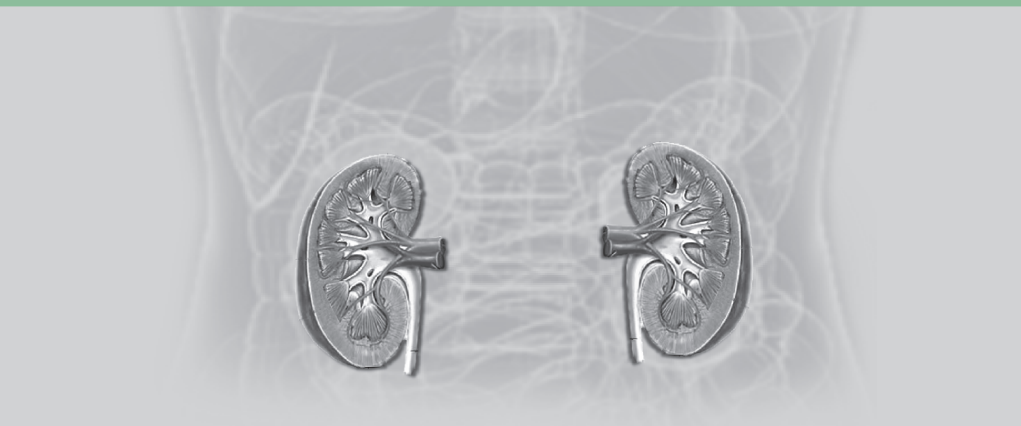
CLINICAL PRACTICE GUIDELINES

June 2011

MOH/P/PAK/217.11 (GU)

MANAGEMENT OF CHRONIC KIDNEY DISEASE IN ADULTS



Ministry of Health Malaysia

Malaysian Society of Nephrology

Academy of Medicine of Malaysia

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.

These guidelines are issued in 2011 and will be reviewed in 2015 or sooner if new evidence becomes available.

CPG Secretariat
Health Technology Assessment Section
Medical Development Division
Ministry of Health Malaysia
4th Floor, Block E1, Parcel E
62590 Putrajaya

Electronic version available on the following websites:
http://www.moh.gov.my
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http://msn.org.my

TABLE OF CONTENTS

TABLE OF CONTENTS

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

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The Development Group (DG) for this Clinical Practice Guidelines (CPG) was from the Ministry of Health (MOH), Ministry of Higher Education and private sector. They consisted of nephrologists, a general physician, an endocrinologist, a cardiologist, an obstetrician & gynaecologist, family medicine specialists, a public health physician, a general practitioner, pharmacists, a dietitian and a nursing matron. There was active involvement of a multidisciplinary Review Committee (RC) during the process of development of these guidelines.

Literature search was carried out at the following electronic databases: Guidelines International Network (G-I-N); Pubmed; Medline, Cochrane Database of Systemic Reviews (CDSR), Journal full text via OVID search engine; International Health Technology Assessment websites (refer to **Appendix 1** for Search Terms). In addition, the reference lists of all retrieved literatures and guidelines were searched to identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were officially conducted between 10 September 2009 and 31 March 2010. 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.

Reference was also made to other guidelines on Chronic Kidney Disease (CKD) such as Scottish Intercollegiate Guidelines Network (SIGN) - Diagnosis and Management of Chronic Kidney Disease (2008), National Institute of Clinical Excellence (NICE), London – Chronic Kidney Disease (2008), Kidney Health Australia - Chronic Kidney Disease Management in General Practice (2007), Royal College of Physicians, London - Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral (2006), Ministry of Health Malaysia - Diabetic Nephropathy (2004) and National Kidney Foundation-KDOQI - Clinical Practice Guidelines for Chronic Kidney Disease (2002). These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) prior to them being used as references.

The clinical questions were developed under three sections with 13 clinical questions. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for Clinical Questions). The DG members met a total of 21 times throughout the development of these guidelines. All literatures retrieved were appraised by at least two

members, presented in evidence tables and further discussed during DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. These CPG are 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 modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network .

On completion, the draft guideline was sent for review by external reviewers. It was posted on the MOH Malaysia official website for feedback from any interested parties. It was also presented at the 27th Malaysian Society of Nephrology Annual Congress held in May 2011 for further review. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MOH Malaysia for review and approval.

OBJECTIVES

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

a) Prevention and reduction in risk of developing chronic kidney disease (CKD)
b) Screening and early detection of CKD
c) Treatment of early CKD to prevent its progression to end-stage renal disease
d) Reduction in risk of cardiovascular disease

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion criteria

Adults at risk of/with CKD

b. Exclusion criteria

Dialysis and renal transplant patients

The CPG will not address treatment for specific renal diseases or complications of CKD such as anaemia, renal bone disease and metabolic acidosis.

TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders in all levels of healthcare in the management of CKD in adults including:

i. Doctors with emphasis on primary and secondary care
ii. Allied health professionals
iii. Trainees and medical students
iv. Policy makers
v. Patients and their advocates
vi. Professional societies

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

DEVELOPMENT GROUP

Chairperson

Dr. Ong Loke Meng
Consultant Nephrologist, Hospital Pulau Pinang

Members (alphabetical order)

Dr. Ang Hock Aun
Consultant Physician
Hospital Seberang Jaya, Pulau Pinang

Dr. Anita Bhajan Manocha
Consultant Nephrologist
Hospital Seberang Jaya, Pulau Pinang

Dr. Ching Chen Hua
Consultant Nephrologist
Hospital Sultanah Bahiyah, Kedah

Mdm. Eezsafryna Azalin Nordin
Dietitian
Hospital Pulau Pinang, Pulau Pinang

Dr. Gnanasegaran Xavier
General Practitioner
Klinik Xavier, Pulau Pinang

Dr. Kow Fei Ping
Family Medicine Specialist
Klinik Kesihatan Bandar Baru Air Itam
Pulau Pinang

Dr. Liew Yew Fong
Consultant Nephrologist
Hospital Pulau Pinang, Pulau Pinang

Mdm. Lim Chooi Eng
Nursing Matron
Hospital Pulau Pinang, Pulau Pinang

Dr. Mohd. Aminuddin Mohd. Yusof
Public Health Physician
Health Technology Assessment Section
Ministry of Health

Dr. Mohd. Faudzi Abdullah
Consultant Family Medicine Specialist
Klinik Kesihatan Padang Serai, Kedah

Mdm. Ng Boon Yah
Pharmacist
Hospital Pulau Pinang, Pulau Pinang

Ms. Ng Ru Shing
Pharmacist
Hospital Pulau Pinang, Pulau Pinang

Dr. Ong Hean Teik
Consultant Cardiologist
HT Ong Heart Clinic, Pulau Pinang

Dato' Dr. Rozina Mohamed Ghazalli
Senior Consultant Nephrologist
Hospital Pulau Pinang, Pulau Pinang

Dr. Sunita Bavanandan
Consultant Nephrologist
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Sharmini Diana Parampalam
Consultant Obstetrician & Gynaecologist
Hospital Seberang Jaya, Pulau Pinang

Assoc. Prof. Dr. Yeow Toh Peng
Consultant Endocrinologist
Penang Medical College, Pulau Pinang

REVIEW COMMITTEE

The draft guidelines were reviewed by a panel of independent expert referees, from both public and private sectors, and also a patient advocate who were asked to comment primarily on the comprehensiveness and accuracy in the interpretation of evidence supporting the recommendations in the guidelines.

Chairperson

Datuk Dr. Ghazali Ahmad
Senior Consultant Nephrologist
Hospital Kuala Lumpur, Kuala Lumpur

Members (alphabetical order)

Prof. Dr. Abdul Rashid A Rahman
Consultant Physician
Cyberjaya University College of Medical Sciences, Selangor

Dr. Inderjeet Kaur Gill
Senior Principal Assistant Director
Medical Services Unit
Medical Services Development Section, MOH

Mdm. Lee Day Guat
Manager
National Renal Registry

A. Prof. Dr. Kamaliah Mohd. Daud
Consultant Nephrologist
Universiti Sains Malaysia, Kelantan

Dato' Dr. K. Aris Chandran
Senior Consultant General Physician
Hospital Raja Permaisuri Bainun, Perak

Dr. Mohd. Fozi Kamarudin
Family Medicine Specialist
Klinik Kesihatan Kangar, Perlis

Prof. Dr. Nor Azmi Kamaruddin
Consultant Endocrinologist,
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur

Mdm. Norkasihan Ibrahim
Pharmacist
Hospital Selayang, Selangor

Dr. Philip N. Jeremiah
Consultant Nephrologist &
past President Malaysian Society of Nephrology

Datin Dr. Rugayah Bakri
Deputy Director
Health Technology Assessment Section
Medical Development Section, MOH

Dr. Siti Sharina Anas
Pathologist
Hospital Putrajaya, Putrajaya

Dato' Syed Sidi Idid Syed Abdullah Idid
Member of National Kidney Foundation &
Patient Advocate

Prof. Dr. Taufiq Teng Cheong Lieng
Consultant Family Medicine Specialist
International Medical University, Kuala Lumpur

A. Prof. Dr. Winnie Chee Siew Swee
Consultant Dietitian
International Medical University, Kuala Lumpur

Dato' Dr. Zaki Morad Mohamad Zaher
Consultant Nephrologist &
Chairman National Kidney Foundation

EXTERNAL REVIEWERS (alphabetical order)

The following external reviewers provided feedback on the draft:

Prof. Dr. Amir Khir
Dean & Senior Consultant Endocrinologist
Penang Medical College

Dr. Baizury Bashah
Family Medicine Specialist
Klinik Kesihatan Bandar Alor Setar

Dr. Bavanandan Naidu Gopal
Fetal-Maternal Consultant
Hospital Sultanah Bahiyah, Alor Setar

Dato' Dr. Chew Soon Ping @ David Chew
Senior Consultant Cardiologist
Institut Jantung Negara, Kuala Lumpur

Dr. Hooi Lai Seong
Senior Consultant Nephrologist
Hospital Sultanah Aminah, Johor Bahru

Dr. Kevin Harris
Medical Director & Honorary Consultant Nephrologist
Leicester General Hospital, United Kingdom

Prof. Dr. Khoo Ee Ming
Senior Lecturer & Primary Care Physician
Pusat Perubatan Universiti Malaya, Kuala Lumpur

Ms. Manjulaa Devi Subramaniam
Pharmacist
Hospital Kuala Lumpur

Dr. Marianne Vennegoor
Emeritus Renal Dietitian
Chair of the Educational Sub Committee of the
International Federation of Kidney Foundations (IFKF)

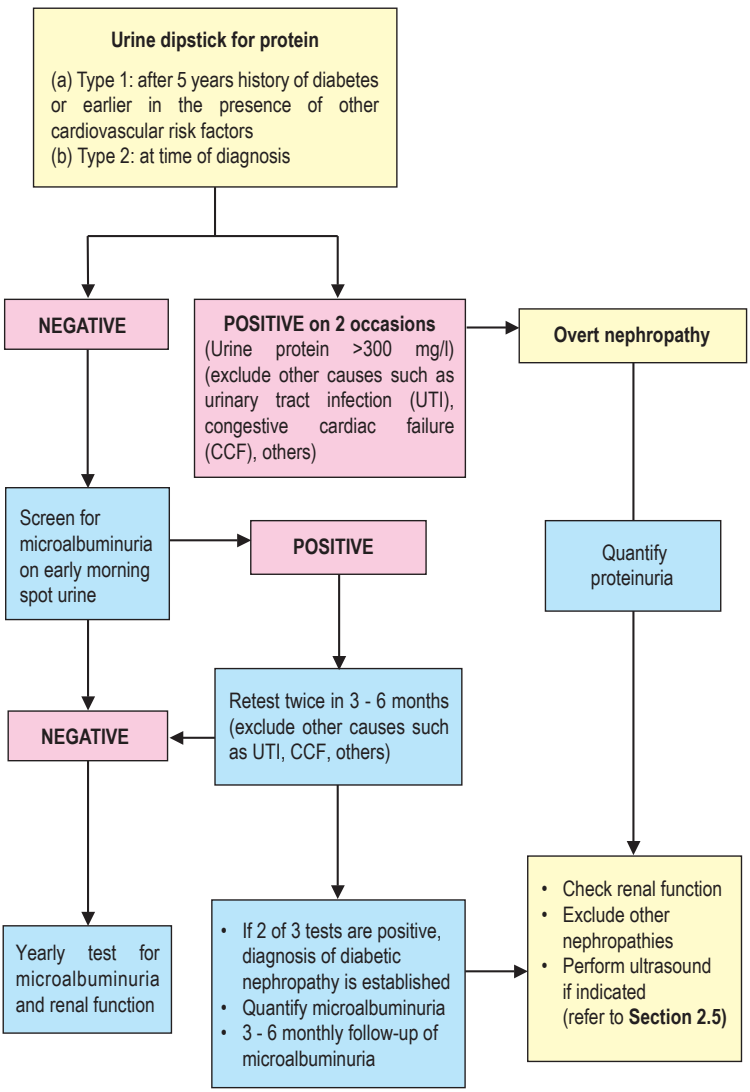
Datin Nor Sharita Mohd. Saad
Dietitian
Hospital Kuala Lumpur

