CLINICAL PRACTICE GUIDELINES

2018 MOH/P/PAK/394.18(GU)

MANAGEMENT OF CHRONIC KIDNEY DISEASE

(SECOND EDITION)

Ministry of Health Malaysia

Malaysian Society of Nephrology

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2018 and will be reviewed in a minimum period of four years (2022) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

Risk factors

- Patients with diabetes mellitus and/or hypertension should be screened at least yearly for chronic kidney disease (CKD).
- Screening for CKD may be considered for patients with:
  - age >65 years old
  - obesity
  - cardiovascular disease
  - metabolic syndrome
  - drugs e.g. nephrotoxic drugs, long-term use of proton-pump inhibitors or analgesics
  - family history of CKD or hereditary kidney disease
  - gout
  - multisystem diseases with potential kidney involvement e.g. systemic lupus erythematosus
  - structural renal tract disease, renal calculi or prostatic hypertrophy
  - opportunistic (incidental) detection of haematuria or proteinuria

Assessment and classification

- Renal function should be assessed using estimated glomerular filtration rate (eGFR) based on the 2009 CKD-epidemiology (CKD-EPI) creatinine equation.
- Serum creatinine **should not** be used alone in the assessment of renal function.
- Kidney Disease Improving Global Outcomes (KDIGO) staging should be used to classify chronic kidney disease.

Treatment

- Blood pressure target for chronic kidney disease (CKD) should be aimed at*:

Proteinuria / Cause	≥1 g/day	<1 g/day
Diabetic Kidney Disease (DKD)	≤130/80 mmHg (SBP 120 to 130 mmHg)	≤130/80 mmHg (SBP 120 to 130 mmHg)
Non-DKD	≤130/80 mmHg (SBP 120 to 130 mmHg)	≤140/90 mmHg* (SBP 120 to 140 mmHg)

SBP=systolic blood pressure

*Blood pressure targets should be individualised according to co-morbidities and age.

- Angiotensin-Converting Enzyme Inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB) should be used as first-line agent in:
  - diabetic kidney disease (DKD) with albuminuria
  - non-DKD when urinary protein excretion ≥1.0 g/day
  - non-DKD with hypertension when urinary protein excretion ≥0.5 g/day
- The target HbA1c should be ≤7% in DKD but this should be individualised according to co-morbidities and age.
- Statin should be offered to patients with CKD for primary and secondary prevention of cardiovascular events.
- Aspirin should be used in patients with CKD for secondary prevention of cardiovascular disease (CVD).
- Aspirin should not be used as primary prevention of CVD in CKD.
- Combination of clopidogrel with aspirin should be avoided in patients with CKD unless compelling indications are present.

Pregnancy

- All female patients of reproductive age with chronic kidney disease (CKD) should receive pre-pregnancy care.
- Pregnancy should be avoided in women with either:
  - moderate to severe renal impairment
  - poorly controlled hypertension
  - heavy proteinuria
  - active systemic disease
- All pregnant women with CKD should be co-managed by a multidisciplinary team.

Referral

- A patient with chronic kidney disease (CKD) with any of the following criteria should be referred to a nephrologist/physician:
  - persistent heavy proteinuria [urine protein ≥1 g/day or urine protein: creatinine ratio (uPCR) ≥100 mg/mmol*] despite optimal treatment
  - persistent isolated microscopic haematuria after excluding urogynaecological cause
  - persistent haematuria with proteinuria (urine protein ≥0.5 g/day or uPCR ≥50 mg/mmol*)
  - rapidly declining renal function [loss of estimated glomerular filtration rate (eGFR) >5 ml/min/1.73 m^2 in one year or >10 ml/min/1.73 m^2 within five years]
  - eGFR <30 ml/min/1.73 m^2 (eGFR categories G4 - G5)
  - resistant hypertension (failure to achieve target blood pressure despite three antihypertensive agents including a diuretic)
  - suspected renal artery stenosis
  - suspected hereditary kidney disease
  - pregnant or when pregnancy is planned
  - persistent abnormalities of serum potassium
  - unexplained cause of CKD

*This is an estimation for practical purpose. The actual conversion of urine protein 1 g/day=uPCR 113 mg/mmol.

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH), Ministry of Higher Education and private healthcare. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

The CPG update was done based on the first edition of evidence-based CPG on Management of Chronic Kidney Disease (CKD) in Adults, issued in 2011. In the update, certain methodology was used e.g. GRADE principles, and the scope expanded/added on risk factors, classification, treatment, pregnancy and complications (e.g. anaemia and CKD-Mineral Bone Disease). Dietary interventions and lifestyle modification were not included. A literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published in the last four years, on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted from 13 May 2016 to 10 October 2016. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 December 2017 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were made to other CPGs on CKD e.g.

- KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (Kidney Disease: Improving Global Outcomes CKD Work Group, 2013)
- Chronic kidney disease in adults: assessment and management (National Institute for Health and Care Excellence, 2014)
- Chronic Kidney Disease (CKD) Management in General Practice (3rd Edition) (Kidney Health Australia, 2015)

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to being used as references.

A total of 11 main clinical questions were developed under four different sections (screening, treatment, referral and CKD-related complications). Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 19 times throughout the development of

these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in DG meetings. All statements and recommendations subsequently formulated were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG strictly follows the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/penerbitan/mymahtas/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objectives of the CPG are to provide recommendations on the following:

- Identification of risk in developing CKD
- Screening and early detection of CKD
- Treatment of early CKD to prevent progression
- Reduction in risk of cardiovascular disease in CKD
- Management of CKD in special populations
- Indications and timing for referral
- Screening for CKD-related complications

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion Criteria

- Adults at risk of/with CKD

b. Exclusion Criteria

- CKD patients on dialysis and transplant

The CPG will also not address detail treatment for CKD-related complications and specific renal diseases.

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of CKD in adults including:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. policy makers
v. patients and their advocates
vi. professional societies

HEALTHCARE SETTINGS

Primary and secondary/tertiary care settings

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The draft guidelines were reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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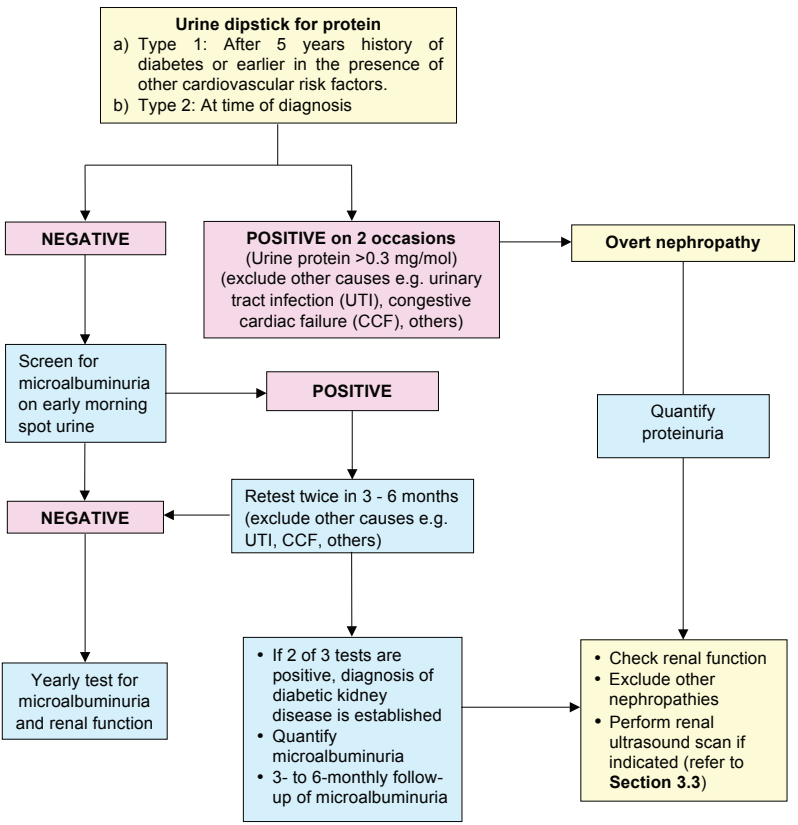
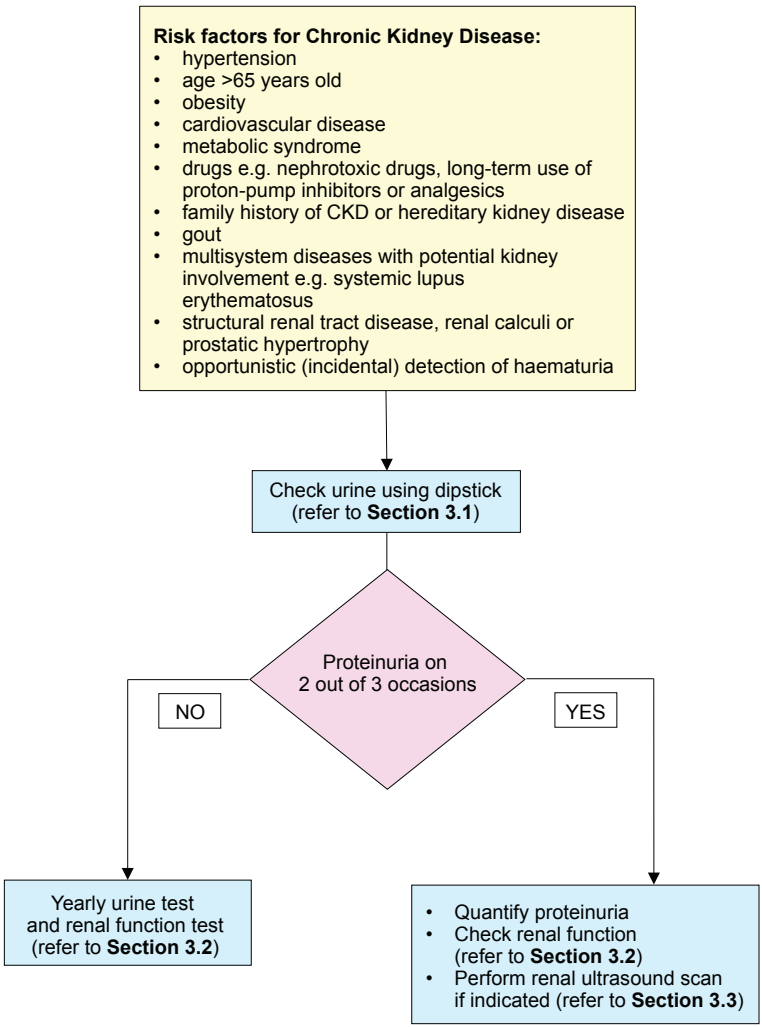
ALGORITHM 1. SCREENING AND INVESTIGATIONS FOR CHRONIC KIDNEY DISEASE IN ADULTS WITH DIABETES



