustained fall in eGFR • eGFR < 30 ml/min per 1.73 m^2 (GFR categories G4-G5) • Rapid Progression of CKD (the reduction in GFR is more than 25% below the baseline value) • Urinary red cell casts, RBC >20 per high power field sustained and not readily explained • CKD and hypertension refractory to treatment with four or more antihypertensive agents • Persistent abnormalities of serum potassium • Recurrent or extensive nephrolithiasis • Hereditary kidney disease • Absence of retinopathy (in T1D) NICE 2021 guidelines • Adults with CKD should be referred for specialist assessment (taking into account their wishes and comorbidities) if they have any of the following: ◦ A 5-year risk of needing KRT of >5% (measured using KFRE) ◦ UACR ≥700 mg/g, unless known to be caused by diabetes and already appropriately treated ◦ UACR ≥300 mg/g (albuminuria category A3), together with hematuria ◦ A sustained decrease in eGFR ≥25% and a change in the eGFR category within 12 months ◦ A sustained decrease in eGFR of 15 ml/min per 1.73 m^2 or more per year ◦ Poorly controlled hypertension (above the person's target) despite the use of at least four antihypertensive medicines at therapeutic doses ◦ Known or suspected rare or genetic causes of CKD ◦ Suspected kidney artery stenosis	• Early referral to nephrology services and timely preparation for KRT can be made for individuals found to progress rapidly despite intervention during regular monitoring • CKD Referral Criteria: ◦ CKD of the uncertain cause or etiology ◦ Persistent and severe albuminuria (stage A3; UACR ≥300 mg/g) or proteinuria (PCR ≥500–1000 mg/g) in Vietnam ◦ AKI or abrupt sustained fall in eGFR ◦ eGFR < 30 ml/min per 1.73 m^2 (GFR categories G4–G5); irrespective of UACR ◦ Rapid Progression of CKD (the reduction in GFR is more than 25% below the baseline value) ◦ CKD and hypertension refractory to treatment with four or more antihypertensive agents ◦ Persistent abnormalities of serum potassium ◦ Recurrent or extensive nephrolithiasis ◦ Hereditary kidney disease Practice points • Scale up the current nephrology workforce by training qualified providers by implementing evidence-based, competence-based, and community-oriented curricula • Develop a robust methodology to collect data and monitor the current and future nephrology workforce • Increase participation of allied health professionals to increase efficiency and decrease the load on nephrologists • In regions where there is a shortage of nephrologists, protocol driven management of individuals with CKD and shared care with PCPs could be considered to mitigate the high workload, with nephrology oversight • Leverage cost-effective technology to increase access to specialist care while building the scope of PCPs and other allied health professionals in managing and improving outcomes of kidney patients • Augment research and scholarly activity in nephrology workforce development, management, and maintenance • Apply different proposed referral criteria for patients with CKD to specialist nephrology services results in differences in referral rates and costs. Referral criteria need to be evaluated in terms of available workforce and resources but also regarding over- and underutilization of nephrology services

AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KFRE, Kidney Failure Risk Equation; KRT, kidney replacement therapy; NICE, National Institute for Health and Care Excellence; PCP, primary care physician; PCR, protein-creatinine ratio; RBC, red blood cell; T1D, type 1 diabetes mellitus; UACR, urine albumin-to-creatinine ratio.

prescription of SGLT2 inhibitors is limited to nephrologists. Use of SGLT2 inhibitors in early CKD at primary care settings is thus subject to local Health Authority approval.

The implementation of referral guidelines leads to an increased workload for specialist nephrology services. There is a shortage of nephrology care providers across all World Bank income groups, particularly in the LMICs.[188] Therefore, a shared service model of care may be adopted to increase early referral of individuals to nephrologists.

Shared Service Model

According to the National Kidney Foundation, quality management of kidney disease and its comorbidities improves clinical outcomes and reduces mortality.[128]

Table 7. Barriers and solutions for early referral in Asia[18]

Barriers	Resolutions
Lack of adequate knowledge and awareness of CKD among HCPs and patients	Increasing HCP education; creating awareness among the general population for kidney disease with informative guides In the Philippines, public awareness programs include the distribution of small informative talks and videos over social media platforms. Opportunistic screenings are conducted on World Kidney Day as well as Philippines Kidney Month to increase awareness In Taiwan, similar to the Philippines, opportunistic screening is conducted for hepatitis and kidney disease during Kidney Month to increase awareness In Vietnam, CKD related information for diagnosis and treatment is publicly available through website
Delayed diagnosis	Incorporation of national screening programs In Taiwan, PCPs and endocrinologists are recruited for 'pay-for-performance' programs where patients are tested for CKD and referred for nephrology services
Inadequate patient-provider communication regarding CKD	Provision of CKD-related supplies and HCP training
Self-medication and use of herbal/alternative medicines	Patient counseling and education
Inadequate mechanisms for CKD referral and follow-up	A system approach to care coordination M-health technology to improve CKD care
Lack of nephrologists in the region	Participation of allied HCPs with high standards of accreditation and training in nephrology care to maintain the quality of patient care

CKD, chronic kidney disease; HCP, healthcare practitioners; PCP, primary care physician.

Organizing multiprofessional team care, including nursing staff and allied healthcare professionals for screening, and patient education could improve CKD prognosis. When the eGFR of advanced patients with CKD reduces to less than 15 ml/min per 1.73 m^2, the shared decision-making for KRT should be activated and the case should be discussed with a specialist. In situations where nephrology consultation is required, PCPs should aim for a shared care model in which they do not lose the relationship with their patient, even in cases requiring ongoing nephrology follow-up, especially because patients with CKD require ongoing preventive care (e.g., cancer screening, vaccinations), management of acute and other chronic medical conditions, and mental health counseling, all of which are most suitably provided at the primary care level.[189] Protocol driven management of individuals with CKD and shared care between nephrologists and PCPs will benefit patients.

FRAMEWORK FOR MANAGEMENT OF COMPLICATIONS

Recommendation Summary

- All individuals with CKD should be considered at increased risk for CVD.
- The level of care for ischemic heart disease offered to individuals with CKD should not be prejudiced by their existing CKD.
- In adults with newly identified CKD, hemoglobin (Hb) levels should be routinely measured to screen for anemia and individuals with Hb <11.0 g/dl should be investigated and appropriate treatment considered.
- The route of iron administration for patients with anemia and CKD should be based on the severity of the iron deficiency, availability of venous access, response to previous oral iron therapy, side effects with previous oral or i.v. iron therapy, patient compliance, and cost.
- Potential benefits and risks should be evaluated before initiating erythropoiesis-stimulating agents (ESAs).
- Serum levels of electrolytes, calcium, phosphate, parathyroid hormone, and alkaline phosphatase should be routinely monitored in individuals with CKD stages 3a to 5 with an individualized frequency of testing.