Prof. Dr. Peter G Kerr
Director of Nephrology
Monash Medical Centre, Australia

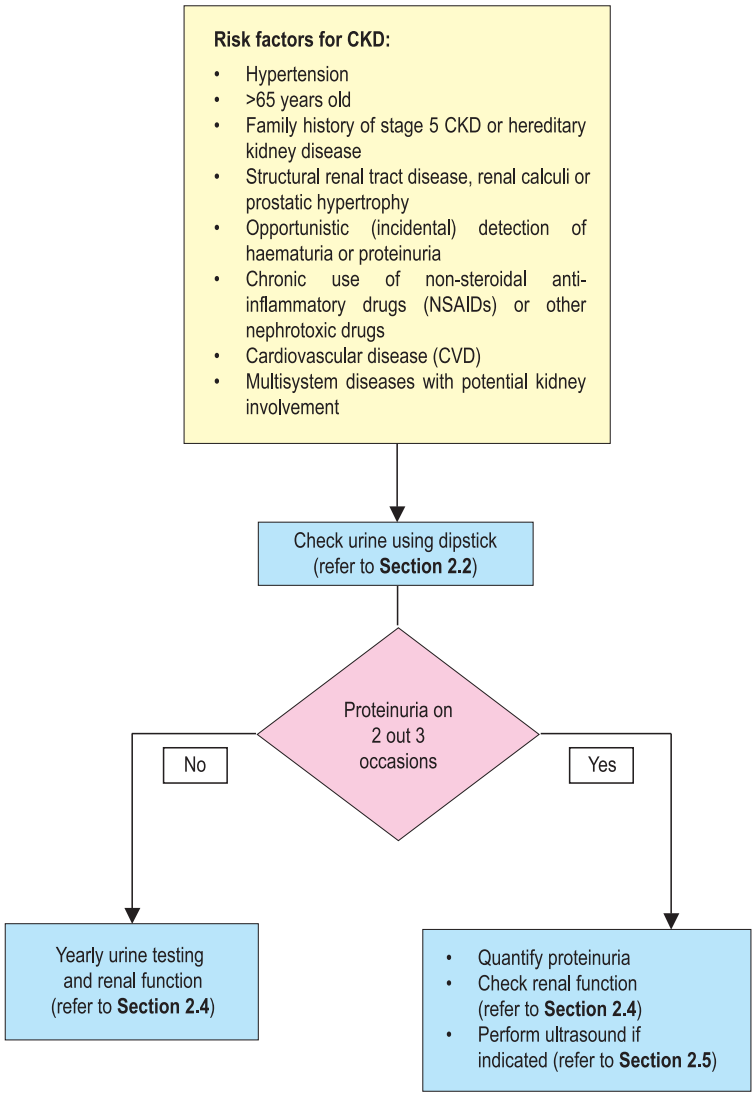
Dr. Wong Hin Seng
Senior Consultant Nephrologist, Hospital Selayang &
President of Malaysian Society of Nephrology

ALGORITHM 1: SCREENING AND INVESTIGATIONS FOR CKD IN PATIENTS WITH DIABETES

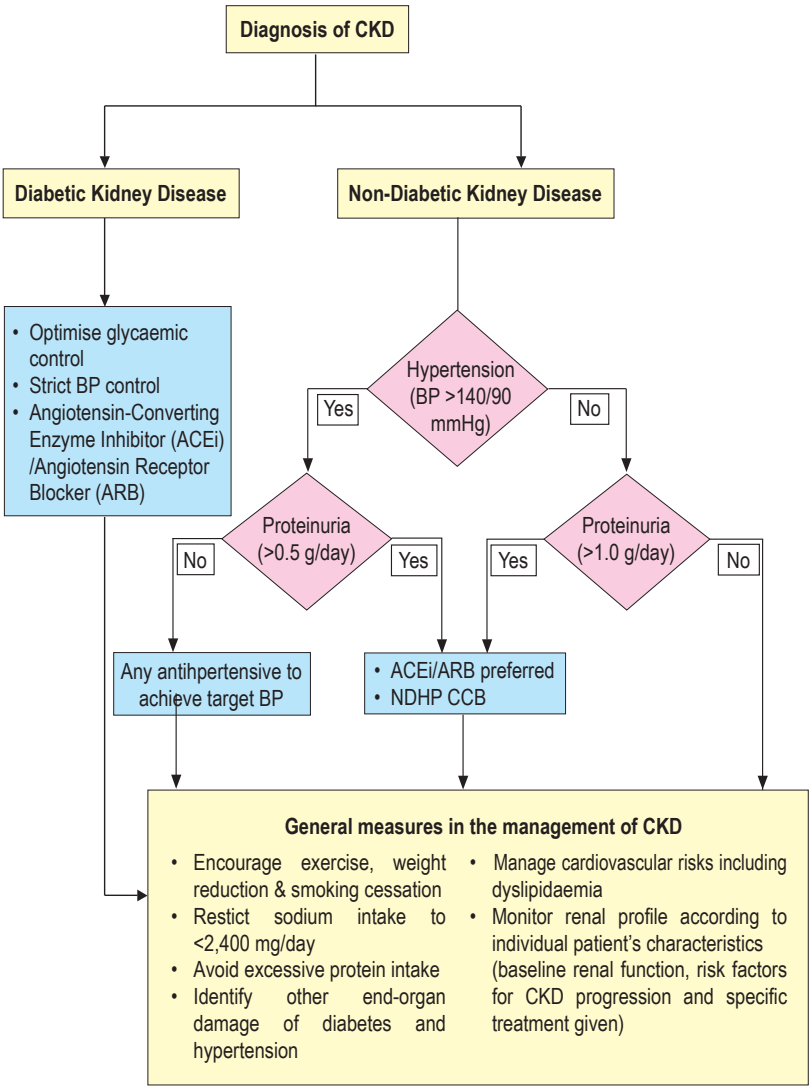
(Adapted: Ministry of Health Malaysia. Diabetic Nephropathy: Putrajaya: MOH; 2004)



ALGORITHM 2: SCREENING AND INVESTIGATIONS FOR CKD IN PATIENTS WITHOUT DIABETES



ALGORITHM 3: TREATMENT FOR CHRONIC KIDNEY DISEASE



1. INTRODUCTION

Chronic kidney disease (CKD) is an irreversible loss of renal function for at least three months and poses a major public health problem.

The prevalence of CKD and end-stage renal disease (ESRD) is increasing worldwide. The estimated prevalence of CKD in the US was 16.8% while in Asia the prevalence ranged from 12.1% to 17.5%.[1 - 4, level III] In Malaysia, the incidence and prevalence of patients with ESRD on dialysis had increased from 88 and 325 per million population (pmp) respectively in 2001 to 170 and 762 pmp respectively in 2009.[5, level III] The increase in ESRD was largely driven by the increasing incidence of diabetic kidney disease (DKD) accounting for 58% of new patients accepted for dialysis.[5, level III] The growing number of ESRD places an enormous human, economic and social burden on the healthcare system. In an economic evaluation among Ministry of Health dialysis centres in Malaysia, the cost of dialysis and erythropoietin was RM2,500 per month.[6, level III] In the US, the cost of medical care was 1.7 times higher in patients with CKD stage 3 and 2.6 times higher in those with stage 4 CKD compared with controls.[7, level II-2]

Early kidney disease is largely asymptomatic and patients often present late with complications of CKD. As such, targeted screening and early intervention will be necessary to reduce the burden of the disease. Primary care providers play a key role in the early identification, treatment and improving the outcome of patients with CKD. Awareness of CKD among primary care providers should be increased and they should be equipped to treat these patients. As the prevalence of diabetes is increasing and DKD remains the most common cause of CKD, optimal control of diabetes will be necessary to prevent CKD. The most important strategies to improve the outcome of CKD are the control of hypertension and proteinuria. As CKD is also associated with increased cardiovascular disease (CVD), therapy will also need to address the treatment and reduction of CVD.

The aim of these Clinical Practice Guidelines (CPG) is to provide an evidence-based guidance for primary care physicians and other healthcare providers to identify the appropriate and cost-effective measures to screen for CKD and to commence therapy early to ameliorate or even halt the progression of CKD before relentless deterioration begins. CPG alone would be insufficient. Rather it should be used by the stakeholders as an arsenal in our armamentarium to combat the scourge of CKD.

2. SCREENING AND INVESTIGATIONS

Patients with early stage of CKD are generally asymptomatic. Many of such cases remain undiagnosed and later progress to ESRD. To reduce the prevalence of ESRD, effective screening and treatment methods for CKD should be established. Refer to **Algorithm 1** and **Algorithm 2** (page viii - ix).

2.1 WHO SHOULD BE SCREENED?

Recommendation 1:

- Patients with diabetes mellitus and/or hypertension should be screened at least yearly for chronic kidney disease (CKD). **(Grade C)**
- Screening can be considered for patients with:
  - Age >65 years old
  - Family history of stage 5 CKD or hereditary kidney disease
  - Structural renal tract disease, renal calculi or prostatic hypertrophy
  - Opportunistic (incidental) detection of haematuria or proteinuria
  - Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) or other nephrotoxic drugs
  - Cardiovascular disease (CVD)
  - Multisystem diseases with potential kidney involvement such as systemic lupus erythematosus. **(Grade C)**

Early detection and intervention of high risk groups may prevent the development and progression of CKD. Epidemiological evidence has identified the following factors:

A. Diabetes Mellitus (DM)

DM is significantly associated with increased risk for CKD.[8 - 10, level III; 11, level II-2] In Malaysia, DKD is a major cause of CKD, contributing to 58% of new patients requiring dialysis in 2009.[5, level III]

B. Hypertension

Large studies showed that patients with hypertension had a significantly higher risk of developing CKD compared with normotensive patients.[10, level III; 12 - 13, level III] Hypertension may be a cause or consequence of renal failure. It accelerates the progression of renal disease and may lead to ESRD.

C. Metabolic Syndrome

Metabolic syndrome has been shown to be an independent risk factor for CKD. Large studies suggested that metabolic syndrome was significantly associated with CKD.[14 - 15, level II-2; 16, level III] The number of metabolic syndrome components was proportional to the prevalence of CKD[16, level III] and negatively correlated to estimated glomerular filtration rate (eGFR).[16 - 17, level III] There was also a significant association of metabolic syndrome and the risk of CKD in subjects without diabetes and hypertension.[14 - 15, level II-2]

D. Age

People aged >65 years old have an increased risk of renal impairment and decline in renal function.[9 - 10, level III; 12 - 13, level III; 25, level III]

E. Family History

A longitudinal study with 25 years follow-up showed that a family history of kidney disease in a first degree relative had a 40% increased risk of CKD.[18, level II-2]

F. Cardiovascular Disease (CVD)

Patients with atherosclerotic vascular disease had 1.4 times greater risk of developing CKD compared with those without the disease in a 2 year follow-up study.[12, level II-2]

G. Chronic Use of NSAIDs and Analgesics

There was conflicting evidence in the association between chronic NSAIDs, aspirin and paracetamol usage and the development of CKD. In a case-control study, an average intake >500 g/year of aspirin was associated with over 3-fold increase of developing CKD.[19, level II-2] In contrast, one prospective cohort study of physicians showed that occasional to moderate analgesic intake of aspirin, paracetamol, or NSAIDs did not appear to increase the risk of decline in kidney function during a period of 14 years follow-up.[20, level II-2] An 11-year follow-up of Nurses' Health study had shown higher lifetime use of aspirin and NSAIDs was not associated with renal function decline, but high paracetamol (>3,000 g) use may increase the risk of loss of renal function.[21, level II-2]

H. Other Risk Factors

Other possible risk factors include autoimmune disease, nephrolithiasis,[2, level III] low birth weight of <2,500g,[22, level II-2] central obesity,[2, level III] smoking,[11, level III; 23 - 24, level III] low socioeconomic status,[25, level III] anaemia, hyperuricaemia, nocturia,[18, level II-2] and physical inactivity,[24, level III] Certain herbal products including those containing aristolochic acid had also been associated with CKD.[26, level III]

2.2 METHODS OF SCREENING

Screening for CKD should include assessment for proteinuria, haematuria and renal function.