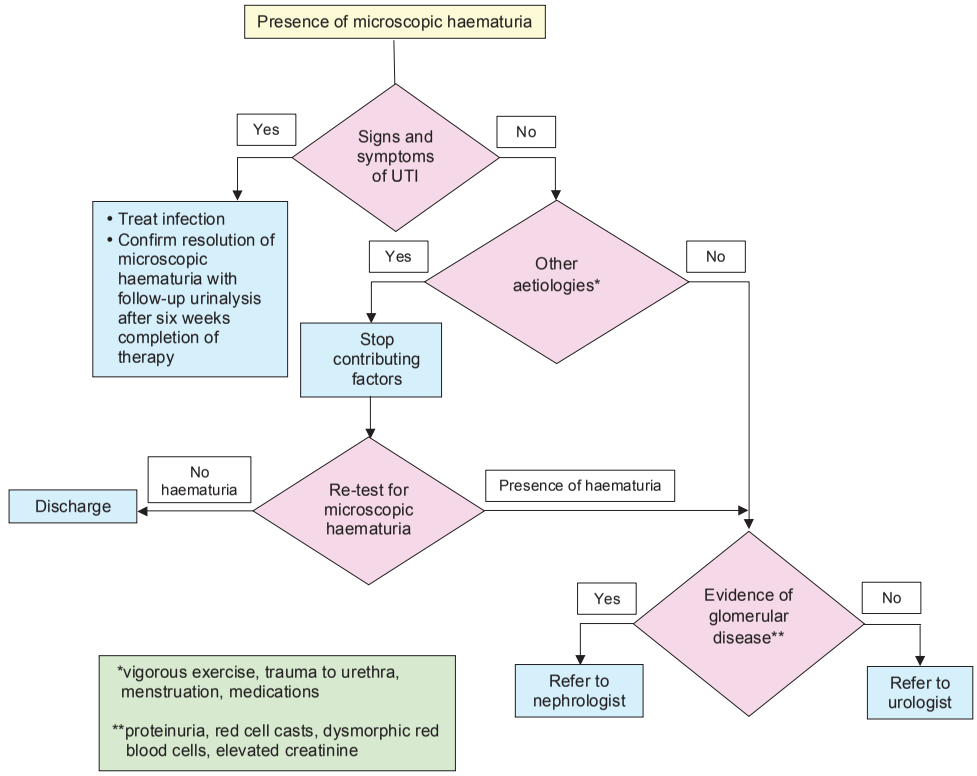
Source: Ministry of Health Malaysia. Management of Chronic Kidney Disease in Adults. Putrajaya: MoH; 2011

ALGORITHM 2. SCREENING AND INVESTIGATIONS FOR CHRONIC KIDNEY DISEASE IN ADULTS WITHOUT DIABETES

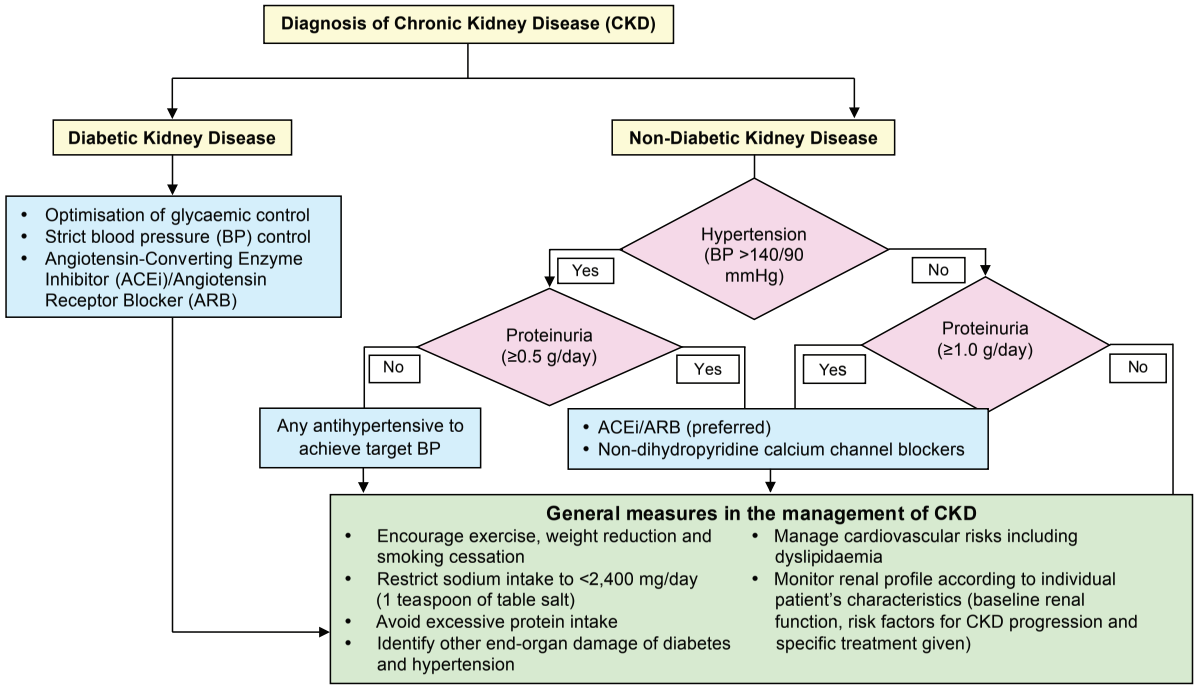


Source: Ministry of Health Malaysia. Management of Chronic Kidney Disease in Adults. Putrajaya: MoH; 2011

ALGORITHM 3. EVALUATION OF HAEMATURIA IN CHRONIC KIDNEY DISEASE IN ADULTS



ALGORITHM 4. TREATMENT FOR CHRONIC KIDNEY DISEASE IN ADULTS



Source: Ministry of Health Malaysia. Management of Chronic Kidney Disease in Adults. Putrajaya: MoH; 2011

1. INTRODUCTION

Chronic kidney disease (CKD) has emerged as a global public health problem because of the increasing number of patients with CKD, risk of progression to end-stage renal disease (ESRD), and high morbidity and mortality.[1] This growing figure will impose enormous socio-economic burdens on the healthcare system.

CKD is a **common** but **silent** and often **under-recognised** condition. The Malaysian National Health and Morbidity Survey 2011 showed a prevalence of 9.07% in adults with CKD, and only 4% of respondents were aware of the diagnosis.[2] There were 37,183 patients on regular dialysis in 2015, with 7,595 new patients entering dialysis.[3] The number of Malaysians with CKD is projected to significantly increase in the future mainly due to the increasing prevalence of diabetes, hypertension and the aging population.

CKD is a strong risk factor for mortality and coronary events.[4, 5] However, it is **preventable** and **treatable**. If CKD is detected early and managed appropriately, the deterioration in kidney function can be reduced by as much as 50%.[6] Lifestyle changes, initiation of Angiotensin-Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB) are proven interventions to delay renal disease progression and also reduce cardiovascular disease (CVD) risk.

In Taiwan, the prevalence of CKD was estimated to be 11.9% while awareness was only 3.5%.[7] After the introduction of a nationwide CKD Preventive Project in 2001, consisting of screening high-risk populations, patient education and multidisciplinary team care, the prevalence rate was greatly reduced and the annual growth rate of patients requiring dialysis decreased from 6% to 3%.[8] This is a successful CKD prevention programme that can be emulated in Malaysia.

Early detection at primary care and timely intervention are important strategies in delaying CKD progression. **Shared decision making** and **close collaboration between different levels of healthcare** should be implemented in the management of CKD locally.

The aim of this CPG is to provide an evidence-based guidance for healthcare providers to screen for CKD and commence early interventions to ameliorate or even halt the progression of CKD. It can also be used as a reference for the relevant stakeholders when forming public health plans for comprehensive CKD management.

2. RISK FACTORS

Early detection and intervention on patients at risk of CKD may prevent the development and progression of the disease.

Recommendation 1

- Patients with diabetes mellitus and/or hypertension should be screened at least yearly for chronic kidney disease (CKD).
- Screening for CKD may be considered for patients with:
  - age >65 years old
  - obesity
  - cardiovascular disease
  - metabolic syndrome
  - drugs e.g. nephrotoxic drugs, long-term use of proton-pump inhibitors or analgesics
  - family history of CKD or hereditary kidney disease
  - gout
  - multisystem diseases with potential kidney involvement e.g. systemic lupus erythematosus
  - structural renal tract disease, renal calculi or prostatic hypertrophy
  - opportunistic (incidental) detection of haematuria or proteinuria

The risk factors of CKD are as follows:

A. Diabetes mellitus

Diabetes mellitus (DM) is an established risk factor for CKD. Patients with DM should be screened at least yearly for CKD.[9]

B. Hypertension

Hypertension may be a cause or consequence of CKD and may accelerate the progression of renal disease leading to ESRD. Patients with hypertension should also be screened at least yearly for CKD.[9]

C. Age

Individual >65 years are at increased risk of CKD.[9]

D. Obesity

Obesity increases the risk of developing low estimated glomerular filtration rate (eGFR) with RR of 1.18 (95% CI 1.09 to 1.28) and albuminuria with RR of 1.51 (95% CI 1.36 to 1.67), independent of metabolic syndrome.[10, level II-2]

E. Cardiovascular Disease

Patients with atherosclerotic vascular disease have 1.4 times greater risk of developing CKD compared with those without the disease in a 2-year follow-up.[9]

F. Metabolic Syndrome

Metabolic syndrome is a risk factor for CKD as shown by a large meta-analysis of 11 cohort studies (OR=1.55, 95% CI 1.34 to 1.80). The strength of the association increases as the number of components of metabolic syndrome increases (p=0.02).[11, level II-2]

G. Drugs

There is conflicting evidence in the association between chronic non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and paracetamol usage and the development of CKD.[9] However, among the most common risk factors for acute decline in GFR for patients with established CKD is NSAIDs, including cyclooxygenase-2 inhibitors.[12]

Use of proton pump inhibitors (PPI) has been shown to significantly increase the risk of developing CKD (RR/OR range of 1.10 to 1.50)[13 - 15, level II-2] and progression of CKD (HR between 1.26 to 1.32).[15 - 16, level II-2] The risk correlates with cumulative dose of exposure.[14 - 16, level II-2] However, this association was not evident with cumulative dose of H_2-blocker.[16, level II-2]

- Certain herbal products including those containing aristolochic acid are associated with CKD.[9]

H. Family history

Family history of kidney disease in first degree relatives increases the risk of CKD by 40% in a 25-year follow-up.[9]

I. Other risk factors

Gout[17, level II-2] and asymptomatic hyperuricaemia[18, level II-2] are associated with CKD.

