

VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF CHRONIC KIDNEY DISEASE IN PRIMARY CARE

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

Version 2.0 – 2007

Prepared by:

The Management of CKD Working Group

With support from:

The Office of Quality and Performance, VA, Washington, DC

&

Quality Management Directorate, United States Army MEDCOM

Table of Contents

	<i>Page</i>
Introduction	1
Guideline Update Working Group	6
Key Elements Addressed by the Guideline	7
Algorithm and Annotations	8
Appendices	
Appendix A: Guideline Development Process	
Appendix B: Assessment	
Appendix C: Slowing Progression of CKD	
Appendix D: Pharmacotherapy	
Appendix E: Complications of Kidney Disease	
Appendix F: Nutrition	
Appendix G: Patient Education	
Appendix H: Follow-up for Chronic Kidney Disease	
Appendix I: Acronym List	
Appendix J: Participant List	
Appendix K: Bibliography	
Tables	
Table 1.1. Definitions of Chronic Kidney Disease.....	11
Table 1.2. Classification of Chronic Kidney Disease Stages	12
Table 2.1. Prevalence of CKD (eGFR in VA Patient Population)	14
Table 4.1. Stages of Chronic Kidney Disease (CKD)	19
Table 4.2. Classification of Chronic Kidney Disease (eGFR).....	20
Table 4.3. Urine Dipstick: Interpretation.....	24
Table 4.4. Evaluation of Proteinuria.....	24
Table 10.1. Summary of Number of Antihypertensive Agents Required to Reach Target Blood Pressure.....	35
Table 10.2. Herbal Products that May Cause Renal Problems	43
Table 11.1. Potassium Content of Foods (see Appendix F-2. Potassium).....	48
Table 11.2. Results of randomized trials of anemia management in CKD, not on dialysis (includes only trials of > 6 months duration and with N > 50).....	56
Table 11.3. Recommended Intake of Protein, Energy, and Minerals in CKD.....	60
Table 14.1. Classification of CKD and Follow-Up Frequency by Primary Care	67

Introduction

The Clinical Practice Guideline for the Management of Chronic Kidney Disease (CKD) was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs (VA). VHA and DoD define clinical practice guidelines as:

“Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes:

- Determination of appropriate criteria such as effectiveness, efficacy, population benefit, or patient satisfaction; and
- Literature review to determine the strength of the evidence in relation to these criteria.”

The intent of the guideline is to:

- Reduce current practice variation and provide facilities with a structured framework to help improve patient outcomes
- Provide evidence-based recommendations to assist providers and their patients in the decision-making process for patients with CKD
- Identify outcome measures to support the development of practice-based evidence that can ultimately be used to improve clinical guidelines.

BACKGROUND

Chronic Kidney Disease (CKD)

- Chronic kidney disease (CKD) is a frequently unrecognized condition that can be progressive, and is often accompanied by multiple other comorbidities. These include diabetes, hypertension, renal osteodystrophy, anemia, cardiovascular disease, and malnutrition. Early recognition of CKD and treatment of complications can improve long-term outcomes.
- Kidney disease is the ninth leading cause of death in the United States (Arias et al., 2003). Approximately 19 million Americans older than 20 years have non-dialysis dependent CKD and an additional 435,000 have end-stage kidney disease (ESKD) requiring chronic dialysis or kidney transplant. An estimated 80,000 new cases of non-dialysis dependent CKD are diagnosed annually and the incidence of ESKD, has doubled every decade since 1980 (USRDS, 2006).
- To estimate the prevalence of CKD in the United States (overall and by health risk factors and other characteristics), the Centers for Disease Control and Prevention analyzed the most recent data from the National Health and Nutrition Examination Survey (NHANES). The total crude (i.e., not age-standardized) CKD prevalence estimate for adults aged ≥ 20 years in the United States was 16.8 percent. By age group, CKD was more prevalent among persons aged ≥ 60 years (39.4%) than among persons aged 40 to 59 years (12.6%) or 20 to 39 years (8.5%). CKD prevalence also was greater among persons with diabetes than among those without diabetes (40.2% versus 15.4%), among persons with cardiovascular disease than among those without cardiovascular disease

(28.2% versus 15.4%), and among persons with hypertension than among those without hypertension (24.6% versus 12.5%). In addition, CKD prevalence was greater among non-Hispanic blacks (19.9%) and Mexican Americans (18.7%) than among non-Hispanic whites (16.1%). This racial/ethnic disparity was most pronounced among participants with early CKD (MMWR, 2007).

Evidence-Based Sources

The National Kidney Foundation's Chronic Kidney Disease Guidelines (KDOQI, 2002) proposes a staging system for CKD and a management approach that is based primarily on stage. The guideline defines five stages of CKD defined by level of estimated glomerular filtration rate (eGFR) and the presence or absence of urinary protein. A similar approach has subsequently been presented in a number of different guidelines from a variety of other professional societies. The evidence-based guidelines referenced in this updated version of the VA/DoD Clinical Practice Guideline include:

- The National Kidney Foundation Kidney Disease Outcomes Quality Initiative - which will be referred to throughout this guideline as **KDOQI** and can be accessed at <http://www.kidney.org/professionals/KDOQI/guidelines.cfm>.
- The Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association, and the Royal College of General Practitioners. Chronic kidney disease in adults: UK guidelines for identification, management and referral. London: Royal College of Physicians, 2006 – which will be referred to throughout this guideline as **UK**.
- Caring for Australians with Renal Impairment - which will be referred to throughout this guideline as **CARI** and can be accessed at: <http://www.cari.org.au/guidelines.php>.

Key Changes in the Update to the 1999 VA/DoD Guideline for ESKD

The revised guideline recommendations continue to support the approach initially advocated in the 1999 version of the VA/DoD guideline for ESKD; however, a goal of the current update is to provide guidance to primary care providers in the management of CKD in the primary care setting. The emphasis of the current guideline has thus shifted away from the management of severe CKD (eGFR < 30 ml/min/1.73m²) and toward the management of earlier stage CKD (eGFR ≥ 30 ml/min/1.73m²). In addition, the evidence published from randomized trials in recent years allowed the Working Group to make firmer recommendations in the following areas:

- Diagnostic Workup:
 - Classification of CKD based on eGFR rather than levels of serum creatinine.
- A unified approach to management of common aspects of kidney disease that is not dependent on the underlying etiology of the CKD:
 - Complications of CKD (anemia, cardiovascular disease, dyslipidemia).
 - Strategies to slow the decline of eGFR.

Target population

Adult patients with CKD: This guideline applies to both patients presenting for the first time with CKD and to patients already being followed for CKD. In both instances, CKD is defined as the presence of decreased eGFR or proteinuria or structural renal damage as determined by radiologic imaging or kidney biopsy, which can occur together or independently.

Audiences

The guideline is relevant to all healthcare professionals who have direct contact with patients with CKD, and make decisions about their care. This version of the guideline was specifically tailored to provide what would be of greatest value to the primary care provider.

Scope of Guideline

- Offers best practice advice on the care of adults who have a clinical working diagnosis of CKD.
- Covers diagnostic criteria for CKD.
- Focuses on identification of susceptibility factors (i.e., adult patients at increased risk for developing CKD).
- Specifies key elements in the evaluation of patients with CKD (including assessment of disease progression).
- Focuses on identification of risk factors for progression of CKD.
- Addresses approaches to slowing the progression of CKD.
- Addresses pharmacotherapy, nutrition, and management of comorbidities in patients with CKD.
- Addresses indications for consultation and referral to a nephrologist.
- Does *not* cover the management of patients with ESKD (i.e., hemodialysis, peritoneal dialysis, kidney transplantation), or detailed management of patients with severe CKD (eGFR < 30 ml/min/1.73m²), nor does it cover pediatric patients.

Development Process

The development process of this guideline follows a systematic approach described in “Guideline-for-Guideline,” an internal working document of VHA’s National Clinical Practice Guideline Counsel. [Appendix A](#) clearly describes the guideline development process.

The literature was critically analyzed and evidence was graded using a standardized format. The evidence rating system for this document is based on the system used by the U.S. Preventative Services Task Force.

Evidence Rating System

A	A strong recommendation that the clinicians provide the intervention to eligible patients. <i>Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.</i>
B	A recommendation that clinicians provide (the service) to eligible patients. <i>At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.</i>
C	No recommendation for or against the routine provision of the intervention is made. <i>At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.</i>
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. <i>At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</i>
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. <i>Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</i>

Lack of Evidence – Consensus of Experts

Where existing literature was ambiguous or conflicting, or where scientific data were lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on “Working Group Consensus.”

This Guideline is the product of many months of diligent effort and consensus-building among knowledgeable individuals from the VA, DoD, and academia, and a guideline facilitator from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The draft document was discussed in 3 face-to-face group meetings. The content and validity of each section was thoroughly reviewed in a series of conference calls. The final document is the product of those discussions and has been approved by all members of the Working Group.

The list of participants is included in [Appendix J](#) to the guideline.

Implementation

The guideline and algorithms are designed to be adapted to individual facility needs and resources. The algorithm will serve as a guide that providers can use to determine best interventions and timing of care for their patients to optimize quality of care and clinical outcomes. This should not prevent providers from using their own clinical expertise in the care of an individual patient. Guideline recommendations are intended to support clinical decision-making but should never replace sound clinical judgment.

Although this guideline represents the state of the art practice at the time of its publication, medical practice is evolving and this evolution will require continuous updating of published information. New technology and more research will improve patient care in the future. The clinical practice guideline can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of clinical practice guidelines such as these may lead to the development of new practice-based evidence.

Outcomes

1. Progressive loss of kidney
 - a. Decrease in eGFR
 - b. Increasing proteinuria
 - c. Progression to ESKD
2. Development/progression of cardiovascular disease
3. Mortality
4. Health Related-Quality of Life (HR-QOL)
5. Utilization of healthcare (hospitalization)
6. Control of metabolic implications (anemia, bone disease, acid base balance, malnutrition)

REFERENCES

- Arias E, Anderson RN, Kung HC, Murphy SL, Kochanek KD. Deaths: final data for 2001. Natl Vital Stat Rep 2003 Sept 18;52(3):1-115.
- KDOQI. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 suppl 1):S1-S266.
- U.S. Renal Data System, USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2006. Available from: <http://www.usrds.org/adr.htm>

Guideline Update Working Group

Guideline Update Working Group*	
VA	DoD
Arianna M. Aoun MS, RD, CSR	Kevin Abbott, MD
Magna Brito, RD	Angela V. Klar, MSN, RN, ANP-CS
Peter G. Carson, MD	Parnell C. Mattison, DO
John Dooley, MD	Eric Sawyers, MD, LCDR USN
Elaine M. Furmaga, PharmD	Mark Stephens, MD, MS, FAAFP
James S. Kaufman, MD, Co-Chair	Fred Yeo, MD
Mary Ellen Nugent, RN, MSN	
Ann M. O'Hare, MA, MD, Co-Chair	
Carlos E. Palant, MD	
Christine Pasquariello, MD	
Thakor G. Patel, MD, MACP	
Kevin T. Stroupe, PhD	
FACILITATOR Oded Susskind, MPH	
RESEARCH TEAM – EVIDENCE APPRAISAL RTI INTERNATIONAL NORTH CAROLINA Linda Lux, MPA Meera Viswanathan, PhD Kathleen Lohr, PhD	HEALTHCARE QUALITY INFORMATICS, INC. Martha D'Erasmus, MPH Rosalie Fishman, RN, MSN, CPHQ Joanne Marko, MS, SLP

* *Bolded names are members of the Editorial Panel.*

Additional contributor contact information is available in [Appendix J](#).

Key Elements Addressed by the Guideline

1. Diagnostic criteria and identification of early disease.
2. Identification of susceptibility factors (adult patients at increased risk for developing CKD).
3. Identification of progression factors (adult patients at high risk for worsening kidney damage and subsequent loss of kidney function).
4. Evaluation of patients with kidney disease (estimate of GFR, blood pressure, and assessment of proteinuria as a marker of kidney damage).
5. Slowing the progression of CKD and prevention of conditions that exacerbate chronic disease.
6. Management of comorbidities.
7. Indication for consultation and referral to a nephrologist.
8. Outline of patient education and preparation for kidney replacement therapy.

STRUCTURE OF THE GUIDELINE

The algorithm describes the step-by-step process of clinical decision-making and intervention that should occur in patients with CKD. General and specific recommendations for each step in the algorithm are included in an annotation section following the algorithm. The links to these recommendations are embedded in the relevant specific steps in the algorithm.

Each annotation includes a brief discussion of the research supporting the recommendations and the rationale behind the grading of the evidence and determination of the strength of the recommendations.