A. Proteinuria

Recommendation 2:
- Urine dipsticks should be used to screen for proteinuria. **(Grade C)**
- In patients with diabetes, albumin: creatinine ratio (ACR) on an early morning spot urine sample should be performed at least annually to screen for microalbuminuria if urine dipstick is negative. **(Grade C)**

Refer to **Algorithm 1 and 2**

Proteinuria has both diagnostic and prognostic value in CKD.[27, level II-1] However, it shows considerable biological variation. Therefore, the presence of proteinuria should be confirmed by a repeat test within three months. Factors affecting urinary albumin excretion should be taken into consideration when screening for proteinuria (refer to **Table 1**).

Table 1: Factors Affecting Urinary Protein Excretion

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

Source:

1. Phillipou G, Phillips PJ. Variability of urinary albumin excretion in patients with microalbuminuria. Diabetes Care. 1994 May;17(5):425-7
2. Mogensen CE, Vestbo E, Poulsen PL et al. Microalbuminuria and potential confounders. A review and some observations on variability of urinary albumin excretion. Diabetes Care. 1995 Apr;18(4):572-81

Urine dipstick testing is convenient, cheap and widely available. It is often the initial measure used to detect CKD. However its accuracy may be affected by fluctuations in urine concentration. Automated urinalysis has greater predictive values for significant proteinuria (>0.3 g/24 hours) when compared with urine dipstick[28, level II-2] and is the preferred method.

Although 24-hour urinary protein or albumin excretion is considered a 'gold standard' for the quantification of proteinuria, it is cumbersome and error may arise from incomplete collection. In a study involving non-diabetic CKD patients, protein: creatinine ratio (PCR) measured on early morning or random urine sample was as good as 24-hour urine protein estimation at predicting the rate of Glomerular Filtration Rate (GFR) loss. In the same group of patients, measurement of PCR may be used to predict risk of progressive disease.[29, level III]

Microalbuminuria refers to the presence of a small amount of albumin in the urine, which cannot be detected with the usual urine dipstick. It is defined as urinary albumin excretion rate 20 - 200 µg/min/24 hour or 30 - 300 mg/24 hour. Overt proteinuria (macroalbuminuria) is defined as albumin excretion rate of >200 µg/min/24 hour or >300 mg/24 hour. Further classification of proteinuria by method of screening is shown in **Table 2**.

Microalbuminuria is the earliest sign of DKD and predicts increased cardiovascular (CV) mortality and morbidity, and ESRD. Diabetes patients should be screened for microalbuminuria at least annually (refer to **Algorithm for Screening of Microalbuminuria in Diabetes Patients**). It is also a marker of renal insufficiency in non-diabetes subjects.[30, level III]

Urine ACR is highly sensitive and specific for microalbuminuria.[31, level III] This should be performed on an early morning urine sample to minimise the effect of posture and exercise on urine albumin excretion.

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 mcg/min (mg/24 hour)
Normal	Negative	<15	<0.15	<2.5 (male) <3.5 (female)	<20 (<30)
"Trace" protein (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		
Overt proteinuria (Macroalbuminuria)	1+	45 - 149	0.45 - 1.49	>30	>200 (>300)
	2+	150 - 449	1.50 - 4.49		
	3+	≥450	≥4.50		

Adapted: Scottish Intercollegiate Guidelines Network. Diagnosis and management of chronic kidney disease. Edinburgh: SIGN; 2008

B. Haematuria

Recommendation 3:
- A positive dipstick test (1+ or more) for blood requires repeat testing for confirmation. **(Grade C)**
- Visible or persistent non-visible haematuria requires urological investigation after excluding urinary tract infection. **(Grade C)**

Refer to **Algorithm 2**

Haematuria may indicate significant pathology including infection, renal calculi, primary glomerulonephritis, malignancy and other forms of kidney damage. Isolated non-visible haematuria is associated with a modest increased risk of progressive kidney disease[13, level III; 32, level II-2] and therefore should be evaluated.

Urine dipsticks have 98% sensitivity[33, level III] and are commonly used for detecting haematuria. However a single positive dipstick test is not sufficient to indicate pathology.[34, level III] Non-visible haematuria must be confirmed by the presence of a positive dipstick test (1+ or more) for blood on two out of three occasions and may warrant a microscopic examination.

Urine microscopy (preferably phase contrast microscopy) on a fresh specimen can be used to differentiate between glomerular and non-glomerular haematuria. Presence of dysmorphic red blood cells and red cell casts indicate glomerular disease (refer to **Section 5**).

2.3 COST-EFFECTIVENESS OF SCREENING

Screening allows early detection of CKD to enable timely intervention to improve outcome. However, it should be directed towards the high risk groups as it is not cost-effective to screen the general population.[35, level III]

A study among US population aged 50 - 75 years found that early detection of urine protein to slow progression of CKD was not cost-effective unless selectively directed towards high-risk groups (older people and patient with hypertension) or conducted at an infrequent interval of 10 years.[36, level III]

In an Australian study, primary care screening of 50 - 69 years old for diabetes, hypertension, and proteinuria, with subsequent intensive management including ACE inhibitors for all patients with proteinuria was cost-effective.[37, level II-2]

In a Canadian study, screening for hypertension and overt proteinuria in patients with Type 1 diabetes mellitus (T1DM) was more cost-effective than screening for microalbuminuria in patients with hypertension but without diabetes.[38, level III] Another study had shown that screening for microalbuminuria was cost-effective in patients with diabetes or hypertension, but was not cost-effective for patients with neither diabetes nor hypertension unless screening is conducted at longer intervals or as part of existing physician visits.[39, level II-2]

A decision analysis by National Institute of Clinical Excellence (NICE) suggested that case-finding of CKD among high-risk groups was cost-effective. Use of ACR, without prior reagent strip, appeared to be the most cost-effective option.[40] Reporting eGFR may also be beneficial, but this benefit was reversed when there was a reduction in quality of life caused by incorrect diagnosis of CKD.[41, level II-2]

2.4 RENAL FUNCTION

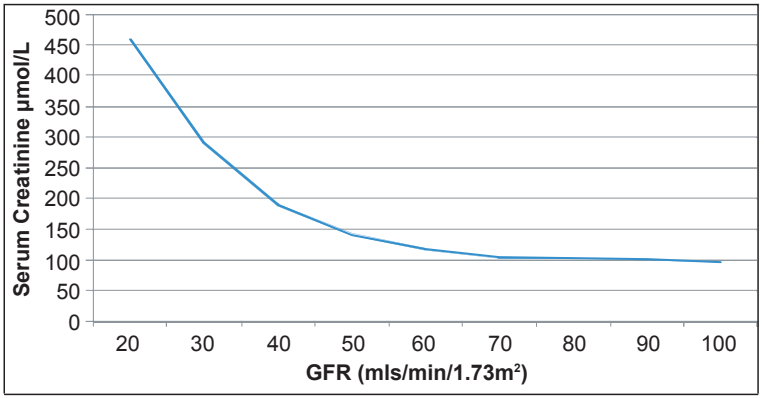
Recommendation 4:

- Renal function should be assessed with estimated Glomerular Filtration Rate (eGFR) based on the 4-variable MDRD*. **(Grade C)**
- Serum creatinine should be used in combination with eGFR in the assessment of renal function. **(Grade C)**
- Laboratories should provide automated eGFR estimation in addition to serum creatinine. **(Grade C)**
- When eGFR is not available, other methods of estimation may be used. **(Grade C)**

Refer to **Equations for estimation of renal function** box.

**Modification of Diet in Renal Disease*

Serum creatinine has been routinely used in clinical practice to estimate renal function. However, it is affected by many other variables (such as age, gender, ethnicity, muscle mass and protein meal) and should not be used as an independent marker of kidney function. Furthermore, serum creatinine is not a sensitive marker of early CKD as it will rise only after a reduction of renal function by at least 50% (refer to **Figure 1**). When eGFR is >60 ml/min/1.73m^2, consider a rise of 20% in serum creatinine as a significant indicator of reduction in renal function.



Source: Salifu MO, Ifudu O. Azotemia. emedicine. c2009 [Updated Sept 2009]. Available from: http://emedicine.medscape.com/article/238545-overview

Due to this limitation, other formulae to estimate renal function was developed (refer to the yellow box below). The 4-variable MDRD equation has been shown to be better than Cockcroft-Gault equation in estimating renal function.[42, level I; 43 - 45, level III] However, the MDRD equation may be inaccurate when the GFR rate was greater than 60 ml/min/1.73m^2.[44, level III] Recently, a new CKD-epi (CKD-epidemiology) equation was found to be significantly superior over the MDRD equation especially at higher GFR and therefore could replace the latter equation for routine clinical use in the future.[46, level III] Until further validation is available, the 4-variable MDRD equation is preferred. However, these equations are still dependent on serum creatinine level and thus may over-estimate (such as in amputees) or under-estimate (such as in bodybuilders) renal function when muscle mass is abnormal.

Serum creatinine is subjected to intra- and inter-laboratory analytical variations. Laboratories should calibrate measurement of serum creatinine to the gold standard method of isotope dilution mass spectrophotometry to minimise variations.

Cystatin C has been used as a marker for GFR assessment and it is independent of muscle mass, age, sex, weight, height or meat intake. However, it has not been able to demonstrate superiority to the 4-variable MDRD and Cockcroft-Gault formulae.[47] Furthemore, it is expensive and not widely available.

Equations for estimation of renal function:

i. **MDRD eGFR =**
175 x standardised $sCr^{-1.154}$ x $age^{-0.203}$ x 1.212 [if black] x 0.742 [if female], where GFR is expressed as ml/min/1.73m^2 of body surface area and sCr is expressed in mg/dl

ii. **CKD-epi eGFR =**
$141 \times \min(sCr/\kappa, 1)^{\alpha} \times \max(sCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if black], κ = 0.7 (females) and 0.9 (males), α = -0.329 (females) and -0.411 (males), min indicates the minimum of sCr /κ or 1, and max indicates the maximum of sCr /κ or 1

iii. **Cockcroft-Gault Creatinine Clearance**

$$CrCl\ (ml/min) = \frac{(140 - age\ (yrs)) \times body\ weight\ (kg)}{sCr\ (\mu mol/l)} \times Constant$$

where the constant is 1.23 in male or 1.04 in female

sCr =Serum Creatinine *CrCl = Creatinine Clearance*

2.5 RENAL TRACT ULTRASOUND

Ultrasound is a useful first line test for imaging the renal tract in patients with CKD. It identifies obstructive uropathy, renal size and symmetry, renal scarring and polycystic disease.[48, level III]

Indications for renal ultrasound in patients with CKD:[49]
- a rapid deterioration of renal function (eGFR >5 ml/min/1.73m^2 within one year or 10 ml/min/1.73m^2 within five years)
- visible or persistent non-visible haematuria
- symptoms or history of urinary tract obstruction
- a family history of polycystic kidney disease and age over 20 years
- stage 4 or 5 CKD
- when a renal biopsy is required

3. CLASSIFICATION

Recommendation 5:
- Classification of chronic kidney disease (CKD) should be based on the existing NKF-KDOQI* staging (refer to **Table 3**). **(Grade C)**
- The suffix (p) should be added to denote the presence of proteinuria when staging CKD. **(Grade C)**