The progression of CKD is associated with multiple complications. These complications are associated with poor quality of life as well as an increase in mortality. The complications and comorbidities associated with CKD generally accelerate in late-stage CKD and nephrologists provide holistic care. The primary goals for the management of complications include prevention and management of CVD; anemia, MBD, electrolyte imbalance and acidosis; and management of other symptoms of CKD with appropriate referral to subspecialties as required.

CVD

There is a high prevalence of CVD in individuals with CKD. Approximately 50% of individuals with stage 4 and 5 CKD have CVD,[190] making CKD an independent risk factor for CVD. CVD is responsible for mortality in 40% to 50% of individuals with advanced-stage CKD.[191-193] Individuals with CKD also have a high risk of atherosclerosis-related complications such as MI and stroke; CV death can occur because of heart failure and fatal arrhythmias.[194] CV complications among patients with CKD result in substantial morbidity and affect their quality of life.[193] Several risk factors for CVD are usually prevalent in individuals with CKD, including hypertension,[88] insulin resistance or diabetes,[195] electrolyte imbalance, dyslipidemia,[196] vascular calcification,[197] and lifestyle factors such as smoking and obesity.[198,199] The management of CVD in individuals with CKD focuses primarily on the management of risk factors and the prevention of CV adverse events.

The recommendations for lifestyle modification, control of BP, and diabetes are discussed in earlier sections. In CV outcome trials, glucagon-like peptide-1 receptor agonists, and SGLT2 inhibitors have demonstrated reductions in CV events, emerging as key disease-modifying therapy to prevent the progression of CKD. The recommendations and supporting evidence for SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists in prevention of CV events are elaborated in the section 'Framework for Treatment of T2D in CKD.' This section will focus on initiating lipid-lowering therapies as well as antiplatelet and anticoagulant therapies. The recommendations are presented in Table 8.[13,200-205]

Rationale

A strong and linear association between CVD and CKD has been established in large cohort studies. In individuals with an eGFR of 45 to 59 ml/min per 1.73 m^2, CV risk is increased by 43% and in those with eGFR below 15 ml/min per 1.73 m^2, the risk is increased by 343%.[7] Although the risk is higher in patients with lower eGFR, considering that the majority of the population with CVD will be in the range of 45 to 59 ml/min per 1.73 m^2, the number of CV events in this category will surpass the severe CKD category. Other large studies confirming the increased risk of CVD in CKD include The CKD Prognosis Consortium,[206] Micro-Heart Outcomes Prevention Evaluation,[108] HUNT-2,[207] Losartan Intervention For Endpoint Reduction in Hypertension,[208] and Modification of Diet in Renal Disease.[209]

Table 8. Recommendations for screening and management of CVD in individuals with CKD[134]

Recommendation for Asia
All individuals with CKD be considered at increased risk for CVD [1A]
We recommend that the level of care for ischemic heart disease offered to individuals with CKD should not be prejudiced by their CKD [1A]
Use of antiplatelet agents
Individuals with CKD and atherosclerotic events be offered treatment with antiplatelet agents for secondary prevention unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits [2B]
Management of dyslipidemia
In adults with newly identified CKD, we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) [1C]
Practice Point: The frequency of routine monitoring should be individualized based on cardiovascular risk of the patient and subject to country-specific reimbursement status
In adults aged ≥50 years with eGFR ≤60 ml/min per 1.73 m^2 but not treated with chronic dialysis (GFR categories G3a–G5), we recommend treatment with a statin or statin/ezetimibe combination [1A]
In adults aged ≥50 years with CKD and eGFR ≥60 ml/min per 1.73 m^2 (GFR categories G1–G2), we recommend treatment with a statin [1B]
In adults aged 18–49 years with CKD, we suggest statin treatment in individuals with one or more of the following [2A]:
• known coronary disease (MI or coronary revascularization)
• diabetes mellitus
• prior ischemic stroke
• the estimated 10-year incidence of coronary death or nonfatal MI >10%

CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.

Antiplatelet/Anticoagulant Therapy. In patients with coronary artery disease without CKD, antiplatelet therapy is well-established to reduce CV risk, but in CKD, the benefit is less clear.[210] In the *post hoc* analysis of the Hypertension Optimal Treatment trial, among every 1000 persons with eGFR <45 ml/min per 1.73 m^2 treated with aspirin for 3.8 years, 76 major CV events and 54 all-cause deaths will be prevented and 27 excess major bleeds were projected to occur.[211] Although aspirin increases the risk of bleeding, the benefit versus risk should be considered when prescribing aspirin for secondary prevention of atherosclerotic events. In a recent Cochrane review, the results indicated insufficient available evidence for use of antiplatelet treatment in primary prevention in individuals with CKD, whereas efficacy of antiplatelet therapies for secondary prevention against MI or stroke in individuals with CKD was established in a few studies.[212]

As per KDIGO guidelines, aspirin is indicated for secondary prevention of CVD but not primary prevention.

Lipid-lowering Therapy. In the Study of Heart and Renal Protection study, the largest randomized clinical trial in individuals with CKD, lipid-lowering therapy with simvastatin and ezetimibe resulted in a 17% reduction in atherosclerotic events, as compared to placebo.[213] *Post hoc* analyses of 3 studies (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events - low-density lipoproteins, Treating to New Targets, and Scandinavian Simvastatin Survival Study) show a reduction in risk of CV events and all-cause death in individuals receiving statins compared to placebo.[214] In addition to the subanalysis of the Study of Heart and Renal Protection study (in patients undergoing dialysis)[213], AURORA[215] and 4D[216] studies did not report a significant impact on major CV events as well as all-cause mortality. Considering the role of lipid-lowering drugs for prevention of CVD, evaluation of lipid profile in individuals with CKD is recommended. However, no recommendations have been provided for the frequency of evaluation. Adding a low-to-moderate-dose statin for prevention of CV events is recommended by KDIGO[13,189] as well as other guidelines.[217]

Asia Perspective

Several studies in the Asian population have also shown an increased risk of CVD and metabolic diseases in individuals with CKD.[201–204] Thus, patients should undergo complete CV assessment at time of diagnosis of CKD and all individuals with CKD should be considered at an increased risk for CVD.