Individuals with incidental detection of proteinuria and/or haematuria during opportunistic medical screening need to be investigated for CKD.[9]

Other possible risk factors include autoimmune disease, nephrolithiasis, structural renal tract disease, prostatic hypertrophy, low birth weight of <2,500 g, smoking, low socioeconomic status, anaemia, nocturia and physical inactivity.[9]

3. ASSESSMENT

3.1 Screening

CKD screening includes urinalysis and renal function.

3.1.1 Proteinuria

Recommendation 2
- Urine dipstick should be used to screen for proteinuria and haematuria.
- In patients with diabetes, albumin: creatinine ratio on an early morning spot urine sample should be performed to screen for microalbuminuria if urine dipstick for protein is negative.

Proteinuria has both diagnostic and prognostic value in CKD. Presence of proteinuria should be confirmed by a repeat test within three months. Refer to **Algorithm 1** and **2** on **Screening and Investigations for CKD in Adults with and without Diabetes.**

Urine protein excretion may be influenced by factors as shown in **Table 1**.

Table 1. Factors affecting urinary protein excretion

Increases protein excretion	Decreases protein excretion
• Strenuous exercise • Uncontrolled DM • Uncontrolled hypertension • Heart failure • UTI • Acute febrile illness • Haematuria • Menstruation • Pregnancy	• ACEi/ARB • NSAIDs

Source: Ministry of Health Malaysia. Management of Chronic Kidney Disease in Adults. Putrajaya: MoH; 2011

Albumin concentration should be reported as a ratio to urinary creatinine concentration [urine albumin: creatinine ratio (ACR) in mg/mmol or mg/g].[12] Urine ACR is highly sensitive and specific for microalbuminuria. An early morning urine sample is preferred to minimise the effect of posture and exercise.[9]

The proposed albuminuria categories A1-3 are more clinically meaningful than the term microalbuminuria. The term microalbuminuria is discouraged as it can be misleading in suggesting that the albumin may be small or different in some way.[12]

24-hour urine collection should be used for protein quantification. However, an early morning urine protein: creatinine ratio (uPCR) can be used as an alternative.[12]

The diagnosis of proteinuria is shown in **Table 2**.[9]

Table 2. Diagnosis of abnormal protein or albumin excretion

Class	Urine dipstick reading	Urine PCR in mg/mmol	Urine total protein excretion in g/24 hour	Urine ACR in mg/mmol	Urine albumin excretion in µg/min (mg/24 hour)
Normal	Negative	<15	<0.15	<2.5 (male) <3.5 (female)	<20 (<30)
Microalbuminuria	Negative	<15	<0.15	≥2.5 to 30 (male) ≥3.5 to 30 (female)	20 - 200 (30 - 300)
	Trace	15 - 44	0.15 - 0.44		
Macroalbuminuria	1+	45 - 149	0.45 - 1.49	>30	>200 (>300)
	2+	150 - 449	1.50 - 4.49		
	3+	≥450	≥4.50		

Source: Ministry of Health Malaysia. Management of Chronic Kidney Disease in Adults. Putrajaya: MoH; 2011

Refer to **Algorithm 1** and **2** on screening and investigations in CKD.

3.1.2 Haematuria

Persistence microscopic haematuria may indicate significant pathology such as infection, glomerulonephritis, renal calculi, malignancy and other forms of kidney damage. A positive dipstick test for blood on two out of three occasions warrant a full microscopic examination.

Urine microscopy (preferably phase contrast microscopy) on a fresh specimen can be used to differentiate haematuria of glomerular or non-glomerular origin. Non-glomerular haematuria warrants a urological evaluation. Refer to **Algorithm 3** on **Evaluation of Haematuria in Chronic Kidney Disease in Adults**.

3.2 Renal Function

Recommendation 3
- Renal function should be assessed using estimated glomerular filtration rate (eGFR) based on the 2009 CKD-epidemiology (CKD-EPI) creatinine equation.
- Serum creatinine **should not** be used alone in the assessment of renal function.

Serum creatinine (SCr) is not sensitive to diagnose early CKD as it is affected by age, gender, ethnicity, muscle mass and dietary protein intake. It will only rise after a 50% decline of eGFR.[9] (Refer to **Figure 1**)

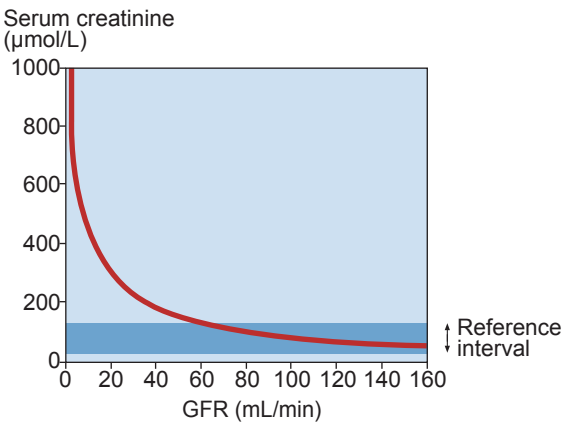


Figure 1. The relationship between glomerular filtration rate and serum creatinine concentration

Adapted: Investigation of renal function (1) (Available at https://clinicalgate.com/investigation-of-renal-function-1/)

There are various formulae to evaluate eGFR. CKD-epidemiology (CKD-EPI) creatinine equation validated in the Western population has shown superiority over the Modification of Diet in Renal Disease (MDRD) equation especially at higher eGFR (>60 ml/min/1.73 m^2).[19, level III] A study in Malaysian population showed that CKD-EPI creatinine equation had better accuracy over MDRD in patients with eGFR <60 ml/min/1.73 m^2 and ≥90 ml/min/1.73 m^2, using Cr-51-EDTA as a reference. However, both formulae were comparable in those with eGFR between 60 and 89 ml/min/1.73 m^2.[20, level III]

In the elderly (age >65 years), there is no accurate method to assess renal function. The Cockcroft-Gault Creatinine Clearance equation, MDRD

equation and cystatin C have the highest correlation to the gold standards e.g. inulin, Cr-51-EDTA, Tc-DTPA or iohexol assays.[21, level III] More studies are required to address the best formula for this age group.

The Cockcroft-Gault equation has been traditionally used for drug dosing based on creatinine clearance. In recent practice, CKD-EPI equation is used for drug dosing based on eGFR especially for newer generation drugs. However drug dosing adjustment should be done according to the United States Food and Drug Administrative- or European Medicines Agency-approved product labelling.

Cystatin C is used for eGFR assessment and it is independent of muscle mass, age, sex, weight, height or dietary protein intake.[9] The combination of SCr and serum cystatin C is more accurate than either marker alone for eGFR. Cystatin C is expensive and not widely available. It may be used for confirmation of CKD in adults with eGFR of 45 - 59 ml/min/1.73 m^2 with no other markers of kidney damage.[22, level III]

Equations for Estimation of Renal Function

i. **2009 CKD-EPI creatinine equation =**
   141 x min (Scr/κ,1)$^{\alpha}$ x max (Scr/κ,1)$^{-1.209}$ x 0.993^{Age} [x 1.018 if female] [x 1.159 if black], where Scr is serum creatinine (in mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1

ii. **Cockcroft-Gault Creatinine Clearance =**
   CrCl (ml/min/1.73 m^2) = (140 - age (yrs)) x body weight (kg)/SCr (umol/l) x Constant where the constant is 1.23 in male or 1.04 in female

When creatinine-based equations are used, calibration of SCr should confer to the isotope dilution mass spectrophotometry method to minimise variations in results.[9]

3.3 Renal Ultrasound

Ultrasound is a useful first-line test for renal tract imaging. It provides information on:

- renal size and symmetry
- cortical thickness and echogenicity
- urinary tract obstruction
- solid or cystic lesions

- General indications for renal ultrasound:[9]
  - rapid deterioration of renal function (loss of eGFR >5 ml/min/1.73 m^2 within one year or 10 ml/min/1.73 m^2 within five years)
  - haematuria
  - symptoms or history of urinary tract obstruction
  - family history of polycystic kidney disease and age over 20 years
  - when a renal biopsy is indicated

3.4 Classification

Recommendation 4
- Kidney Disease Improving Global Outcomes (KDIGO) staging should be used to classify chronic kidney disease.

The current classification of CKD is based on KDIGO 2012 guidelines which has health and prognostic implications.[12]

- CKD is defined as:
  - eGFR <60 ml/min/1.73 m^2 that is present >3 months with or without evidence of kidney damage*

    OR
  - evidence of kidney damage* that is present >3 months with or without eGFR <60 ml/min/1.73 m^2

*Markers of kidney damage are:
a. albuminuria (AER ≥30 mg/24 hours or ACR ≥3 mg/mmol)
b. urine sediment abnormalities
c. electrolyte and other abnormalities due to tubular disorders
d. abnormalities detected by histology
e. structural abnormalities detected by imaging
f. history of kidney transplantation

- CKD in itself is NOT a diagnosis. There should be attempts to identify the underlying cause.