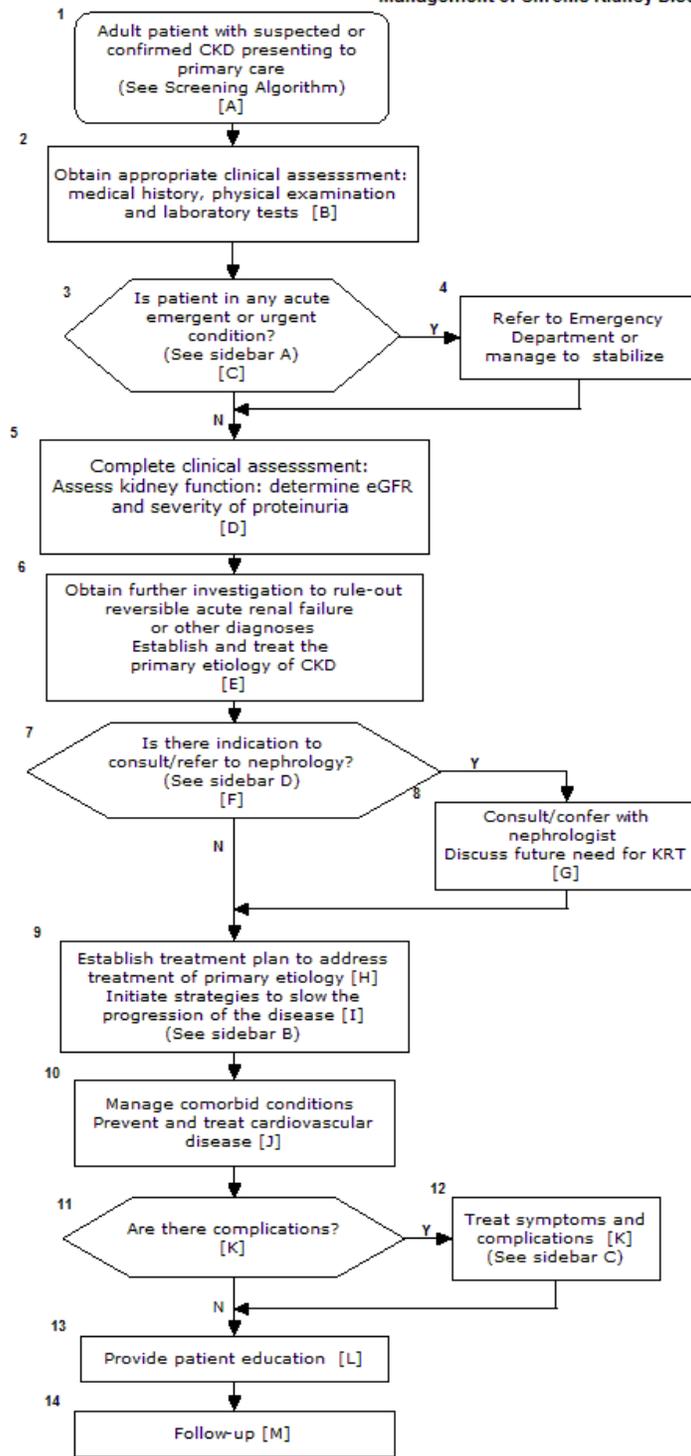
Algorithm and Annotations

Table of Contents

	<i>Page</i>
1. DEFINITION OF CHRONIC KIDNEY DISEASE.....	11
1.1. Patient with Suspected or Confirmed Chronic Kidney Disease (CKD)	11
1.2. CKD Classification	11
2. EARLY DETECTION OF KIDNEY DISEASE.....	13
2.1. Case Identification/Screening.....	13
3. EVALUATION OF PATIENTS WITH CKD.....	15
3.1. Medical History	15
3.2. Physical Examination.....	16
3.3. Laboratory Tests.....	17
4. ASSESSMENT OF KIDNEY FUNCTION	18
4.1. Measuring Disease Progression.....	18
4.2. Estimating GFR.....	19
4.3. Assessing Proteinuria	22
4.4. Imaging the Kidney	25
5. URGENT/EMERGENT CONDITIONS	25
6. REVERSIBLE CONDITIONS.....	26
7. PRIMARY ETIOLOGY OF KIDNEY DISEASE.....	27
8. CONSULTATION WITH/REFERRAL TO NEPHROLOGY	30
9. MANAGEMENT OF CKD – PROMOTION OF GENERAL HEALTH	32
10. STRATEGIES TO SLOW THE PROGRESSION OF THE DISEASE	33
10.1. Control of Hypertension	33
10.2. Use of an ACEI or ARB.....	36
10.3. Protein Restriction.....	39
10.4. Control of Hyperglycemia in Patients with Diabetes	41
10.5. Avoidance of Nephrotoxic Drugs and Adjustment of Medication Doses as Indicated	41
10.6. Smoking Cessation	44
10.7. Control of Dyslipidemia	45
11. COMPLICATIONS OF CKD	47
11.1. Disorders of Potassium Balance	47
11.2. Disorders of Bone Mineral Metabolism	49
11.3. Acid Based Abnormalities.....	51
11.4. Hematologic Abnormalities (Anemia)	52
11.5. Volume Overload	57

11.6. Disorders of Nutrition	59
11.7. Adjustment of Medication Doses	61
11.8. Immunization	61
12. THE RISK FOR CARDIOVASCULAR DISEASE.....	62
13. PATIENT EDUCATION	65
14. FOLLOW-UP.....	66

VA/DoD Clinical Practice Guideline
Management of Chronic Kidney Disease



Stage	eGFR (ml/min/1.73m ²)	Description
1	> 90	Kidney damage with normal or increased GFR
2	60-89	Kidney damage with mildly decreased GFR
3	30-59	Moderately decreased GFR
4	15-29	Severely decreased GFR
5	< 15 or dialysis	Kidney failure

Sidebar A: Urgent/Emergent Conditions

- Acute unexplained decline in kidney function
- Heart failure/volume overload
- Hyperkalemia (potassium ≥ 6 mEq/L)
- Signs or symptoms of uremia

Sidebar B: Strategies to Slow Progression

1. Control of hypertension
2. Use of ACEI/ARB
3. Control of hyperglycemia
5. Avoid toxic drugs
6. Smoking cessation
7. Control of dyslipidemia

Sidebar C: Prevention and Treatment of Complications

- Metabolic disorders:
 - potassium balance
 - calcium, phosphate balance
 - acidosis
- Anemia
- Volume overload
- Overuse of renally excreted drugs
- Nutrition

Sidebar D: Indications for Nephrology Consultation

1. eGFR <30 ml/min/1.73m²
2. Rapid decline of GFR
3. Severe complications of CKD (e.g., recalcitrant anemia, calcium or phosphorus abnormalities)
4. Nephrotic range proteinuria (>3.5 grams/24 hours)
5. Underlying cause of CKD is unclear after basic work-up
6. Kidney biopsy is indicated
7. Patient's level of disease exceeds the level of comfort of the primary care provider

ACEI - Angiotensin-Converting Enzyme Inhibitor , ARB - Angiotensin II Receptor Blockers , DM - Diabetes Mellitus, eGFR - Estimated Glomerular Filtration Rate, KRT - Kidney Replacement Therapy.

6/2/2008

Annotations

Annotation A

Adult Patient with Suspected or Confirmed CKD Presenting to Primary Care

1. DEFINITION OF CHRONIC KIDNEY DISEASE

1.1. Patient with Suspected or Confirmed Chronic Kidney Disease (CKD)

BACKGROUND

This guideline should be used for patients in need of further diagnostic work-up and follow-up. These patients present to primary care and are found to have one of the following (see [Table 1.1. Definitions of Chronic Kidney Disease](#)):

Table 1.1. Definitions of Chronic Kidney Disease

<ul style="list-style-type: none">• Persistent decreased eGFR < 60 ml/min/1.73m² on two tests at least three months apart <i>or</i>• Proteinuria ($> 1+$) on dipstick or urine protein-to-creatinine ratio > 0.2, confirmed on two tests at least three months apart <i>or</i>• Microalbuminuria defined as albumin-to-creatinine ratio > 30, confirmed on two out of three urine tests in patients with diabetes mellitus (DM) <i>or</i>• Known structural kidney disease defined by imaging or pathologic examination (e.g., polycystic kidney disease [PCKD]) <p><i>Estimated glomerular filtration rate (eGFR) is the preferred method to assess kidney function.</i></p>

DEFINITIONS

This guideline is intended to apply both to patients presenting for the first time with CKD and to patients with existing CKD. In both instances, CKD is defined as the presence of decreased eGFR or proteinuria, which can occur together or independently, or the presence of microalbuminuria in patients with diabetes or structural kidney disease. The presence of proteinuria may indicate kidney disease even with a normal eGFR. Any of these patients has a potentially serious kidney disease that might progress to kidney failure.

Note: Pure hematuria without proteinuria is usually a urologic problem. If a referral is needed after the initial work-up by primary care, it should be to urology and not nephrology.

1.2. CKD Classification

- **The most common criterion for chronic kidney disease** is an eGFR < 60 ml/min/1.73m² for at least 3 months.
- **In patients with eGFR > 60 ml/min/1.73m²**, the presence of CKD should be established based on the presence of kidney damage indicated by pathological abnormalities on kidney biopsy, proteinuria (or microalbuminuria in patients with diabetes), or imaging studies.

- **Patients who meet criteria for CKD** may be assigned to a CKD stage based on the presence or absence of abnormalities on urinalysis or imaging and their estimated level of glomerular filtration rate (eGFR).
- **Classification System** of Chronic Kidney Disease (see [Table 1.2. Classification of Chronic Kidney Disease Stages](#)): Defining stages of CKD requires “categorization” of continuous measures of kidney function, and the “cut-off levels” of eGFR for each stage are inherently arbitrary. Nonetheless, staging of CKD may facilitate the application of clinical practice guidelines (CPG), clinical performance measures, and quality improvement efforts to the evaluation and management of CKD.

Table 1.2. Classification of Chronic Kidney Disease Stages

Stage	Description	eGFR (ml/min/1.73m ²)	Common complications
1	Kidney damage with normal eGFR	Normal or ≥ 90 ml/min/1.73m ² with other evidence of chronic kidney damage *	Hypertension more frequent than amongst patients without CKD
2	Mild impairment	60 - 89 ml/min/1.73m ² with other evidence of chronic kidney damage *	Hypertension frequent
3	Moderate impairment	30 - 59 ml/min/1.73m ²	Hypertension common Decreased dietary calcium absorption Reduced renal phosphate excretion Elevation of parathyroid hormone Altered lipoprotein metabolism Reduced spontaneous protein intake Anemia Left ventricular hypertrophy Salt and water retention Decreased renal potassium excretion
4	Severe impairment	15 - 29 ml/min/1.73m ²	As above but more pronounced plus: Metabolic acidosis
5	Established renal failure	< 15 ml/min/1.73m ² or on dialysis	All the above (with greater severity) plus: Salt and water retention causing edema and apparent heart failure Anorexia Nausea, Vomiting Pruritus (itching without skin disease) Neuropathy, altered mental status

Based on KDOQI, 2002

* The “other evidence of chronic kidney damage” may be one of the following:

- Persistent microalbuminuria in a diabetic
- Persistent proteinuria
- Persistent hematuria of renal origin
- Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g., polycystic kidney disease, reflux nephropathy
- Biopsy-proven chronic kidney disease such as glomerulonephritis or interstitial nephritis (most of these patients will have microalbuminuria or proteinuria, hematuria or low eGFR)

2. EARLY DETECTION OF KIDNEY DISEASE

2.1. Case Identification/Screening

BACKGROUND

- Chronic kidney disease (CKD) is a frequently unrecognized condition that can be progressive, and is often accompanied by multiple other comorbidities. These include diabetes, hypertension, renal osteodystrophy, anemia, cardiovascular disease, and malnutrition. Early recognition of CKD and treatment of complications can improve long-term outcomes.
- The National Kidney Foundation's Chronic Kidney Disease Guidelines (KDOQI, 2002) proposes a staging system for CKD and a management approach that is based primarily on stage. The guidelines define five stages of CKD defined by level of estimated glomerular filtration rate and the presence or absence of urinary protein.
- Applying this classification system to the general non-institutionalized US population, the total crude (i.e., not age-standardized) CKD prevalence estimate for adults aged ≥ 20 years in the United States was 16.8 percent (MMWR). By disease stage, the prevalences were as follows: stage 1, 5.7 percent; stage 2, 5.4 percent; stage 3, 5.4 percent; stages 4/5, 0.4 percent. By age group, CKD (all stages) was more prevalent among persons aged ≥ 60 years (39.4%) than among persons aged 40 to 59 years (12.6%) or 20 to 39 years (8.5%). By education level, CKD (all stages) was more prevalent among persons with less than a high school education (22.1%) than persons with at least a high school education (15.7%). CKD prevalence also was greater among persons with diabetes than among those without diabetes (40.2% versus 15.4%), among persons with cardiovascular disease than among those without cardiovascular disease (28.2% versus 15.4%), and among persons with hypertension than among those without hypertension (24.6% versus 12.5%). In addition, CKD prevalence was greater among non-Hispanic blacks (19.9%) and Mexican Americans (18.7%) than among non-Hispanic whites (16.1%). This racial/ethnic disparity was most pronounced among participants with stage 1 CKD. In that group, Mexican Americans had a prevalence of 10.2 percent and non-Hispanic blacks had a prevalence of 9.4 percent, compared with 4.2 percent for non-Hispanic whites (MMWR, 2007).

RECOMMENDATIONS

1. Patients with hypertension, diabetes, cardiovascular disease, or a family history of kidney disease should be screened annually for the presence of kidney disease. [C]
2. Screening for CKD may be considered in patients with other conditions that have shown high incidence of CKD. [C]
 - a. Persistent hematuria (after exclusion of other causes, e.g., urological disease)
 - b. Recurrent urinary tract infections or urinary obstruction
 - c. Systemic illness that can affect the kidney (e.g., Human Immunodeficiency Virus (HIV), Systemic Lupus Erythematosus, hyperuricemia, multiple myeloma)
3. Testing for kidney disease includes urinalysis and estimation of the glomerular filtration rate (eGFR). [B]
4. Patients with diabetes who have a negative urine protein by dipstick should be tested for the presence of microalbuminuria. [B]

(Screening can be performed using a microalbumin-sensitive dipstick or measurement of microalbumin-to-creatinine ratio in a morning urine sample.)

See [Appendix B-1 – Screening Algorithm for CKD](#)

DISCUSSION

The KDOQI guidelines (2002) recommend assessing all patients for kidney disease risk factors. Further screening is performed in patients with identified risk factors. Although screening methods for CKD have not been evaluated in randomized controlled trials (RCT), the high prevalence of the disease in at-risk populations, the ease of screening, and the availability of effective treatments during early asymptomatic stages of the disease provide a sufficient rationale for screening. Nonetheless, screening rates for patients with known risk factors for CKD are as low as 20 percent (KEEP, 2003; McClellan et al., 2003).

Early treatment of CKD has the potential to delay or prevent disease progression. Consequently, detection of CKD by primary care providers represents a critical first step in the process of intervening at an early stage. However, data from national screening programs suggest that many patients are not tested for CKD even when they have access to primary care (KEEP, 2003; McClellan et al., 2003).

In a cross-sectional study of the VA patient population in fiscal year 2002, over 20 percent of users of VA healthcare met the criteria for CKD (eGFR < 60 ml/min/1.73m²) (see [Table 2.1. Prevalence of CKD \(eGFR in VA Patient Population\)](#)). Furthermore, in this study, CKD was present among approximately 1/3 of patients 70 years and older. CKD was significantly more common among individuals of older age, male gender, and white race as well as those with diabetes and hypertension. The prevalence of CKD among this population greatly exceeds recent prevalence estimates for other adult Americans even among similar demographic and disease subgroups.

Table 2.1. Prevalence of CKD (eGFR in VA Patient Population)

	eGFR		
	30 – 60	15 – 30	< 15
OVERALL	19.1%	1.5%	0.6%
Age (years)			
< 60	5.4%	0.5%	0.4%
60 – 70	19.5%	1.2%	0.7%
70	32.7%	2.7%	0.8%
Gender			
Female	14.7%	0.7%	0.3%
Male	19.3%	1.6%	0.6%
Race			
Black	11.0%	1.8%	1.6%
White	20.6%	1.7%	0.6%
Disease			
Diabetes	18.9%	1.8%	0.5%
Hypertension	22.9%	1.5%	0.6%
Diabetes + Hypertension	27.0%	3.0%	1.5%
Neither	10.7%	0.6%	0.2%

Source: Fischer et al., 2005

A cost analysis (Boulware et al., 2003) suggested that screening all patients older than 60 years is cost-effective even when other risk factors for CKD are absent; screening low-risk patients younger than 60 years does not appear to be cost-effective.