Antiplatelet Drugs. The Australia CARI guidelines suggest that aspirin therapy should not be routinely recommended because it is unclear if the benefits outweigh the risks for primary prevention of CVD in patients with early (stage 1–3) CKD (2C).[218] Malaysian CKD guidelines recommend use of antiplatelet agents such as aspirin in patients with CKD for secondary prevention of CVD. Aspirin should not be used for the primary prevention of CVD in CKD. A combination of clopidogrel with aspirin should be avoided in patients with CKD unless compelling indications are present.[17] These recommendations are similar to the KDIGO recommendations and thus have been incorporated in our framework for use of antiplatelet agents for management of CVD in CKD.

Lipid-lowering Therapy. Because there are no formal recommendations about the frequency of evaluation of lipid profile in CKD, the frequency of routine monitoring should be individualized based on CV risk of the patient and is subject to country-specific reimbursement status. The Philippines CPGs for Management of

Dyslipidemia recommends statins for the prevention of CV events in individuals not on dialysis.[17] As per the Malaysia guidelines, statins should be preferred in individuals with CKD for primary as well as secondary prevention of CV events.[17] The Australian CARI guidelines strongly recommend use of statins (with or without ezetimibe) to reduce the risk of atherosclerotic events (1A).[218] Statin therapy in a majority of Asian countries is cost-effective and may be reimbursed or subsidized by government, thus increasing their accessibility. However, none of the guidelines provide target lipid and cholesterol levels in individuals with CKD. Though most of the statins have proven to be safe and well-tolerated, caution should be exercised in initiating high-dose statins in individuals with advanced CKD.[219,220]

Anemia

Anemia is a common complication in patients with CKD and is associated with increased mortality and reduced quality of life.[221] The development of anemia in CKD is due to reduced erythropoietin production and resistance, sometimes coupled with iron deficiency.[222] Hepcidin, elevated during inflammation, plays a critical role in the impairment of iron absorption and utilization and derangement in the oxygen sensing mechanism via the hypoxia-inducible factor pathway in CKD-related anemia.[223] Anemia is more common in advanced-stage CKD than in early CKD. However, in the clinical setting, anemia may be underdiagnosed due to the relatively asymptomatic nature of the condition.[224-226] The detailed guidelines for the management of anemia in individuals with CKD are provided in KDIGO CPG for Anemia in CKD 2012.[227] The current recommendations for anemia diagnosis and management are presented in Table 9.[227-229]

Rationale

Screening. Though there is scarce evidence on the frequency of screening patients with CKD for anemia, it has been observed that there is a gradual decline in Hb values in patients with CKD, thus requiring regular surveillance. Regular monitoring is recommended for patients with CKD stage ≥3.[227-229]

Diagnosis. The international guidelines differ in Hb concentration requiring therapy and laboratory tests for diagnosis of anemia. As per KDIGO[228] guidelines, treatment should be considered for individuals with Hb level <13 g/dl (<12 g/dl in females), after being diagnosed with anemia. Although initiating treatment at Hb <13 g/dl is debatable, more recent NICE (2020)[228] guidelines and Renal Association CPGs–Anemia of CKD (2017)[229] take more conventional approach by suggesting that a Hb level <11 g/dl should be considered for management strategies. As per KDIGO guidelines, along with complete blood count, serum ferritin, transferrin saturation, vitamin B12, and folate levels should be checked for investigating the severity of anemia. Complete blood count and vitamin levels assist in identifying the type and causality of anemia,[230-233] whereas evaluating transferrin saturation and ferritin is critical for understanding iron deficiency and metabolism disorders.[234-236]

Management of Anemia. Replenishing the iron or vitamin deficiency and treating with ESAs are 2 major strategies in individuals with need for pharmacotherapy for anemia management. It is recommended that the treatment of anemia should be individualized as per availability, cost of therapy, and personal choice.[227-229] Recently, hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI) have been approved in some countries for the treatment of anemia in CKD.[131] Currently 3 HIF-PHIs, roxadustat, daprodustat, and vadadustat, are approved in some markets. In non-dialysis individuals, roxadustat was superior to placebo in raising Hb,[237] and daprodustat and vadadustat were noninferior to darbepoetin alpha[238,239]; whereas in individuals undergoing dialysis, roxadustat was noninferior to epoetin alfa,[240] and vadadustat and daprodustat were noninferior to darbepoetin alfa[241] and ESAs[242] in raising Hb. A few safety concerns including gastrointestinal bleeding, malignancy, retinopathy, liver dysfunction, and CV events have been reported with HIF-PHI. Therefore, the place in the management of anemia is yet to be formalized in the guidelines. However, the KDIGO working group has recognized its value in the treatment of anemia in CKD.[243]

Asia Perspective

In Asia, almost all countries follow the KDIGO guidelines for anemia diagnosis and treatment.[17,244-246] We have graded the recommendations as per KDIGO guidelines based on the LOE presented. However, considering the recent advances in the management of anemia, regrading of recommendations is warranted. For the management of anemia in individuals with need for pharmacotherapy, iron supplementation and ESAs are preferred. With consideration of costs, oral iron supplementation is preferred. However, i.v. supplementation provides rapid improvement with fewer doses.[244] As per Malaysian guidelines, nephrologist referral is important before initiating ESAs.[17] Recently, nephrologists from the Asia-Pacific region convened to discuss the current status and management of patients undergoing peritoneal dialysis.[247] The group established that iron supplementation and ESA treatment are cornerstones for the treatment of anemia. The group also recognized the emerging evidence for HIF-PHI in

Table 9. Recommendations for diagnosis and management of anemia[8]