Classification of CKD should be based upon cause, GFR category and albumin category (CGA).

a. Cause

The cause of CKD is based on the presence or absence of a systemic disease and the location within the kidney of observed or presumed histopathology findings.

b. GFR category

GFR category is based upon the following table:

Table 3. GFR categories in CKD

Stages of CKD		
GFR category	**GFR (ml/min/1.73 m²)**	**Term**
G1	≥90	Normal or high
G2	60 - 89	Mildly decreased
G3a	45 - 59	Mildly to moderately decreased
G3b	30 - 44	Moderately to severely decreased
G4	15 - 29	Severely decreased
G5	≤15	Renal failure

c. Albuminuria category

Albuminuria category is based upon the following table:

Table 4. Albuminuria categories in CKD

Stages of CKD				
Category	**AER**	**ACR**		**Terms**
	(mg/24 hours)	(mg/mmol)	(mg/g)	
A1	<30	<3	<30	Normal to mildly increased
A2	30 - 300	3 - 30	30 - 300	Moderately increased
A3	>300	>30	>300	Severely increased

Albuminuria is an independent CV risk factor at any stage of CKD. Presence of albuminuria significantly increases the risk of CV events by ≥85% in stage 1 and 2 diabetic kidney disease (DKD).[9]

Presence and the degree of proteinuria predicts progression of CKD and development of ESRD. In a Japanese cohort study, proteinuria significantly increased the risk of ESRD by more than four times. Another study showed that presence of higher level of albuminuria conferred a higher risk of developing ESRD compared with lower level (HR of 47.2 vs 13.0).[9]

The prognosis of CKD is based upon four factors (refer to **Table 5**):

a. cause of CKD
b. GFR category
c. albuminuria category
d. other risk factors and co-morbid conditions

Table 5. Prognosis of CKD by GFR and albuminuria category

				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
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60 - 89			
	G3a	Mildly to moderately decreased	45 - 59			
	G3b	Moderately to severely decreased	30 - 44			
	G4	severely decreased	15 - 29			
	G5	Renal failure	<15			

Green - low risk, Yellow - moderate risk, Orange - high risk, Red and Deep Red - very high risk

Modified: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150

CKD-EPI creatinine equation is a better predictor of risk than the MDRD study equation. Risk implications include:[23, level III]

- all-cause mortality
- CV mortality
- ESRD
- acute kidney injury (AKI)
- progressive CKD

Risks of ESRD and mortality are higher with larger eGFR decline [24 - 25, level III] and higher albuminuria levels.[25, level III]

4. INTERVENTIONS IN DELAYING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

The aim of CKD treatment is to delay its progression, reduce CV risk and manage CKD-related complications.

Optimal blood pressure (BP) and blood glucose control and, use of renin-angiotensin system (RAS) blockers in proteinuric-CKD are the main strategies to delay CKD progression. Lifestyle modifications (smoking cessation, reduction of weight, low salt diet and other dietary interventions) and avoidance of potentially nephrotoxic agents are additional measures that should be instituted.

Refer to **Algorithm 4** for **Treatment for Chronic Kidney Disease in Adults**.

4.1 Treatment of Hypertension and Proteinuria for Renoprotection

The majority of CKD patients (70 - 80%) have hypertension (usually systolic) which is more severe than non-CKD patients.[9] Control of hypertension and proteinuria are the two most important interventions in delaying renal disease progression.

Any class of antihypertensive agents can be used to control BP in CKD.[9] However, some antihypertensive agents have additional anti-proteinuric effect.

ACEi/ARB should be the first-line therapy in DKD because they have additional renoprotective effect apart from BP reduction. ACEi/ARB is also the preferred antihypertensive agent in non-diabetic, hypertensive CKD patients with proteinuria. However, in the absence of significant proteinuria, there is no preferred class of antihypertensive agent as long as the target blood pressure is achieved.

Proteinuria is an independent predictor for renal disease progression. The magnitude of baseline proteinuria has a linear relationship with progression of CKD and risk of CV events. The degree of proteinuria reduction correlates with the degree of delaying CKD progress and CVD mortality reduction.[9]

4.1.1 Blood Pressure Target

Recommendation 5

- Blood pressure target for chronic kidney disease should be aimed at:

Proteinuria / Cause	≥1 g/day	<1 g/day
Diabetic Kidney Disease (DKD)	≤130/80 mmHg (SBP 120 to 130 mmHg)	≤130/80 mmHg (SBP 120 to 130 mmHg)
Non-DKD	≤130/80 mmHg (SBP 120 to 130 mmHg)	≤140/90 mmHg* (SBP 120 to 140 mmHg)

SBP=systolic blood pressure
*Blood pressure targets should be individualised according to co-morbidities and age.

*Based on SPRINT (Systolic Blood Pressure Intervention Trial) study (median follow-up of 3.3 years), lowering SBP towards 120 mmHg can be considered in non-DKD patients with high CV risk, in whom BP lowering is well-tolerated.[27, level I]

BP lowering has an impact on all-cause mortality, CV events, stroke risk and progression of kidney disease. A target BP of ≤140/90 mmHg has been universally adopted since 2011 as there is no strong data to support further benefits with more intensified therapy. On the other hand, there have been concerns on harmful effects particularly on CV outcomes with the more intensified approach.

In patients with DKD, a post-hoc analysis of the Reduction of Endpoints in Non-insulin-dependent DM (RENAAL) study showed that patients who achieved SBP <130 mmHg had a significantly lower risk of reaching the combined endpoint of doubling of SCr, ESRD or mortality compared with those achieving SBP 140 - 159 mmHg. However, there was no difference in those with BP 130 - 139 mmHg.[9] This is supported by another recent post-hoc analysis in Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT) where the renoprotection effect was significant in those with proteinuria >1 g/day.[26, level I]

In SPRINT study that included hypertensive non-diabetic patients with high CV risk, more intensified BP lowering had demonstrated significant positive impact on CV outcomes and all-cause mortality.[27, level I] In the CKD subgroup, more intensified BP lowering showed significant reduction in all-cause mortality but not on CV and renal outcomes.[28, level I] These findings were further confirmed by systematic reviews and meta-analyses published later.[15, level I; 29 - 30, level I]

In general, BP target for CKD patients should be tailored based on diabetic status, level of proteinuria and CV risk profile. Recent data demonstrated that lowering systolic BP towards 120 mmHg conferred some CV benefits in non-DKD patients with high CV risk.[27, level I] However, physicians need to be cautious on adverse effects from intensified BP lowering e.g. symptomatic hypotension and AKI.

4.1.2 Pharmacological Agents

Recommendation 6

- Any class of antihypertensive agents may be used to treat hypertension in chronic kidney disease (CKD) patients without proteinuria. The choice will depend on the patient's co-morbidity.
- Angiotensin-Converting Enzyme Inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB) should be used as first-line agent in:
  - diabetic kidney disease (DKD) with albuminuria
  - non-DKD when urinary protein excretion ≥1.0 g/day
  - non-DKD with hypertension when urinary protein excretion ≥0.5 g/day
- Renal profile should be carefully monitored following initiation or dose escalation of ACEi/ARB.
- Dual renin-angiotensin system blockade should only be used in carefully selected non-DKD patients with proteinuria* under close supervision by nephrologists.

*Refer to text in **Subchapter 4.1.2b**.

a. Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker

ACEi and ARB confer both renoprotective and cardioprotective effects. A systematic review of randomised controlled trials (RCTs) on ACEi in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), and ARB in T2DM with kidney disease showed that the risk of ESRD was significantly reduced by 40% with ACEi and 22% with ARB when compared with placebo or no treatment. ACEi and ARB also significantly reduced progression of micro- to macroalbuminuria and induced regression from micro- to normoalbuminuria (RR of 3.1 and 1.4 respectively). This benefit was seen regardless of baseline BP.[9]

There was conflicting evidence on the use of ACEi or ARB in non-proteinuric DKD. In a meta-analysis of diabetes patients with normoalbuminuria, ACEi reduced the development of DKD by 42%. In a subsequent combined analysis of three RCTs, the use of candesartan did not prevent microalbuminuria in normotensive normoalbuminuric T1DM or T2DM.[9]

For proteinuric non-DKD, a meta-analysis of RCTs showed that after adjustment for levels of systolic BP and urine protein excretion, the risk for kidney disease progression was lower in patients assigned to ACEi therapy (RR=0.67, 95% CI 0.53 to 0.84) compared with other antihypertensive agents. However, there was no benefit of ACEi use for non-DKD with hypertension if proteinuria <0.5 g/day.[9]

Good quality evidence on the beneficial effects of ACEi/ARB in advanced CKD is lacking. There is difference in opinion as to whether once a patient has advanced CKD, the potential gain of eGFR with ACEi/ARB cessation could improve morbidity and mortality by delaying the need for RRT or whether this would cause an increase in adverse CV outcomes. Hence there is an on-going trial (STOP-ACEi) that addresses the benefits and safety of these agents in advanced progressive CKD (stage 4 - 5).[31, level I]

Health economic evidence has established that ACEi and ARB confer both health gains and net cost savings compared with non-ACEi therapy in CKD. While there is no evidence to support the superiority of one ACEi over another or ARB over ACEi, health economic evidence suggests increased cost-effectiveness for ACEi vs ARB. Hence ACEi should be prescribed first and changed to an ARB only if there is non-renal adverse drug reaction.[9]

- Renal profile should be reassessed within two weeks upon initiation or dose escalation of ACEi/ARB therapy. The interval depends on the baseline renal function.
- ACEi/ARB should be titrated to the maximum recommended dose to achieve optimal BP and anti-proteinuric targets provided:
  - SCr levels remain <30% from the baseline (or eGFR reduces <25%) or
  - serum potassium <5.6 mmol/L
- Consider to reduce or discontinue ACEi/ARB within two months upon commencement (after excluding other precipitating factors) when
  - SCr levels remain ≥30% from the baseline (or eGFR reduces ≥25%) or
  - serum potassium ≥5.6 mmol/L

b. Dual Renin-Angiotensin System Blockade

Dual RAS blockade has additional reduction in proteinuria and hospitalisation for heart failure in both diabetes and non-diabetes patients.[32, level I] However, it does not reduce mortality.[32 - 33, level I] There are mixed results for hard end-points e.g. progression of CKD and ESRD.[33 - 34, level I] Data for outcome of ESRD are restricted mainly to patients who have macroalbuminuria and those with T2DM.[34, level I] Dual RAS blockade has higher risk of adverse events e.g. hyperkalaemia, hypotension and AKI compared with monotherapy.[32 - 33, level I]

Hence, dual RAS blockade should not be prescribed routinely. However, it may be considered in non-DKD patients who remain hypertensive with persistent proteinuria >0.5 g/day provided that serum potassium is within normal range. They should be under close supervision by nephrologists.[9]

c. Calcium Channel Blockers

Calcium Channel Blockers (CCBs) are effective antihypertensive agents but the evidence for its renoprotective effect is not conclusive. Previous meta-analysis showed that non-dihydropyridine (NDHP) CCBs such as verapamil and diltiazem had greater anti-proteinuric effect than dihydropyridine (DHP) CCBs in both DKD and non-DKD. However, the evidence on long-term renal outcomes is lacking.[9]

