MANAGEMENT OF CHRONIC KIDNEY DISEASE IN ADULTS
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.

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Electronic version available on the following website:
http://www.moh.gov.my
http://www.acadmed.org.my
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### LEVELS OF EVIDENCE

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<td>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</td>
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<td>III</td>
<td>Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees</td>
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**SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE**

### GRADES OF RECOMMENDATION

<table>
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<th>Description</th>
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<tr>
<td>A</td>
<td>At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population</td>
</tr>
<tr>
<td>B</td>
<td>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</td>
</tr>
<tr>
<td>C</td>
<td>Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality</td>
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**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

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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.

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


Urine dipstick for protein

(a) Type 1: after 5 years history of diabetes or earlier in the presence of other cardiovascular risk factors
(b) Type 2: at time of diagnosis

NEGATIVE

POSITIVE on 2 occasions
(Urine protein >300 mg/l)
(exclude other causes such as urinary tract infection (UTI), congestive cardiac failure (CCF), others)

Overt nephropathy

NEGATIVE

Screen for microalbuminuria on early morning spot urine

POSITIVE

Quantify proteinuria

NEGATIVE

Retest twice in 3 - 6 months
(exclude other causes such as UTI, CCF, others)

Yearly test for microalbuminuria and renal function

• If 2 of 3 tests are positive, diagnosis of diabetic nephropathy is established
• Quantify microalbuminuria
• 3 - 6 monthly follow-up of microalbuminuria

• Check renal function
• Exclude other nephropathies
• Perform ultrasound if indicated (refer to Section 2.5)
ALGORITHM 2: SCREENING AND INVESTIGATIONS FOR CKD IN PATIENTS WITHOUT DIABETES

Risk factors for CKD:
- Hypertension
- >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

Check urine using dipstick (refer to Section 2.2)

Proteinuria / haematuria on 2 out 3 occasions

No

Yearly urine testing and renal function (refer to Section 2.4)

Yes

- Quantify proteinuria
- Check renal function (refer to Section 2.4)
- Perform ultrasound if indicated (refer to Section 2.5)
**ALGORITHM 3: TREATMENT FOR CHRONIC KIDNEY DISEASE**

**Diagnosis of CKD**

- **Diabetic Kidney Disease**
  - Optimise glycaemic control
  - Strict BP control
  - Angiotensin-Converting Enzyme Inhibitor (ACEi) /Angiotensin Receptor Blocker (ARB)

- **Non-Diabetic Kidney Disease**
  - Hypertension (BP >140/90 mmHg)
    - Yes
      - Proteinuria (>0.5 g/day)
        - Yes
          - Any antihypertensive to achieve target BP
        - No
          - ACEi/ARB preferred
            - NDHP CCB
      - No
    - No

**General measures in the management of CKD**

- Encourage exercise, weight reduction & smoking cessation
- Restrict sodium intake to <2,400 mg/day
- Avoid excessive protein intake
- Identify other end-organ damage of diabetes and hypertension
- Manage cardiovascular risks including dyslipidaemia
- Monitor renal profile according to individual patient’s characteristics (baseline renal function, risk factors for CKD progression and specific treatment given)
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%. 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. 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. 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. 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.

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. The number of metabolic syndrome components was proportional to the prevalence of CKD and negatively correlated to estimated glomerular filtration rate (eGFR). There was also a significant association of metabolic syndrome and the risk of CKD in subjects without diabetes and hypertension.

D. **Age**
People aged >65 years old have an increased risk of renal impairment and decline in renal function.

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.

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.

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. 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. 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.

H. **Other Risk Factors**
Other possible risk factors include autoimmune disease, nephrolithiasis, low birth weight of <2,500g, central obesity, smoking, low socioeconomic status, anaemia, hyperuricaemia, nocturia, and physical inactivity. Certain herbal products including those containing aristolochic acid had also been associated with CKD.
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**

<table>
<thead>
<tr>
<th>Increases protein excretion</th>
<th>Decreases protein excretion</th>
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<tbody>
<tr>
<td>• Strenuous exercise</td>
<td>• ACEi/ARB</td>
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<tr>
<td>• Poorly controlled DM</td>
<td>• NSAIDs</td>
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<tr>
<td>• Heart failure</td>
<td></td>
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<td>• UTI</td>
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<tr>
<td>• Acute febrile illness</td>
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<tr>
<td>• Uncontrolled hypertension</td>
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<td>• Haematuria</td>
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<tr>
<td>• Menstruation</td>
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<td>• Pregnancy</td>
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Source:

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Urine dipstick reading</th>
<th>Urine PCR in mg/mmol</th>
<th>Urine total protein excretion in g/24 hour</th>
<th>Urine ACR in mg/mmol</th>
<th>Urine albumin excretion in mcg/min (mg/24 hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Negative</td>
<td>&lt;15</td>
<td>&lt;0.15</td>
<td>&lt;2.5 (male) &lt;3.5 (female)</td>
<td>&lt;20 (&lt;30)</td>
</tr>
<tr>
<td>“Trace” protein</td>
<td>Negative</td>
<td>&lt;15</td>
<td>&lt;0.15</td>
<td>≥2.5 to 30 (male) ≥3.5 to 30 (female)</td>
<td>20 - 200 (30 - 300)</td>
</tr>
<tr>
<td>(Microalbuminuria)</td>
<td>Trace 15 - 44</td>
<td>0.15 - 0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt proteinuria</td>
<td>1+ 45 - 149</td>
<td>0.45 - 1.49</td>
<td></td>
<td>&gt;30</td>
<td>&gt;200 (&gt;300)</td>
</tr>
<tr>
<td>(Macroalbuminuria)</td>
<td>2+ 150 - 449</td>
<td>1.50 - 4.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3+ ≥450</td>
<td>≥4.50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(^{13, \text{level III; 32, level II-2}}\) and therefore should be evaluated.

Urine dipsticks have 98% sensitivity\(^{33, \text{level III}}\) and are commonly used for detecting haematuria. However a single positive dipstick test is not sufficient to indicate pathology.\(^{34, \text{level III}}\) 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.\(^{35, \text{level III}}\)

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.\(^{36, \text{level III}}\)

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.\(^{37, \text{level II-2}}\)
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

<table>
<thead>
<tr>
<th>Recommendation 4:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Renal function should be assessed with estimated Glomerular Filtration Rate (eGFR) based on the 4-variable MDRD*. (Grade C)</td>
</tr>
<tr>
<td>• Serum creatinine should be used in combination with eGFR in the assessment of renal function. (Grade C)</td>
</tr>
<tr>
<td>• Laboratories should provide automated eGFR estimation in addition to serum creatinine. (Grade C)</td>
</tr>
<tr>
<td>• When eGFR is not available, other methods of estimation may be used. (Grade C)</td>
</tr>
</tbody>
</table>

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/1.73m², consider a rise of 20% in serum creatinine as a significant indicator of reduction in renal function.
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. However, the MDRD equation may be inaccurate when the GFR rate was greater than 60 ml/min/1.73m². 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. 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.
Equations for estimation of renal function:

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

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

iii. **Cockcroft-Gault Creatinine Clearance**
   \[
   \text{CrCl (ml/min)} = \frac{(140 - \text{age (yrs)}) \times \text{body weight (kg)}}{\text{sCr (µmol/l)} \times \text{Constant where the constant is 1.23 in male or 1.04 in female}}
   \]

**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.\(^{48, \text{level III}}\)

**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/1.73m² 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**

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Normal or increased GFR, with other evidence of kidney damage</td>
</tr>
<tr>
<td>2</td>
<td>60 - 89</td>
<td>Slight decrease in GFR, with other evidence of kidney damage</td>
</tr>
<tr>
<td>3A</td>
<td>45 - 59</td>
<td>Moderate decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>3B</td>
<td>30 - 44</td>
<td>Moderate decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>4</td>
<td>15 - 29</td>
<td>Severe decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Established renal failure</td>
</tr>
</tbody>
</table>

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

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/1.73m², 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. 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. 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.
The degree of proteinuria reduction achieved also correlates with the degree of CKD retardation and CVD mortality reduction.\textsuperscript{61 - 66, level I} Lowering BP can reduce proteinuria to some extent.\textsuperscript{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.\textsuperscript{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.\textsuperscript{69, level I} However, in a meta-analyses of 7,603 patients with normoalbuminuria, ACEi reduced the development of DKD by 42%.\textsuperscript{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).\textsuperscript{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.\textsuperscript{73, level I} There was also no benefit of ACEi use for non-diabetic CKD with hypertension if proteinuria <0.5 g/day.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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.

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.