KDIGO[13] guidelines	NICE 2020 Guidelines and Renal Association Clinical Practice Guidelines–Anemia of CKD (2017)	Recommendations for Asia
Screening for anemia		
For patients with CKD without anemia, measure Hb concentration when clinically indicated and (Not Graded): at least annually in patients with CKD 3 at least twice per year in patients with CKD 4–5 not on dialysis	Hb levels should be routinely measured to screen for anemia: • at least annually in patients with CKD G3 • at least twice a year in patients with CKD G4–5 not on dialysis [2B]	Recommendation: We suggest that Hb levels should be routinely measured to screen for anemia: • at least annually in patients with CKD G3 • at least twice a year in patients with CKD G4–5 not on dialysis (Not Graded)
Diagnosis of anemia		
Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females (Not Graded)	All patients with chronic anemia associated with CKD should be investigated for the cause and possible treatment, irrespective of the stage of kidney disease or requirement for renal replacement therapy if: • their Hb levels are <110 g/l (<105 g/l if younger than 2 years) or • they develop symptoms attributable to anemia This is to ensure the correct diagnosis and management of anemia [1A]	Recommendation: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females Practice Point: We recommend that all patients with chronic anemia associated with CKD should be investigated for the cause and possible treatment, irrespective of the stage of kidney disease. Physicians to check patients' Hb levels and compare them to age-based norms within their country/region before initiating therapy
In patients with CKD and anemia (regardless of age and CKD stage), including the following tests in the initial evaluation of the anemia (Not Graded): CBC, which should include Hb concentration, RBC indices, WBC count and differential, and platelet count Absolute reticulocyte count Serum ferritin level Serum TSAT Serum vitamin B12 and folate levels	Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements every 3 months The measurement of erythropoietin levels should not routinely be considered for the diagnosis or management of anemia for patients with CKD [1A] Do not request TSAT or serum ferritin measurement alone to assess iron deficiency status in individuals with anemia of CKD.	Recommendation: The following blood tests are recommended in patients with CKD: CBC including Hb concentration, RBC indices, WBC count and differential, and platelet count (Not graded) Practice Point: Consider the following blood tests as per the availability and resources: Absolute reticulocyte count Serum ferritin level Serum TSAT Serum vitamin B12 and folate levels
Treatment of anemia – iron supplements		
When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks) (Not graded) For CKD nondialysis patients who require iron supplementation, select the route of iron administration based on the severity of the iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost (Not graded) Guide subsequent iron administration in patients with CKD based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness, and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status (Not graded) Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted (Not graded)	Offer iron therapy to individuals with anemia of CKD who are receiving ESAs to achieve: • percentage of hypochromic RBC less than 6% (unless ferritin is greater than 800 μg/l) • reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 μg/l) If these tests are not available or the person has thalassemia or thalassemia trait, iron therapy should maintain TSAT greater than 20% and serum ferritin level greater than 100 μg/l (unless serum ferritin is greater than 800 μg/l) Most adults will need 500 to 1000 mg of iron (equivalent doses for children) in a single or divided dose depending on the preparation. Intravenous iron should be administered in a setting with facilities for resuscitation	Recommendations: For CKD nondialysis patients who require iron supplementation, select the route of iron administration based on the severity of the iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or i.v. iron therapy, patient compliance, and cost (Not graded) Practice Points: Physicians should balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm to individual patients Physicians evaluate iron status routinely during iron supplementation. In regions where TSAT and ferritin cannot be evaluated, physicians can consider Hb and CBC parameters for evaluating the effectiveness
Treatment of anemia – ESAs		
In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, and hypertension) [1B] We recommend using ESA therapy with great caution, if at all, in patients with	We recommend that treatment with ESA should be offered to patients with anemia of CKD who are likely to benefit in terms of quality of life and physical function and avoid blood transfusion [1B] We recommend that the decision on the choice of ESA is based on the local	Recommendation: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, and hypertension) [1B]

(Continued on following page)

Table 9. (Continued) Recommendations for diagnosis and management of anemia[8]

KDIGO[13] guidelines	NICE 2020 Guidelines and Renal Association Clinical Practice Guidelines–Anemia of CKD (2017)	Recommendations for Asia
CKD with active malignancy—in particular when cure is the anticipated outcome—[1B], a history of stroke [1B], or a history of malignancy [2C] For adult CKD nondialysis patients with Hb concentration ≥10.0 g/dl (≥100 g/l), we suggest that ESA therapy not be initiated [2D] For adult CKD nondialysis patients with Hb concentration ≤10.0 g/dl (≤100 g/l), we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia [2C] For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when Hb is between 9.0 and 10.0 g/dl (90–100 g/l) [2B]	availability of ESAs [1B] We suggest that patients with CKD on ESA therapy should achieve Hb between: • 100 and 120 g/l in adults, young individuals, and children aged 2 years and older [2B]	Practice Point: Physicians can consider hypoxia-inducible factor-prolyl hydroxylase inhibitors as an alternative to ESA in correcting and maintaining Hb levels for renal anemia in non-dialysis-dependent patients with CKD as well, based on the new data concerning its efficacy and safety

CBC, complete blood count; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; RBC, red blood cell; TSAT, transferrin saturation; WBC, white blood cell.

the treatment of anemia in CKD. The APSN recently provided recommendations for use of HIF-PHI in patients with CKD and anemia.[131] However, we have added the HIF-PHI treatment as a practice point for this recommendation considering that these drugs are yet to be approved in all markets.

MBD

MBD is a common complication of CKD. MBD in CKD is associated with an increased risk of CVD. MBD involves 3 categories, namely bone abnormalities, laboratory abnormalities, and vascular calcification.[248] MBD is frequently accompanied by calcium, phosphorous, and vitamin D dysregulation along with hyperparathyroidism resulting in bone pain, abnormalities in bone turnover, fractures, and extraskeletal calcification.[249] The detailed guidelines for diagnosis and management of MBD in individuals with CKD are provided in the KDIGO 2017 CPG Update for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD.[250]

Rationale

Several observational studies support the recommendation (1C) for screening for abnormalities in calcium, phosphate, alkaline phosphatase, and parathyroid hormone in individuals with CKD.[251-253] The frequency of monitoring the parameters is not graded and will depend on the stage of CKD and the degree of baseline abnormality. The recommended frequency of monitoring is detailed in Table 10.[250]

Criteria for the diagnosis of osteoporosis were revised in the 2017 KDIGO clinical practice guidelines based on increased fracture rate[254-256] and related mortality and morbidity in individuals with CKD.[257-259] The guidelines update data regarding dual-energy x-ray absorptiometry measures of bone mineral density to estimate fracture risk in CKD.[260,261]

Management of MBD

The 2017 KDIGO guidelines for the treatment of mineral abnormalities suggest that elevated phosphate levels should be lowered to the normal range (2C). Both elevated and decreased phosphate levels are associated with increased mortality in patients with G3 to G5 CKD,[262,263] showing a U-shaped correlation.[264] Similarly, hypercalcemia should be avoided in CKD (2C) because increased calcium is associated with nonfatal CV events.[265,266]

For correction of parathyroid hormone, calcimimetics, calcitriol, or vitamin D analogues, or a combination of calcimimetics with calcitriol or vitamin D analogues are recommended (2B) based on results from the EVOLVE study.[250,267] The recommendations for the treatment of osteoporosis are not supported by a high LOE studies, thus the World Health Organization

Table 10. Frequency of testing for abnormalities in calcium, phosphate, alkaline phosphatase, and PTH[250]

Bone Mineral Abnormality	Stage 3a and b	Stage 4	Stage 5
Calcium and phosphate	6–12 mos	3–6 mos	1–3 mos
Alkaline phosphatase	-	12 months or more frequently based on PTH	12 months or more frequently based on PTH
PTH	Based on baseline	6–12 mos	3–6 mos

PTH, parathyroid hormone.

criteria for osteoporosis management in the general population are applied to individuals with CKD.