Recent meta-analysis addressing different subtypes of DHP CCBs reported that L/T- and L/N-type CCBs, as add-on therapy to RAS blockers, offered better renal outcome. The eGFR was lower (MD=0.23 ml/min/1.73 m^2, 95% CI 0.11 to 0.35), in addition to decrease in albuminuria and proteinuria (net change= -1.01 g, 95% CI -1.78 to -0.23). Common T-type and N-type CCBs include lercanidipine, azelnidipine, efonidipine, benidipine and cilnidipine. However, most studies included in the meta-analysis had small sample size with short study duration.[35, level I]

In clinical practice, CCBs as an add-on therapy to RAS blockers in the management of CKD is a reasonable and safe approach to optimise blood pressure control. NDHP CCBs and certain subtypes of DHP CCBs may have additional anti-proteinuric effect. However, effect on CKD progression and ESRD cannot be ascertained based on current evidence.

d. Aldosterone Antagonists

Evidence has shown that aldosterone antagonists (AA) reduced proteinuria and BP in CKD patients on RAS blockers. The main adverse effects of non-selective AA are hyperkalaemia and/or gynaecomastia, which occur less in selective AA e.g. eplerenone and finerenone.[9; 36, level I] In DKD patients on RAS blockade, additional finerenone reduces urine ACR in dose-dependent manner compared with placebo. However there is a drop in eGFR at higher doses.[37, level I] There is no long-term data on renal outcomes and mortality.[9; 36, level I]

e. Direct Renin Inhibitors

Direct renin inhibitors were developed to provide an alternative for RAS blockade. However in several RCTs [Veterans Affairs Nephropathy in Diabetes (VA Nephron D) and Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE)], the use of this agent in addition

to standard RAS blockade did not confer additional benefits but was associated with more adverse events.[9; 33, level I; 38, level I]

4.2 Glycaemic Control for Renoprotection

Recommendation 7
- The target HbA1c should be ≤7% in diabetic kidney disease but this should be individualised according to co-morbidities and age.

Optimal glycaemic control should be attained to reduce the complications of diabetes. Lowering HbA1c to approximately 6.5% to 7% reduces the development of micro- and macroalbuminuria. However, aggressive glycaemic control in patients with established CVD increase the risks of hypoglycaemia and death due to impaired drug metabolism.[9]

Regular blood glucose measurements are advised for more accurate assessment of diabetic control as HbA1c maybe falsely low in CKD due to anaemia.[9]

For the appropriate choice and dosing adjustment of oral anti-diabetic agents in CKD, refer to **Appendix 3** on **Dosage Recommendation in CKD for Commonly Prescribed Oral Medications**.

Recent trials on sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to reduce CV outcomes and may have renoprotective effect.
- In Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG Outcome) trial on patients with T2DM at high CV risk and eGFR of ≥30 ml/min/1.73 m^2, empagliflozin reduced incident or worsening nephropathy by 39% at four years (HR=0.61, 95% CI 0.53 to 0.70).[39, level I]
- There was also a possible benefit of canagliflozin in reducing the progression of albuminuria (HR=0.73, 95% CI 0.67 to 0.79). It also reduced the composite outcome of a sustained 40% reduction in eGFR, need for renal replacement therapy (RRT) or death from renal causes (HR=0.60, 95% CI 0.47 to 0.77) in Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-R studies. However, there was an increased risk of amputation primarily at the level of the toe or metatarsal (HR=1.97, 95% CI 1.41 to 2.75).[40, level I]

4.3 Protein Restriction for Renoprotection

Recommendation 8
- Low protein diet (0.6 - 0.8 g/kg/day) with adequate energy intake (30 - 35 kcal/kg/day) may be given in chronic kidney disease stage 3 - 5.
- Dietary protein restriction should be supervised by a dietitian.

Protein restriction is one of the supportive measures to delay CKD progression. Low protein diet of 0.8 g/kg/day is recommended in DKD vs 0.6 - 0.8 g/kg/day in non-DKD. The benefits in slowing down the progression should be weighed against the risks of protein-calorie malnutrition and death. Low protein diet (0.6 g/kg/day) is not advised in overt DKD due to the risk of malnutrition.[9; 41, level III]

Very low protein diet (VLPD) with keto-acid supplementation may be considered in patients with non-DKD stage 4 - 5 (pre-dialysis). Earlier evidence shows conflicting results on VLPD of 0.3 g/kg/day supplemented with keto-acid in CKD.[9] However, in a recent RCT, vegetarian VLPD supplemented with keto-acid among non-DKD deferred dialysis initiation in patients with Unit eGFR <20 ml/min/1.73 m^2 and was also nutritionally safe. Over the 18 months period of the study, RRT initiation was required in a lower proportion in the keto-acid diet group compared with control (11% vs 30%, p<0.001).[42, level I]

- Only patients who adhere to VLPD may benefit from keto-acid supplements at the recommended dose (1 tablet for every 5 kg body weight/day). They should be carefully supervised by a dietitian (preferably renal-trained) to monitor nutritional status and ensure compliance.

4.4 Lipid Lowering for Renoprotection

There is insufficient evidence to support the use of statin therapy for delaying CKD progression or proteinuria reduction.

In a Cochrane systematic review, statin therapy [median dose equivalent to simvastatin 20 mg (ranged from 5 to 80 mg/day)] had uncertain effects on kidney function or risk of progression to ESRD even though it had some proteinuria reduction (MD= -0.47 g/24 h, 95% CI -0.75 to -0.19) compared with control.[43, level I]

In another meta-analysis, high-intensity statin (atorvastatin 40 - 80 mg/day) minimally improved eGFR (MD rate of eGFR was 0.10 ml/min/1.73 m^2 per year, 95% CI 0.09 to 0.12). However, no safety concerns were addressed.[44, level I]

4.5 Uric Acid Reduction for Renoprotection

There is emerging evidence to suggest uric acid reduction is a potential strategy to delay CKD progression. However, more RCTs are needed to confirm the renoprotective effect.

One meta-analysis which included publications of all languages reported that uric acid reduction mainly by allopurinol led to higher eGFR and lower SCr compared with control in CKD.[45, level I] Another meta-analysis that included only English papers showed non-significant difference in GFR change between allopurinol and control in patients with various baseline kidney function.[46, level I]

An RCT reported that febuxostat potentially improved renal outcome of CKD with asymptomatic hyperuricemia. However, the duration of the study is short i.e. six months.[47, level I]

4.6 Miscellaneous Agents for Renoprotection

There is no conclusive evidence on pentoxifylline, vitamin D analogues and traditional medications in improving renal outcomes.

In two meta-analyses, pentoxifylline reduced proteinuria and improved eGFR minimally.[48 - 49, level I] However, the primary papers used were of low to moderate quality, generally small sample sizes and short duration of follow-up.

Although vitamin D analogues were found to reduce proteinuria against the background of RAS blockade,[50 - 51, level I] there was a trend towards hypercalcemia.[51 - 52, level I] More RCTs are needed to address its efficacy and safety on hard end-points e.g. mortality, CV events, doubling of SCr and ESRD.

There were many studies on traditional medications for renoprotection. In a Cochrane systematic review, Cordyceps preparations (*Cordyceps sinensis*), used as adjuvant therapy to conventional medicine, decreased SCr levels and reduced 24-hour proteinuria.[53, level I] A meta-analysis of eight trials in China demonstrated that puerarin (*Pueraria lobate*) decreased the urinary AER in DKD with few adverse effects.[54, level I] However, definitive conclusions could not be made as most studies in these reviews were of low methodological quality.

4.7 Special Precautions

CKD patients often have multiple co-morbidities, thus may be exposed to potentially nephrotoxic agents. Therefore, the following precautions should be taken:[9]

i. Review all prescribed medications regularly to ensure the dose is appropriate to current renal function (refer to **Appendix 3** on **Dosage Recommendation in CKD for Commonly Prescribed Oral Medications**).
ii. Avoid NSAIDs including cyclooxygenase-2 inhibitors [e.g. mefenamic acid, diclofenac acid, ibuprofen, naproxen, indomethacin, ketoprofen, salicylic acid (high dose), meloxicam, celecoxib and etoricoxib]
iii. Avoid long-term PPI use unless with clear indication.
iv. Adhere to risk mitigation strategies to avoid contrast-induced AKI.
    - Avoid radio-contrast agents in high risk patients if possible. They are those with pre-existing renal impairment (SCr ≥132 μmol/L or an eGFR <60 ml/min/1.73 m^2), DM, volume depletion, CCF, nephrotic syndrome, decompensated liver cirrhosis or concurrent NSAIDs/diuretic use.
    - Consider an alternative imaging study e.g. ultrasound, non-contrasted computerised tomography scan or magnetic resonance imaging.
    - Use isotonic saline peri-procedure.
    - There is insufficient evidence to support the use of N-acetylcysteine and sodium bicarbonate.
    - Use non-ionic contrast media with low osmolarity (e.g. ioversol and iopamidol) or iso-osmolarity (e.g. iodixanol).
    - Use the lowest dose of contrast possible and avoid repeated studies within 48 hours.
v. Gadolinium should be avoided in patients with impaired renal function (eGFR <30 ml/min/1.73 m^2) due to increased risk of nephrogenic systemic fibrosis.
vi. Avoid using oral sodium phosphate (FLEET®) in bowel preparation for colonoscopy in CKD with eGFR <60 ml/min/1.73 m^2 due to increased risk of acute hyperphosphataemia.[12] Use alternative preparations e.g. macrogol (FORTRANS®).

5. INTERVENTIONS IN REDUCING THE RISK OF CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE

Patients with CKD are at high risk for CV morbidity and mortality. The risk factors e.g. high BP and hyperlipidaemia should be appropriately controlled and anti-platelet agents should be used for the secondary prevention of CVD.

5.1 Lipid Lowering Agents

Recommendation 9
- Statin should be offered to patients with chronic kidney disease for primary and secondary prevention of cardiovascular events.

Beneficial effects of statin in primary and secondary prevention of CV events (total mortality, CV mortality and non-fatal CV events) were significant in patients with CKD:[9]

- In the primary prevention of CV event, the SHARP (Study of Heart and Renal Protection) study supported the use of lipid-lowering therapy in CKD stages 3 - 5. In this large study, patients on ezetimibe/simvastatin had a 17% reduction of major atherosclerotic events compared with placebo.
- In the secondary prevention of CV event, post-hoc analyses of three studies [ALLIANCE (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events)-LDL, TNT (Treating to New Targets) and 4S (Scandinavian Simvastatin Survival Study)] showed that patients with and without CKD had reduction of CV events with statin treatment.
- Statin use was not associated with an increased incidence of adverse events or drug discontinuation in patients with CKD.