Screening Test

Current KDOQI guidelines recommend screening for CKD with a serum creatinine measurement for use in GFR estimation and analysis of a random urine sample for proteinuria. Both measurements are needed to exclude the diagnosis of CKD because both conditions can exist independently. An analysis of data from the third National Health and Nutrition Examination Survey (NHANES III) showed that 20

percent of persons with diabetes, and 43 percent of persons with hypertension with an eGFR below 30 ml/min/1.73m², had no proteinuria (Garg et al., 2002).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Screening for patients with risk factors	USRDS, 2006	II	Fair	C
2	Screening patients older than 60 is cost effective	Boulware et al., 2003	II	Fair	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

Annotation B	Obtain Appropriate Clinical Assessment: Medical History, Physical Examination, and Laboratory Tests
--------------	---

3. EVALUATION OF PATIENTS WITH CKD

For every newly discovered patient with kidney disease and those with acute worsening of CKD, the history, physical examination, and basic laboratory evaluation remain the cornerstone for establishing etiology and ruling out reversible causes. Clinical assessment will help identify the clinical markers that indicate kidney disease and outline basic diagnostic testing required in all patients.

Once CKD has been identified, goals include determining the severity of the disease, establishing the most likely cause (or causes), and evaluating associated complications and comorbid conditions.

3.1. Medical History

BACKGROUND

Although there are no RCTs demonstrating the value of a medical history, this is the critical first step in the evaluation of any condition including CKD. The identification of underlying conditions may reveal a treatable cause.

RECOMMENDATIONS

1. The patient with CKD should be evaluated for underlying (causative or contributory) medical conditions. A targeted history to detect the presence and possible contribution of conditions present in a patient with new or established CKD includes: [I]
 - a. History of diabetes, hypertension, cardiovascular disease, lower urinary tract symptoms suggestive of urinary obstruction, hepatitis B or C, HIV, kidney stones, urinary tract infections, symptoms suggestive of a systemic vasculitis (e.g., rash, arthritis, serositis), or chronic pain syndrome (raising suspicion for analgesic abuse), genito-urinary malignancy, history of abdominal/pelvic surgery or radiation, exposure to environmental toxins.
 - b. There are no symptoms that are specific to and diagnostic of CKD itself. When patients develop the following symptoms in the presence of renal failure (eGFR < 15 ml/min/1.73m²) these symptoms are usually attributed to their CKD.
 - Sleep disturbance

- Decreased attentiveness
 - Nausea, vomiting, anorexia, weight change
 - Dyspnea, orthopnea, leg swelling
 - Fatigue, muscle cramps, restless legs, peripheral neuropathy
 - Pruritus.
- c. Medications should be reviewed to identify those that may be contributing to renal impairment including: nonsteroidal anti-inflammatory drugs (NSAIDs), other analgesics, diuretics, lithium, cyclosporine, tacrolimus, antiviral agents, chemotherapeutic agents, antibiotics, allopurinol, and dietary and herbal supplements (see [Appendix D-2](#)).
- Note: Angiotensin-converting enzyme inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB), which are generally preferred agents in CKD due to their renoprotective effects, may cause an acute decline in the eGFR due to hemodynamic effects in some cases requiring discontinuation of the drug.
- d. Family history of ESKD or of a particular kidney disease (e.g., polycystic kidney disease [PCKD]).

3.2. Physical Examination

BACKGROUND

Although there are no clinical trials that demonstrate a benefit of specific elements of the physical examination, a focused physical examination may provide clues to relevant underlying conditions or help identify complications of CKD. Key elements of the exam include overall and vital sign assessment, volume assessment, and focused assessment of specific organs. In addition, the global assessment of a patient's appearance as acutely ill, chronically ill, or well can provide a valuable measure of a patient's overall health and functional status. A full set of vital signs, including body mass index should be obtained at every visit. Serial weights are important in assessing both volume status and adequacy of nutrition. Other potentially useful elements of volume assessment include checking for rales, jugular venous distension, and peripheral edema.

An abdominal or femoral bruit may indicate the presence of renal artery stenosis. A palpable bladder or enlarged prostate may suggest the presence of urinary tract obstruction. A rash or inflammatory arthritis may suggest an underlying rheumatologic disorder. A cardiac rub may indicate pericarditis in a patient with advanced CKD. Patients with diabetes should be assessed for retinopathy in order to gauge the likelihood that diabetic nephropathy is the most likely cause of their CKD, although diabetic nephropathy may occur in the absence of retinopathy, particularly in type II diabetes.

RECOMMENDATIONS

1. The physical examination should include the following: [I]
 - a. Height, weight, and body mass index
 - b. Vital signs, including orthostatic blood pressure and pulse
 - c. Volume assessment (rales, jugular venous distension, peripheral edema, and cardiac heave/gallop/rub)
 - d. Abdominal findings (mass, bruit, palpable bladder, and flank tenderness)
 - e. Integument (rash, stigmata of atheroembolic disease, or ischemia)
 - f. Extremities: foot examination, femoral artery (bruit), joints (arthritis).

3.3. Laboratory Tests

BACKGROUND

Laboratory testing is critical in ascertaining the stage, course, chronicity, and complications (and associated comorbid conditions) of CKD. In addition, laboratory testing may help identify a specific etiology of CKD.

RECOMMENDATIONS

1. Routine laboratory testing for diagnosis and routine follow-up of patients with CKD should include: [I]
 - a. Urinalysis and examination of urinary sediment as indicated
 - b. Random microalbumin-to-creatinine ratio in patients with diabetes (urine protein-to-creatinine ratio is acceptable if there is overt proteinuria on dipstick)
 - c. Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine (S_{Cr}) and eGFR, glucose, calcium, phosphorous, albumin, total protein, and lipid profile
 - d. Complete blood count with differential
 - e. Additional tests may be indicated depending on the differential diagnosis for CKD or particular complications in a given patient.

See [Appendix B-3 – Specialized Laboratory Studies for the Diagnosis of Kidney Disease](#).

See [Section 4.4 for the recommendation regarding ultrasound](#).

DISCUSSION

Chem 7, Urinalysis, Calcium, Phosphorus, and Albumin

- Use of creatinine alone to identify the stage of CKD is not recommended, because it can be an unreliable marker for true GFR particularly in patients with reduced muscle mass (e.g., small body size, female, elderly) (CARI, 2005; KDOQI, 2002).
- The use of the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate GFR is recommended. The equation is based on serum creatinine level in combination with race, age, and sex. This formula has reasonable accuracy for true GFR in a wide variety of different sub-groups at eGFR levels <60 ml/min/1.73m² (Stevens et al., 2007). Use of the MDRD equation to differentiate between different levels of renal function at eGFR levels above 60 is not recommended as the equation was not developed for this purpose.
- Urinalysis and microscopic examination of the urine.
- Red cell casts may indicate glomerulonephritis.
- White cells may indicate infection or interstitial nephritis.
- Check the random urine protein-to-creatinine ratio. A value of > 3.5 gm protein/day is indicative of nephrotic-range proteinuria indicating the presence of glomerular disease. Urine protein-to-creatinine and albumin-to-creatinine ratios provide accurate estimates of protein and albumin excretion rates (KDOQI, 2002).
- Calcium and phosphorus should be monitored in all patients with CKD. If there are abnormalities in calcium or phosphorus or if their eGFR < 45 ml/min/1.73m² parathyroid hormone (PTH) levels should be measured (KDOQI, 2002; UK guideline, 2006).

- Albumin, prealbumin: Hypoalbuminemia can occur as part of a nephrotic syndrome and is also a marker both for inflammation and malnutrition and thus should be monitored in patients with CKD. Low levels of albumin and prealbumin at the initiation of dialysis are predictors of increased mortality risk (KDOQI, 2000).

Lipid Panel

- All adults with CKD should be evaluated for dyslipidemia with a complete fasting lipid panel (KDOQI, 2002).

Anemia

- Anemia is common in patients with CKD. A complete blood count can help determine whether anemia is present, how severe the anemia is and whether the patient would benefit from treatment. All patients with CKD should have hemoglobin measured at least annually (KDOQI, 2002).

Other

- Depending on the patient’s history and clinical presentation, testing for HIV, Hepatitis B and C, ANA (double stranded DNA), complement, anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody, serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), and determination of serum free light chain ratio may be helpful in making a diagnosis or monitoring the course of the disease and response to therapy. However, these tests are not needed in all patients with CKD.

<i>Annotation D</i>	<i>Complete Clinical Assessment: Assess Kidney Function: Determine eGFR and Severity of Proteinuria (Rate of Decline)</i>
---------------------	---

4. ASSESSMENT OF KIDNEY FUNCTION

4.1. Measuring Disease Progression

BACKGROUND

Developing an operational definition of CKD and its stages is intended to guide clinicians in evaluating and managing CKD and defining individuals at greatest risk of CKD progression (see [Table 4.1. Stages of Chronic Kidney Disease \(CKD\)](#)).

Table 4.1. Stages of Chronic Kidney Disease (CKD)

Stage	eGFR (ml/min/1.73m ²)	Description	Action*
1	≥ 90	Kidney damage with normal or increased GFR	Diagnosis and treatment. Treatment of comorbid conditions, slowing progression, CVD risk reduction
2	60-89	Kidney damage with mildly decreased GFR	Estimating progression
3	30-59	Moderately decreased GFR	Evaluating and treating complications
4	15-29	Severely decreased GFR	Preparation for kidney replacement therapy
5	< 15 or dialysis	Kidney failure	Replacement (if uremia present)

* Includes action from the preceding stages

The eGFR is a measure of the filtering capacity of the kidneys. In patients with CKD, eGFR declines over time and is associated with an increased risk of adverse outcomes including death. Thus, both the baseline level of eGFR and the rate of change in eGFR are key pieces of information that should inform the management of patients with CKD.

While not a perfect reflection of true GFR, eGFR calculated using the MDRD equation has the advantage of being easily communicable to patients who might be encouraged to “know their number.” Staging provides a systematic and uniform classification of CKD. Patients in more advanced stages are more likely to progress to the point of needing dialysis and are also more likely to experience complications related to CKD, which are relatively uncommon at earlier stages. To accommodate the fact that at any stage of CKD there can be considerable variability in disease progression between individuals, the rate of loss of eGFR should also be incorporated into the clinical management of patients with CKD at any stage.

Note: The term end-stage kidney disease (ESKD) refers to patients on dialysis or with a kidney transplant, similar to the term end stage renal disease (ESRD) used elsewhere. ESRD is an administrative term used in the U.S., where the Medicare program finances the care of most dialysis and transplant patients. ESRD overlaps with but is not identical to CKD Stage 5.

4.2. Estimating GFR

BACKGROUND

Direct measurement of GFR is too cumbersome of a procedure to be widely applied in the clinical setting. Serum creatinine serves as a marker for true GFR. However, due to the dependence of serum creatinine on muscle mass, substantial decrements in true GFR may be present despite a normal serum creatinine level. GFR can be more accurately estimated using the MDRD equation which includes terms for serum creatinine, age, race and gender. Accurate estimation of GFR is important both for the dosing of renally excreted medications and for clinical goals.

RECOMMENDATIONS

1. The severity of CKD should be classified based on the level of the estimated glomerular filtration rate (eGFR) (see [Table 4.2. Classification of Chronic Kidney Disease \(eGFR\)](#)).

2. Kidney function in patients with CKD should be assessed by formula-based estimation of GFR (eGFR), preferably using the 4-variable Modification of Diet in Renal Disease (MDRD) equation. [A]
3. Serum creatinine alone should NOT be used as a measure of kidney function. [B]
4. All clinical laboratories should report an estimate of GFR (4-variable MDRD, 6-variable MDRD, or Cockcroft-Gault equations) alongside a measurement of serum creatinine. [Expert Opinion]
5. In clinical laboratories without the ability to automatically incorporate race into the MDRD calculation, adjusted values for race should be determined (multiply by 1.21 for African-Americans). [B]
6. There is no need to collect 24-hour urine samples to measure creatinine clearance. [D]

Clinicians without access to automated reporting of eGFR can:

1. Use a web-based tool at :
http://www.nkdep.nih.gov/professionals/gfr_calculators/index.htm
2. Calculate eGFRs using the actual MDRD equation:

$$eGFR = 186 \times [S_{Cr}]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if female}] \times [1.210 \text{ if black}]$$

Key: GFR=glomerular filtration rate; MDRD=Modification of Diet in Renal Disease;
S_{Cr}=Serum creatinine concentration

3. For laboratories using an isotopic dilution mass spectrometry (IDMS) traceable measurement of serum creatinine, the following formula should be used:

$$eGFR = 175 \times [S_{Cr}]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if female}] \times [1.210 \text{ if black}]$$

Key: GFR=glomerular filtration rate; MDRD=Modification of Diet in Renal Disease;
S_{Cr}=Serum creatinine concentration

Table 4.2. Classification of Chronic Kidney Disease (eGFR)

Stage	eGFR (ml/min/1.73m ²)
1	≥ 90
2	60 – 89
3	30 – 59 Known to be stable ^a Newly diagnosed or progressive ^b
4	15 – 29 Known to be stable ^a Newly diagnosed or progressive ^b
5	< 15
^a Stable kidney function is defined as a change of eGFR of <15% (< 2 ml/min/1.73m ²) over 6 months or more ^b Progressive decline in kidney function is defined as 15% fall in eGFR (> 2 ml/min/1.73m ²) over 6 - 12 months or longer	

DISCUSSION

The eGFR is the best overall measure of kidney function in patients with CKD and has replaced serum creatinine measurement as the diagnostic test of choice for CKD. GFR can be directly measured using a variety of different assays, but none are feasible for widespread use in the clinical setting. A variety of different prediction equations have been developed including the MDRD (4- and 6-variable) and Cockcroft-Gault Formulas. While estimates of GFR may be unreliable at the extremes of age, muscle mass and weight, and at eGFR levels above 60 ml/min/1.73m², eGFR is reasonably accurate measure of true GFR in most patients with moderate or more severe CKD (Stevens et al., 2007). Both the abbreviated and full MDRD and the Cockcroft-Gault equations are acceptable for use in the clinical setting (see CARI, 2005; KDOQI, 2002). However, for uniformity, the use of the abbreviated MDRD equation is recommended (Levey et al., 2006).

There are preliminary data to support the value of automated eGFR reporting. Akbari et al. (2004) examined the impact of automated eGFR reporting and education of primary care physicians among 324 patients 65 years and older with an eGFR 30 to 59 ml/min/1.73m² in outpatient family medicine practice. Excluded were 476 patients who did not have prior or subsequent creatinine measurements within 3 years. Recognition of CKD by the primary care provider increased from 22.4 to 85.1 percent. However, it was unclear to what extent improved recognition reflected the impact of the educational intervention vs. eGFR reporting per se.