Asia Perspective

Most Asian countries follow the KDIGO recommendations except for Japan which has developed the Japanese Society for Dialysis Therapy CPG for CKD-MBD[268] and Malaysia (CKD-MBD and parathyroidectomy CPG and standard of practice).[269] In Vietnam, it is recommended that calcium, phosphate, and parathyroid levels be evaluated every 12 months in individuals with stage 3 CKD. In stage 4 CKD, patients should be routinely evaluated every 3 months, whereas in stage 5 CKD, the frequency of evaluation for calcium and phosphate should be increased to per month (Guidance for diagnosis and treatment some nephrology and urology diseases [Ministry of Health, 2015]). We recommend adopting all the KDIGO recommendations for MBD in Asia with the same grading because there is limited evidence from Asia for the management of MBD in individuals with CKD. The Asian perspective on the KDIGO recommendations is presented in Table 11.[250]

Fluid Imbalance and Metabolic Acidosis

Fluid imbalance is prevalent in an advanced-stage of CKD because individuals are susceptible to both hypervolemia and hypovolemia. Fluid overload in CKD is associated with hypertension, left ventricular hypertrophy and mortality in CKD.[271] Electrolyte imbalance in individuals with CKD has been discussed in earlier sections. Electrolyte imbalance is reported in 3% to 11% of individuals with CKD.[272] Although no specific

Table 11. Recommendations for management of CKD-MBD and Asia perspective[250]

KDIGO[250] guidelines	Asia perspective
Diagnosis of CKD-MBD	
We recommend monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G3a [1C] In patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if the results will impact treatment decisions [2B] In patients with CKD G3a–G5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover [2B] In patients with CKD G3a–G5D, we suggest not routinely measuring bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) [2C] In patients with CKD G3a–G5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging [2C]	In Taiwan, a referral to a nephrologist is mandatory for CKD G3 patients; upon referral, all biochemical tests are reimbursed. All biochemical tests for CKD-MBD including calcium, phosphorus, and alkaline phosphatase are performed every 3 months, and PTH testing every 6 to 12 months starting from CKD G4 Thailand offers partial reimbursement for PTH testing In Singapore, individuals with CKD G3a are referred to nephrologists under National CKD Program. Though there is variability in PTH testing currently, a standardization in monitoring is excepted with the referral
Treatment of CKD-MBD – biochemical abnormalities	
In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range [2C] In adult patients with CKD G3a–G5D, hypercalcemia should be avoided [2C] In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders [2B] In patients with CKD G3a–G5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication [1C] In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments [2D]	Regional variations in diet also need to be considered while calculating calcium intake and prescribing calcium-based phosphate binders since China, India, and Indonesia have the world's lowest average calcium intake[270] Also, consideration of the availability of non-calcium-based phosphate binders is required since these drugs may not be reimbursed in all countries. Aluminum-based phosphate binders are still used in some Asian countries
Treatment of CKD-MBD – bone abnormalities	
In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management for the general population [1A] In patients with CKD G3a–G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment for the general population [2B]	The access to calcimimetics for management is not uniform in Asia due to its high cost. For example, cinacalcet for the suppression of PTH is reimbursed in Japan, South Korea, and in selected cases in Hong Kong, but not in some countries like Vietnam

BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

recommendations have been outlined in KDIGO for the management of electrolyte and fluid imbalance, dietary restrictions and appropriate supplements for electrolytes should be constituted as a first-line treatment. PCPs should be engaged in regular monitoring of electrolytes and acid-base biochemistry profiles for individuals with CKD and prescribe low-potassium diets for patients with hyperkalemia and low-phosphorus diets for patients with hyperphosphatemia.[227,273] Individuals with CKD should be screened for metabolic acidosis with arterial blood gas measurements. For fluid overload, patients should be counseled about restricting fluid and sodium intake. Dietary restrictions for sodium intake discussed earlier also assist in maintaining the fluid and electrolyte balance by limiting thirst.

Metabolic acidosis increases as kidney function decline in patients with CKD. Metabolic acidosis is associated with increased protein catabolism, uremic bone disease, muscle wasting, chronic inflammation, impaired glucose homeostasis, impaired cardiac function, progression of CKD, and increased mortality.[274–278] Correction of acidosis with sodium bicarbonate was associated with improved prognosis in individuals with CKD.[278–280] Serum bicarbonate concentration <22 mmol/l is associated with an increased risk of CKD progression and increased risk of death. Conversely, high serum bicarbonate concentration >32 mmol/l is associated with an increased risk of death irrespective of the level of kidney function.[13] Therefore, KDIGO guidelines' proposed recommendation is treatment with oral bicarbonate supplementation to maintain serum bicarbonate within the normal range unless contraindicated for individuals with CKD and serum bicarbonate concentrations of less than 22 mmol/l (2B). For Asia, we recommend few practice points for regulating electrolyte and fluid balance as follows: (1) dietary sodium restriction should be emphasized; (2) loop diuretics are preferred when GFR is <40 ml/min per 1.73 m^2; (3) the addition of spironolactone or eplerenone might be beneficial, especially in proteinuric patients already on maximum ACEi or ARB therapy, but serum potassium levels should be monitored frequently for the development of hyperkalemia; and (4) adjusting diuretic dose and frequency based on the patient's accurate weight and BP should be preferred.

SUCCESSFUL IMPLEMENTATION AND INTENDED IMPACT OF LOCAL GUIDELINES FOR CKD

Recommendation Summary

- CKD should be recognized as an important cause of death and disability by national health authorities.
- CKD prevention, screening, diagnosis, and management should be integrated into existing or planned public health initiatives.
- Increase government funding for CKD detection and prevention.
- Engage national or regional nephrology societies with global societies.
- Train PCPs in early diagnosis, referral pathways; and community management for kidney care.
- Use web-based applications for educating PCPs about CKD guidelines and faster and wider dissemination of the guidelines.
- Use standardized management algorithms or referral pathways for CKD prevention and management with clear treatment decision points enlisted in action plan formats, checklists, and levels of referral according to the local healthcare infrastructure.
- Shared decision-making can slow disease progression, improve outcomes, and manage resources more effectively.