A meta-analysis showed an additional 30 - 39% reduction in proteinuria comparing combination of ACEi and ARB group to monotherapy. 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.
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.\textsuperscript{82, level III}

**D. Aldosterone Antagonist (AA)**

Plasma aldosterone level has been shown to correlate with the rate of progression of kidney disease.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
  - in patients with proteinuria ≥1 gram/day. (Grade A)
  - 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\textsuperscript{96, level I} or by targeting SBP<120 for the CKD population in the AASK study.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{96, level I} patients with DKD\textsuperscript{98, level II-2} or in elderly patients with CKD stage 3 - 4.\textsuperscript{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.\textsuperscript{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’.\textsuperscript{102, level I} However, these findings were not reproduced in the PRoFESS study.\textsuperscript{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.\textsuperscript{96, level I}

In the general CKD population, several large-scale studies showed no significant difference in decline in GFR,\textsuperscript{60, level I; 104 - 105, level I} or in progression to ESRD\textsuperscript{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).\textsuperscript{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.\textsuperscript{107, level II-2} There was a non-significant difference in risk for this combined endpoint 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,\textsuperscript{108, level I} the benefit of antihypertensive treatment was significant only in patients with an entry SBP ≥140 mmHg. Similar findings were obtained when stratification was based on the presence or absence of a history of hypertension.\textsuperscript{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
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. 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.

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. 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.

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%.

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.
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. If renal function remains stable within these limits, ACEi/ARB may be titrated until BP goal and optimal antiproteinuric targets are achieved.

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:

- 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 HbA1c 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. Lowering HbA1c to approximately 6.5% to 7% reduces the development of micro- and macroalbuminuria. The effect of intensive blood glucose control and BP lowering is independent and additive for reducing the risk of new or worsening nephropathy. However, aggressive glycaemic control in patients with established CVD has been shown to increase the risks of hypoglycaemia and death. 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 HbA1c values without a change to glycemic control in patients with DM and CKD. HbA1c 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.\(^\text{121}\) - \(^\text{122}\), level I; 130, level I Three post hoc analyses showed no significant difference between statin (lovastatin, pravastatin, atorvastatin) and comparators,\(^\text{124}\) - \(^\text{125}\), 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.\(^\text{120}\), level I

In contrast, Huskey J et al. demonstrated reduction in GFR was significantly lower in patients on simvastatin compared to patients on placebo.\(^\text{128}\), 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.\(^\text{123}\), 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.\(^\text{129}\), level I

ii. Changes in proteinuria

Three meta-analyses showed that statin treatment significantly reduced protein excretion compared to placebo.\(^\text{121}\) - \(^\text{122}\), level I; 132, level I However, significant heterogeneity was found in two of the meta-analyses.\(^\text{121}\) - \(^\text{122}\), 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.\(^\text{123}\), level II-1; 130, level I

B. Antiplatelet Agent

<table>
<thead>
<tr>
<th>Recommendation 11:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aspirin should be used in patients with chronic kidney disease (CKD) for secondary prevention of cardiovascular disease. (Grade B)</td>
</tr>
<tr>
<td>• Combination of clopidogrel with aspirin should be avoided in patients with CKD unless compelling indications are present. (Grade B)</td>
</tr>
</tbody>
</table>

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%, ischaemic strokes by 22% and total mortality by 10%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. \(^{141, \text{level I}}\)

### 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. \(^{142, \text{level I}}\)

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. \(^{143, \text{level I}}\)

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. \(^{144, \text{level I}}\)

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. \(^{145, \text{level I}}\) 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)

Exercise152, level III; 153, level I and weight loss154, 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 m²), 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

<table>
<thead>
<tr>
<th>Fetal Outcomes</th>
<th>Maternal Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity %</td>
<td>Low Birth Weight/ Small for Gestational Age %</td>
</tr>
<tr>
<td>17 - 90</td>
<td>19 - 64</td>
</tr>
</tbody>
</table>

Source:
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:
  - 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
  - haematuria with proteinuria (urine protein ≥0.5 g/day or uPCR ≥0.05 g/mmol)
  - rapidly declining renal function (loss of glomerular filtration rate/GFR >5 ml/min/1.73m² in one year or >10 ml/min/1.73m² within five years)
  - resistant hypertension (failure to achieve target blood pressure despite three antihypertensive agents including a diuretic)
  - suspected renal artery stenosis
  - suspected glomerular disease
  - suspected genetic causes of CKD
  - pregnant or when pregnancy is planned
  - estimated GFR <30 ml/min or serum creatinine >200 µmol/L
  - unclear cause of CKD.