** National Kidney Foundation-Kidney Disease Outcomes Quality Initiative*

Large population studies demonstrated that declining renal function of <60 ml/min/1.73m^2 was associated with increased risk of mortality, hospitalization and CV events. The NKF-KDOQI classification is commonly practiced (refer to **Table 3**). It is based on three factors: GFR (level of kidney function), pathological changes (kidney damage) and presence of the abnormality for at least three months. The kidney damage is defined as either:

a. Persistent microalbuminuria
b. Persistent proteinuria
c. Persistent haematuria
d. Radiological evidence of structural abnormalities of the kidneys
e. Biopsy proven glomerulonephritis

Table 3: Staging of Chronic Kidney Disease

Stages of CKD		
Stage	**GFR (ml/min/1.73m^2)**	**Description**
1	≥90	Normal or increased GFR, with other evidence of kidney damage
2	60 - 89	Slight decrease in GFR, with other evidence of kidney damage
3A	45 - 59	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30 - 44	
4	15 - 29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure

The respective suffices should be added:
- suffix ‘p’ if overt proteinuria present (refer to **Table 2**)
- suffix ‘d’ if patient is on dialysis
- suffix ‘t’ if patient has been transplanted

Adapted: National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S000, 2002 (suppl 1)

At any stage of CKD, the presence of proteinuria was associated with doubling of CV risk and mortality. In a study conducted in the diabetes population, despite eGFR of ≥90 ml/min/1.73m^2, patients with albuminuria had a significantly 85% increased risk of CV events compared to those without albuminuria. Similarly, the study showed that albuminuria increased CV events by 89% in patients with stage 2 disease.[50, level II-2]

At any stage of CKD, persistence of proteinuria predicts its progression and development of ESRD. In a Japanese cohort study, proteinuria significantly increased the risk of ESRD by more than four times. The 7-year cumulative incidence per 1,000 subjects of ESRD gradually increases with declining renal function in stage 3 and 4 of CKD.[51, level II-2] A study by Hallan SI et al. demonstrated that combining the effect of GFR and albuminuria for classifying CKD significantly improved prediction of ESRD. The hazard ratio (HR) was 13 if the patient had microalbuminuria compared to 47.2 if the patient had macroalbuminuria.[52, level II-2] Evidence from longitudinal population studies and meta-analysis of progression risk and level of proteinuria suggested that an ACR ≥30 mg/mmol should be used as a marker for increased risk for progression of CKD (equivalent to a PCR ≥50 mg/mmol or proteinuria values ≥0.5 g/day).[53, level II-2; 54, level I] Therefore, the suffix (p) is important to be added to denote the presence of proteinuria when staging CKD.

A suffix (d) should be added if the patient is on dialysis and (t) should be added if the patient has been transplanted.[55, level III]

The diagnosis of CKD in the elderly should not solely rely on eGFR estimation. The NKF-KDOQI classification may lead to overdiagnosis of CKD particularly in the elderly. Elderly patients (age >70 years old) with stable stage 3A of kidney disease are not likely to develop CKD-related complications.[56, level III]

4. TREATMENT

The aim of treatment of CKD is to retard the progression of renal disease, reduce CVD risk and manage CKD-related complications. The latter aspect of CKD management is beyond the scope of this guideline. Refer to **Algorithm 3** for summary of treatment (page x).

4.1 TREATMENT OF HYPERTENSION AND PROTEINURIA

Recommendation 6:

- Any class of antihypertensive agents can be used to treat hypertension in chronic kidney disease (CKD) patients without proteinuria. **(Grade C)** 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:
  - o non-diabetic CKD with urinary protein excretion ≥0.5 g/day in the presence of hypertension. **(Grade A)**
  - o non-diabetic CKD when urinary protein excretion ≥1.0 g/day irrespective of the presence of hypertension. **(Grade A)**
  - o all diabetes patients with albuminuria (micro- or macroalbuminuria) irrespective of the CKD stage and presence of hypertension. **(Grade A)**

Renal profile should be carefully monitored following introduction of ACEi/ARB (refer to **Recommendations in Section 4.4**)

The majority (70 - 80%) of patients with CKD have hypertension, which is usually systolic and more severe than in non-CKD patients.[57, level II-3; 58, level III] Control of hypertension and proteinuria are the two most important interventions for retardation of renal disease progression.

Any class of antihypertensive agents can be used to lower blood pressure (BP) in CKD.[59] However, some antihypertensive agents have additional renal or cardiac protection besides BP lowering effect. ACEi/ARB should be the first line therapy in DKD because they have additional renoprotective effect over and above 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.[50, level II-2; 60, level I

The degree of proteinuria reduction achieved also correlates with the degree of CKD retardation and CVD mortality reduction.[61 - 66, level I] Lowering BP can reduce proteinuria to some extent.[60, level I; 67, level I] However, some antihypertensive agents have additional antiproteinuric effect. Other agents may reduce proteinuria without affecting BP.

A. Angiotensin-Converting Enzyme Inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB)

ACEi and ARB confer both renoprotective and cardioprotective effects.

A systematic review (SR) of 36 RCTs looking at the effect of ACEi in both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM), and ARB in only 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 reduced progression of micro to macroalbuminuria by 45% while ARB reduced the progression by 51%. Both ACEi and ARB induced regression from microalbuminuria to normoalbuminuria with RR of 3.1 and 1.4 respectively. This benefit was regardless of baseline BP.[68, level I]

The use of ACEi or ARB in diabetes patients without proteinuria is not well established. In the study by Bilous R et al., the use of candesartan over 4.7 years did not prevent microalbuminuria in normotensive normoalbuminuric T1 or T2DM.[69, level I] However, in a meta-analyses of 7,603 patients with normoalbuminuria, ACEi reduced the development of DKD by 42%.[70, level I] The UK CKD guidelines recommend ACEi and ARBs as first line therapy only for diabetes with microalbuminuria (ACR=2.5 and 3.5 mg/mmol for male and female respectively).[71 ; 72, level I]

A meta-analysis of 11 RCTs conducted in non-diabetic CKD patients showed that there was no significant risk of renal disease progression when proteinuria was <1 g/day at any BP level. For those with proteinuria >1 g/day, the risk of renal disease progression became significant when SBP >130 mmHg.[73, level I] There was also no benefit of ACEi use for non-diabetic CKD with hypertension if proteinuria <0.5 g/day.[74, level I]

Health economic evidence from post hoc analysis of several RCTs and meta-analyses found that ACEi and ARB conferred both health gains and net cost savings compared with non-ACEi therapy. There was no evidence to support the superiority of one ACEi over another or ARB over ACEi.[68, level I] However, health economic evidence suggested an increased cost-effectiveness for ACEi vs ARBs, indicating that ACEi should be prescribed first and changed to an ARB only if there is non-renal ACEi intolerance.[49]

B. Calcium Channel Blocker (CCB)

CCBs are effective antihypertensive agents but the evidence for its renoprotective effect is not conclusive. One meta-analysis concluded that non-dihydropyridine CCB (NDHP CCB) such as verapamil and diltiazem had greater antiproteinuric effect than dihydropyridine (DHP) CCBs in both diabetes and non-diabetes, hypertensive patients.[75, level I] However, a recent study using fixed-dose combinations of an ACEi with either NDHP CCB (trandolapril/verapamil slow release) or DHP CCB (benazepril/amlodipine) showed that both were equally effective in reducing albuminuria in T2DM hypertensive patients with kidney disease; nevertheless there were differences in BP lowering between the groups.[76, level I]

NDHP CCB (diltiazem or verapamil) can be considered in hypertensive CKD patients with proteinuria either as an alternative in patients who are intolerant/contraindicated to ACEi or ARB or in combination with in ACEi or ARB for additional proteinuria reduction is required.

C. Combination of ACEi and ARB

There is insufficient evidence to warrant the use of combined ACEi and ARB for BP control or to improve renal outcomes. Current available studies were either of small sample size or results did not reach statistical significance.[77 - 80, level I]

A meta-analysis showed an additional 30 - 39% reduction in proteinuria comparing combination of ACEi and ARB group to monotherapy.[80, level I] However, there is no reliable evidence for hard end-point reduction such as progression to ESRD or mortality. On the other hand, there are some concerns regarding safety issues such as risk of hyperkalaemia, hypotension and acute renal failure. In a RCT, the combination of telmisartan and ramipril reduced proteinuria to a greater extent than monotherapy, but increased the incidence of hypotensive symptoms and acute renal deterioration without increasing major chronic renal outcomes. The study was conducted in patients with high vascular risk or patients with DM and with end-organ damage but did not include those who were at high renal risk or those with creatinine >265 mmol/l.[81, level I]

Therefore, this combination is not recommended in patients with CKD without significant proteinuria. However, dual blockade may be considered in CKD patients, who remain hypertensive with persistent proteinuria >0.5 g/day provided that serum potassium is within normal range.[82, level III]

D. Aldosterone Antagonist (AA)

Plasma aldosterone level has been shown to correlate with the rate of progression of kidney disease.[83 - 84, level II-2] Several RCTs conducted in patients with proteinuria with or without diabetes showed that spironolactone significantly reduced proteinuria without significant change in GFR when added to ACEi or ARB compared to placebo. Three studies showed no significant change in GFR but one study reported a significantly decreased eGFR with spironolactone compared to placebo.[85 - 88, level I]

Meta-analysis of 11 trials showed that AA significantly reduced proteinuria and BP in CKD patients on ACEi and/or ARB compared to placebo, but increased the risk of hyperkalaemia with no significant effect on GFR. Hence, current available evidence should be interpreted with caution as all studies had a small sample size (n=21 to 165) and short follow-up periods (2 months to 1 year). Long-term effects on renal outcome, mortality and safety need to be established.[89, level I]

E. Renin Inhibitor

Oral direct renin receptor inhibitors provide another alternative for blockade of renin-angiotensin-aldosterone system (RAAS) besides ACEi, ARB and aldosterone inhibitor. Aliskiren has been licensed as antihypertensive agent. However, its effect on renoprotection has not yet been established.

There is only one RCT in hypertensive, T2DM patients with proteinuria on maximal dose of losartan showing that treatment with 300 mg aliskiren significantly reduced mean urinary ACR by 20% compared to placebo. The aliskiren group had a smaller decline in kidney function which was not statistically significant.[90, level I] Recommendations cannot be made until the results of ongoing larger scale RCTs such as VA Nephron D and ALTITUDE studies with longer follow-up and hard renal outcomes are available.

F. Miscellaneous Agent

Sulodexide has not been proven to be an effective antiproteinuric agent. Earlier small-scale, short duration studies indicated that sulodexide had promising antiproteinuric effects.[91 - 92, level I] However, subsequent evidence failed to confirm the findings. Two pilot studies were conducted using sulodexide as antiproteinuric agent in T2DM who were already on maximal dose of RAAS blockade, one group with microalbuminuria (SUN-Micro-Trial) and another group with macroalbuminuria (SUN-Macro-Trial). SUN-Micro-Trial failed to achieve a significant difference between groups in the primary end point of conversion from microalbuminuria to normoalbuminuria or more than 50% reduction of microalbuminuria.[93, level III] SUN-Macro-Trial was prematurely terminated due to the negative results from SUN-Micro-Trial. There was no difference in protein excretion at 6 and 12 months at the time of termination.[93, level III] Thus, sulodexide cannot be currently recommended for reduction of proteinuria.

There are some preliminary evidence for the antiproteinuric effect of paricalcitol and pentoxyphylline.[94 - 95, level I] However, further studies need to be conducted.

4.2 OPTIMAL BLOOD PRESSURE RANGE

Recommendation 7:

- Target blood pressure (BP) should be <140/90 (SBP range 120 - 139) mmHg. **(Grade A)**
- Target BP should be <130/80 (SBP range 120 - 129) mmHg
  - o in patients with proteinuria ≥1 gram/day. **(Grade A)**
  - o in patients with diabetic kidney disease. **(Grade B)**

SBP = systolic blood pressure

Blood pressure lowering is important to retard the progression of CKD and reduce CVD risk. However, reducing BP below the above-mentioned targets may not be beneficial or may even be harmful.[60, level I; 73, level I; 96 level I; 97, level II-2; 98, level I; 101, level II-2] There appears to be a dichotomous risk in which strict BP lowering is better for renal disease and stroke reduction, but seems worse for CVD outcomes. Interpretation of data on target BPs needs to take into account the possible confounding effect of BP and adverse outcomes due to reverse causality.