Importantly, serum creatinine may not rise above the normal range until creatinine clearance has declined to less than half of normal in patients with low muscle mass. For every 50 percent reduction in GFR, the serum creatinine concentration (S_{Cr}) approximately doubles. It should be recognized that since serum creatinine is determined both by kidney function and muscle mass, patients with normal serum creatinine and low muscle mass may have significant impairment of kidney function. Patients with a serum creatinine level above the normal range but under 2.0 mg/dL have significant kidney disease but are less likely to have electrolyte disturbances, anemia, or bone disease than those with a creatinine level of ≥ 2.0 mg/dL.

Novel Markers (Cystatin C)

Cystatin C is a novel marker of kidney function. It is a non-glycosylated low molecular weight protein constitutively produced by all nucleated cells (Barrett, 1985). Like serum creatinine, cystatin C is freely filtered by the glomerulus. Unlike serum creatinine, cystatin C is subsequently reabsorbed and catabolized by the tubular epithelium with only a small amount excreted in the urine. Cystatin C was first proposed as a marker of renal function in the mid-1980s (Grubb et al., 1985; Simonsen et al., 1985).

As a measure of GFR, cystatin C appears to be either similar to or slightly superior to serum creatinine. A meta-analysis of studies that compared the relationship of both creatinine and cystatin C with measured GFR reported that 1/cystatin C correlates better than 1/creatinine with GFR. Also, the meta-analysis found that receiver operator characteristic (ROC)-plot area under the curve for 1/Cystatin C was significantly greater than the ROC plot AUC for serum 1/Creatinine, demonstrating that 1/Cystatin C had greater identity with the reference test for GFR (Kharnidharka et al., 2002). However, the authors did not employ rigorous inclusion criteria, including abstracts and at least one unpublished study. Furthermore, the majority of studies were in pediatric patients, renal transplant patients, patients at risk for reduced muscle mass (spinal cord injury and cirrhosis) and patients with normal renal function. Furthermore, given the now widespread use of creatinine-based eGFR, the more relevant question may be whether cystatin C is superior to true eGFR as a measure of actual GFR. If anything, cystatin appears to be a more accurate indicator of GFR in patients with preserved renal function. While more accurate identification of patients with very early decrements in eGFR may be of value in research studies and in specialized populations where creatinine is known to be inaccurate, the more widespread clinical utility of cystatin C for identifying and stratifying patients with CKD is presently unclear and awaits the results of clinical trials testing the efficacy of interventions in patients with very early stage CKD.

In a variety of different studies, serum cystatin C levels display a more linear association with mortality and cardiovascular events than serum creatinine. Plasma cystatin C is not related to the formation of creatinine and, unlike creatinine, is not influenced by muscle mass. It has been argued that the more linear association of cystatin C with mortality supports its role as a more accurate marker of renal function in patients with low serum creatinine (Shlipak et al., 2005). However, this assertion has not been substantiated since these studies did not include a gold standard measure of renal function leaving open the possibility that cystatin C is a marker for mortality independent of level of renal function. Furthermore, in a recent analysis of the prognostic significance of cystatin C in the MDRD study, cystatin C was a stronger predictor of mortality than the gold standard of measured GFR and a weaker predictor of onset of ESKD (Menon et al., 2007). These findings suggest the possibility that the association of Cystatin C with mortality reported previously may not simply represent an association of measured GFR with mortality.

4.3. Assessing Proteinuria

BACKGROUND

Protein excretion in the urine is an indicator of abnormal kidney function and should be assessed in all patients with CKD and in patients with diabetes as an early indicator of CKD.

RECOMMENDATIONS

1. Proteinuria should initially be assessed using a conventional dipstick. A first morning specimen is preferred, but random urine specimens are acceptable.
 - a. If the dipstick is 1+ or greater, a quantitative test should be performed using the random urine protein-to-creatinine ratio
 - b. A protein-to-creatinine ratio of > 0.2 is considered abnormal (> 200 mg protein/g creatinine).
2. Microalbuminuria – in patients with diabetes – should be assessed using a laboratory method expressed as an albumin-to-creatinine ratio. If dipsticks designed to detect urinary microalbumin are used, positive tests should be followed by laboratory confirmation.
3. The diagnosis of microalbuminuria cannot be reliably made in the presence of an acute medical condition. As far as it is practicable, the best possible metabolic control of diabetes should be achieved before evaluating for microalbuminuria. Patients should not be screened during intercurrent illness or after heavy exercise.
4. It is important to consider other causes of increased albumin excretion, especially in the case of Type 1 diabetes present for < 5 years. In addition to the previously mentioned conditions, other causes can include menstrual contamination, vaginal discharge, uncontrolled hypertension, and heart failure.
5. A 24-hour urine collection for protein and creatinine is not needed for quantitation of proteinuria, as it is more cumbersome for patients and prone to collection errors.

24-hour urine collection may be considered for: pregnant women, extreme age and weight, malnutrition, skeletal muscle disease, paraplegia or quadriplegia, patients with a vegetarian diet and rapidly changing kidney function.

DISCUSSION

Very small amounts of protein are normally excreted in the urine. Persistently increased protein excretion is a marker of kidney damage and one of the diagnostic criteria for CKD. Two classes of proteins may appear in the urine, albumin and globulins. The excretion of specific types of protein appearing in the urine depends on the severity and type of kidney disease present. The small amount of protein that may normally appear in the urine is a globulin secreted by a renal tubular cell (Tamm-Horsfall glycoprotein). With renal injury, the normal glomerular barrier may be altered and albumin

may leak into the urine, resulting in microalbuminuria, an early functional abnormality in diabetic nephropathy. With more severe renal injury, or in specific diseases, globulins may also pass the glomerular barrier and appear in the urine. Proteinuria has been demonstrated to be a potent independent risk factor for progression of renal disease and a potent independent cardiovascular risk factor.

Urinalysis Using Protein Dipsticks

Protein excretion displays considerable biological variability. Standard urine dipsticks estimate protein concentration and are therefore dependent on patient hydration or how concentrated the urine sample is. This test can only give a rough indication of the presence or absence of pathological proteinuria. The test only measures albumin and will be falsely negative if the urine protein is globulin, such as often found in paraproteinemia. The “trace” block on the dipstick corresponds to approximately 150 mg/L of total protein and 1+ block to 300 mg/L. Significant proteinuria is deemed present when greater than the trace block (i.e., > 300 mg/L). The specificity of urinalysis using protein dipsticks for the detection of proteinuria is approximately 67 percent. Positive dipstick tests (1+ or greater) should be confirmed in the laboratory by quantitative measurement. Key interpretations of dipsticks tests are summarized in [Table 4.3. Urine Dipstick: Interpretation](#).

Random Urine Collection for Assessing Proteinuria

Twenty-four hour urine collection has been the longstanding “gold standard” for the quantitative evaluation of proteinuria. The recognized difficulty in collecting reliable 24-hour urine samples makes routine use problematic and assessment of random urine samples an attractive and practical alternative. Urine albumin-to-creatinine ratio or urine protein-to-creatinine ratio can be assessed in random urine samples. The measurement of urinary albumin is more precise than urinary protein at lower protein concentrations, but it is more expensive and many of the studies of the natural history or treatment of kidney disease stratified patients by urine total protein, rather than by albumin excretion. Therefore, the more cost effective urine protein-to-creatinine ratio is recommended for use in assessment of proteinuria except in screening for renal disease in diabetics, in whom urine microalbumin-to-creatinine ratio should be used.

Several studies have demonstrated a close correlation between the random urine protein-to-creatinine ratio and 24-hour urine protein collection. This correlation is near unity with a relatively narrow standard deviation until daily protein excretion exceeds 3.5 g/24-hour in patients with diabetes, and even then it distinguishes patients with nephrotic syndrome from those without (Rodby et al., 1995) making it useful for the broad characterization of urine protein excretion. The correlation is most accurate when testing the first morning voided urine, e.g., a urine protein-to-creatinine ratio of 1.0 g/g is equivalent to a 24-hour urine protein excretion rate of 1g; a ratio of 0.2 g/g would be the equivalent of 200 mg/24-hours, etc. A urine protein-to-creatinine ratio > 0.2 should be considered a positive test for proteinuria (Keane et al., 1999).

See the [VA/DoD CPG for Management of Diabetes Mellitus](#) for a discussion of microalbuminuria.

The urinalysis reagent dipstick for protein and blood can provide important initial information regarding the type of disease that may be causing kidney disease or proteinuria (see [Table 4.3. Urine Dipstick: Interpretation](#)).

The degree of proteinuria is also helpful in defining the cause of the persistent elevated creatinine and/or the cause of the abnormal proteinuria (see [Table 4.4. Evaluation of Proteinuria](#)) and may further narrow the differential diagnosis. Results of urine testing for proteinuria should be interpreted in the context of the microscopic examination of the urine, level of eGFR, and overall history and physical examination. An etiologic evaluation should be guided by history and physical, urinary sediment, and degree of proteinuria (see [Appendix B-2](#)). A guide to specialized laboratory studies for the diagnosis of kidney disease can be found in [Appendix B-3](#).

Table 4.3. Urine Dipstick: Interpretation

Protein	Blood	Consider
Negative	Negative	Rule-out false negative, microalbuminuria, multiple myeloma and other paraproteinuria Heart failure, volume depletion or obstruction, ischemic nephropathy
Positive	Negative	Rule-out false positive, benign, or orthostatic proteinuria Consider diabetes, HTN, tubulo-interstitial diseases, nephrotic syndrome Quantitate proteinuria
Positive	Positive	UTI, pyelonephritis, RPGN, GN, HIV, vasculitis, pulmonary-kidney syndrome, HUS, TTP, malignant HTN, nephrotic syndrome, nephrolithiasis with obstruction, atypical DM, PCKD
Negative	Positive	Look for urologic cause of hematuria

Key: DM: Diabetes Mellitus; GN: Glomerulonephritis; HTN: Hypertension; HUS: Hemolytic Uremic Syndrome; PCKD: Polycystic Kidney Disease; RPGN: Rapidly Progressive Glomerulonephritis; TTP: Thrombotic Thrombocytopenic Purpura; UTI: Urinary Tract Infection

Table 4.4. Evaluation of Proteinuria

A	Random urine protein-to-creatinine ratio estimates 24-hour excretion of protein in grams/24 hours. To perform the test, a random urine sample is submitted to the laboratory for protein concentration (in mg/dL) and creatinine concentration (in mg/dL). The protein concentration is divided by the creatinine concentration, and the unit-less number is the estimated daily protein excretion in gm/24 hours.						
B	Further define cause based on the degree of proteinuria/albuminuria: <table border="1" style="margin-left: 20px;"> <tr> <td>Normal:</td> <td>< 150 mg/24 hours or < 0.2 protein-to creatinine ratio</td> </tr> <tr> <td>Microalbuminuria:</td> <td>30 – 300 mg/24 hours (specifically albumin; usually measured in diabetics)</td> </tr> <tr> <td>Nephrotic range proteinuria:</td> <td>> 3 g/24 hours</td> </tr> </table>	Normal:	< 150 mg/24 hours or < 0.2 protein-to creatinine ratio	Microalbuminuria:	30 – 300 mg/24 hours (specifically albumin; usually measured in diabetics)	Nephrotic range proteinuria:	> 3 g/24 hours
Normal:	< 150 mg/24 hours or < 0.2 protein-to creatinine ratio						
Microalbuminuria:	30 – 300 mg/24 hours (specifically albumin; usually measured in diabetics)						
Nephrotic range proteinuria:	> 3 g/24 hours						
C	Degree of proteinuria and differential diagnosis <ol style="list-style-type: none"> 1. Overflow proteinuria: Trace or negative dipstick protein but a disproportionate larger amount on a 24-hour test. Its presence suggests: light-chain proteinuria as seen in multiple myeloma or lymphoproliferative process, or hemolysis (only if dip also blood +), since dipstick only measures albumin not globulins, such as light chains. 2. Proteinuria: 150 mg – 2000 mg/24 hours. <ol style="list-style-type: none"> a. May occur with interstitial diseases as well as glomerular disease b. Interstitial diseases resulting in proteinuria include analgesic nephropathy, collagen vascular diseases (Sjogren’s syndrome, lupus), heavy metal toxicity, interstitial nephritis (drugs or infectious), or granulomatous diseases 3. Proteinuria greater than 3,500 mg/24 hours suggests glomerular proteinuria and these patients should be referred to a nephrologist. Rule-out diabetes nephropathy, hepatitis, HIV, vasculitis, malignancy, and GN 4. Massive proteinuria (> 6 gm/24 hours). Focus history and physical to rule out HIV, severe focal glomerulosclerosis or minimal change disease. Refer to a nephrologist. 						
Key: GN: Glomerulonephritis; IEP: Immuno-Electrophoresis; UPEP: Urine Protein Electrophoresis; UTI: Urinary Tract Infection							

4.4. Imaging the Kidney

BACKGROUND

Renal ultrasound helps establish the diagnosis and prognosis by documenting the size of the kidneys. Normal size indicates kidney disease that may be amenable to medical treatment. Large kidneys (e.g., > 13 cm) can be seen in diabetes, amyloid, infiltrative diseases and HIV-associated nephropathy (HIV-AN). Small echogenic kidneys (< 8 cm) suggest irreversible disease. Asymmetry in size suggests renovascular disease or ureteral obstruction and can also be due to a congenital abnormality.

RECOMMENDATIONS

1. Consider kidney ultrasound in cases of unknown etiology to evaluate for kidney size, anatomical abnormality, or urinary tract obstruction.

DISCUSSION

Selected patients with risk factors for kidney disease should be screened with renal ultrasonography. Indications for this study include suspected urinary tract obstruction, recurrent urinary tract infections, vesicoureteral reflux, and a family history of PCKD (KDOQI, 2002).

<i>Annotation C</i>	<i>Is Patient in Any Acute Emergent or Urgent Condition?</i>
---------------------	--

5. URGENT/EMERGENT CONDITIONS

BACKGROUND

Because patients with CKD (or acute renal failure), particularly those with an eGFR < 30 ml/min/1.73m², can develop life-threatening complications, the initial evaluation should focus on identifying conditions or abnormalities that require emergent or urgent interventions.

RECOMMENDATIONS

1. Evaluation should identify complications of CKD that may require immediate treatment. These may include:
 - a. Acute renal failure
 - b. Fluid overload, especially pulmonary edema
 - c. Hyperkalemia (potassium \geq 6.0 mEq/L)
 - d. Metabolic acidosis (bicarbonate \leq 16 mEq/L)
 - e. Pericarditis
 - f. Encephalopathy
 - g. Uremic symptoms, such as nausea, vomiting, and anorexia.