Healthcare research and development of CPGs aim to improve patient care and clinical outcomes by collating evidence-based recommendations for physicians, and to bring about appropriate and timely community-level policy changes that reduce disease burden to society, leading to lesser expenditure on patients as well as overall lesser healthcare costs. CPGs standardize real-world practices, decrease inappropriate variability, and help propagate best practices for maximum patient benefit.[281–285]

Guidelines for CKD aim at both diagnosis and staging of individuals with CKD followed by optimum management of the condition and its comorbidities to delay progression to kidney failure. The guidelines also direct PCPs to the appropriate time for referring patients to nephrology services and help in the shared decision-making process for patients in whom KRT needs to be initiated. The challenge in LMICs lies in the effective population-level implementation of these guidelines and policies to ensure the intended impact on the community at large. The barriers to the implementation of guidelines are presented in Figure 5.[286,287] Poor implementation may lead to suboptimal clinical outcomes because of unsuccessful prevention strategies and missed or failed execution of beneficial therapy regimens while wasting already limited healthcare resources.[288] The reasons for inadequate implementation are multifold and warrant specific strategies to overcome them. The proposed strategies to ensure the effective implementation of guidelines in local clinical practice in LMICs are described below.

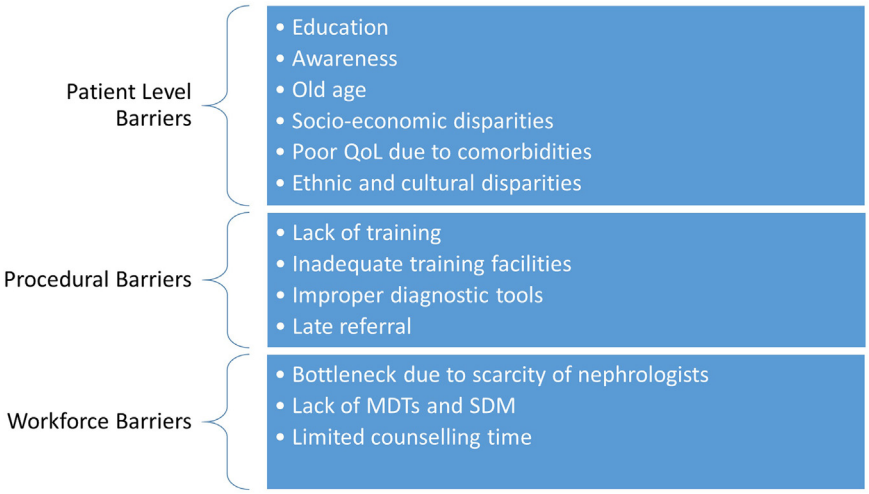

Figure 5. Barriers to implementation of guidelines.[286,287] MDT, multidisciplinary team; QoL, quality of life; SDM, shared decision-making.

Strategies to Ensure the Optimal Implementation of Guideline-Based Health Policies

Screening and Surveillance Programs

- Identification of stakeholders that include the target population and their families/support networks, governmental and not-for-profit allies, pharmaceutical industry, professional societies, and the medical fraternity
- Integration of CKD prevention, risk factor control, screening, diagnosis, and management into existing or planned public health initiatives
- Special focused initiatives for CKDu; CKD due to environmental toxins, herbs, and illicit use specific to some countries or ethnicities
- Health economics and outcomes research into the burden of untreated disease or disease that has progressed into advanced stages may re-enforce the need for early identification and intervention and provide an economic rationale for this undertaking
- Recognition of CKD as an important cause of death and disability by national health authorities
- Increase government funding for CKD detection and prevention
- Engagement of national or regional nephrology societies with global societies. A case in point is a successful collaboration between a Pan-American health organization and the Latin American Society of Nephrology and Hypertension that resulted in the inclusion of CKD within the annals of prevention of CVD in the Americas and the creation of a task force for the study of the CKD epidemic in Central America[289,290]
- Establishing and maintaining robust CKD-specific registries and end-stage kidney disease registries with details on the availability of dialysis and/or transplant
- Training PCPs and allied healthcare professionals for effective screening, diagnosis, referral, and adherence to treatment strategies through shared care model
- Increase patient awareness about CKD
- Increase awareness about CKD among the general population
- Country-wide dissemination of guidelines through local publications, participation in local conferences/symposia, or workshops in collaboration with local pharmaceutical companies or nephrology societies
- "Train the trainers" sessions and exemplary case presentations could be an effective implementation tool[291]
- Use web-based applications for educating PCPs about CKD guidelines and electronic diagnosis and management assistance to PCPs in CKD
- In resource-constrained countries with limited access to KRT, emphasis should be on the development of effective surveillance systems to track data on risk factors, disease burden, care pathways, and clinical outcomes for acute kidney injury and nondialysis-dependent CKD
- Ensure maintenance of adequate screening tools for an effective screening program through approaches, such as questionnaires, risk stratification, physical assessments or measurements, and laboratory tests to identify patients with CKD.[251,292]
- Appropriate follow-up of patients who have screened positive for CKD as well as rescreening for patients at high risk of CKD (continuing care)
- Promote appropriate lifestyle changes through mass public dissemination drives such as healthier eating, including a reduction in consumption of salt and sugar, increased physical activity, weight loss (if