The important outcomes in the studies of BP lowering are all-cause mortality, coronary artery disease, cerebrovascular disease and progression of CKD.

A. All-Cause Mortality

No benefit was observed by targeting BP<135/85 mmHg in the general population[96, level I] or by targeting SBP<120 for the CKD population in the AASK study,[60, level I] On the contrary, there was a suggestion of harm from the post hoc analysis of IDNT where SBP<120 mmHg is associated with increased risk of CVD and all-cause mortality in proteinuric DKD.[98, level I] A lower BP of <110/70 mmHg was also found to be a marker of higher mortality in older individuals with advanced CKD.[99, level II-2]

B. Coronary Artery Disease

There was no difference noted in CVD mortality risk between intensive (Mean Arterial Pressure [MAP] <92 mmHg) vs usual (MAP 102 - 107 mmHg) BP control from AASK study.[60, level I]

In T2DM patients at high risk of CV events, the ACCORD-BP study showed that targeting a SBP <120 mmHg as compared with 140 mmHg did not reduce the rate of a composite outcome of fatal and nonfatal major CVD. Instead it incurred a significantly higher rate of serious adverse events.[100, level I] This concurred with the IDNT post hoc analysis where a significantly higher risk of CVD mortality and CCF for patients with achieved SBP <120 mmHg was observed.[98, level II-2]

A SR in the general hypertensive population showed lower BP targets (≤135/85 mmHg) instead of standard targets (≤140 - 160/90 - 100 mmHg) did not significantly change myocardial infarction, CCF or major CVD.[96, level I]

C. Cerebrovascular Disease

There are conflicting findings on intensive vs less intensive BP control. There was no significant benefit of intensive BP control in reducing risk of cerebrovascular disease among hypertensive patients,[96, level I] patients with DKD[98, level II-2] or in elderly patients with CKD stage 3 - 4.[101, level II-2] In a study by Weiner DE et al., SBP <120 mmHg significantly increased risk of cerebrovascular disease compared with SBP 120 - 129 mmHg.[101, level II-2] In contrast, the PROGRESS study showed BP-lowering therapy with perindopril-indapamide reduced risk of recurrent cerebrovascular disease in patients with CKD (stage 3 or greater) and pre-existing cerebrovascular disease.

This occurred irrespective of baseline BP levels with no evidence of a 'J-curve'.[102, level I] However, these findings were not reproduced in the PRoFESS study.[103, level I]

D. Prevention of Renal Disease Progression

In the hypertensive population, lowering BP to <135/80 does not significantly reduce the development of ESRD compared with a target BP of <140-160/90.[96, level I]

In the general CKD population, several large-scale studies showed no significant difference in decline in GFR,[60, level I; 104 - 105, level I] or in progression to ESRD.[60, level I; 104, level I] between intensive vs usual BP control. Intensive vs usual BP targets in these trials were MAP ≤92 vs 102 - 107 mmHg (AASK study), BP <130/80 vs DBP <90 mmHg (REIN-2 study), and MAP ≤92 vs ≤107 mmHg for patients aged 18 - 60 years and ≤98 vs ≤113 mmHg for patients aged >61 years (MDRD study). In the MDRD trial, only those with proteinuria >3 g/day had a significant benefit from the lower BP target in terms of decline in GFR. Recent long-term follow-up data of the AASK study has also shown that aiming for intensive BP control of <130/80 has no effect on kidney disease progression except in those with baseline proteinuria of PCR >0.22 (equivalent to proteinuria of 300 mg/day).[106, level I]

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 compared to those achieving SBP 140 - 159 mmHg had a significantly lower risk of reaching the combined endpoint of doubling of serum creatinine, ESRD or mortality.[107, level II-2] There was a non-significant difference in risk for this combined end-point for those with BP 130 - 139 vs SBP <130 mmHg.

Although the ADVANCE study reported that lowering SBP levels to even <110 mmHg was associated with progressively lower rate of renal events with no BP threshold below which renal benefit was lost,[108, level I] the benefit of antihypertensive treatment was significant only in patients with an entry SBP ≥140mmHg. Similar findings were obtained when stratification was based on the presence or absence of a history of hypertension.[109, level III]

The relationship of the level of BP with risk of CKD progression varies with the level of proteinuria. The greatest beneficial effect for BP reduction on GFR decline is seen in patients with high urinary protein

excretion.[73, level I; 105, level I] The AIPRD meta-analysis by Jafar TH et al. showed that for prevention of CKD progression in non-diabetes patients with proteinuria >1 g/day, the optimal SBP was 110 - 129 mmHg.[73, level I] However, the lower limit of SBP reduction is however set at 120 mmHg in view of the increased risks of CV events associated with lowering BP below this level.

4.3 OPTIMAL PROTEINURIA REDUCTION

Patients with CKD and proteinuria should be treated with ACEi/ARB to reduce proteinuria in order to retard renal disease progression (refer to **Section 4.1**). Currently, there is no consensus on the target proteinuria reduction but the available evidence suggests that proteinuria should be reduced to <1 g/day for non-diabetic CKD and to normoalbuminuria for DKD if this can be safely achieved.

Urine protein excretion is a modifiable risk factor for CKD progression. The progression correlates closely to proteinuria and its retardation correlates with the degree of proteinuria reduction.[61 - 62, level I; 66, level I]

In a meta-analysis of 11 RCTs in non-diabetic CKD with proteinuria ranging from <0.5 g/day to >6 g/day, each 1 g/day proteinuria reduction is associated with 80% reduction in the risk of CKD progression/ESRD.[66, level I] However, when proteinuria is <1 g/day, there was little relationship between the risk for kidney disease progression and current systolic BP ranging from 110 to 159 mmHg.[73, level I]

Post hoc analysis of IDNT study by Atkins et al. in T2DM showed that baseline urinary protein excretion of <1 g/day, 2 - 4 g/day and >8 g/day was associated with 7.7%, 22.9% and 64.9% risk of progression to ESRD at three years. Each 50% reduction of proteinuria at one year of follow-up reduced the risk of ESRD at three years by 56%.[61, level I]

In addition, evidence from longitudinal population studies and meta-analysis of progression of risk and level of proteinuria suggested that an ACR ≥30 mg/mmol (equivalent to a PCR ≥50 mg/mmol or proteinuria value ≥0.5 g/day) should be used as a marker of the increased risk of doubling CVD risk and mortality.[53, level II-2; 54, level I]

4.4 MONITORING OF RENAL FUNCTION

Recommendation 8:

- Renal profile should be reassessed within two weeks upon initiation or escalation of Angiotensin-Converting Enzyme Inhibitor (ACEi)/ Angiotensin Receptor Blocker (ARB) therapy. The interval should be determined by baseline renal function. **(Grade B)**
- If there is a sustained rise in creatinine levels above 30% (or estimated glomerular filtration rate reduces >25%) from the baseline or serum potassium is >5.6 mmol/l during the first two months after commencement of ACEi/ARB therapy, reduce or discontinue the ACEi/ARB after excluding other precipitating factors and refer to a nephrologist/physician. **(Grade B)**

Although it is important to ensure that patients with CKD receive optimal therapy with ACEi/ARB, care should be taken to avoid adverse effects.

Serum potassium and creatinine should be checked prior to, and within two weeks after initiating an ACEi/ARB and after each dose increase. After initiation of therapy, there may be increase in serum creatinine of ≤30% and this usually occurs within the first two weeks.[110; 111, level I] If renal function remains stable within these limits, ACEi/ARB may be titrated until BP goal and optimal antiproteinuric targets are achieved.[110]

The frequency and interval of monitoring should be tailored according to the individual's baseline renal function and risk of hyperkalaemia.

ACEi/ARB should be avoided or used with caution in patients with conditions which predispose to worsening of renal function or hyperkalaemia. These conditions include:[110; 111, level I]

- renal artery stenosis
- elderly
- concomitant NSAIDs use
- concomitant medications predisposing to hyperkalaemia (such as beta blockers and aldosterone antagonists)
- hypoperfusion states (such as congestive cardiac failure, dehydration and sepsis)

These patients should be monitored more frequently.

4.5 OPTIMAL GLYCAEMIC CONTROL

Recommendation 9:
- The target HbA_{1c} should be ≤7% in patients with diabetes but this should be individualised according to co-morbidities. **(Grade A)**

Tight glycaemic control should be attained to reduce the complications of diabetes if it can be achieved safely.[112; 113 - 115, level I] Lowering HbA_{1c} to approximately 6.5% to 7% reduces the development of micro- and macroalbuminuria[113, level I; 116, level I; 117] The effect of intensive blood glucose control and BP lowering is independent and additive for reducing the risk of new or worsening nephropathy.[118, level I] However, aggressive glycaemic control in patients with established CVD has been shown to increase the risks of hypoglycaemia and death.[172, level I] Patients with CKD often have co-existing CVD and are more prone to severe hypoglycaemia due to impaired drug excretion.

Iron and erythropoetin treatment can cause a significant fall in HbA_{1c} values without a change to glycemic control in patients with DM and CKD.[119, level II-2] HbA_{1c} may be underestimated in patients with advanced CKD and regular capillary glucose measurements are needed for a more accurate assessment of glycaemic control.

For the appropriate choice and dosing adjustment of hypoglycaemic agents in CKD, refer to **Appendix 3**.

4.6 CORONARY ARTERY DISEASE

CVD is the most common cause of death in patients with CKD. Patients with CKD are at high risk for CV morbidity and mortality. Therefore, the risk factors for CVD namely high blood pressure and hyperlipidaemia should be appropriately controlled and anti-platelet agents should be used for the secondary prevention of CVD.

A. Hyperlipidaemia

Recommendation 10:
- Statin should be offered to patients with chronic kidney disease for primary and secondary prevention of cardiovascular events. **(Grade A)**

CKD is associated with dyslipidaemia, a known risk factor for CVD. In the past, many lipid trials either excluded patients with CKD or evidence for the beneficial effects of lipid lowering therapy for reduction in risk of CV events had to be derived from post hoc analysis of CKD

subpopulations. However, the SHARP study has recently provided evidence to support the use of lipid-lowering therapy in CKD stages 3 - 5.[120, level I]

Two meta-analyses, one RCT and five post hoc analyses reviewed the use of statin in primary and/or secondary prevention of CV outcomes.

Beneficial effects of statin in primary and secondary prevention of CV events were significant in patients with CKD as reported in two meta-analyses. Statin significantly reduced the risk of total mortality, CV mortality and non-fatal CV events.[121 - 122, level I]

The use of atorvastatin for primary prevention of CVD had resulted in significant reduction in major CV events by 42%.[123, level II-1] In addition, a post hoc analysis of AFCAPS/TexCAPS study showed a 69% reduction in the risk of CV events between patients with CKD on lovastatin compared with placebo.[124, level I]

In the SHARP study of 9,438 CKD stage 3 to 5 patients, compared to placebo, those on ezetimibe/simvastatin had a significant 17% reduction of major atherosclerotic events.[120, level I]

Statin should be recommended to patients with CKD for secondary prevention of CV events. Atorvastatin therapy in CKD patients showed a significant decrease in risk of CV events by 28% as compared to the usual care in a post hoc analysis of ALLIANCE-LDL study.[125, level I] Findings from another post hoc analysis of TNT study demonstrated that atorvastatin 80 mg significantly reduced the risk of major CV events by 32% compared to atorvastatin 10 mg in CKD patients.[126, level I] In a post hoc analysis of CKD patients in 4S, simvastatin significantly reduced total mortality by 31% compared to placebo.[127, level I]

Three post hoc analyses showed that patients with and without CKD had similar reduction of CV events with statin treatment.[123, level II-1; 124, level I; 127, level I]

Compared with placebo, statin use was not associated with an increased incidence of adverse events or drug discontinuation in patients with CKD.[121, level I; 124 - 125, level I; 127 - 129, level I] In the TNT trial, both 10 and 80 mg doses were well tolerated in CKD and non-CKD patients.[126, level I]

There is no conclusive evidence of lipid lowering in retarding the progression of CKD or reduction of proteinuria.

i. Changes in GFR

Three meta-analyses showed that statin therapy did not significantly slow the reduction in GFR. However, these meta-analyses were subjected to significant heterogeneity.[121 - 122, level I; 130, level I] Three post hoc analyses showed no significant difference between statin (lovastatin, pravastatin, atorvastatin) and comparators.[124 - 125, level I; 131, level I] In the SHARP study, there was no significant reduction in development of ESRD between CKD patients on ezetimibe/simvastatin compared to placebo.[120, level I]

In contrast, Huskey J et al. demonstrated reduction in GFR was significantly lower in patients on simvastatin compared to patients on placebo.[128, level I] A post hoc analysis of RCT by Colhoun HM et al. revealed a significant modest beneficial effect of atorvastatin on eGFR particularly in those with albuminuria.[123, level I] Another post hoc analysis showed a modest reduction on the rate of kidney function loss by pravastatin in patients with or at risk for cardiovascular disease.[129, level I]

ii. Changes in proteinuria

Three meta-analyses showed that statin treatment significantly reduced protein excretion compared to placebo.[121 - 122, level I; 132, level I] However, significant heterogeneity was found in two of the meta-analyses.[121 - 122, level I]

A meta-analysis by Sandhu et al. and a post hoc analysis of CARDS study showed no significant difference between placebo and statin groups in proteinuria changes.[123, level II-1; 130, level I]

B. Antiplatelet Agent

Recommendation 11:

- Aspirin should be used in patients with chronic kidney disease (CKD) for secondary prevention of cardiovascular disease. **(Grade B)**
- Combination of clopidogrel with aspirin should be avoided in patients with CKD unless compelling indications are present. **(Grade B)**

CKD is a recognised risk factor for the development of CVD. Patients with CKD are often prescribed antiplatelet medications.