DISCUSSION

There is no clear relationship between eGFR and clinical manifestations of CKD, but they tend to occur at lower levels of eGFR (e.g., < 30 ml/min/1.73m²). They include volume overload manifested by congestive heart failure or severe hypertension; severe hyperkalemia (serum potassium > 6.0 mEq/L); severe acidemia (e.g., pH < 7.2) with a serum bicarbonate < 16 mEq/L; severe anemia; and

symptomatic hypocalcemia. In addition, patients with very low eGFR (e.g., < 15 ml/min/1.73m²) can develop clinical manifestations of uremia such as pericarditis or encephalopathy. Several of these manifestations require immediate evaluation, usually in an emergency room, and often require admission to the hospital and initiation of dialysis. Evaluation and treatment of these complications are more fully described in [Section 11](#).

Annotation E

*Obtain Further Investigation to Rule-Out Reversible Acute Renal Failure or Other Diagnoses;
Establish and Treat the Primary Etiology of CKD*

6. REVERSIBLE CONDITIONS

BACKGROUND

Patients with CKD can develop acute renal failure. Acute renal failure is a clinical syndrome characterized by a rapid rise in creatinine occurring over a period of hours or days. Acute renal failure is associated with an increased risk of mortality and may speed progression of underlying CKD. Some forms of acute renal failure may be completely or partially reversible. In some instances, acute renal failure will only reverse with specific interventions.

Some drugs and acute medical conditions may result in an acute deterioration of renal function that may be completely or partially reversible with cessation of the drug or treatment of the underlying condition. Identifying the causes for acute renal failure can indicate treatment that may reverse the condition.

RECOMMENDATIONS

1. Any rapid reduction in eGFR in a patient with CKD should be considered acute kidney failure and evaluated promptly. [I]
2. Before ascribing deterioration in kidney function to progression of the patient's underlying chronic disease, evaluate for reversible causes such as: [I]
 - a. Volume depletion
 - b. Severe heart failure
 - c. Urinary tract obstruction
 - d. Acute tubular necrosis occurring in the setting of hypotension or nephrotoxic agents, such as radiocontrast or antibiotics.
 - e. Acute interstitial nephritis, often due to drugs such as NSAIDs or antibiotics.

DISCUSSION

Acute renal failure is best identified by evaluating prior measurements of serum creatinine to identify the rate of progression. In the absence of prior measurements, there may be clues in the history or physical examination that suggest the possibility of a reversible cause of renal deterioration, particularly volume depletion and the use of nephrotoxic agents, two of the most common causes of reversible renal dysfunction.

Most, but not all causes of acute renal failure, are completely or partially reversible and many require urgent interventions, including referral to an emergency department, an urgent nephrology consultation, and admission to the hospital.

Information about the patient's recent baseline creatinine levels and urinalysis results is necessary to determine the acuity of the kidney process. Clues to the diagnosis of these conditions can be obtained

by careful evaluation of the presenting history, physical examination, and screening laboratory evaluation. Since some conditions require specific treatments to reverse the kidney failure, every effort should be made to ensure that the patient receives timely care for these conditions. Clues to the diagnosis of specific acute processes include the following:

- a) **Volume depletion** is frequently accompanied by a history of anorexia, vomiting, diarrhea, diuretic use, or blood loss. Physical examination may show tachycardia, hypotension, or postural changes in pulse and blood pressure. The laboratory tests demonstrate elevated BUN and creatinine levels, often with BUN elevated out of proportion to creatinine (BUN to creatinine ratio > 20 to 1).
- b) **Severe congestive heart failure** is usually diagnosed based on the history and physical examination.
- c) **Urinary tract obstruction** can be accompanied by symptoms of hesitancy, urgency, post-void dribbling, dysuria, hematuria, or decreased urinary output. The physical exam may reveal a palpable bladder. The diagnosis is typically made by demonstrating hydronephrosis on kidney ultrasound. Check for a large post void residual urinary volume using ultrasound of the bladder or catheterization if indicated.
- d) **Acute tubular necrosis** is frequently associated with hypotension, infection, surgery, or exposure to nephrotoxic agents. Muddy brown casts may be present in the urine.
- e) **Acute interstitial nephritis** is often drug related. Patients may also have a fever, rash, history of arthralgias, eosinophilia, and sterile pyuria or eosinophiluria. Non-nephrotic proteinuria is frequently present. Nephrotic syndrome may be seen in patients with acute interstitial nephritis due to NSAIDs.
- f) **Acute pyelonephritis** is accompanied by symptoms related to infection including fever and costovertebral angle tenderness. The urinalysis may show white blood cells, red cells, and white blood cell casts. Urine cultures are positive.
- g) **Acute glomerulonephritis** may be accompanied by the history and findings of sudden onset of edema, hypertension, and microscopic or macroscopic hematuria. The urinalysis may show proteinuria, red blood cells, and red blood cell casts.
- h) **Atheroembolic disease** is typically seen following arteriography, vascular or cardiac surgical procedures, or in patients on anticoagulant or thrombolytic therapy. The physical examination may show livedo reticularis, ischemia of distal extremities, and retinal plaques. Urinalysis may show eosinophiluria.

7. PRIMARY ETIOLOGY OF KIDNEY DISEASE

BACKGROUND

The most common causes of CKD are hypertension and diabetes. In most instances, it will be possible to identify the most likely etiology of CKD using the history, physical examination; urinalysis, laboratory, and imaging test. In some patients, optimal management will require definitive diagnosis with a kidney biopsy (see [Appendix B, Tables B-2 and B-3](#)). Although there are treatments that are applied to all patients with CKD, such as the use of ACEI/ARBs, some etiologies may require specific treatment and referral to a nephrologist.

RECOMMENDATIONS

1. Use history, physical examination, laboratory tests, and imaging procedures to establish most likely etiology. [I]
2. Patients with CKD not related to hypertension or diabetes or in whom the etiology is uncertain may benefit from a referral to a nephrologist for evaluation and treatment. [I]
3. A kidney biopsy should be considered in patients with nephrotic range proteinuria (urine protein-to-creatinine ratio > 3.5), particularly in the absence of diabetes, to determine the histopathology of the kidney disease.
4. Urology should be consulted for patients with urinary tract obstructions. [I]

DISCUSSION

Diabetes and hypertension are the two leading causes of CKD in the United States. Patients with known diabetes, particularly those with retinopathy and with pre-existing proteinuria, can usually be assumed to have diabetic nephropathy in the presence of urine sediment without cellular elements or casts. Similarly, patients with long-standing hypertension, low grade proteinuria (< 1 gm/day) and urine sediment without cells or casts may be assumed to have hypertension as the cause of their kidney disease (AASK Study, 2002). The presence of an active urine sediment (hematuria, pyuria, red or white cell casts), obstructive symptoms, or rapid deterioration in eGFR (e.g., >50% in 6 months) in any patient whether or not they have diabetes or hypertension should prompt a search for other causes of CKD and requires a nephrology referral.

For some etiologies, treatment of the underlying disorder leading to kidney disease may delay, prevent, or reverse the progression of CKD. Specific treatments include the following:

- **Hypertension:** see the [VA/DoD CPG for Management of Hypertension](#).
- **Diabetes Mellitus:** see the [VA/DoD CPG for Management of Diabetes Mellitus](#).
- **Glomerulonephritis (GN):** can be caused by a heterogeneous group of diseases that may require different treatments. Patients suspected, or known, to have GN should be referred to a nephrologist for definitive diagnosis and subsequent appropriate treatment.
- **Polycystic kidney disease (PCKD):** Because of the systemic nature of PCKD and the implications of this diagnosis for both the patient and their family, patients with PCKD should be referred to nephrology, at least for initial evaluation and recommendations.
- **Urinary tract obstruction (UTO):** The key intervention in any patient with UTO is to relieve the obstruction (which may require referral to urology or interventional radiology). The patient with UTO may also have an infection, which should be treated.

Patients should receive follow-up after diagnosis and relief of urinary obstruction to determine whether the kidney function has normalized. Serum creatinine may require several weeks to reach a steady state and may never return to normal. Should kidney failure not resolve within weeks, alternative causes for kidney dysfunction, or new acute kidney failure should be considered.

- **Analgesic nephropathy:** Analgesic nephropathy is caused by chronic use of NSAIDs (e.g., indomethacin, fenoprofen, naproxen, ibuprofen, etc.) or abuse of combination analgesics (e.g., aspirin, acetaminophen). Depending on the chronicity of analgesic use, the severity of CKD, and the presence of other underlying causes of CKD discontinuing the offending agent(s) may not necessarily result in an improvement in eGFR.

- **HIV-associated nephropathy (HIV-AN) and HCV-related kidney disease:** Evidence of kidney abnormalities (elevated serum creatinine, proteinuria and/or hematuria) in HIV infected individuals requires early referral to a nephrologist. There is a broad spectrum of kidney disease seen in HIV positive patients that includes HIV-AN, immune-complex mediated GN, and acute renal failure syndromes all of which require different interventions. Therefore, kidney biopsy is often required to guide management of renal dysfunction in patients with HIV.

HCV can be associated with a variety of different glomerulonephritides, classically membranoproliferative glomerulonephritis (MPGN) with or without cryoglobulins. Thus a patient with HCV who develops CKD should be referred to a nephrologist. Low complement levels and the presence of cryoglobulins in patients with a chronic HCV are considered by some to be sufficient evidence of the presence of MPGN. Depending on the clinical context, and usually in consultation with the patient's hepatologist, a kidney biopsy may help to guide management of patients with HCV either to confirm the etiology of the kidney disease when this is uncertain or to assess the severity and chronicity of kidney involvement. Treatment of this entity may include alpha interferon and ribavirin depending on the patient's level of eGFR.

- **Renovascular disease (RVD):** The indications for the treatment of renal artery stenosis associated with CKD are controversial. Although there is some evidence that intervention with surgery or angioplasty may reverse or stabilize kidney function, the natural history of untreated atherosclerotic renal artery stenosis is not well characterized. In the absence of randomized controlled studies, patients with known renal artery stenosis should be referred to a nephrologist if they have hypertension that is difficult to control (i.e., the patient requires more than four drugs), or if they experience an increase in Cr of > 50 percent in less than six months (Dean et al., 1991).

The patient with bilateral renal artery stenosis is at risk for development of worsening kidney function or hyperkalemia with the use of an ACEI (Hricik et al., 1983) or ARB. Nevertheless, ACEIs and ARBs can be beneficial in patients with renal artery stenosis in terms of slowing progression of CKD and lowering blood pressure. Because of the potential for acute worsening of eGFR and hyperkalemia, these drugs should be used with caution in patients with known or suspected renal artery stenosis (RAS). Specifically, serum creatinine and potassium should be measured within 1 to 2 weeks of initiating therapy or increasing dosage.

- **Multiple myeloma with monoclonal immunoglobulin light chain-related kidney disease:** Decreased eGFR may be the initial presentation of a plasma cell dyscrasia. These include multiple myeloma, undefined plasma cell dyscrasia, amyloidosis, monoclonal gammopathy of undetermined significance (MGUS) and chronic lymphocytic leukemia. Depending on the clinical context, a kidney biopsy may play a critical role in guiding management of the underlying plasma cell dyscrasia. Since subsequent management is usually directed by the hematologist (or oncologist), the diagnostic work up of CKD in these patients should be undertaken by the nephrologist in close consultation with the treating specialty.

Annotation F

Is there Indication to Consult/Refer to Nephrology?

8. CONSULTATION WITH/REFERRAL TO NEPHROLOGY

8.1. Referral to nephrology

BACKGROUND

Nephrology consultation or referral can serve a variety of different purposes: identifying the underlying etiology of kidney disease, initiating therapies to slow progression of CKD and identifying reversible processes leading to rapid loss of eGFR, managing the complications of kidney disease, and preparing patients for renal replacement therapy. On the other hand, not all patients with CKD will benefit from nephrology consultation or referral. This section is intended to guide the primary caregiver as to when nephrology referral is likely to be most beneficial to the patient.

Nephrology referral is always appropriate when the primary care provider is not comfortable managing a patient with CKD. Specific indications for nephrology referral include an eGFR < 30 ml/min/1.73m², rapid progression of CKD (or superimposed acute renal failure in a patient with established CKD), when the patient has a known or suspected kidney condition requiring specialized nephrology care (e.g., glomerulonephritis), and for diagnostic work up when the etiology is unclear, or if the primary care provider suspects that a kidney biopsy may be indicated

Indications for a nephrology referral in CKD:

- Underlying cause is unclear after the basic work-up
- Kidney biopsy is indicated
- eGFR < 30 ml/min/1.73m²
- Rapid progression of CKD
- Superimposed acute kidney failure
- Management is beyond the comfort of the individual provider

RECOMMENDATIONS

Nephrology consultation for help in diagnosis and treatment is indicated in:

1. Patients with eGFR < 30 ml/min/1.73m² to facilitate education and planning for renal replacement therapy (dialysis or kidney transplant).
2. Patients with kidney function that is deteriorating rapidly (e.g., eGFR decline of 50% eGFR from previous measure over 6 months or less) without obvious cause.
3. Patients with metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism).
4. Patient has CKD of unclear etiology after initial work up, or has a known or suspected kidney condition requiring specialized care (e.g., a glomerulonephritis).

RATIONALE

Patients with $eGFR < 30 \text{ ml/min/1.73m}^2$ are at highest risk for progression to ESKD ($eGFR < 15 \text{ ml/min/1.73m}^2$), and for development of metabolic complications. For these reasons, these are the patients most likely to benefit from nephrology referral, particularly if their metabolic complications are severe and their CKD is progressive. In general, it takes at least six months to adequately prepare patients for renal replacement therapy.

DISCUSSION

In observational studies, late nephrology referral among patients with severe CKD is associated with worse outcomes after initiation of dialysis (Astor et al., 2001; Avorn et al., 2002; Cleveland et al., 2002; Huisman, 2004; Roderick et al., 2002a; Roderick et al., 2002b; Winkelmayr et al., 2002; Winkelmayr et al., 2003). Adverse outcomes linked to late referral to nephrology include higher early mortality after initiation of dialysis, lower transplant rates, higher rates of catheter use at the time of initiation of dialysis, and longer duration of catheter use after dialysis initiation. While these studies are observational in nature and results may reflect a selective referral of patients who are felt to be the best candidates for dialysis, it seems plausible that there may be a causal connection between referral to nephrology and improved clinical outcomes because critical elements of pre-ESKD care such as referral for pre-dialysis vascular access, discussion of dialysis modality, and referral for renal transplant are generally only provided by nephrologists.

<i>Annotation G</i>	<i>Discuss Future Need for KRT</i>
---------------------	------------------------------------

8.2. Future Need for KRT

BACKGROUND

Patients who are expected to experience progressive loss of renal function to the point of requiring renal replacement therapy within the time frame needed to prepare for dialysis are likely to benefit from referral to nephrology. Nephrologists are usually in the best position to facilitate informed decision-making in this area and are generally charged with key referrals for vascular access placement and transplant evaluation. Because progression to ESKD increases dramatically at $eGFR$ levels $< 30 \text{ ml/min/1.73m}^2$ and metabolic complications related to CKD are more common and more severe among patients with an $eGFR$ in this range, an $eGFR < 30 \text{ ml/min/1.73m}^2$ serves as a reasonable threshold for recommending referral to a nephrologist.