5.2 Antiplatelet Agents

Recommendation 10
- Aspirin should be used in patients with chronic kidney disease (CKD) for secondary prevention of cardiovascular disease (CVD).
- Aspirin should not be used as primary prevention of CVD in CKD.
- Combination of clopidogrel with aspirin should be avoided in patients with CKD unless compelling indications are present.

Aspirin is beneficial for secondary prevention of CVD in both general and CKD population. In a meta-analysis on secondary prevention trials, aspirin lowered the risk of major coronary events by 20%, ischaemic strokes by 22% and total mortality by 10%. In a cohort with renal disease, heart failure and coronary artery disease, aspirin significantly

reduced 1-year mortality by 16% in patients with CrCl 30 - 59 ml/min compared with non-use of aspirin but non-significant in those with CrCl <30 ml/min.[9]

CKD patients are at increased risk of bleeding compared with the general population. The UKHARP (United Kingdom Heart and Renal Protection)-1 study showed that aspirin 100 mg daily in CKD patients was associated with a 3-fold increase in minor bleeding but not significant in major bleeding.[9]

A recent meta-analysis of three low-to-moderate quality RCTs concluded that there was no clear benefit of aspirin in primary prevention of CV events in CKD and no statistically significant reduction in mortality. Aspirin is likely to increase the risk of major bleeding events.[55, level I]

Post-hoc analysis of CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial showed that the combination of aspirin and clopidogrel was associated with significant increase in overall mortality by 60% compared with aspirin alone in DKD. In post-hoc analysis of CREDO (Clopidogrel for the Reduction of Events During Observation) trial on CKD patients scheduled for elective percutaneous coronary intervention, this combination was associated with a slight increase in major or minor bleeding.[9]

6. CHRONIC KIDNEY DISEASE WITH PREGNANCY

Recommendation 11

- All female patients of reproductive age with chronic kidney disease (CKD) should receive pre-pregnancy care*.
- Pregnancy may be considered in women with mild renal impairment (serum creatinine <124 µmol/L), well controlled blood pressure and without significant proteinuria (<1 g/day).
- Pregnancy should be avoided in women with either:
  - moderate to severe renal impairment
  - poorly controlled hypertension
  - heavy proteinuria
  - active systemic disease
- All pregnant women with CKD should be co-managed by a multidisciplinary team.

*Pre-Pregnancy Care (PPC) is a set of healthcare and interventions given to women in their reproductive age before conception occur. Components of pre-pregnancy care:[56]

- screening for medical conditions and medical risk factors
- management and optimisation of medical conditions and risk factors
- nutrition and supplementations
- family planning

Pregnancy in CKD is associated with increased risk of adverse maternal outcomes (gestational hypertension, pre-eclampsia, eclampsia and maternal death) and foetal outcomes (premature birth, intra-uterine growth retardation, small-for-gestational age, low birth weight, still birth and neonatal mortality). The risks begin at CKD stage I and increased with more advanced stage of CKD. Baseline hypertension, baseline proteinuria (>1 g/day), and presence of systemic disease are significant predictors of adverse maternal-foetal outcomes.[57, level III]

Rate of renal function deterioration and worsening of proteinuria during pregnancy correlates significantly with CKD stages.

- Renal function deteriorates more in CKD stage 3/4 compared with stage 2 (60% vs 14.3%).[58, level III]
- Doubling of proteinuria as CKD stage progresses are 20.5%, 86.5% and 70% in stage 1, 3 and 4 - 5 respectively.[57, level III]

Adverse maternal outcomes (pre-eclampsia, hypertension and caesarean delivery) are significantly higher as CKD stage advances. Risks of pre-term delivery and IUGR correlate with maternal renal function and level of proteinuria.[58 - 59, level III] Thus, the decision to continue with pregnancy should be individualised.

Pregnancy may be considered in women with CKD having mild renal impairment (SCr <124 µmol/L) and blood pressure well controlled.[9; 57 - 60, level III]

- Pregnancy in patients with CKD should be planned, taking into consideration the clinical status of the woman, with pre-conception review of medication and early referral for combined specialist care.
- ACEi and ARB should be avoided in pregnancy. Refer to **Appendix 4** on **United States Food and Drug Administration (FDA) Pharmaceutical Pregnancy Categories**.

7. REFERRAL

Recommendation 12

- A patient with chronic kidney disease (CKD) with any of the following criteria should be referred to a nephrologist/physician:
  - persistent heavy proteinuria [urine protein ≥1 g/day or urine protein: creatinine ratio (uPCR) ≥100 mg/mmol*] despite optimal treatment
  - persistent isolated microscopic haematuria after excluding urogynaecological cause
  - persistent haematuria with proteinuria (urine protein ≥0.5 g/day or uPCR ≥50 mg/mmol*)
  - rapidly declining renal function [loss of estimated glomerular filtration rate (eGFR) >5 ml/min/1.73 m^2 in one year or >10 ml/min/1.73 m^2 within five years]
  - eGFR <30 ml/min/1.73 m^2 (eGFR categories G4 - G5)
  - resistant hypertension (failure to achieve target blood pressure despite three antihypertensive agents including a diuretic)
  - suspected renal artery stenosis
  - suspected hereditary kidney disease
  - pregnant or when pregnancy is planned
  - persistent abnormalities of serum potassium
  - unexplained cause of CKD

*This is an estimation for practical purpose. The actual conversion of urine protein 1 g/day=uPCR 113 mg/mmol.

Referral to nephrologist is indicated when a healthcare provider feels that additional expert input is required for patient's management. The aim may be:

- to rule out AKI
- to delay CKD progression
- to prepare for RRT

There is no clear evidence to recommend indications of referral to nephrologist. However, several published guidelines have recommended referral criteria as listed in the recommendation box above.[9, 12, 61, 62, 63]

Early referral to nephrologist has the benefit in reducing mortality and hospital stay, achieving higher haemoglobin (Hb) levels and better dialysis preparation compared with late referral.[64, level II-2] Shared-care with effective communication between the nephrologist and primary healthcare provider is strongly encouraged.

- It is important to look at the trend of SCr and eGFR when deciding on the urgency of referral. The optimal time depends on the aim of referral which must always be individualised, taking into consideration the patient's co-morbidities, functional status and life expectancy.
- Immediate discussion with nephrologist is indicated in patients with:[9]
  - AKI superimposed on CKD
  - newly detected ESRD
  - accelerated or malignant hypertension
  - life-threatening hyperkalaemia
  - suspected rapidly progressive glomerulonephritis
- Patients with CKD and renal outflow obstruction should be referred to urological services.[9]
- When referring to a nephrologist, ensure patient has:[9]
  - serial blood chemistry and urine analysis
  - preferably a recent renal ultrasound report

Special issues in elderly

- An eGFR <60 ml/min/1.73 m^2 is common in elderly people which may be physiological or age-appropriate.
- Elderly patients with stable eGFR and low risk of CKD progression (proteinuria ≤1 g/day, optimal BP and glycaemic control) can be managed in primary care setting in collaboration with a nephrologist.
- In elderly patients with advanced CKD, referral with the aim of RRT initiation should take into consideration the co-morbidity, functional status, life expectancy, family support and patient's wishes because RRT may not confer better quality of life and survival.

8. SCREENING FOR COMPLICATIONS

CKD patients are prone to develop a host of complications, reflecting the loss of exocrine and endocrine function of the kidneys.

The two most common complications i.e. anaemia and Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) are discussed here.

The evidence on the screening and monitoring of these complications are scarce. Thus, the recommendations in this CPG are mainly adapted from pre-existing international CPGs.

Recommendation 13
- In chronic kidney disease (CKD), screening for:
  - anaemia should be done when estimated Glomerular Flitration Rate (eGFR) <60 ml/min/1.73 m^2
  - CKD-mineral and bone disorder when eGFR <45 ml/min/1.73 m^2

8.1 Anaemia

Anaemia is defined as a Hb concentration of <13 g/dL in adult males and <12 g/dL in adult females.[12, 65]

Renal anaemia is a common complication of CKD due to reduced erythropoietin production by the kidney and reduced absorption of iron. It usually starts to develop when the eGFR is <60 ml/min/1.73 m^2. The prevalence of anaemia increases markedly with decreasing eGFR.[61] When the eGFR is ≥60 ml/min/1.73 m^2, the anaemia is more likely to be related to other causes.[66]

Iron deficiency and other causes of anaemia e.g. vitamin B12 and folate deficiency, bone marrow suppression, hypothyroidism and haemoglobinopathies should be excluded during the work-up for renal anaemia.[12, 61, 67]

The frequency of Hb monitoring is influenced by kidney function (refer to **Table 6**), underlying disease process, initial Hb concentration and rate of change in Hb concentration.[12, 65]

Table 6. Suggested Hb monitoring in CKD

	Stage 3	Stage 4	Stage 5 ND*
CKD without anaemia	At least annually	At least twice a year	At least twice a year
CKD with anaemia (not treated with erythropoiesis-stimulating agent (ESA)	At least every 3 months	At least every 3 months	At least every 3 months

*ND=non-dialysis

Treatment with ESA must be commenced by or in consultation with a nephrologist.[61]

The optimal Hb target in CKD is 10.0 - 12.0 g/dL. However, it should be individualised based on symptoms and co-morbidities.[66]

8.2 Chronic Kidney Disease-Mineral and Bone Disorder

CKD-MBD is a common complication of CKD. Changes in the metabolism of calcium, phosphate, parathyroid hormone (PTH) and alkaline phosphatase (ALP) typically start to occur when eGFR <60 ml/min/1.73 m^2.[61]

KDIGO recommends to start monitoring serum levels of corrected calcium, phosphate and ALP at CKD stage G3a.[68] However it may be more relevant to initiate the monitoring when eGFR <45 ml/min/1.73 m^2 in local setting.

Frequency of monitoring of the above parameters depends on stage of CKD, its treatment, presence and magnitude of abnormalities, and rate of progression of CKD.[68, 69]

The suggested frequency of monitoring for CKD-MBD is outlined in **Table 7**.