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
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**

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

- **Percentage of diabetes patients screened for proteinuria**

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

- **Percentage of diabetic CKD patients with BP <130/80**

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

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

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

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

  \[ \text{Percentage} = \frac{\text{Number of patients with hypertension and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of hypertension and proteinuria in the same period}} \times 100\% \]

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

  \[ \text{Percentage} = \frac{\text{Number of patients with diabetes and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of diabetes and proteinuria in the same period}} \times 100\% \]
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.
REFERENCES


41


SEARCH TERMS

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


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
      - 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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dose</th>
<th>Dose Adjustment in Renal Failure</th>
<th>Note</th>
<th>US FDA Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild (GFR 60-90 ml/min)</td>
<td>Moderate (GFR 30-59 ml/min)</td>
<td>Severe (GFR &lt;30 ml/min)</td>
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<tr>
<td><strong>HMG-CoA reductase inhibitors</strong></td>
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<tr>
<td>Atorvastatin</td>
<td>10 – 80 mg od</td>
<td>No dosage adjustment necessary</td>
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<td></td>
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<tr>
<td>Fluvastatin</td>
<td>20 – 80 mg od</td>
<td>No dosage adjustment necessary</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
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<td>No dosage adjustment necessary</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10 – 40 mg od</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5 – 40 mg od</td>
<td>No dosage adjustment necessary</td>
<td>Avoid</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20 – 80 mg od</td>
<td>No dosage adjustment necessary</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td><strong>Fibric acid derivatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>145 – 300 mg od (depends on formulations)</td>
<td>50%</td>
<td>25%</td>
<td>15 – 30: 25% &lt;15: Avoid</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>600 mg bd</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>10 mg od</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazide diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5 – 50 mg od</td>
<td>No dosage adjustment necessary</td>
<td>&lt;10: Avoid</td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>500 – 1000 mg/day in 1 – 2 doses</td>
<td>No dosage adjustment necessary</td>
<td>&lt;10: Avoid</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>12.5 – 50 mg od</td>
<td>No dosage adjustment necessary</td>
<td>&lt;10: Avoid</td>
<td></td>
</tr>
<tr>
<td>Indapamide</td>
<td>1.25 – 5 mg od</td>
<td>No dosage adjustment necessary</td>
<td>&lt;10: Avoid</td>
<td></td>
</tr>
</tbody>
</table>

*Statin should be started at low dose and titrated upwards in order to minimise the adverse effects (such as myopathy).*

*May increase serum creatinine*

*Thiazide diuretics are unlikely to be of use once GFR <30 ml/min*
### Management of Chronic Kidney Disease in Adults

**Sulfonpyrazone**

Sulfonpyrazone should be used cautiously because it increases the risk of hypoglycemia. First-generation sulfonylureas, generally, should be avoided. Due to increased half-life and risk of hypoglycemia in patients with CKD, glinides 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.

### Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Loop diuretics</th>
<th>Potassium sparing diuretics</th>
<th>Sodium channel inhibitors</th>
<th>Alpha-glucosidase inhibitors</th>
<th>Meglitinides</th>
<th>Repaglinide</th>
<th>Nateglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>0.5 – 4 mg/day in 2 – 3 doses</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide</td>
<td>40 – 240 mg/day in 2 – 3 doses</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>5 – 10 mg/day in 1 – 2 doses</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25 – 100 mg/day in 1 – 2 doses</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1 – 4 mg od</td>
<td>15 – 30: 50%</td>
<td>15 – 30: q12 – 24h</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2.5 – 15 mg od</td>
<td>15 – 30: 50%</td>
<td>15 – 30: q12 – 24h</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>80 – 160 mg bd</td>
<td>15 – 30: 50%</td>
<td>15 – 30: q12 – 24h</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>5 – 10 mg od</td>
<td>15 – 30: 50%</td>
<td>15 – 30: q12 – 24h</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Acarbose</td>
<td>25 – 100 mg tds</td>
<td>15 – 30: 50%</td>
<td>15 – 30: q12 – 24h</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Metformin</td>
<td>500 – 1,000 mg bd</td>
<td>15 – 30: 50%</td>
<td>15 – 30: q12 – 24h</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

**Note:***
- ADEC = A, D, E, C
- C = Cautious use
- B = Use with caution
- Avoid = Avoid use

**US FDA Pregnancy Category**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mild (GFR 60-90 ml/min)</th>
<th>Moderate (GFR 30-59 ml/min)</th>
<th>Severe (GFR &lt;30 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Frusemide</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Amiloride</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Glipizide</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Acarbose</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Metformin</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