Early referral to nephrology and pre-dialysis education has been associated with:

- Improved vocational outcomes
- Delay in the need to initiate ESKD therapy
- Increased proportion of patients initiating dialysis who have permanent dialysis access, particularly arteriovenous fistula (which has a much longer useful life)
- A difference in modality selection (i.e., increased likelihood of selecting peritoneal dialysis)
- Reduced need for urgent dialysis
- Reduced need for inpatient initiation of dialysis
- Better metabolic parameters
- Improved patient choice regarding transplantation or peritoneal dialysis.

RECOMMENDATIONS

1. ESKD and kidney replacement therapy (KRT) should be discussed with patients by the primary care provider while referring to nephrology for assistance in evaluation and treatment:
 - a. Discuss the progression of kidney disease to ESKD, in general terms
 - b. Explain why the patient needs to see the nephrologist
 - c. Reinforce and review the information provided to the patient by the nephrologist
 - d. Discuss the principles of dialysis (peritoneal dialysis or hemodialysis) and transplantation, in general terms
 - e. Maintain consistency of information between the primary care provider and the nephrologist.

Annotation H

Establish Treatment Plan to Address Treatment of Primary Etiology

9. MANAGEMENT OF CKD – PROMOTION OF GENERAL HEALTH

BACKGROUND

The treatment plan in primary care for patients diagnosed with CKD should include routine monitoring of kidney function and promotion of general health, addressing cardiovascular risk factors as related to CKD. Referral to a nephrologist is not necessary in most patients with CKD. For indications for referral see [Annotation 8](#).

RECOMMENDATIONS

1. Treatment plan for patients diagnosed with CKD should include routine monitoring of kidney function and promotion of general health, addressing cardiovascular risk factors as related to CKD. These may include:
 - a. Regular measurement of kidney function (eGFR) to assess the severity of kidney impairment (see [Section 4](#))
 - b. Management of the primary etiology
 - c. Initiation of strategies to slow the progression of the disease
 - d. Prevention and management of complications
 - e. Management of co-existing comorbid conditions (e.g., diabetes, hypertension, cardiovascular disease).
2. There is insufficient evidence to support a particular management strategy for reducing cardiovascular risk in patients with CKD, although the prevalence of cardiovascular disease is high in this population. In the absence of evidence to support a tailored approach in patients with renal insufficiency, strategies applicable to the general population should be considered.

10. STRATEGIES TO SLOW THE PROGRESSION OF THE DISEASE

BACKGROUND

Reduction of protein excretion results in a reduction in the risk of progressive kidney failure, and is therefore an important therapeutic target for all adults with CKD, irrespective of age.

The progression of kidney disease may be slowed with the use of non-invasive interventions.

- 10.1 Control of hypertension
- 10.2 Use of an ACEI or ARB
- 10.3 Protein restriction
- 10.4 Control of hyperglycemia in patients with diabetes
- 10.5 Avoidance of nephrotoxic drugs and adjusting medication doses as indicated
- 10.6 Smoking cessation
- 10.7 Control of dyslipidemia

10.1. Control of Hypertension

BACKGROUND

The goals of lowering blood pressure include a reduction of mortality and cardiovascular events and slowing the progression of CKD. Several studies have been undertaken to determine what blood pressure target is appropriate for patients with CKD. Based on these studies, consensus guidelines currently recommend blood pressure targets of < 130/80 mm Hg in patients with CKD, both with and without diabetes. The evidence to support a further blood pressure lowering to < 125/75 mm Hg in patients with > 1 g/day proteinuria is inconclusive.

Level I evidence in support of these recommendations is unavailable; they are the expert opinion of several CKD workgroups in the United States and abroad.

Uncontrolled hypertension not only increases the risk of serious cardiovascular morbidity or mortality but is also associated with a more rapid progression of CKD. Treatment of hypertension in CKD patients with antihypertensive drugs therefore has two aims: reduction of the risk of cardiovascular disease and reduction of the risk of progressive loss of kidney function. Studies have suggested that a lower blood pressure target has a greater impact on the progression of CKD than on cardiovascular disease risk. There is considerable uncertainty about the ideal blood pressure target in patients with CKD. First, few patients with CKD have been included in larger scale trials of hypertension and renal outcomes are often not examined. Second, there have been very few RCTs of the effect of blood pressure lowering to specific targets in patients with CKD. Among these, most have shown no difference in the progression of renal disease with lower than conventional blood pressure targets.

In the absence of good evidence, it proved impossible to reconcile all existing sources of guidance and opinions, largely due to a poor definition of the intervention thresholds and optimal blood pressure goals in some of the guidelines.

The preferred antihypertensive agents are discussed in [Section 10.2](#).

RECOMMENDATIONS

1. Blood pressure should be closely monitored in all patients with CKD and checked at each visit. [I]
2. Blood pressure measurement should conform to published standards (see [VA/DoD CPG for Management of Hypertension](#)). [C]
3. Treatment of high blood pressure in CKD should include identification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease and development of cardiovascular disease.
4. Antihypertensive therapy should be adjusted to achieve blood pressure of < 130/80 mm Hg. [C]

Non Pharmacologic Interventions

5. All patients with CKD with hypertension should be offered life-style advice, including maintenance of normal body weight (body mass index 18.5 to 24.9 kg/m²), reduction in dietary sodium intake (< 2 g/day), regular aerobic physical exercise, smoking cessation, and limitation of alcohol intake. [B]

Pharmacologic Interventions

6. ACEIs or ARBs are the preferred agent for patients with kidney disease and hypertension. ACEIs may be preferred based on cost. ARBs may be substituted for patients with an ACEI induced cough. [A]
7. Many patients will require two or more medications to achieve their target blood pressure control. A diuretic should be used when a second blood pressure medication is needed, or if hyperkalemia occurs. Thiazide diuretics may be used if estimated GFR > 30 ml/min/1.73m², but loop diuretics are usually needed for patients with lower eGFR. Potassium-sparing diuretics should be used with caution in patients with CKD (see [Table 10.1. Summary of Number of Antihypertensive Agents Required to Reach Target Blood Pressure](#)).
8. An increase of serum creatinine, as much as 30 percent above baseline after ACEI or ARB initiation, may be tolerated. ACEIs or ARBs should not be discontinued for this situation, since these medications are renoprotective.
9. Patients with resistant hypertension, defined as inability to achieve goal blood pressure despite combination therapy with three drugs from complementary classes (including a diuretic), may benefit from an evaluation by a specialist in hypertension.

RATIONALE

There is Level III evidence (opinion) to suggest that blood pressure should be maintained at < 130/80 mm Hg in patients with non-diabetic CKD. Level I evidence (based on RCTs) to support this low blood pressure is lacking. There is Level II evidence that in patients with > 1 g proteinuria, more aggressive lowering of blood pressure may slow progression of CKD, although the optimal blood pressure level is unknown.

DISCUSSION

Numerous RCTs in patients without diabetes (Giatras et al., 1997; The GISEN Group, 1997; Hebert et al., 1997; Klahr et al., 1995) and with diabetes (Brenner et al., 2001; Crepaldi et al., 1998; Estacio et al., 2000; Lewis et al., 1993; Lewis et al., 1999; Lewis et al., 2001; Parving et al., 2001; Weidmann et al., 1995) with CKD have clearly shown that blood pressure lowering is associated with substantial reductions (1.1 to 6.2 ml/min/1.73m² per year) in GFR decline. Meta-regression analyses have indicated that blood pressure reduction accounts for 50 percent of the variance in GFR decline and that each 10-mm Hg reduction in mean arterial pressure (down to 92 mm Hg) confers a benefit in eGFR preservation of 3.7 to 5.0 ml/min/1.73m² per year (Bakris & Weir, 2000; Jafar et al., 2001; Maki et al., 1995).

The degree of renal protection afforded by blood pressure reduction appears to be proportional to the degree of baseline proteinuria (The GISEN Group, 1997; Klahr et al., 1994; Ruggenenti et al., 1998) and its reduction following treatment (Klahr et al., 1994). In the multicentre Modification of Diet in Renal Disease (MDRD) study, the differences in mean GFR decline between the low and standard blood pressure groups were greatest in patients with proteinuria > 3 g/day (approximately 4 ml/min/1.73m² per year), intermediate in patients with proteinuria 1 to 3 g/day (approximately 2 ml/min/1.73m² per year) and least in patients with proteinuria <1 g/day (0 ml/min/1.73m² per year) (Kasiske et al., 1993). Moreover, each 1 g/day decrease in protein excretion following antihypertensive treatment was associated with a reduction from 0.9 to 1.3 ml/min/1.73m² per year in eGFR decline.

Based on these studies (particularly the MDRD study), the guidelines currently recommend blood pressure targets in patients without diabetes of ≤ 130/80 mm Hg if proteinuria is < 1 g/day and ≤ 125/75 mm Hg if proteinuria is >1 g/day.

For a summary of studies supporting the recommendations – see [Appendix C-1](#).

Table 10.1. Summary of Number of Antihypertensive Agents Required to Reach Target Blood Pressure

Study, Year	Target Blood Pressure (mm Hg)	Achieved Blood Pressure	Mean Number of Agents
IDNT, 2001	Systolic < 135	Systolic 138	2.6
RENAAL, 2001	Systolic < 140	Systolic 141	2.7
ABCD, 2000	Diastolic < 75 or 80-89 ^a	132/78 and 138/86 ^a	2.4
CSG Captopril Trial, 1993	Systolic < 140, Diastolic < 90	Mean arterial pressure 96±8 and 100±8 ^b	1-3 ^b

^a Denotes intensive blood pressure control group and moderate blood pressure control group, respectively.
^b Denotes captopril and placebo groups, respectively, number of agents inferred from report; there were approximately 25% normotensive participants.
Source: KDOQI Diabetes and CKD, 2007

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	CKD alone Target for blood pressure 140/90 mm Hg	AASK, 2002	I	Good	A
2	CKD with cardiovascular risk or type 2 DM Target for blood pressure 130/80 mm Hg	KDOQI, 2002	III	Poor	C
3	CKD with > 300 g proteinuria Target for blood pressure > 130/80 mm Hg	KDOQI, 2002	III	Poor	C
4	CKD with > 1 g proteinuria Target for blood pressure 125/75 mm Hg	MDRD (post analyses)	III	Poor	C
5	Diabetic nephropathy Target for blood pressure 130/80 mm Hg	ABCD, 2000 ADA, 2003a JNC 7, 2003 KDOQI, 2002	III	Poor	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

10.2. Use of an ACEI or ARB

BACKGROUND

The angiotensin-converting enzyme inhibitors (ACEIs) have beneficial effects in patients with diabetic nephropathy and other kidney diseases. These drugs slow the progression of kidney disease independent of their effect on blood pressure. The ACEIs reduce proteinuria, an effect that may be renoprotective. The agents reduce proteinuria at any given level of blood pressure reduction more than other antihypertensive drugs. In general, the angiotensin II receptor blockers (ARBs) are a class of drugs which may be used in patients who are intolerant of an ACEI.

RECOMMENDATIONS

1. Patients with non-DM CKD with hypertension or diabetes with macroalbuminuria should be treated with an ACEI or ARB to slow the progression of kidney disease [A] and reduce proteinuria [A].
(See [VA/DoD CPG for Management of Diabetes Mellitus](#))
2. Patients with diabetes and microalbuminuria should be treated with an ACEI or ARB to slow the progression from microalbuminuria to macroalbuminuria, considered a surrogate for progression to CKD. [A]
3. ACEIs and ARBs should be initiated at low doses and titrated to moderate to high doses as used in clinical trials. [A]
4. There is insufficient evidence to recommend combination therapy with an ACEI and ARB to slow the progression of kidney disease except in a limited population of non-DM CKD. [C]
5. Creatinine and potassium levels should be monitored one to two weeks after initiation or after a change in dose of ACEI or ARB therapy and periodically to maintain a normal range. [C]
6. Treatment with an ACEI or ARB should not be initiated in patients with hyperkalemia (> 5.5). [D]
7. People who develop cough on an ACEI should be switched to an ARB. Some people who develop angioedema on an ACEI may be switched to an ARB but require careful monitoring since some may also develop angioedema on an ARB. [C]
8. In most patients, an ACEI or ARB should be continued unless:
 - a. There is an acute GFR decline of > 30 percent within the first two weeks after initiation. [B]
 - b. Serum potassium is ≥ 6 mEq/L, despite appropriate treatment. [B]
9. If ACEIs and ARBs are not tolerated, a nondihydropyridine calcium channel blocker, either verapamil or diltiazem, may be considered to reduce proteinuria. [B]

DISCUSSION

There is good evidence that ACEI therapy slows the progression of non-DM CKD in patients with proteinuria. There is insufficient evidence to support use of an ACEI in patients without concomitant hypertension, as the majority of these trials enrolled patients with hypertension; although there continued to be benefit from the ACEI after adjustment for blood pressure. There is fair evidence to suggest that ARBs lower blood pressure and proteinuria, at least as well as ACEIs in individuals with non-DM CKD. Only in patients with immunoglobulin A (IGA) nephropathy is there good evidence that the combination of an ACEI and ARB is more effective than either medication alone in decreasing the progression of non-DM CKD.

- For medication dosage and information see [Appendix D-1](#).
- For prevention and management of hyperkalemia, see [Section 10.2 – Use of an ACEI or ARB](#).