Table 7. Suggested frequency of monitoring for CKD-MBD

	Stage 3	Stage 4	Stage 5 non-dialysis
Calcium and phosphate	6 - 12 monthly	3 - 6 monthly	3-monthly, more frequent if indicated
ALP	6 - 12 monthly	3 - 6 monthly	3-monthly, more frequent if indicated

Elevated phosphate level should be lowered towards the normal range and hypercalcaemia should be avoided in most stages of CKD.[68]

In hyperphosphataemia, dietary restriction of phosphate is recommended.[61, 68, 69] In persistent hyperphosphataemia, patient's compliance to dietary phosphate restriction should be re-assessed before considering the use of phosphate binders.

Excess calcium administration (in the form of calcium-based phosphate binders) and vitamin D analogue should be avoided as this may be associated with increased risk of vascular calcification in CKD.[61, 68]

9. IMPLEMENTING THE GUIDELINES

The management of CKD in adults should be guided by evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

9.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

a. National Healthy Kidneys Action plan (2017 - 2025) - upcoming
b. extensive networking of nephrologists nationwide
c. collaboration between primary and secondary/tertiary health care
d. availability of CPGs in hardcopy and softcopy (online)
e. active involvement of local NGOs in screening and educational activities

Existing barriers for application are:

a. inadequate support or attention on CKD prevention programme from various stakeholders
b. inadequate human resources to form dedicated CKD teams to focus on CKD management
c. lack of CKD database for planning of services

9.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:

a. ensure widespread distribution of the CPG to health care personnel via printed copies, electronic websites, etc.
b. reinforce training of health care personnel by regular seminars or workshops to ensure information is made available
c. develop multidisciplinary teams at hospital and community level to include involvement of specialists, primary care doctors, medical officers, pharmacists, dietitians and nurse educators
d. ensure screening and monitoring facilities are available at all sites
e. ensure availability of the drugs mentioned in the CPG
f. develop coordinated linkage between specialists and primary health care teams to facilitate referral and management
g. have a national database on CKD
h. ensure widespread distribution of patient education materials

The following is proposed as clinical audit indicator for quality management of CKD:

- Percentage of diabetes patients screened for proteinuria/ microalbuminuria

$$= \frac{\text{Number of diabetes patients screened for proteinuria/microalbuminuria within a year}}{\text{Total number of diabetes patients on follow up in the same period}} \times 100\%$$

- Percentage of hypertensive patients screened for proteinuria

$$= \frac{\text{Number of hypertensive patients screened for proteinuria within a year}}{\text{Total number of hypertensive patients on follow up in the same period}} \times 100\%$$

- Percentage of diabetic CKD patients with BP ≤130/80

$$= \frac{\text{Number of diabetic CKD patients with BP } \leq 130/80 \text{ within a year}}{\text{Total number of diabetic CKD patients in the same period}} \times 100\%$$

- Percentage of non-diabetic CKD patients with BP ≤140/90

$$= \frac{\text{Number of non-diabetic CKD patients with BP } \leq 140/90 \text{ within a year}}{\text{Total number of non-diabetic CKD patients in the same period}} \times 100\%$$

- Percentage of patients with hypertension and proteinuria receiving treatment with ACEi or ARB

$$= \frac{\text{Number of patients with hypertension and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of hypertension and proteinuria in the same period without contraindications to ACEi or ARB}} \times 100\%$$

- Percentage of patients with diabetes and proteinuria receiving treatment with ACEi or ARB

$$= \frac{\text{Number of patients with diabetes and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of diabetes and proteinuria in the same period without contraindications to ACEi or ARB}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the blood pressure targets in chronic kidney disease?

1. Renal Insufficiency, Chronic/
2. Kidney Failure, Chronic/
3. (chronic adj1 (kidney disease* or kidney insufficienc* or renal disease* or renal insufficienc*)).tw.
4. ckd.tw.
5. Renal Insufficiency/
6. ((kidney or renal) adj1 (failure* or insufficienc*)).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Blood Pressure/
9. (blood adj1 pressure*).tw.
10. (systolic adj1 pressure*).tw.
11. (diastolic adj1 pressure).tw.
12. or/8-11
13. reduc*.tw.
14. aim*.tw.
15. target*.tw.
16. control*.tw.
17. or/13-16
18. 12 and 17
19. 7 and 18
20. limit 19 to (english language and humans and yr="2010 -Current" and "all adult (19 plus years)")
21. limit 20 to systematic reviews

Appendix 2

CLINICAL QUESTIONS

A. Screening

1. Who are at high risk of developing chronic kidney disease?
2. Who should be screened for chronic kidney disease?
3. What methods should be used for screening chronic kidney disease?
   - urine dipstick
   - urine protein/albumin-creatinine ratio
   - time urine collection
4. What methods should be used to assess renal function?
   - serum creatinine
   - 24-hour urine creatinine clearance
   - prediction equation e.g. MDRD, Cockcroft-Gault, CKD-epi (in elderly, stages of CKD)
   - serum and urine cystatin C

   *Classification of CKD

B. Treatment

5. What are the effective and safe interventions in slowing down the progression of chronic kidney disease?
   - reduction in blood pressure and proteinuria
     - ACEi/ARB
     - calcium channel blockers
     - combined Renin-Angiotensin System Blockade
     - aldosterone antagonists
     - direct renin inhibitors
   - glycaemic control
   - lipid lowering
   - uric acid reduction
   - miscellaneous agents
     - pentoxifylline
     - protein restriction (ketoacid)
     - supplement agents
     - traditional medication
   - smoking cessation
   - salt restriction
   - weight reduction
   - exercise
   - sulodexide
   - sodium bicarbonate
6. What are the blood pressure targets in chronic kidney disease?
7. What are the effective interventions in reducing the risk of cardiovascular disease in CKD?
   - as above
   - aspirin
8. How should pregnancy with chronic kidney disease be managed?

C. Referral

9. When should a patient with chronic kidney disease be referred to a nephrologist?

D. CKD-related Complications

10. When to screen complications in chronic kidney disease (anaemia and mineral bone disease)?
11. How to screen complications in chronic kidney disease?

DOSAGE RECOMMENDATION IN CKD FOR COMMONLY PRESCRIBED ORAL MEDICATIONS

Medication		Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
			Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
HMG-CoA reductase inhibitors Statin should be started at low dose and titrated upwards in order to minimise the adverse effects (e.g.myopathy)							
^HI	Rosuvastatin	20 - 40 mg OD	No dosage adjustment necessary		15 - 29: 5 - 10 mg OD <15: Avoid (no data)		X
+MI	Rosuvastatin	5 - 10 mg OD					
^HI	Atorvastatin	40 - 80 mg OD	No dosage adjustment necessary				X
+MI	Atorvastatin	10 - 20 mg OD					
+MI	Simvastatin	20 - 40 mg OD	No dosage adjustment necessary		10 - 20 mg OD (Initial dose: 5 mg OD)		X
~LI	Simvastatin	10 mg OD					
+MI	Pravastatin	40 - 80 mg OD	No dosage adjustment necessary		10 - 40 mg OD	Severe impairment: 10 mg OD	X
~LI	Pravastatin	10 - 20 mg OD					
+MI	Fluvastatin	20 - 80 mg OD	No dosage adjustment necessary	10 - 80 mg OD	10 - 40 mg OD		X
~LI	Fluvastatin	20 - 40 mg OD					
+MI	Lovastatin	40 mg OD	No dosage adjustment necessary	10 - 40 mg OD	10 - 20 mg OD		X
~LI	Lovastatin	20 mg OD					
Fibric acid derivatives							
Fenofibrate		145 mg OD	50%	25%	15 - 30: 25% <15: Avoid	May increase serum creatinine	C
Gemfibrozil		600 mg BD	No dosage adjustment necessary	50%	15 - 30: 50% <15: Avoid		C
Cholesterol absorption inhibitor							
Ezetimibe		10 mg OD	No dosage adjustment necessary				C

Medication	Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
		Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
Thiazide diuretics						
Chlorthalidone	12.5 - 50 mg OD	No dosage adjustment necessary		<10: Avoid	Thiazide diuretics are unlikely to be of use once GFR <30 ml/min	B
Chlorothiazide	500 - 1000 mg/day in 1 - 2 doses	No dosage adjustment necessary		<10: Avoid		C
Hydrochlorothiazide	12.5 - 50 mg OD	No dosage adjustment necessary		<10: Avoid	#	B
Indapamide	12.5 - 5 mg OD	No dosage adjustment necessary		1.25 - 2.5 mg <10: Avoid		B
Loop diuretics						
Bumetanide	0.5 - 4 mg/day in 2 - 3 doses	No dosage adjustment necessary				C
Frusemide	40 - 240 mg/day in 2 - 3 doses	No dosage adjustment necessary				C
Potassium sparing diuretics						
Amiloride	5 - 10 mg/day in 1 - 2 doses	No dosage adjustment necessary	50%	10 - 30: 50% <10: Avoid	Serum potassium needs to be monitored	B
Spironolactone	25 - 100 mg/day in 1 - 2 doses	≥50: 12.5 - 25 mg OD/ BD	30 - 49: 12.5 mg OD/EOD	<30: Avoid	# Serum potassium needs to be monitored	C
Sulfonylureas Sulfonylureas should be used cautiously due to increased risk of hypoglycaemia. **First-generation sulfonylureas** generally should be avoided due to increased half-life and risk of hypoglycaemia in patients with CKD. Glipizide and gliclazide are the preferred agents among the **second-generation sulfonylureas** as they do not have active metabolites and have lower risk of hypoglycaemia in CKD patients.						
Glimepiride	1 - 4 mg OD	Initiate at low dose: 1 mg OD	15 - 30: Initiate at low dose, 1 mg OD <15: Avoid			C
Glipizide	2.5 - 15 mg OD	No dosage adjustment necessary				C
Gliclazide	80 - 160 mg BD	No dosage adjustment necessary		Contraindicated	#	*ADEC - C
Glibenclamide	5 - 10 mg OD	Use with caution	Avoid			C