**Dose Adjustment in Renal Failure**

- Mild (GFR 60-90 ml/min): No dosage adjustment necessary
- Moderate (GFR 30-59 ml/min): No dosage adjustment necessary
- Severe (GFR <30 ml/min): Serum potassium needs to be monitored
<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dose</th>
<th>Dose Adjustment in Renal Failure</th>
<th>Note</th>
<th>US FDA Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild (GFR 60-90 ml/min)</td>
<td>Moderate (GFR 30-59 ml/min)</td>
<td>Severe (GFR &lt;30 ml/min)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>15 – 30 mg od</td>
<td>No dosage adjustment necessary</td>
<td>May worsen fluid retention</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incretin mimetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>5 – 10 mcg bd</td>
<td>100%</td>
<td>50 – 100% Dose escalation from 5 – 10 mcg should proceed conservatively</td>
<td>Avoid (increase frequency and severity of GI side effects)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Starting dose: 0.6 mg SC od x 1 week Maintainence dose: 1.2 – 1.8 mg SC od</td>
<td>100%</td>
<td>(limited data)</td>
<td>(limited data)</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg od</td>
<td>100%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50 mg od – bd</td>
<td>100%</td>
<td>(limited data)</td>
<td>(limited data)</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5 – 5 mg od</td>
<td>100%</td>
<td>2.5 mg od</td>
<td>2.5 mg od</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiamoebic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>200 – 400 mg q8 - 12h</td>
<td>No dosage adjustment necessary</td>
<td>15 – 30: No dosage adjustment necessary &lt;15: 50%</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Usual Dose</td>
<td>Dose Adjustment in Renal Failure</td>
<td>US FDA Pregnancy Category</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------</td>
<td>----------------------------------</td>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild (GFR 60-90 ml/min)</td>
<td>Moderate (GFR 30-59 ml/min)</td>
<td>Severe (GFR &lt;30 ml/min)</td>
</tr>
<tr>
<td><strong>Antifungal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200 – 400 mg q24h</td>
<td>No dosage adjustment necessary</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>100 – 200 mg q12h</td>
<td>No dosage adjustment necessary</td>
<td>15 – 30: No dosage adjustment necessary</td>
<td>&lt;15: 50%</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>200 mg q24h</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiviral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>200 mg q4h (herpes simplex)</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>800mg q4h (herpes zoster)</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>75 mg q12h</td>
<td>No dosage adjustment necessary</td>
<td>10 – 30: 75 mg q24h</td>
<td>&lt;10: No recommendation</td>
</tr>
<tr>
<td><strong>Cephalosporin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>250 – 500 mg q8h</td>
<td>100%</td>
<td>50 – 100%</td>
<td></td>
</tr>
<tr>
<td>Ceftibuten</td>
<td>400 mg q24h</td>
<td>100%</td>
<td>50%</td>
<td>&lt;15: 25%</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>250 – 500 mg q12h</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>250 – 500 mg q6h</td>
<td>q8h</td>
<td>q12h</td>
<td></td>
</tr>
<tr>
<td><strong>Fluoroquinolone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500 – 750 mg q12h</td>
<td>100%</td>
<td>50 – 75%</td>
<td>15 – 30: 50 – 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;15: 50%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg q24h</td>
<td>100%</td>
<td>250 mg q24 – 48h</td>
<td>15 – 30: 250 mg q24 – 48h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(500 mg initial dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;15: 250 mg q48h (500 mg initial dose)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg q24h</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Usual Dose</td>
<td>Dose Adjustment in Renal Failure</td>
<td>Note</td>
<td>US FDA Pregnancy Category</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>---------------------------------</td>
<td>------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400 mg q12h</td>
<td>q12h</td>
<td>q12 – 24h</td>
<td>15 – 30: q12 – 24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;15: q24h</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200 – 400 mg q12h</td>
<td>100%</td>
<td>200 – 400 mg q24h</td>
<td>15 – 30: 200 – 400 mg q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;15: 200 mg q24h</td>
</tr>
<tr>
<td>Lincosamide</td>
<td>Clindamycin</td>
<td>150 – 300 mg q6h</td>
<td>No dosage adjustment necessary</td>
<td>B</td>
</tr>
<tr>
<td>Macrolide</td>
<td>Azithromycin</td>
<td>250 – 500 mg q24h</td>
<td>No dosage adjustment necessary</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>500 – 1,000 mg q12h</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>(ethylsuccinate) 400 mg q6h or 800 mg q12h (stearate) 250 mg q6h or 500 mg q12h</td>
<td>100%</td>
<td>100%</td>
<td>15 – 30: 100% &lt;15: 50 – 75%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Nitrofurantoin</td>
<td>50 – 100 mg q6h</td>
<td>No dosage adjustment necessary</td>
<td>Avoid</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Amoxicillin</td>
<td>250 – 500 mg q8h</td>
<td>q8h</td>
<td>q8 – 12h</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin + Clavulanic Acid (Augmentin)</td>
<td>625 mg q12h</td>
<td>No dosage adjustment necessary</td>
<td>15 – 30: No dosage adjustment necessary &lt;15: q24h</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>250 mg – 2 g q6h</td>
<td>q6h</td>
<td>q6 – 12h</td>
</tr>
<tr>
<td></td>
<td>Sultamicillin / Ampicillin + Sulbactam (Unasyn)</td>
<td>375 – 750 mg q12h</td>
<td>No dosage adjustment necessary</td>
<td>15 – 30: q12h &lt;15: q24h</td>
</tr>
<tr>
<td></td>
<td>Cloxacillin</td>
<td>250 – 500 mg q6h</td>
<td>No dosage adjustment necessary</td>
<td>B</td>
</tr>
<tr>
<td>Medication</td>
<td>Usual Dose</td>
<td>Dose Adjustment in Renal Failure</td>
<td>Note</td>
<td>US FDA Pregnancy Category</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>---------------------------------</td>
<td>------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild (GFR 60-90 ml/min)</td>
<td>Moderate (GFR 30-59 ml/min)</td>
<td>Severe (GFR &lt;30 ml/min)</td>
</tr>
<tr>
<td>Penicillin V / Phenoxymethyl-penicillin</td>
<td>250 – 500 mg q6h</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamide + Trimethoprim</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>100 mg q12h</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td>15 – 30: q18h</td>
</tr>
<tr>
<td>&lt;15: q24h</td>
<td></td>
<td></td>
<td>&lt;30 ml/min: Close monitoring of blood count</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole + Trimethoprim</td>
<td>960 mg q12h</td>
<td>Normal dose up to 960 mg q12h for 14 days, then up to 960 mg/day</td>
<td></td>
<td>15 – 30: q18h</td>
</tr>
<tr>
<td>&lt;15: q24h</td>
<td></td>
<td></td>
<td>&lt;15: q24h</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg q24h</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td>D</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg q12h</td>
<td>No dosage adjustment necessary</td>
<td></td>
<td>D</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>250 – 500 mg q6h</td>
<td>q8 – 12h</td>
<td>q12 – 24h</td>
<td>15 – 30: q12 – 24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;15: Avoid</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies in women fail to demonstrate a risk to fetus in the first trimester, and the possibility of fetal harm appears remote.</td>
</tr>
<tr>
<td>B</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>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.</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of human fetal risk exists, but benefits in certain situations (e.g., 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.</td>
</tr>
<tr>
<td>X</td>
<td>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.</td>
</tr>
</tbody>
</table>
# Australian Drug Evaluation Committee (ADEC) Pregnancy Categories