- For a summary of studies supporting the recommendations see [Appendix C-2](#).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Use ACEI to slow the progression of kidney disease in patients with non-DM CKD and hypertension	AASK, 2002 AIPRD, 2003 Jafar et al., 2001 REIN, 1997 REIN-2, 2005	I	Good	A
2	Use ACEI or ARB to reduce proteinuria in patients with non-DM CKD and hypertension	Del Vecchio et al., 2004 Iino et al., 2004 Ishimitsu et al., 2005 Luno et al., 2002 Matsuda et al., 2003 Nielsen et al., 1997 Plum et al., 1998 REIN, 1997 Remuzzi et al., 1999	I	Good	A
3	Use ACEI or ARB to slow the progression of CKD in patients with DM and macroalbuminuria	IDNT, 2001 KDOQI DM, 2007 Lewis et al., 1993 RENAAL, 2001	I	Good	A
4	Use ACEI or ARB to slow the progression of CKD in patients with DM and microalbuminuria	ACEI/DN Trialists, 2001 IRMA-2, 2001 Laffel et al., 1995 Lovell, 2001 KDOQI DM, 2007 Viberti et al., 1994	I	Good	A
5	Initiate ACEI and ARB at low doses and titrate to moderate to high doses as used in clinical trials	AASK, 2002 Aranda et al., 2005 DETAIL, 2004 Esnault et al., 2005 IDNT, 2001 IRMA-2, 2001 Lewis et al., 1993 KDOQI DM, 2007 RENAAL, 2001	I	Good	A
6	Initiate therapy with an ACEI; an ARB should be used as an alternative agent	Andersen et al., 2000 DETAIL, 2004 Lacourciere et al., 2000 Muirhead et al., 1999 Nielsen et al., 1997 KDOQI DM, 2007 KDOQI HTN, 2004	I	Fair	B
7	There is insufficient evidence to recommend combination therapy with an ACEI and an ARB in non-DM or DM CKD to slow the progression of kidney disease except in patients with IGA nephropathy	Campbell et al., 2003 COOPERATE, 2003 MacKinnon et al., 2006 Mogensen et al., 2000 KDOQI DM, 2007 KDOQI HTN, 2004	I	Fair	C
8	Monitor for adverse effects (including hypotension, hyperkalemia, decreased GFR) in patients treated with an ACEI or ARB	Bakris et al., 2000 Morimoto et al., 2004 Raml et al., 2001 KDOQI HTN, 2004	I II-2 II-3 III	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

10.3. Protein Restriction

BACKGROUND

The World Health Organization defines normal dietary protein intake as 0.8 g/kg/day. Low-protein diets (≤ 0.8 g/kg/day) have long been advocated as a potential means of slowing the rate of progression of kidney disease, delaying the onset of uremic symptoms and thereby delaying the need for dialysis. Available evidence does not provide strong support for protein restriction as a means of slowing the progression of CKD. RCTs provide insufficient evidence that protein restriction slows loss of GFR and a meta-analysis demonstrated only a weak effect. However, other meta-analyses examining the separate outcome of renal death, usually defined as time to death or treatment for ESKD, have reported a lower incidence of this outcome among patients receiving a protein restricted diet. This apparent paradox is perhaps explained by the possibility that while protein restriction does not slow the progression of renal disease it may delay the onset of uremic symptoms and forestall the need for dialysis. Decision-making in this area is further complicated by the need to balance any perceived benefit of protein restriction with the risk of compromising nutritional status and/or the greater intensity of dietitian input that may be required to ensure that this does not happen. Any dietary prescription should take into account the spontaneous tendency for patients with CKD to reduce protein and caloric intake.

RECOMMENDATIONS

1. There is insufficient evidence to recommend the routine implementation of a low protein diet (≤ 0.6 g/kg/day) to slow the loss of GFR in patients with CKD. [D]
2. A low protein diet may delay the onset of uremic symptoms in patients close to needing dialysis but this benefit must be weighed against the risk of protein malnutrition. [B]

RATIONALE

In the 1980-1990s there were a number of RCTs examining the impact of protein restriction on the progression of renal disease. These trials were quite heterogeneous in their design and did not show a consistent benefit of protein restriction. While some small RCTs (mostly in patients with diabetes) and some larger RCTs primarily in non-diabetic patients have reported slower loss of GFR in patients on a low protein diet, most RCTs, including the MDRD study which was the largest and most definitive to date, reported no difference in the loss of GFR or surrogate measures of GFR comparing the intervention and control arms. In addition, the additional benefit of protein restriction over ACE inhibition was not addressed in most of these trials. The impact of protein restriction on loss of GFR remains somewhat controversial because patients with PCKD—who usually do not experience heavy proteinuria and thus are less likely than other groups to benefit from protein restriction—were over represented in the MDRD study and because the study may have been underpowered due to slower than expected progression among participants.

Paradoxically, several meta-analyses have demonstrated a strong association between protein restriction and longer time to renal death (onset of ESKD or death). However, because most of these trials were not set up to examine renal death as a primary outcome and because this outcome is in part a treatment decision, it is difficult to know how to interpret this finding. In addition, several showed significant publication bias in favor of a protein-restricted diet.

EVIDENCE STATEMENTS

RCTs on protein restriction are quite heterogeneous in terms of entry criteria, specific intervention and outcome measures. While several small RCTs in patients with diabetes (Ciaverella et al., 1987, Dullaart et al., 1993; Raal et al., 1994; Zeller et al., 1991) and some RCTs in patients without diabetes (D'Amico et al., 1994; Ihle et al., 1989, Meloni et al., 2002; Rosman et al., 1984) demonstrated slower loss of GFR among protein restricted patients, most RCTs of protein restriction report no sustained

difference between protein-restricted and non-restricted groups in loss of kidney function (Hansen et al., 2002; Jungers et al., 1987; Klahr et al., 1994; Locatelli et al., 1991; Pijls et al., 2002; Rosman et al., 1989; Williams et al., 1991). The MDRD study was the largest of these studies and found no difference between intervention and control arms in the rate of change in GFR or in the incidence of the composite outcome of doubling of serum creatinine or onset of ESKD. Because the overall rate of progression in the MDRD study population was low and the study included a large percentage of patients with PCKD, generalizability may be limited and it is possible that the study was underpowered to examine differences between control and treatment groups. The few RCTs that did report an effect of protein restriction on loss of renal function (Ciaverella et al., 1987; D'Amico et al., 1984; Dullaart et al., 1993; Ihle et al., 1989; Raal et al., 1994; Rosman et al., 1984; Zeller et al., 1991) do not provide compelling evidence to counteract the results of this study, though the possibility does remain that there may be a benefit among patients with diabetes. Finally, an important factor limiting the clinical relevance of RCTs of protein restriction is that most were conducted in an era of less widespread use of ACEIs and/or did not account for differential use of ACEI in study participants. Thus, none of these trials address the question of what additional benefit protein restriction provides among patients receiving ACEIs or ARBs—the most clinically relevant question in our current era of widespread ACEI and ARB use. A meta-analysis of 13 trials that included relatively few patients with diabetes demonstrated a very modest slowing of progression of renal decline by 1.53 ml/min/year with protein restriction (Kasiske et al., 1998). This study also reported evidence for a publication bias favoring studies with positive, rather than negative results.

Paradoxically, some clinical trials (Hansen et al., 2002; Ihle et al., 1989; Jungers et al., 1987) and meta-analyses (Fouque et al., 2006) (updated from the 1992 and 2000 versions of the review) showed a lower odds of progression to renal death in patients on a low protein diet. However, this association must be interpreted with some caution; interpretation of the outcome of renal death defined in part by onset of ESKD is complicated because ESKD is a treatment decision and results may be explained by variation in treatment decisions in patients on a lower protein diet (these trials were not blinded). It is generally assumed that these results indicate that protein restriction can reduce uremic symptoms and slow onset of ESKD; these trials were for the most part not optimally designed to test this hypothesis.

In general, a low protein diet was well tolerated in most of the studies described, although in several studies, patients in the protein-restricted arm experienced worsening nutritional status during the course of the trial (Ihle et al., 1989; Meloni et al., 2002). Thus, any perceived benefits of protein restriction must be weighed against the competing goal of maintaining good nutrition among patients with severe CKD and renal failure in whom there may be a spontaneous tendency to restrict protein intake and thus greater need for intensive monitoring by a nutritionist to ensure that patients do not become malnourished on a low protein diet.

Spontaneous Protein Restriction and Risk of Malnutrition

Another concern regarding dietary protein restriction in patients with CKD is the spontaneous reduction in dietary protein intake with declining GFR. Ikizler et al. (1995) noted that mean spontaneous dietary intakes averaged 1.1 g/kg/day for patients with creatinine clearances > 50 ml/min, 0.85 g/kg/day at 25 to 50 ml/min, 0.70 g/kg/day at 10 to 25 ml/min and 0.54 g/kg/day at < 10 ml/min. These changes raise questions regarding the safety of further restricting protein intake.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Protein restriction does not show consistent benefit in change in GFR	D'Amico et al., 1994 Hansen et al., 2002 Ihle et al., 1989 Jungers et al., 1987 Kasiske et al., 1998 Klahr et al., 1994 Locatelli et al., 1991 Meloni et al., 2002 Pijls et al., 2002 Rosman et al., 1984, 1989 Williams et al., 1991	I	Fair	D
2	Strong association between protein restriction with delayed onset of renal death	Fouque et al., 2006 Kasiske et al., 1998 Pedrini et al., 1996	I	Fair	B

QE = Quality of Evidence; SR = Strength of Recommendations (See Appendix A)

10.4. Control of Hyperglycemia in Patients with Diabetes

BACKGROUND

Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) confirmed that improved glycemic control in type 1 and type 2 DM can prevent the development of microalbuminuria. The evidence of a benefit of intensive glycemic control on the progression from microalbuminuria to overt nephropathy is controversial.

RECOMMENDATIONS

1. In patients with diabetes, glycemic control should be managed according to the [VA/DoD CPG for Management of Diabetes Mellitus](#).
2. In patients with CKD, the use of antidiabetic agents should be reviewed and modified since several are renally excreted (see [Appendix D](#)).

10.5. Avoidance of Nephrotoxic Drugs and Adjustment of Medication Doses as Indicated

BACKGROUND

Some drugs are potentially toxic to the kidney and can worsen kidney function, precipitating acute deterioration of renal function.

The clearance of drugs that are excreted by the kidney may be impaired in the presence of reduced kidney function. This can lead to drug accumulation with toxic effects specific to the drug. Some medications therefore require dosage adjustments according to the level of kidney function.

RECOMMENDATIONS

1. Use of prescription and over-the-counter drugs, including herbal supplements, should be reviewed and doses modified or adjusted to the level of kidney function (per CrCl or sCr) in patients with CKD. [C]

2. Avoid or limit exposure to nephrotoxic drugs. [D]
3. Patients with CKD should preferentially undergo imaging studies that do not require the use of iodinated contrast. If iodinated contrast cannot be avoided, low- or iso-osmolar non-ionic agents should be used. Consider the use of measures to prevent contrast nephropathy, including intravenous fluids. [B]

Clinicians should also be aware of recent FDA warnings on the risk for nephrogenic systemic fibrosis with the use of gadolinium-based contrast agents in patients with acute or severe chronic kidney disease.

(See [Appendix D-2](#))

DISCUSSION

Several commonly used drugs may be nephrotoxic in patients with CKD. These include NSAIDs, aminoglycosides, various cancer chemotherapeutic drugs, lithium, some of the bisphosphonates, cyclosporine, and tacrolimus. Other drugs are not themselves nephrotoxic, but have toxicities that may be accentuated in CKD. These toxicities include hyperkalemia (ACEI, ARB, potassium-sparing diuretics, trimethoprim, digoxin, and heparin) and lactic acidosis (metformin). It is not possible to specify GFR thresholds for the use of all drugs. According to the manufacturer, the use of metformin is contraindicated in men with a serum creatinine greater than 1.5 and in women with a serum creatinine greater than 1.4. There are no formal recommendations for the use of metformin based on the GFR level.

Many commonly used drugs require dose adjustment in patients with CKD. The extent of dose reduction depends on the level of kidney function. Dose adjustments are most often based on the patient's calculated CrCl or sCr (as opposed to eGFR), according to recommendations established based on these parameters and as per the product information for the medication. Medications requiring dose adjustment include most antibiotics (macrolides, clindamycin, and metronidazole are exceptions), heparin, glyburide, chlorpropamide, insulin, atenolol, digoxin, tramadol, meperidine, gabapentin, paroxetine, allopurinol, colchicine, H₂-blockers, and antiviral agents. Starting at a lower dose and titrating upward gradually is prudent. When available, monitoring parameters (such as drug levels, blood sugar, and heart rate) should be utilized.

Certain patients with CKD may be at higher risk than others for drug nephrotoxicity. Concurrent diabetes, advanced age, volume depletion or states of effective volume depletion and concomitant use of multiple nephrotoxic drugs have been implicated. Repeated and frequent use, and higher doses of nephrotoxic drugs may increase risk (specific data are lacking, however).

Contrast nephropathy is the decline in kidney function following exposure to iodinated contrast. The decline is usually mild and transient but can necessitate dialysis acutely or even chronically. The risk of contrast nephropathy is higher in patients with diabetes, advanced heart failure or other states of hypovolemia or effective hypovolemia), and a higher total dose of contrast. Assuring adequate hydration by the infusion of normal saline or sodium bicarbonate solutions in the peri-procedure period may reduce the incidence of nephrotoxicity (Weisbord et al., 2008). The use of N-acetylcysteine may be effective in reducing the incidence of contrast nephropathy, although results have been inconsistent (Briguori et al., 2002, 2003, 2004a, 2004b, 2005; Cigarroa et al., 1989; Davidson et al., 1989; Lameier, 2006; Lautin et al., 1991; Mehran et al., 2004; Parfrey et al., 1989; Rihal et al., 2002; Rudnick et al., 1995; Sandhu et al., 2006; Schwab et al., 1989; Stacul, 2005).

The use of gadolinium for contrast magnetic resonance imaging has been associated with toxicity, specifically nephrogenic systemic fibrosis, especially in patients with severe CKD (Grobner & Prischl, 2007). First observed in 1997, it is characterized by thickening, induration, and hardening of the skin most commonly involving the distal extremities and the trunk, and may also involve internal organs. The vast majority of patients with the disorder have been receiving chronic maintenance dialysis, although patients with acute kidney injury, hepatorenal syndrome, liver or kidney transplants, and patients with eGFR < 30 ml/min/1.73m² may also be at risk. Although rare patients have been

described who have not received gadolinium, the FDA has issued several alerts and has required the manufacturers of gadolinium to include a black box warning. This warning describes the patients at risk and recommends that renal function be assessed either by history or laboratory determination of serum creatinine prior to the administration of gadolinium. Gadolinium should be avoided in patients with known risks unless the diagnostic information is essential and cannot be obtained using other diagnostic procedures.

NSAIDs, including cyclooxygenase-2 inhibitors, may cause kidney damage in a number of ways. These include a predictable reversible reduction in GFR as well as idiosyncratic reactions such as acute renal failure, interstitial nephritis, and nephrotic syndrome. The benefits of these drugs must be weighed carefully against the possible adverse effects on kidney function. There is no well established GFR threshold for the use of NSAIDs.

There is little data on nephrotoxicity due to herbal medications (see [Table 10.2. Herbal Products that May Cause Renal Problems](#)). The Chinese herbs *Stephania tetrandia* and *Magnolia officinalis* have been implicated. Vanherweghem et al. (1993) described a series of nine young women with advanced and progressive renal disease following chronic use of these herbs for weight loss.