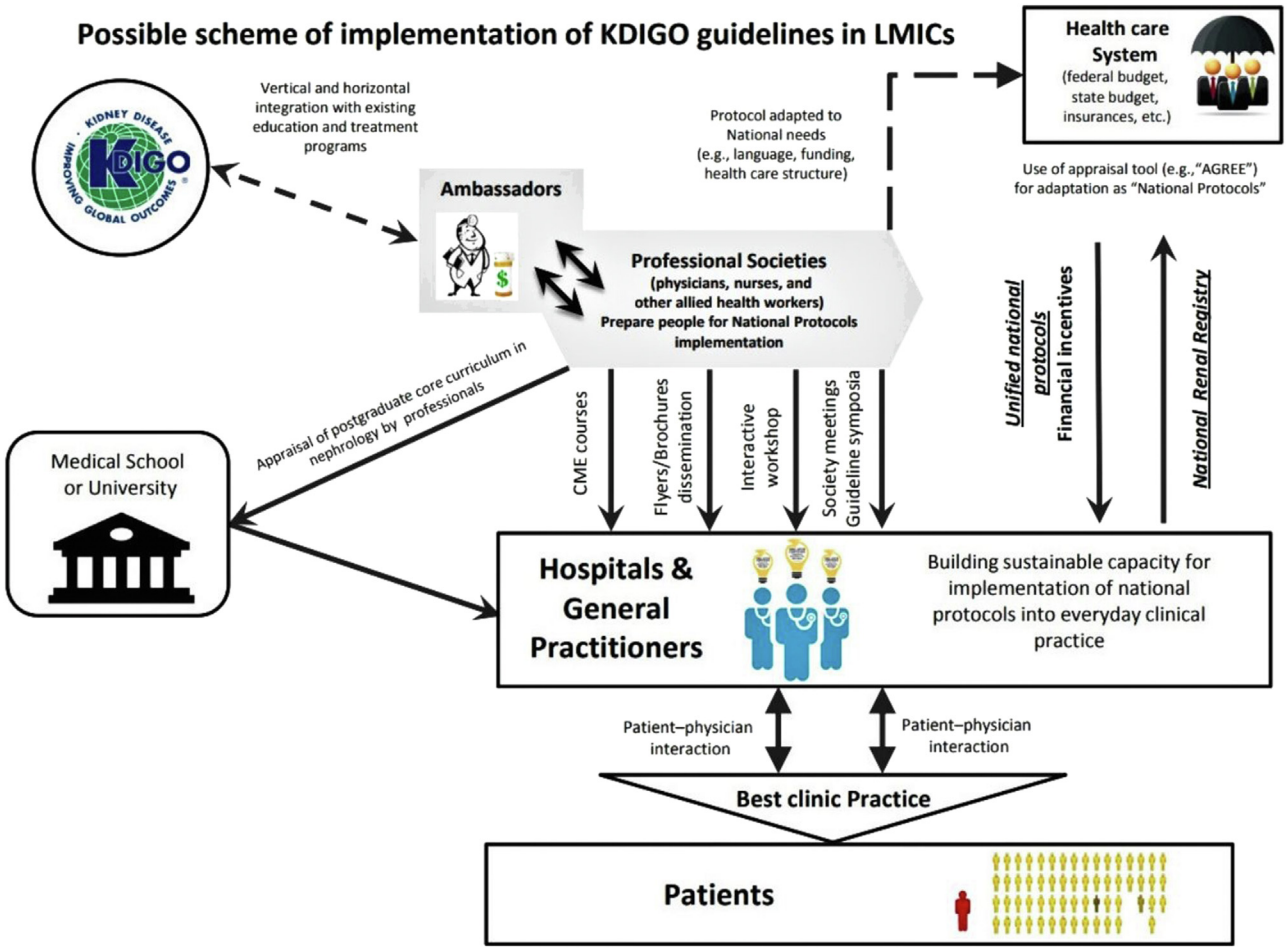

Figure 6. Key players in the implementation of KDIGO guidelines in LMICs.[291] KDIGO, Kidney Disease: Improving Global Outcomes; LMIC, low and middle-income countries.

indicated), tobacco cessation, and education about drug usage (nephrotoxin).

Effective Care and Management Strategies

- Standardized management algorithms or referral pathways for CKD prevention and management with clear treatment decision points enlisted in action plan formats, checklists, and levels of referral according to the local healthcare infrastructure[293]
- Developing and training renal healthcare workforce across all domains such as diagnostics, PCPs, specialists, nurses, and other health workers
- Adequate healthcare workforce financing[294]
- Roll out of universal healthcare or national insurance schemes covering CKD treatment
- Constituting a multidisciplinary team, including PCPs who are the initial clinical contacts, nephrologists, nurses, psychosocial workers/counselors, dieticians, other allied health professionals, and community leaders
- Shared decision-making involving patients, caregiver, and healthcare professional involvement to slow progression, improve outcomes, and manage resources effectively[295]
- Country-specific priority setting in care pathways to allow the government to offer treatment options that are best suited for the patient based on individual countries' unique treatment landscapes. For example, in Thailand, the implementation of a "peritoneal dialysis first" universal coverage policy in which all eligible patients are offered peritoneal dialysis with the more costly hemodialysis restricted to patients with a clinical indication or private insurance coverage has led to the expansion of end-stage kidney disease care.[296] In Taiwan, the National Health Insurance program provides full coverage for dialysis therapy.[297]
- Nationwide key performance indicators with trackable care quality index, to improve daily monitoring of the patients and keeping track of their data as per a country's enrollment and reimbursement policies.

Although KDIGO has been instrumental in developing evidence-based best practice guidelines to optimize the management of patients with CKD, the

Figure 7. Intended impact of implementation of guidelines for CKD. CKD, chronic kidney disease; PROs, patient-reported outcomes.

adoption of recommendations and guidelines especially in LMICs has been challenging. Policy makers need to be alerted that the large part of the disease burden of diabetes, hypertension, and obesity is compounded through the development of CKD.[298] Adaption of KDIGO guidelines to local guidelines can be instrumental in making CKD care accessible and improving outreach and patient compliance, because they are experience-based. Therefore, an integrated approach that involves policy makers, payers, and caregivers is essential for the successful implementation of regionally effective CKD guidelines. The KDIGO Controversies conference suggested a scheme for the implementation of guideline-based care in routine clinical practice in LMICs (Figure 6).[291]

Intended Impact of Guidelines Implementation

The intended impact of the implementation of guidelines is presented in Figure 7. Implementation of KDIGO guidelines in LMICs may result in a shortage of nephrologists resulting in severe demand versus supply crises for nephrology services.[299] A team-based, multidisciplinary, and integrated care model is required for CKD management in LMICs.

The introduction of local initiatives in conjunction with PCPs can improve the appropriateness and quality of the referral. Local initiatives combined with national policy and practice changes can lead to an improvement in the outcomes of patients with CKD regardless of the level of resources available. Several national programs and initiatives are being undertaken in all countries for the implementation of guidelines for screening, diagnosis, and management of CKD (Table 12).