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>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.</td>
</tr>
<tr>
<td>B1</td>
<td>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 not shown evidence of an increased occurrence of fetal damage.</td>
</tr>
<tr>
<td>B2</td>
<td>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.</td>
</tr>
<tr>
<td>B3</td>
<td>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.</td>
</tr>
</tbody>
</table>

Sources:
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

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

Servings Distribution

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Exc.</th>
<th>Breakfast (BF)</th>
<th>Lunch (L)</th>
<th>Afternoon Tea (AT)</th>
<th>Dinner (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>9</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fruits</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Skimmed milk</td>
<td>½</td>
<td>½</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Meat</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fish</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Fat</td>
<td>15</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Sample Menu for CKD (1,800 kcal/day)

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

Approximate Nutrient Analysis

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Value</th>
<th>Value</th>
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<tbody>
<tr>
<td>Energy (kcal)</td>
<td>1,610</td>
<td>Iron (mg)</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>36</td>
<td>Thiamin (mg)</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>197</td>
<td>Riboflavin (mg)</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>75</td>
<td>Niacin (mg)</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>995</td>
<td>Vitamin A (RE)</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>982</td>
<td>Vitamin C (mg)</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>413</td>
<td>Dietary Fiber (g)</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>560</td>
<td>11</td>
</tr>
<tr>
<td>1.54</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>318</td>
<td>15</td>
<td></td>
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Source:
## LIST OF ABBREVIATIONS

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

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- Panel of external reviewers who reviewed the draft
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- Technical Advisory Committee for CPG for their valuable input and feedback
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