In the general population, a meta-analysis has shown that aspirin is of substantial net benefit in secondary prevention of CVD. In the meta-analysis of 16 secondary prevention trials involving 17,000 patients,

aspirin significantly lowered the risk of major coronary events by 20%, is chaemic strokes by 22% and total mortality by 10%.[133, level I]

There is no evidence to suggest that antiplatelet drugs are less effective for secondary prevention of CVD in patients with CKD. 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 patients with CrCl <30 ml/min.[134, level II-2]

Patients with CKD are at an increased risk of bleeding compared with the general population. The UKHARP-1 study showed that aspirin 100 mg daily in CKD patients was associated with a 3-fold increase in minor bleeding but no significant increase risk of major bleeding.[135, level I] In two cohort studies of patients with acute coronary syndrome, aspirin was not significantly associated with increased risk of death in patients with CKD Stage 2 and 3. However, in one of the studies, aspirin was associated with a significantly increased risk of death in patients with CKD Stage 4.[136 - 137, level II-2]

There is no study of aspirin in primary prevention of CVD in CKD to establish whether vascular benefits exceed potential adverse outcomes.

Even in the general population, the use of low dose aspirin as primary prevention is of uncertain net value as potential harms (such as hemorrhagic strokes and gastrointestinal bleeding) may outweigh benefits. A recent meta-analysis of six primary prevention trials (95,000 individuals) showed that aspirin significantly lowered major coronary event by 18% with an absolute benefit of only 0.06% per year. There was also no significant reduction in overall vascular mortality or total mortality.[133, level I]

Current evidence suggests that the combination of clopidogrel and aspirin in the general population is associated with a reduction in the risk of CV events compared with aspirin alone in patients with non-ST elevation myocardial infarction (NSTEMI).[138, level I]

In patients with DKD, post hoc analysis of CHARISMA trial showed that the combination of aspirin and clopidogrel was associated with significant increase in overall mortality by 60% compared to aspirin alone.[139, level I] In patients with NSTEMI and GFR <81.2 ml/min, there was a significant increase in risk of minor bleed but nonsignificant risk for life threatening or major bleeding.[140, level I] In a post hoc analysis

of another trial (CREDO) on patients scheduled for elective PCI, this combination of antiplatelet agents was associated with a slight increase of major or minor bleeding in patients with CKD.[141, level I]

4.7 DIETARY INTERVENTION

Dietary intervention in particular protein restriction and adequate energy intake is an important aspect of CKD management to retard disease progression. Sodium restriction is also a useful measure to ensure optimal BP control.

A. Protein restriction

Recommendation 12:
- Low protein diet (0.6 - 0.8 g/kg/day) with adequate energy intake (30 - 35 kcal/kg/day) may be given to patients with chronic kidney disease Stage 3 - 5. **(Grade B)**
- Dietary protein restriction should be supervised by a dietitian. **(Grade B)**

Protein restriction has been used as one of the supportive measures to retard progression of CKD. The benefits of dietary protein restriction in slowing down progression of disease should be weighed against the risks of protein-calorie malnutrition and death when the dietary intervention is considered.

A meta-analysis on patients with DKD showed a significant 73% reduction in risk of ESRD or death with low protein diet [LPD] (0.3 - 0.8 g/kg/day) compared to unrestricted protein intake. However, the compliance was poor as the achieved protein intake was 0.6 - 1.1 g/kg/day in the LPD group.[142, level I]

In another meta-analysis of non-diabetic stage 4 - 5 CKD, protein restriction (0.3 - 0.6 g/kg/day) was associated with a 32% reduction in risk of renal death. However the result may be skewed by publication bias.[143, level I]

In contrast, a recent RCT showed that LPD (0.55 g/kg/day) did not significantly reduce the risk of ESRD and/or death compared with moderate protein diet (0.8 g/kg/day). Patients on LPD did not develop protein-calorie malnutrition in this study.[144, level I]

Finding from one RCT showed a low protein diet (0.6 g/kg/day) was not advised because of the presence of malnutrition risk in overt DKD.[145, level I] However, another RCT showed that there were no signs of malnutrition

with adequate dietary protein restriction (0.8 g/kg/day) in overt diabetic nephropathy and (0.6 g/kg/day) in non-diabetes patients with CKD.[146, level I]

In the long-term report on the MDRD cohort, a low protein diet [LPD] (0.58 g/kg/day) compared to very low protein diet supplemented with keto-acid [SVLPD] (0.28 g/kg/day) did not delay progression to kidney failure but was associated with a significantly greater than 2-fold increased risk of death on dialysis.[147, level I] In contrast, another RCT in patients with Stage 4 - 5 CKD concluded that a SVLPD (0.3 g/ kg/d) helped to postpone renal replacement therapy initiation [4% in SVLPD group compared with 27% in LPD (0.6 g/kg/day)] while preserving nutritional status.[148, level I] This was supported by another RCT where SVLPD preserved GFR, maintained body mass index and mid-arm circumference and increased serum albumin and total protein of CKD patients.[149, level I]

In patients with DKD (microalbuminuria and overt proteinuria), protein restriction of 0.8 - 1.0 g/kg/day may be considered. In a SR by Robertson L et al., LPD lowered albuminuria and was associated with a 73% reduction in risk of ESRD or death. In the same SR, one of the nine studies by Meloni C et al. in 2002 reported a reduction in serum albumin and pre-albumin with a protein intake of 0.6 g/kg/day.[142, level I]

VLPD (0.3 g/kg/day) with keto-acid supplementation may be considered in patients with CKD Stage 3 - 5 (pre-dialysis). To avoid malnutrition, the recommended dose of keto-acid should be used (1 tablet for every 5 kg body weight/day) and the patient should be carefully supervised by a dietitian (preferably renal-trained).

It is important to ensure adequate energy intake to prevent protein-energy malnutrition if protein restriction is prescribed.

B. Sodium restriction

Recommendation 13:

- Sodium restriction (total intake <2,400 mg/day) should be initiated in patients with chronic kidney disease. **(Grade C)**

The available evidence suggests that variations in dietary sodium consumption are directly correlated with albuminuria in which increasing sodium intake is associated with worsening albuminuria.[150, level II-2] A study by Cianciaruso B et al. demonstrated a slower progression of CKD with sodium restriction, but the groups within the study had

different baseline characteristics and diagnoses.[151, level II-2]

In general, sodium chloride added to food should not exceed 5 - 6 g/day (equivalent to 1 level teaspoon of salt) because there is naturally occurring sodium chloride in food and this may be particularly significant in processed foods.

Other dietary measures to address complications of CKD such as hyperkalaemia, hyperphosphataemia and nutritional deficiencies are beyond the scope of this CPG.

Refer to **Appendix 4** for Diet Plan and Menu Suggestion.

4.8 LIFESTYLE MODIFICATION

Recommendation 14:
- Patients with chronic kidney disease should be encouraged to exercise, reduce excess weight and avoid smoking. **(Grade B)**

Exercise[152, level III; 153, level I] and weight loss[154, level I] had been shown in some studies to retard the decline in renal function and reduce proteinuria. In some observational studies, smoking had been associated with decline in renal function and increase in proteinuria [11, level II-2; 23 - 24, level III; 155 - 156, level II-2; 157, level III] but this finding is not universal.[158, level II-2] Smoking cessation had been shown to slow progression of renal disease.[159, level II-1] However, there have been no RCT to show the impact of smoking cessation on progression of CKD. The effect of alcohol consumption on CKD has been variable. [24, level III; 155, level II-2; 160, level II-2; 161, level III] There is lack of evidence on the effectiveness of lifestyle modification in preventing hard renal or CV end-points. Nevertheless, it is prudent to adopt these lifestyle changes in patients with CKD.

4.9 SPECIAL PRECAUTIONS

CKD patients often have multiple medical problems and therefore may be exposed to agents with potential nephrotoxicity. Therefore, the following precautions should be taken:

1. Review all prescribed medication regularly to ensure dose is appropriate (refer to **Appendix 3**).
2. Avoid NSAIDs including COX-2 Inhibitors (such as mefenamic acid, diclofenac, ibuprofen, naproxen, indomethacin, ketoprofen, salicylic acid [high dose], meloxicam, celecoxib and etoricoxib).

3. Avoid radio-contrast agents if possible:
    - Patients undergoing contrast procedure should be assessed for risk of contrast-induced nephropathy. High risk patients are those with pre-existing renal impairment (serum creatinine ≥132 µmol/L or an eGFR <60 ml/1.73 m^2), DM, volume depletion, CCF, nephrotic syndrome, decompensated liver cirrhosis or concurrent NSAIDs/diuretic use.
    - Consider an alternative imaging study such as ultrasound, non-contrasted computerised tomography (CT) scan or magnetic resonance imaging (MRI). Gadolinium should be avoided in patients with advanced renal failure due to increased risk of nephrogenic systemic fibrosis.
    - Use non-ionic contrast media with low osmolarity (such as ioversol and iopamidol) or iso-osmolarity (such as iodixanol).
    - Use the lowest dose of contrast possible and avoid repeated studies within 48 hours.
    - Use isotonic saline or sodium bicarbonate peri-procedure with or without N-acetylcysteine.
4. Avoid using oral sodium phosphate (FLEET®) in bowel preparation for colonoscopy in CKD stage 4 - 5 due to increased risk of hyperphosphataemia. Use alternative preparations such as macrogol (FORTRANS®).

5. PREGNANCY

Recommendation 15:

- Pregnancy may be considered in women with chronic kidney disease (CKD) having mild renal impairment (serum creatinine <124 µmol/L) and well controlled blood pressure. **(Grade C)**
- Women with moderate to severe renal impairment should be counselled to avoid pregnancy due to greater adverse maternal and fetal outcomes. **(Grade C)**
- All pregnant women with CKD should be co-managed by a multidisciplinary team. **(Grade C)**

Pregnancy in women with CKD has varied maternal and fetal outcomes. The main concerns are the effect of pre-existing renal disease on pregnancy and the fetal outcome, and the effect of the pregnancy on the progression of CKD. These outcomes are related to the degree of renal impairment.

A number of observational studies have shown that pregnancy is relatively safe in women having mild renal impairment (serum creatinine <124 mmol/L) with well controlled blood pressure. In this subgroup, 92 to 96% of pregnancies resulted in live births and there was no deterioration in the long term maternal kidney function.[162, level III; 163 - 165, level II-2]

Pregnancy should be avoided in women with moderate to severe renal impairment (serum creatinine >124 mmol/L). Moderate and severe renal disease results in increased risk of adverse maternal and fetal outcomes. Maternal complications include accelerated decline in renal function, hypertension, proteinuria and pre-eclampsia while adverse fetal outcomes include greater fetal loss and pre-term birth. [162, level III; 166, level III] The maternal and fetal outcomes in women with moderate and severe CKD are shown in **Table 4**. However, the decision to allow continuation of pregnancy is individualised.