Medication	Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
		Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
Alpha-glucosidase inhibitors						
Acarbose	25 - 100 mg TDS	50 - 100%	Avoid	Avoid	#	B
Biguanide Metformin is eliminated via kidney and may accumulate in body as kidney function deteriorates - increased risk of lactic acidosis.						
Metformin	500 - 1,000 mg BD	No adjustment	30 - 45: 50%	Avoid		B
Meglitinides						
Repaglinide	0.5 - 4 mg TDS	No dosage adjustment necessary	20 - 40: 0. 5 mg with meal <20: Avoid		#	C
Nateglinide	120 mg TDS	No dosage adjustment necessary			#	C
Thiazolidinediones						
Rosiglitazone	4 - 8 mg OD	No dosage adjustment necessary			May worsen fluid retention	C
Pioglitazone	15 - 30 mg OD	No dosage adjustment necessary			May worsen fluid retention	C
GLP-1 receptor agonists						
Exenatide Immediate Release (Byetta)	5 - 10 µg BD	100%	Use with caution 50 - 100% Dose escalation from 5 - 10 µg should proceed conservatively	Avoid (increase frequency and severity of GI side effects)	#	C
Exenatide Extended Release (Bydureon)	2 mg SC once weekly	No dosage adjustment necessary	Use with caution when initiating or escalating dose	Avoid	#	C
Liraglutide (Victoza)	Starting dose: 0.6 mg SC OD x 1 week Maintenance dose: 1.2 - 1.8 mg SC OD	100%	(limited data)	(limited data)		C
Lixisenatide (Lyxumia)	10 µg SC OD for 14 days followed by 20 µg OD	No dosage adjustment necessary (monitor changes in renal function and GI adverse effects)		15-<30: (limited data) <15: Not recommended	Not indicated for Type 1 DM	-

Medication	Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
		Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
Dipeptidyl peptidase-4 (DPP-4) inhibitors						
Sitagliptin	100 mg OD	100%	30 - 50: 50%	25%	#	B
Vildagliptin	50 mg OD - BD	100%	50 - 59: 100% <50: limited data	(limited data)	#	-
Saxagliptin	2.5 - 5 mg OD	100%	2.5 mg OD	2.5 mg OD	#	B
Linagliptin	2.5 - 5 mg OD	No dosage adjustment necessary				B
Alogliptin	25 mg OD	No dosage adjustment necessary	12.5 mg OD	15 - 30: 6.25 mg OD	#	-
Sodium glucose co-transporter 2 (SGLT-2) inhibitors						
Dapagliflozin	5 - 10 mg OD	No dosage adjustment necessary	Avoid			C
Canagliflozin	100 - 300 mg OD	No dosage adjustment necessary	45 - 60: 100 mg OD <45: Avoid	Avoid		-
Empagliflozin	10 - 25 mg OD	No dosage adjustment necessary	<45: Avoid	Avoid		-
Insulin Doses should be adjusted based on frequent monitoring to balance goals of glycaemic control and avoidance of hypoglycaemia						
Antiamoebic						
Metronidazole	200 - 400 mg q8 - 12h	No dosage adjustment necessary			#	B
Antifungal						
Fluconazole	200 - 400 mg q8 - 12h	No dosage adjustment necessary	50%	50%		C (single dose for vaginal candidiasis) D (all other indications)

Medication	Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
		Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
Itraconazole	100 - 200 mg q12h	No dosage adjustment necessary		15 - 30: No dosage adjustment necessary <15: 50% (use with caution)		C
Ketoconazole	200 mg q24h	No dosage adjustment necessary				C
Antiviral						
Acyclovir	200 mg q4h (herpes simplex)	No dosage adjustment necessary		15 - 30: No dosage adjustment necessary <15: 50% (use with caution)	High doses can cause encephalopathy	
	800 mg q4h (herpes zoster)	No dosage adjustment necessary		>25: No dosage adjustment necessary 10 - 25: 800 mg q8h <10: 800 mg q12h		B
Oseltamivir	75 mg q12h	No dosage adjustment necessary		10 - 30: 75 mg q24h <10: No recommendation		C
Cephalosporin						
Cefaclor	250 - 500 mg q8h	100%	100%	<10: 50%		B
Ceftibuten	400 mg q24h	100%	50%	5 - 29: 25%		B
Cefuroxime axetil	250 - 500 mg q12h	No dosage adjustment necessary				B
Cephalexin	250 - 500 mg q6h	q8h	10 - 50: 500 mg q12 - 24h <10: 250 - 500 mg q12 - 24h			B

Medication	Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
		Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
Fluoroquinolone						
Ciprofloxacin	500 - 750 mg q12h	100%	50 - 75%	15 - 30: 50 - 75% <15: 50%		C
Levofloxacin	500 mg q24h	100%	20 - 50: 500 mg for initial dose, then 250 mg q24h	<20: 500 mg for initial dose, then 250 mg q48h		C
Moxifloxacin	400 mg q24h	No dosage adjustment necessary				C
Norfloxacin	400 mg q12h	q12h	q12 - 24h	15 - 30: q12 - 24h <15: q24h		C
Ofloxacin	200 - 400 mg q12h	100%	20 - 50: q24h	<20: 50% q24h		C
Lincosamide						
Clindamycin	150 - 300 mg q6h	No dosage adjustment necessary				B
Macrolide						
Azithromycin	250 - 500 mg q24h	No dosage adjustment necessary				B
Clarithromycin	500 - 1,000 mg q12h	100%	100%	50%		C
Erythromycin	(ethylsuccinate) 400 mg q6h or 800 mg q12h (stearate) 250 mg q6h or 500 mg q12h	100%	100%	100%		B
Nitrofuran						
Nitrofurantoin	50 - 100 mg q6h	No dosage adjustment necessary	Avoid	Avoid		B

Medication	Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
		Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
Penicillin						
Amoxicillin	250 - 500 mg q8h	q8h	q8 - 12h	10 - 30: q8 - 12h <10: q24h		B
Amoxicillin + Clavulanic Acid (Augmentin)	625 mg q8h	No dosage adjustment necessary		10 - 30: q12h <10: q24h		B
Ampicillin	250 mg - 2 g q6h	q6h	q6 - 12h	15 - 30: q6 - 12h <15: q12 - 24h		B
Sultamicillin/ Ampicillin + Sulbactam (Unasyn)	375 - 750 mg q12h	No dosage adjustment necessary		<15: q24h		B
Cloxacillin	250 - 500 mg q6h	No dosage adjustment necessary				B
Penicillin V/ Phenoxymethyl-penicillin	250 - 500 mg q6h	No dosage adjustment necessary		CrCl <10 ml/minute: 250 mg q6h		B
Sulfonamide + Trimethoprim						
Trimethoprim	100 mg q12h	No dosage adjustment necessary		15 - 30: 50 mg q12H <15: q24h	<30 ml/min: Close monitoring of blood counts	C
Sulfamethoxazole + Trimethoprim (TMP)	960 mg q12h or 15 - 20 mg TMP/kg/day in divided doses q6h	No dosage adjustment necessary		15 - 30: 50% <15: 50% q12 - 24h	Dose to be optimised based on diagnosis	C

Medication	Usual Dose	Dose Adjustment in Renal Failure			Note	US FDA Pregnancy Category
		Mild (GFR 60 - 90 ml/min)	Moderate (GFR 30 - 59 ml/min)	Severe (GFR <30 ml/min)		
Tetracycline						
Doxycycline	100 mg q24h	No dosage adjustment necessary				D
Minocycline	100 mg q12h	No dosage adjustment necessary				D
Tetracycline	250 - 500 mg q6h	q8 - 12h	q12 - 24h	10 - 30: q12 - 24h <10: q24h		D

^HI=High Intensity, +MI=Moderate Intensity, ~LI=Low Intensity, OD=once daily, BD= twice daily, TDS=thrice daily, SC=subcutaneous, q=every, h=hourly
*ADEC = Australian Drug Evaluation Committee Pregnancy Category

Disclaimer:
The list of medication dosage adjustment should be used as a general guides only and is not intended to be comprehensive.
The dosing guide for GFR <10 ml/min does not provide information on dosing in haemodialysis, peritoneal dialysis or continuous RRT patients.
The Cockcroft-Gault equation was used to estimate the renal function for drug dosing unless otherwise indicated.
#Drug dosing calculated using MDRD or CKD-Epi

Source:

1. George RA, William MB, Jeffrey SB, et al. Drug Prescribing in Renal Failure. Dosing Guidelines for Adults and Children, 5th Ed. Philadelphia: American College of Physicians; 2007
2. Drug information handbook. Lexicomp drug reference handbooks, 22nd Ed. American Pharmacists Association; 2013
3. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80(11):1122-3
4. Medication package insert

Appendix 4

UNITED STATES FOOD AND DRUG ADMINISTRATION (FDA) PHARMACEUTICAL PREGNANCY CATEGORIES

CATEGORY	DESCRIPTION
A	Controlled studies in women fail to demonstrate a risk to fetus in the first trimester, and the possibility of fetal harm appears remote.
B	Animal studies do not indicate a risk to the fetus and there are no controlled human studies, or animal studies do show an adverse effect on the fetus but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women.
D	Positive evidence of human fetal risk exists, but benefits in certain situations (e.g. life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.
X	Studies in animals or human have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit.

Modified: Ministry of Health, Malaysia. Management of Chronic Kidney Disease in Adults. MoH: Putrajaya: 2011

LIST OF ABBREVIATIONS

µg	microgramme
µm	micrometre
µmol/L	micromole/litre
AA	Aldosterone Antagonists
ACEi	Angiotensin-Converting Enzyme Inhibitor
ACR	albumin: creatinine ratio
AER	albumin excretion rate
AKI	acute kidney injury
ALP	alkaline phosphatase
ARB	Angiotensin Receptor Blocker
BP	blood pressure
CCBs	calcium channel blockers
CCF	congestive cardiac failure
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease-mineral and bone disorder
CKD-epi	CKD-epidemiology
CI	confidence interval
CPG(s)	clinical practice guidelines
CV(D)	cardiovascular disease
DHP	dihydropyridine
DKD	diabetic kidney disease
DM	diabetes mellitus
(e)GFR	(estimated) glomerular filtration rate
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
dL	desilitre
g	gramme
Hb	haemoglobin
HR	hazard ratio
iPTH	intact parathyroid hormone
MD	mean difference
kg	kilogramme
MDRD	Modification of Diet in Renal Disease
m^2	metre square
mg	milligramme
min	minute
ml	millilitre
mol/L	millimole/litre
mmHg	millimetre mercury
MoH	Ministry of Health
NDHP	non-dihydropyridine
NSAIDS	non-steroidal anti-inflammatory drugs
OR	odds ratio
PPI	proton pump inhibitors
PTH	parathyroid hormone
RAS	renin-angiotensin system
RCT(s)	randomised controlled trial(s)
RR	relative risk
RRT	renal replacement therapy

SBP	systolic blood pressure
SCr	serum creatinine
SGLT2	sodium-glucose co-transporter-2
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
(u)PCR	(urine) protein: creatinine ratio
UTI	urinary tract infection
VLPD	very low protein diet

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