The Asian continent comprises of several countries with a wide diversity in ethnicities, races, and socioeconomic and political conditions. There is substantial heterogeneity in the healthcare facilities across countries as well. Country-wise disparity in government support for KRT has also been observed among Asian countries. Many Asian countries, especially LMICs have inadequate funding for kidney healthcare while bearing a high disease burden.[300,301] In addition, lack of a support system for individuals with CKD is also a concern. Because of the need for continuous medical support, individuals with CKD and their caregivers have to spend considerable amount of time as well as resources on healthcare, thus risk loss of employment, social stigma, and differentiation in addition to financial loss. Because of unavailability of universal

Table 12. Country-level initiatives for implementation of guidelines

Country	Initiatives	National kidney program
Australia	• A call to action for early detection and treatment of CKD • Commissioned a report from Deloitte Access Economics 'Changing the CKD landscape: The economic benefits of early detection and treatment' (Report commissioned by Kidney Health Australia, February 2023) • Initiatives like 'Pathology in Parliament' on World Kidney Day (March 9th) wherein the politicians were tested for their kidney function (BP, eGFR, and serum creatinine).	Target Federal Government, Commonwealth Department of Health National Education Programme for primary care physicians and practice nurses
Hong Kong	• For Hong Kong there have been ad hoc 'screening' activities limited to small regions, mainly to raise public awareness about undiagnosed kidney disease.	
Korea	• National Korean Health Checkup: Children between 7 to 17 years undergo yearly urine dipstick test at school. Adults (>20 years) receive kidney function tests including BP, BUN, creatinine, eGFR, and urine dipstick every 2 years. Nephrologists visit is recommended for individuals with eGFR <60 ml/min per 1.73 m^2	National Korean Health Checkup
Malaysia	• Malaysia Society of Nephrology: early detection and timely intervention of CKD collaborative effort between pharmaceutical industry and medical society (Malaysian Society of Nephrology) embarked on several initiatives aimed at increasing and enhancing the level of knowledge, awareness, and practice amongst primary care physicians in Malaysia.	MyCKDCPG Webapp: a comprehensive one-stop solution providing holistic decision aid approaches for CKD management needs to facilitate early diagnosis and intervention Docquity -MSN Kidney Academy: virtual training platform to uplift and strengthen primary care physician's CKD therapeutic strategies
Philippines	• Stop CKD – an educational program for primary physicians • The Philippines Society of Nephrology is collaborating with other professional organizations Diabetes Phil, Philippine Society of Endocrinology and Metabolism, local chapters of Philippine Academy of Family Physicians to raise awareness about CKD in high-risk population	
Singapore	• Systematically identified and tracks patients with CKD in primary care • Provides individualized education and advice on lifestyle modification • Optimized control of risk factors and medical treatment to delay CKD progression • Shared care management with specialists for more advanced CKD (stage 3B and above)	HALT-CKD
Taiwan	• Educational programs aimed at raising awareness among primary care physicians have been actively implemented • Taiwan CKD Care program (Kidney Care Pioneers Project initiated in 2003, follow by National CKD Care program) • Pay-for-Performance by Taiwan National Health Insurance to encourage nephrologists along with allied healthcare professionals to provide comprehensive care on the basis of the NKF-KDOQI guidelines for patients with an eGFR of <45 ml/min per 1.73 m^2 or severe proteinuria (uPCR >1000 mg/g) • Early-CKD Care: for patients with eGFR between 45 and 59 ml/min per 1.73 m^2 and for those with eGFR ≥60 ml/ min per 1.73 m^2 with accompanying proteinuria; for timely patient enrollment, regular evaluation, and nephrology referral	National CKD Care Program and National Early-CKD Care program
Thailand	• The Effectiveness of Integrated Care on Delaying Progression of stage 3–4 CKD in Rural Communities of Thailand (ESCORT study): an integrated approach demonstrated a delay in CKD progression compared to usual care	
Vietnam	• Pilot CKD surveillance program (CK-NET) based on longitudinal electronic health record data and an intelligent clinical decision support system • Comprehensive, integrated, and systematic roll out of lifestyle and pharmacological interventions, with primary and tertiary shared-care management of CKD (Ministry of Health, 2015) • Guidance for diagnosis and treatment of some nephrology and urology diseases (Ministry of Health, 2015)	HALT-CKD (Holistic Approach in Lowering and Tracking Chronic Kidney Disease) Guidance for diagnosis and treatment of some nephrology and urology diseases
Indonesia	• CKD National Guideline (Ministry of Health collaboration with Medical Society) • CKD prevention guideline from Indonesia Society of Nephrology (InaSN) • Collaboration between government, InaSN and pharmaceutical industry to increase awareness and early screening for patient which have high risk CKD.	Roadshow for InaSN CKD prevention guideline

BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NKF-KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; uPCR, urine protein-creatinine ratio.

healthcare insurance in most LMICs and limited resources, there is a marked imbalance in access to optimal CKD management strategies.[302] It is therefore critical to understand the burden of CKD in Asian countries in order to implement effective strategies. Our framework of guidelines aims at fortifying country-level practices in the light of evidence-based global guidelines in order to assist physicians in providing optimal care for patients with CKD.

DISCLOSURE

CP has received funding for medical writing from AstraZeneca; has received honoraria from AstraZeneca, Boehringer Ingleheim, Otsuka, Vifor, and Astellas; is on an advisory board panel of AstraZeneca, Boehringer Ingleheim, Otsuka, GSK, and Vifor; received travel grant from Boehringer Ingelheim; and is on leadership or fiduciary roles in Chair Kidney Health Australia, Deputy

Chair Australian Organ Tissue, and Transplant Authority and Chair Bureau Health Information. J-yM has received funding and honoria for medical writing from AstraZeneca. PG has received funding for medical writing from AstraZeneca; and is in leadership roles in Scientific Committee, Nephrology Society of Thailand. CHC has received honoraria from AstraZeneca. LG has received honoraria from AstraZeneca, Boehringer Ingelheim, Bayer Pharma, Frasenius Kabi, and Organon Pharma (UK) Limited. TMC has received research grant from Astellas Pharma, travel grant from Bayer, is on an advisory board panel of Novartis and GSK, and is on leadership or fiduciary role in Hong Kong College of Physicians. PN has received honoraria from AstraZeneca, Boehringer Ingelheim, and Otsuka and is on advisory board panel of AstraZeneca, Otsuka, and Novo Nordisk. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Strength of the recommendation and quality of the evidence.

Table S2. Cardiovascular and kidney outcome trials for Sodium-glucose cotransporter-2 inhibitors.

Table S3. Cardiovascular and kidney outcome trials for Sodium-glucose cotransporter-2 inhibitors.

Table S4. Cardiovascular and kidney outcome trials for glucagon-like peptide-1 receptor agonists.

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