Table 4: Fetal and Maternal Outcomes in Women with Moderate and Severe CKD

Fetal Outcomes			Maternal Outcomes		
Prematurity %	Low Birth Weight/ Small for Gestational Age %	Spontaneous Abortion/ Neonatal Death %	Pre-eclampsia %	Irreversible Decline in GFR %	ESRD Within A Year %
17 - 90	19 - 64	6 - 47	40 - 60	20 - 50	2 - 35

Source:

1. Fischer MJ. Chronic kidney disease and pregnancy: maternal and fetal outcomes. Adv Chronic Kidney Dis. 2007 Apr;14(2):132-45
2. Williams D, Davison J. Chronic kidney disease in pregnancy. BMJ. 2008 Jan 6;336(7637):211-5

There is sparse literature about specific contraceptive use in the CKD population. The method of contraception used would depend mainly on the underlying cause of renal disease and the associated co-morbidities. The patient should be counselled about the risks and benefits of each method. Further information from the World Health Organization guidelines "Medical Eligibility Criteria for Contraceptive Use, 4th Edition", which can be accessed from http://whqlibdoc.who.int/publications/2009/9789241547710_eng.pdf

There is no retrievable evidence on referral for pregnant women with CKD. The general consensus is that all pregnant women with CKD should be co-managed by a multidisciplinary team comprising nephrologists/physicians and obstetricians. All women with CKD who intend to get pregnant should inform their doctors for preconception counselling. For the appropriate choice, dosing and safety of medications during pregnancy, refer to **Appendix 3**.

6. REFERRAL

Recommendation 16:

- A patient with chronic kidney disease (CKD) and any of the following criteria should be referred to a nephrologist/physician:
  - o heavy proteinuria (urine protein ≥1 g/day or urine protein: creatinine ratio (uPCR) ≥0.1 g/mmol) unless known to be due to diabetes and optimally treated
  - o haematuria with proteinuria (urine protein ≥0.5 g/day or uPCR ≥0.05 g/mmol)
  - o rapidly declining renal function (loss of glomerular filtration rate/GFR >5 ml/min/1.73m^2 in one year or >10 ml/min/1.73m^2 within five years)
  - o resistant hypertension (failure to achieve target blood pressure despite three antihypertensive agents including a diuretic)
  - o suspected renal artery stenosis
  - o suspected glomerular disease
  - o suspected genetic causes of CKD
  - o pregnant or when pregnancy is planned
  - o estimated GFR <30 ml/min or serum creatinine >200 µmol/L
  - o unclear cause of CKD. **(Grade C)**

Referral to a nephrologist is important to establish the diagnosis and formulate a plan of management for shared care to retard progression of CKD. The nephrologist would also monitor and manage the complications of CKD and plan for timely initiation of renal replacement therapy. Jones C et al. reported that following nephrology referral, there was a significantly slower decline in GFR and a 45% reduction in mortality.[167, level III] In another study, Chen SC et al. showed that nephrology referral was the most significant factor associated with retardation of renal disease progression.[168, level III] In fact, appropriate referral is associated with reduced hospitalisation, decreased patient morbidity and mortality, timely preparation of dialysis access and reduced cost of care.[169] A recent meta-analysis of cohort studies had shown that timing of referral was a significant factor affecting mortality.[170, level II-2]

There is no clear evidence to recommend indications for referral to nephrologist. Nevertheless, several published guidelines have suggested various criteria for referral as shown in the recommendation box above.[49; 71; 110; 169; 171]

Immediate referral is indicated in patients with:

- Acute renal failure superimposed on CKD
- Newly detected ESRD (GFR <15 ml/min/1.73m^2)
- Accelerated or malignant hypertension
- Hyperkalaemia (serum potassium >7 mmol/l)
- Suspected glomerulonephritis

- **Clinical tip 1**: Patients with CKD and renal outflow obstruction should be referred to urological services unless urgent medical intervention is required.
- **Clinical tip 2**: When referring to a nephrologist, ensure patient has a recent renal ultrasound, current blood chemistry and proteinuria quantified.

7. IMPLEMENTING THE GUIDELINES

It is a huge challenge to healthcare policy makers to meet the rising needs of Renal Replacement Therapy for ESRD patients as this is a heavy burden on healthcare resources. It is therefore crucial for all health care personnel to understand the implications of non or late screening of high risk groups and of progressive CKD.

A. Existing Facilitators and Barriers

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

1. Pre-existing Kidney Care Programme (www.msn.org.my)
2. Extensive networking of nephrologists nationwide
3. Availability of related CPGs in hardcopy and softcopy (online)
4. Active involvement of local NGOs in screening and educational activities.

Existing barriers for application are:

1. Poor understanding/limited knowledge of the issues at stake
2. Inadequate training of the healthcare providers
3. Insufficient resources in the management of CKD
4. Lack of coordination between primary and secondary/tertiary health care
5. Lack of CKD database for planning of services.

B. Potential Resource Implications

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

1. Ensure widespread distribution of the CPG to health care personnel via printed copies, electronic websites, etc.
2. Re-enforce training of health care personnel by regular seminars or workshops to ensure information is made available
3. Develop multidisciplinary teams at hospital and community level to include involvement of specialists, primary care doctors, medical officers, pharmacists, dietitians and nurse educators
4. Ensure screening and monitoring facilities are available at all sites
5. Ensure availability of the drugs mentioned in the CPG
6. Develop coordinated linkage between specialists and primary health care teams to facilitate referral and management
7. Have a national database of CKD
8. Ensure widespread distribution of patient education materials.

A study to determine the prevalence of CKD in the population will be carried out in the country in 2011 under the Institute for Public Health/ National Morbidity Health Survey. This will enable health policy makers to estimate resource and cost implications for the future.

A central committee should be established to look at all these issues and liaise with state health services to ensure that all steps are taken to apply the recommendations stipulated in the CPG. A quick reference and a training module that will be developed based on the CPG by the DG should be utilised by all the healthcare personnel.

Clinical audit indicators for quality management proposed are:

- Percentage of diabetes patients screened for proteinuria/ microalbuminuria = $\frac{\text{Number of diabetes patients screened for proteinuria within a year}}{\text{Total number of diabetes patients on follow-up in the same period}} \times 100\%$
- 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 = $\frac{\text{Number of diabetic CKD patients with BP <130/80 within a year}}{\text{Total number. of diabetic CKD patients in the same period}} \times 100\%$
- Percentage of non-diabetic CKD patients with BP <140/90 = $\frac{\text{Number of non-diabetic CKD patients with BP <140/90 within a year}}{\text{Total number of non-diabetic CKD patients in the same period}} \times 100\%$
- Percentage of patients with hypertension and proteinuria receiving treatment with ACEi or ARB = $\frac{\text{Number of patients with hypertension and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of hypertension and proteinuria in the same period}} \times 100\%$
- Percentage of patients with diabetes and proteinuria receiving treatment with ACEi or ARB = $\frac{\text{Number of patients with diabetes and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of diabetes and proteinuria in the same period}} \times 100\%$

Once the actual scope of the problem is known the resources required for manpower, training, screening, etc. can be more clearly identified. Health policy makers will be better informed to ensure these resources including financial requirements are made available to all involved.

Meanwhile screening of high risk groups for proteinuria (refer to **Algorithm 1** and **Algorithm 2**) and the importance of BP control to retard progression of CKD must continue to be emphasised to healthcare personnel and the general public.

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Appendix 1

SEARCH TERMS

The following MeSH terms or free text terms were used either singly or in combination:

"Kidney Failure, Chronic"[Mesh], "chronic kidney disease", "chronic renal disease", "chronic renal failure", CKD, "Risk Factors"[Mesh], "metabolic syndrome", "Proteinuria"[Mesh], "Albuminuria"[Mesh], screen, screening, "albumin creatinine ratio", "protein creatinine ratio", "Hematuria"[Mesh], haematuria, dipstick, urinalysis, "Ultrasonography"[Mesh], "renal ultrasonography", "kidney ultrasonography", ultrasound, "renal ultrasound", "kidney ultrasound", "Glomerular Filtration Rate"[Mesh], GFR, test, "Kidney Function Tests"[Mesh], "Creatinine"[Mesh], "Cystatin C"[Mesh], "Classification"[Mesh], staging, cost-effective, cost-effectiveness, treatment, therapy, drug, agent, medication, "Blood Pressure"[Mesh], BP, "target blood pressure", "optimal blood pressure", "blood pressure threshold", "blood pressure range", "blood pressure control", "blood pressure aim", "Antihypertensive Agents"[Mesh], antihypertensive, anti-hypertensive, "blood pressure lowering", microalbuminuria, macroalbuminuria, reduce, reduction, regress, regression, normalization. normalisation, control, sulodexide, "Glycosaminoglycans"[Mesh], "paricalcitol "[Substance Name], "target proteinuria", prevent, "prevention and control "[Subheading], progress, "Disease Progression"[Mesh], "Angiotensin-Converting Enzyme Inhibitors"[Mesh], ACEi, "angiotensin receptor blocker", "Angiotensin II Type 1 Receptor Blockers"[Mesh], ARB, AIIRA, "A II receptor blocker", "Angiotensin Receptor Blocker", function, "renal function", profile, "renal profile", "renal parameter", "glycaemic control", "glucose control", "glycaemic target", "glucose target", intensive, "Hemoglobin A, Glycosylated"[Mesh], "optimal HbA1c", HbA1c, nephropathy, "diabetes nephropathy", "cardiovascular mortality", "complications "[Subheading], hyperlipidaemia, "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh], statin, "HMG CoA reductase inhibitor", antilipid, anti-lipid, antilipemic, antihyperlipemic. antihyperlipidemic, antihypercholesterolemia, antihypercholesterolaemic, "lipid lowering", "lipid reducing", "cholesterol lowering", "cholesterol reducing", antiplatelet, "Platelet Aggregation Inhibitors"[Mesh], antithrombotic, "Diet"[Mesh], "Diet, Sodium-Restricted"[Mesh]. "low sodium", "reduced sodium" "natrium restricted", "low natrium", "reduced natrium", "salt restricted", "low salt", "reduced salt", "Diet, Protein-Restricted"[Mesh], "low protein", "reduced protein", "hypoproteic diet", "Keto Acids"[Mesh], "keto amino acid", ketoanalogs, keto-analogues, ketosteril, "Life Style"[Mesh], "Smoking"[Mesh], "Obesity"[Mesh], "Exercise"[Mesh], "Weight Loss"[Mesh], "Alcohols"[Mesh], "alcohol cessation", "Referral and Consultation"[Mesh], referral*, "hospital referral", "Pregnancy"[Mesh]

Appendix 2

CLINICAL QUESTIONS

1. Screening

i. Who are at high risk of developing chronic kidney disease?
ii. Who should be screened for chronic kidney disease?
iii. What methods should be used for screening chronic kidney disease?
- urine dipstick
- urine protein/albumin: creatinine ratio
- time urine collection

iv. What methods should be used to assess renal function?
- serum creatinine
- 24-hour urine creatinine clearance
- prediction equation such as MDRD and Cockcroft-Gault
- serum cystatin C

2. Treatment

i. What are the effective interventions in slowing down the progression of chronic kidney disease?
- blood pressure reduction
- ACE inhibitors
- combination of ACE inhibitors and angiotensin receptor blockers
- weight reduction
- exercise
- aldosterone antagonist
- sulodexide
- diabetic control
- smoking cessation
- calcium channel blockers
- salt restriction
- lipid lowering
- angiotensin receptor blockers
- renin inhibitors
- proteinuria reduction
- protein restriction

ii. What are the effective interventions in reducing the risk of CVD in CKD?
- as above
- aspirin

iii. What are the common complications associated with progressive chronic kidney disease? (renal bone disease and anaemia)
iv. How should a pregnant patient with CKD be managed?

3. Referral

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

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 (such as myopathy).						
Atorvastatin	10 – 80 mg od	No dosage adjustment necessary				X
Fluvastatin	20 – 80 mg od	No dosage adjustment necessary		50%		X
Lovastatin	20 – 80 mg od	No dosage adjustment necessary	50%	50%		X
Pravastatin	10 – 40 mg od	No dosage adjustment necessary				X
Rosuvastatin	5 – 40 mg od	No dosage adjustment necessary		Avoid		X
Simvastatin	20 – 80 mg od	No dosage adjustment necessary		50%		X
Fibric acid derivatives						
Fenofibrate	145 – 300 mg od (depends on formulations)	50%	25%	15 – 30: 25% <15: Avoid	May increase serum creatinine	C
Gemfibrozil	600 mg bd	No dosage adjustment necessary				C
Cholesterol absorption inhibitor						
Ezetimibe	10 mg od	No dosage adjustment necessary				C
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	1.25 – 5 mg od	No dosage adjustment necessary		<10: 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)		
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%	15 – 30: 50% <15: Avoid	Serum potassium needs to be monitored	B
Spironolactone	25 – 100 mg/day in 1 – 2 doses	q12h	q12 – 24h	15 – 30: q12 – 24h <15: Avoid		C
Sulfonylureas Sulfonylureas should be used cautiously because increase 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				*ADEC–C
Glibenclamide	5 – 10 mg od	Use with caution	Avoid			C
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, increase risk of lactic acidosis.						
Metformin	500 – 1,000 mg bd	50%	Avoid	Avoid		B
Meglitinides						
Repaglinide	0.5 – 4 mg tds	No dosage adjustment necessary				C
Nateglinide	120 mg tds	Initiate at low dose, 60 mg before each meal		15 – 30: Initiate at low dose, 60 mg before each meal <15: 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)		
				15 – 30: Initiate at low dose, 60 mg before each meal <15: Avoid		
Thiazolidinediones						
Pioglitazone	15 – 30 mg od	No dosage adjustment necessary			May worsen fluid retention	C
Incretin mimetic						
Exenatide	5 – 10 mcg bd	100%	50 – 100% Dose escalation from 5 – 10 mcg should proceed conservatively	Avoid (increase frequency and severity of GI side effects)		C
Liraglutide	Starting dose: 0.6 mg SC od x 1 week Maintainence dose: 1.2 – 1.8 mg SC od	100%	(limited data)	(limited data)		C
DPP-4 inhibitor						
Sitagliptin	100 mg od	100%	50%	25%		B
Vildagliptin	50 mg od – bd	100%	(limited data)	(limited data)		-
Saxagliptin	2.5 – 5 mg od	100%	2.5 mg od	2.5 mg od		B
Insulin Doses should be adjusted based on frequent monitoring to balance goals of glycaemic control with avoiding hypoglycaemia.						
Antiamoebic						
Metronidazole	200 – 400 mg q8 - 12h	No dosage adjustment necessary		15 – 30: No dosage adjustment necessary <15: 50%		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)		
Antifungal						
Fluconazole	200 – 400 mg q24h	No dosage adjustment necessary	50%	50%		C
Itraconazole	100 – 200 mg q12h	No dosage adjustment necessary		15 – 30: No dosage adjustment necessary <15: 50%		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: q12h	High doses can cause encepha-lopathy	B
	800mg q4h (herpes zoster)	No dosage adjustment necessary		15 – 30: q8h <15: q12h		
Oseltamivir	75 mg q12h	No dosage adjustment necessary		10 – 30: 75 mg q24h <10: No recommendation		C
Cephalosporin						
Cefaclor	250 – 500 mg q8h	100%	50 – 100%	15 - 30: 50 – 100% <15: 50%		B
Ceftibuten	400 mg q24h	100%	50%	15 – 30: 50% <15: 25%		B
Cefuroxime axetil	250 – 500 mg q12h	No dosage adjustment necessary				B
Cephalexin	250 – 500 mg q6h	q8h	q12h	q12h		B
Fluoroquinolone						
Ciprofloxacin	500 – 750 mg q12h	100%	50 – 75%	15 – 30: 50 – 75% <15: 50%		C
Levofloxacin	500 mg q24h	100%	250 mg q24 – 48h (500 mg initial dose)	15 – 30: 250 mg q24 – 48h (500 mg initial dose) <15: 250 mg q48h (500 mg initial dose)		C
Moxifloxacin	400 mg q24h	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)		
Norfloxacin	400 mg q12h	q12h	q12 – 24h	15 – 30: q12 – 24h <15: q24h		C
Ofloxacin	200 – 400 mg q12h	100%	200 – 400 mg q24h	15 – 30: 200 – 400 mg q24h <15: 200 mg 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%	75%	15 – 30: 75% <15: 50 – 75%		C
Erythromycin	(ethylsuccinate) 400 mg q6h or 800 mg q12h (stearate) 250 mg q6h or 500 mg q12h	100%	100%	15 – 30: 100% <15: 50 – 75%		B
Nitrofuran						
Nitrofurantoin	50 – 100 mg q6h	No dosage adjustment necessary	Avoid	Avoid		B
Penicillin						
Amoxicillin	250 – 500 mg q8h	q8h	q8 – 12h	15 – 30: q8 – 12h <15: q24h		B
Amoxicillin + Clavulanic Acid (Augmentin)	625 mg q12h	No dosage adjustment necessary		15 – 30: No dosage adjustment necessary <15: 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 – 30: q12h <15: q24h		B
Cloxacillin	250 – 500 mg q6h	No dosage adjustment necessary				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 V / Phenoxymethyl-penicillin	250 – 500 mg q6h	No dosage adjustment necessary				B
Sulfonamide + Trimethoprim						
Trimethoprim	100 mg q12h	No dosage adjustment necessary		15 – 30: q18h <15: q24h	<30 ml/min: Close monitoring of blood count	C
Sulfamethoxazole + Trimethoprim	960 mg q12h	Normal dose up to 960 mg q12h for 14 days, then up to 960 mg/day		15 – 30: q18h <15: q24h		C
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	15 – 30: q12 – 24h <15: Avoid		D

* ADEC: Australian Drug Evaluation Committee Pregnancy Category

Disclaimer:
The medication dosage adjustment listed should be used as general guide only and does not intend to be comprehensive.
The dosing guide for GFR <10 ml/min does not provide information on dosing in haemodialysis, peritoneal dialysis or continuous renal replacement therapy patients.
The Cockcroft-Gault equation was used to estimate the renal function.

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 (egg, life-threatening situations or serious disease 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.

Australian Drug Evaluation Committee (ADEC)
Pregnancy Categories

CATEGORY	DESCRIPTION
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals haven not shown evidence of an increased occurrence of fetal damage.
B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus giving been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Sources:

1. Aronoff GR, Berns JS, Brier ME et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults (Fourth Edition). Philadelphia: American College of Physicians; 1999
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4. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) Guidelines and Commentaries (internet communication, 1 November 2010 at http://www.kidney.org/professionals/kdoqi/guidelines_commentaries.cfm#guideline)
5. Leong WF, Evanglista LF, Romano MB et al (Ed). MIMS.com. 123rd Edition 2010. Hong Kong; CMPMedica: 2010
6. Product package insert

Appendix 4

DIET PLAN AND MENU SUGGESTION

Diet Plan for CKD (1,800 kcal)
60 kg adult: 1,800 kcal/day, 36 g/day @ 0.6 g/kg/day protein, 1 - 3 g sodium

- Carbohydrates = 1,800 x 56% = 1,008 kcal = 252 g (17 exchanges)
- Protein = 1,800 x 8% = 144 kcal = 36 g (5 exchanges)
- Fat = 1,800 x 33% = 648 kcal = 72 g (15 exchanges)

Nutrient Distribution

Food Group	Exc.	Carbohydrates (g)	Protein (g)	Fat (g)	Total Calorie (kcal)
Starch	9	135	18	4.5	675
Fruits	3	45	-	-	180
Skimmed milk	½	7.5	4	-	45
Meat	1	-	7	4	65
Fish	1	-	7	1	35
Fat	15	-	-	75	675
Total (g)		187.5 g	36 g	84.5 g	-
Total (kcal)		750 kcal	144 kcal	761 kcal	1,675 kcal
Total (%)		45 %	9 %	46 %	-

Servings Distribution

Food Group	Exc.	Breakfast (BF)	Lunch (L)	Afternoon Tea (AT)	Dinner (D)
Starch	9	3	3	1	2
Fruits	3	1	1	-	1
Skimmed milk	½	½	-	-	-
Meat	1	-	1	-	-
Fish	1	-	-	-	1
Fat	15	4	4	3	4

Sample Menu for CKD (1,800 kcal/day)

Meal	Food Item	Household Measurement
Breakfast	Sandwich (vegetables)	
	Bread	3 slices (90 g)
	Soft margarine (low salt)	4 teaspoons (20 g)
	Cucumber, tomato	4 slices (4 g)
	Apple	1 medium (110 g)
	Coffee with skimmed milk	½ teaspoon (1 g)
		1½ tablespoons skimmed milk (11 g)
Lunch	White rice	1½ cup (150 g)
	Chicken stir-fried	1 matchbox (30 g)
	Chinese cabbage stir-fried	1 cup (50 g)
	Cooking oil	4 teaspoons (20 g)
	Pear	1 medium (110 g)
Afternoon Tea	Fried popiah (carrot, bean sprouts, yam-bean/*sengkuang*)	1 piece (50 g)
	Cooking oil	3 teaspoons (15 g)
	Plain tea	1 tea bag
Dinner	White rice	1 cup (100 g)
	Fried pomphret (*bawal*) coated with corn flour	1 matchbox (30 g)
	Mustard leaves (*sawi*) stir-fried	1 cup (50 g)
	Cooking oil	4 teaspoons (20 g)
	Guava	½ whole big (150 g)

Approximate Nutrient Analysis

Energy (kcal)	1,610	Iron (mg)	11
Protein (g)	36	Thiamin (mg)	1.54
Carbohydrate (g)	197	Riboflavin (mg)	1.50
Fat (g)	75	Niacin (mg)	13
Sodium (mg)	995	Vitamin A (RE)	150
Potassium (mg)	982	Vitamin C (mg)	318
Phosphorus (mg)	413	Dietary Fiber (g)	15
Calcium (mg)	560		

Source:

1. Malaysian Dietitian Association, Medical Nutrition Therapy Guidelines for Chronic Kidney Disease. Kuala Lumpur: MDA; 2005.
2. Tee ES, Ismail MN, Mohd. Nasir A et al. Nutrient Composition of Malaysian Foods. 4th Edition. Kuala Lumpur; Institute for Medical Research: 1997

LIST OF ABBREVIATIONS

AA	Aldosterone Antagonist
ACEi	Angiotensin-Converting Enzyme Inhibitor
ACR	Albumin: Creatinine Ratio
ARB	Angiotensin Receptor Blocker
bd	Twice Daily
BP	Blood Pressure
CCB	Calcium Channel Blocker
CCF	Congestive Cardiac Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CPG	Clinical Practice Guidelines
CrCl	Creatinine Clearance
CV	Cardiovascular
CVD	Cardiovascular Disease
DG	Development Group
DHP	Dihyhdopyridine
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
EOD	Every Other Day
ESRD	End-Stage Renal Disease
Exc.	Exchange
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
LPD	Low Protein Diet
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
MOH	Ministry of Health
NDHP	Non-Dihydropyridine
NKF-KDOQI	National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSTEMI	Non-ST Elevation Myocardial Infarction
od	Once Daily
PCR	Protein: Creatinine Ratio
PMP	Per Million Population
q6h	Every 6 Hours
q8h	Every 8 Hours
q12h	Every 12 Hours
q24h	Every 24 Hours
QALY	Quality-Adjusted Life Year
RAAS	Renin-Angiotensin-Aldosterone System
RC	Review Committee
RR	Relative Risk
RCT(s)	Randomised Controlled Trial(s)
SBP	Systolic Blood Pressure
SC	Subcutaneous
SR	Systematic Review

SVLPD	Very Low Protein Diet Supplemented With Keto-acid
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
tds	Thrice Daily
uPCR	Urine Protein: Creatinine Ratio
US FDA	United States Food and Drug Administration
UTI	Urinary Tract Infection
VLPD	Very Low Protein Diet
vs	Versus

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Health Technology Assessment Section,
Medical Development Division
Ministry of Health Malaysia,
4th Floor, Block E1,
Parcel E, 62590 Putrajaya
Tel : 603-8883 1246
E-mail : htamalaysia@moh.gov.my