Table 10.2. Herbal Products that May Cause Renal Problems

Aristolochic acid	Contained in Virginian and Texas snakeroot or in Chinese herbs like <i>Stephania tetrandia</i> and <i>Magnolia officinalis</i> . It causes rapidly progressive fibrosing interstitial nephritis and renal failure. It is also linked to urothelial malignancy.
Barberry	Possibly causes interstitial nephritis
Buchu	May cause renal toxicity
Chinese herbal drugs	Contain a variety of herbs, and often aristolochic acid
Juniper	Causes renal fibrosis
Licorice	Is associated with sodium and water retention, hypokalemia and hypertension
Noni juice	Also known as the Och plant (India), Nono (Tahiti), Nonu (Samoa), Nhau (Southeast Asia) and Chinese fruit (Australia), it is associated with hyperkalemia

Source: Kappel & Calissi, 2002

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Medications should be reviewed and doses modified or adjusted to the level of kidney function in patients with CKD	KDOQI, 2002	III	Poor	C
2	Avoid or limit exposure to nephrotoxic drugs	Appel, 1990 Hoitsma et al., 1991 Kintzel, 2001 Markowitz et al., 2000 Schneider et al., 2006 Von Moos, 2005	III III III II-3 II-2 III	Fair	D
3	Avoid hyperosmolar agents to reduce the incidence of contrast nephropathy; if iodinated contrast cannot be avoided, low- or iso-osmolar non-ionic agents should be used	Aspelin et al., 2003 Briguori et al., 2006 Jo et al., 2006 Marenzi et al., 2004 Rudnick et al., 1995	I II-2 I III I	Fair	B
	Consider the use of measures to prevent contrast nephropathy, including intravenous fluids and acetylcysteine	Briguori et al., 2002 Briguori et al., 2004a Briguori et al., 2004b Briguori et al., 2005 Sandhu et al., 2006	I	Fair	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

10.6. Smoking Cessation

BACKGROUND

Besides its adverse effects on cardiovascular risk, lung disease, and cancer, smoking may also increase the rate of progression of CKD.

RECOMMENDATIONS

1. Patients should be advised to stop smoking to reduce cardiovascular risk [A] and slow the progression of kidney disease [C].
(See the [VA/DoD Guideline for Management of Tobacco Use](#).)

DISCUSSION

Several epidemiologic studies have demonstrated a relationship between smoking and more rapid progression of CKD (Biesenbach et al., 1997; Orth et al., 2001; Pinto-Sietsma et al., 2000; Regalado et al., 2000; Sawicki et al., 1994), particularly in patients with diabetes and hypertension. In type 2 diabetes, the adverse effects of smoking on progression of kidney disease are seen even in patients receiving an ACEI, an intervention known to slow the progression of kidney disease (Chuahirun & Wesson, 2002). Although the mechanism is unclear, studies have shown that smoking acutely raises mean arterial pressure, reduces GFR, and increases albuminuria, both in normal subjects and in patients with glomerular disease (Pinto-Sietsma et al., 2000; Ritz et al., 1998). These changes may be due to activation of the sympathetic nervous system, as well as direct toxic effects on the kidney (Odoni et al., 2002; Schiffli et al., 2002). Current and former smoking has been associated with an increased prevalence of proteinuria in the general population (Briganti et al., 2002; Halimi et al., 2000), and proteinuria is a known risk factor for kidney disease progression.

There are limited prospective studies on the effects of smoking cessation on progression of kidney disease. Patients with diabetic nephropathy who quit smoking have a reduction in the rate of increase in albuminuria (Chase et al., 1991). Smoking cessation has been shown to result in the decrease in a surrogate marker of renal damage, urinary excretion of transforming growth factor beta-1 (Chuahirun et al., 2004). There are two prospective cohort studies that assess the effects of smoking cessation on changes in creatinine or GFR. In patients with chronic glomerulonephritis or tubulointerstitial disease, smokers with CKD who stopped smoking within the first six months of the 24 month observation period (n=16) had a slower rate of progression than those who continued to smoke (n=29) (Schiffl et al., 2002). In a one-year prospective cohort study in 93 patients with diabetes, hypertension and diabetic nephropathy progression of kidney disease was less common in patients who quit smoking than those who continued to smoke (Sawicki et al., 1994). Given the beneficial effects of smoking cessation on cardiovascular health, its potential benefits on slowing kidney disease progression and its lack of adverse consequences, smoking cessation should be strongly encouraged.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Cessation of smoking and progression of kidney disease	Chase et al., 1991 Chuahirun et al., 2004 Sawicki et al., 1994 Schiffl et al., 2002	II-2	Fair	C
2	Cessation of smoking and reduction of cardiovascular risk	VA/DoD CPG for Management of Tobacco Use, 2004	I	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

10.7. Control of Dyslipidemia

BACKGROUND

Dyslipidemia is a risk factor for progressive kidney disease. A meta-analysis of 11 small trials showed that lipid lowering therapy amongst patients with CKD with dyslipidemia and proteinuria slowed the progression of the disease. A subanalysis of the CARE study has also suggested that treatment with a statin may slow the decline in kidney function in patients with moderate to severe CKD, especially with proteinuria. However, these results cannot at this time be safely extrapolated to a great majority of patients with CKD without additional evidence.

RECOMMENDATIONS

1. Patients with CKD or diabetic nephropathy who have dyslipidemia should be treated to reduce cardiovascular risk [A] and slow progression of kidney disease [B].
(See [VA/DoD CPG for Management of Dyslipidemia.](#))
2. Statin and fibrate therapies have a higher frequency of adverse events in patients with CKD that warrants careful monitoring. Lower statin doses may be necessary to reduce the risk of myopathy. [I]

DISCUSSION

Prevention of Cardiovascular Events

Lipid abnormalities are commonly associated with CKD and are also considered a risk factor for the development and progression of CKD. In addition, CKD is considered a risk factor for cardiovascular disease (Tonelli et al., 2004). The mortality in CKD is largely associated with cardiovascular disease

(KDOQI Dyslipidemia Guidelines, 2003). Because the lipid mortality trials have mostly excluded CKD patients, the benefit in this group of patients is unknown. A randomized placebo-controlled trial of lipid lowering therapy in diabetic dialysis patients was unable to show a benefit on the composite endpoint of cardiac death, nonfatal myocardial infarction and stroke, despite a 42 percent reduction in LDL (Warner et al., 2005). Despite the lack of high quality evidence for benefit in the patient with CKD but because of the known substantial benefit of lipid lowering in the non-CKD population and the high risk of cardiovascular disease in the CKD population, patients with dyslipidemia and CKD should be treated according to national clinical guideline recommendations established for patients with dyslipidemia (see [VA/DoD CPG for Management of Dyslipidemia](#)).

Dyslipidemia Treatment in the Delay of CKD Progression

The subanalysis of the CARE study (1998) suggests that treatment of dyslipidemia in CKD will slow the progression of kidney disease. Long term, randomized trials on patients with CKD treated with statins and meta-analyses suggest lipid lowering therapies slow the progression of kidney disease (Bianchi et al., 2003; CARI, 2006; Douglas et al., 2006; Fried et al., 2001; Imai et al., 1999; Tonelli et al., 2003; Tonelli et al., 2004). A number of studies were limited by their small numbers and short follow-up times.

A recent meta-analysis including fifteen studies with 1,384 patients and an average treatment of 24 weeks in duration showed that treatment with a statin reduced albuminuria and proteinuria in 13 of the 15 studies. The reduction in excretion was greater in the studies with higher baseline albuminuria or proteinuria: those with excretion < 30 mg/d experienced a change of 2 percent; patients with 30 to 300 mg/d had a reduction of 48 percent; and those with excretion > 300 mg/d experienced a reduction of 47 percent. It was noted that the studies included were not considered to be of high quality. The authors concluded that statins may have a beneficial effect on pathologic albuminuria; however, whether these results translate into a reduction in cardiovascular events or ESKD requires further study (Douglas et al., 2006).

Dyslipidemia Treatment in Diabetic Nephropathy

Dyslipidemia has been associated with a greater decline in GFR in patients with type 1 diabetic nephropathy (Krolewski et al., 1994; Mulec et al., 1990) and is an independent risk factor for progression of nephropathy in patients with type 2 DM and normoalbuminuria (Gall et al., 1997). There is limited evidence to support the treatment of dyslipidemia in diabetic nephropathy to slow the progression of kidney disease (CARI, 2006). There was benefit in one small RCT in patients with dyslipidemia and type 2 DM and nephropathy where there was a decrease in GFR in patients receiving placebo compared to the treatment group (Lam et al., 1995). A large prospective cohort study of 1,600 patients with coronary heart disease including a subgroup of patients with diabetes (N=313) found that treatment of dyslipidemia with a statin reduced all-cause mortality and coronary mortality by 52 percent and 62 percent, respectively (Athyros et al., 2004). It was also reported that patients with various degrees of kidney dysfunction experienced a reduction in the progression of kidney disease (Athyros et al., 2004). A meta-analysis evaluating lipid lowering therapy included 57 percent patients with diabetes and 23 percent with primary renal disease suggested that lipid lowering therapies slow progression of kidney disease (Douglas et al., 2006).

Another meta-analysis of trials in patients with dyslipidemia and renal disease (66% with diabetes) showed that treatment with lipid lowering therapy slowed progression of renal disease (Fried et al., 2001).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Lowering LDL in patients with dyslipidemia reduces cardiovascular events	VA/DoD CPG for Management of Dyslipidemia, 2006	I	Good	A
2	Lowering LDL in patients with CKD may retard the progression of kidney disease	Bianchi et al., 2003 CARI, 2006 Douglas et al., 2006 Fried et al., 2001 Imai et al., 1999 Tonelli et al., 2003 Tonelli et al., 2004	I	Fair	B
3	Lowering LDL in patients with diabetic nephropathy may retard the progression of kidney disease	CARI, 2006 Douglas et al., 2006 Fried et al., 2001 Lam et al., 1995	I	Fair	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

<i>Annotation K</i>	<i>Treat Symptoms and Complications</i>
---------------------	---

11. COMPLICATIONS OF CKD

Maintain normal metabolic levels and homeostasis in patients with kidney disease.

Metabolic abnormalities:

- 11.1** Disorders of potassium balance
- 11.2** Disorders of calcium and phosphate metabolism (bone mineral)
- 11.3** Acid based abnormalities
- 11.4** Hematologic abnormalities (anemia)
- 11.5** Volume overload
- 11.6** Disorders of Nutrition
- 11.7** Adjustment of medication doses
- 11.8** Immunization

11.1. Disorders of Potassium Balance

BACKGROUND

Disorders of potassium homeostasis (both high and low potassium levels) may result in preventable morbidity and mortality. Potassium levels should be checked periodically in patients with kidney disease.

RECOMMENDATIONS

1. Patients with high levels of potassium (> 6 mEq/L) should be referred to the emergency department.

2. Treatment of high levels of potassium should be guided by balancing the benefit and harm to address the most likely etiology:
 - a. Dietary restriction of potassium intake considering a consultation with a dietitian (see [Table 11.1. Potassium Content of Foods](#) (see [Appendix F-2. Potassium](#)))
 - b. Increase urinary potassium excretion using loop diuretics in the absence of volume depletion
 - c. Lower dose or withdraw ACEI/ARBs if the potassium is > 6 mEq/L
 - d. Treating acidosis with oral sodium bicarbonate
 - e. Increase fecal potassium excretion using sodium polystyrene sulfonate (Kayexelate®) (with sorbitol) 30 to 60 g daily or every other day
 - f. Refer to nephrology if etiology is unknown.

DISCUSSION

Hyperkalemia is a common disorder in patients with kidney disease, especially when the eGFR falls below 20 ml/min/1.73m². Hyperkalemia may occur as a result of impaired tubular secretion of potassium in patients with mild CKD. It is more prevalent among patients with diabetes who have Type 4 renal tubular acidosis and is frequently exacerbated by the use of certain drugs such as ACEIs, ARBs, and NSAIDs. Other contributing conditions include volume depletion leading to poor urine flow, severe hyperglycemia, and starvation. Especially in patients with diabetes, poor oral food intake (e.g., fasting in the preoperative periods) resulting in low serum insulin levels may cause or exacerbate hyperkalemia (Allon, 1995). High intake of certain food items can also lead to hyperkalemia in patients with impaired kidney function. Referral to a dietitian for a potassium restricted diet is useful.

Table 11.1. Potassium Content of Foods (see [Appendix F-2. Potassium](#))

Highest content (> 25 mEq/100 g)	Dried figs, molasses, seaweed
Very high content (>12.5 mEq/100 g)	Dried fruit (dates, prunes), nuts, avocados, bran cereals, wheat germ, lima beans
High content (> 6.2 mEq/100 g)	Vegetables: spinach, tomatoes, broccoli, winter squash, beets, carrots, cauliflower, potatoes Fruits: bananas, cantaloupes, kiwi, oranges, mango

Potassium > 6.5 mEq/L

Elevation of potassium above 6.5 mEq/L is a medical emergency and needs immediate attention to prevent life threatening cardiac arrhythmia.

Potassium 5.5 – 6.5 mEq/L

A more conservative approach is generally acceptable if a rapidly reversible cause is identified (e.g., oral potassium supplementation) and the patient is asymptomatic, without ECG manifestations of hyperkalemia. Discontinuation of offending drugs, adequate nutrition, moderate potassium restriction and/or correction of prerenal azotemia or metabolic acidosis with sodium bicarbonate is frequently sufficient. Persistent hyperkalemia may require a more stringent dietary limitation, although very low potassium diets (less than 40 mEq/L/day) may lead to protein malnutrition. If the cause for hyperkalemia is not readily identifiable and the elevation in serum potassium is mild, other measures can be instituted in the outpatient setting. Liberalization of sodium intake, loop diuretics, and thiazides may be used in selected patients although their side effects (volume depletion, hyperuricemia, etc.) must be taken into account. Another option includes the use of sodium polystyrene sulfonate. The usual dose for sodium polystyrene sulfonate is 15 grams (either as a suspension with sorbitol or as a powder for suspension), administered 1 to 4 times daily as needed. Lower doses (5 to 10 grams with meals) can

be used to control chronic mild hyperkalemia (Rose, 2007). Fludrocortisone, a potent mineralocorticoid, may be used in patients with type 4 renal tubular acidosis (De Fronzo, 1980). Refractory hyperkalemia should prompt a referral to a nephrologist.

Since the cause of hyperkalemia may be multifactorial and may differ from patient to patient, the choice of treatment of mild-to-moderate hyperkalemia may require different combinations of the recommendations.

After therapy is instituted, a follow-up potassium level should be performed within one week to ensure the effectiveness of therapy and identify any need for further modification of the treatment regimen.

Hypokalemia Potassium < 3.5 mEq/L

Hypokalemia may occur as a result of diuretic therapy and may cause cardiac arrhythmia and muscle weakness. A fall in serum potassium of 1 mEq/L reflects a loss of about 200 to 400 mEq in total body potassium. Replacement by foods high in potassium (see [Appendix F-2. Potassium](#)) is usually less effective than administration of oral potassium chloride. Slow release tablets or capsules can be used, in the following dosage: (a) for prevention of hypokalemia, potassium chloride 8 to 20 mEq/day; (b) for treatment of potassium depletion, potassium chloride 40 to 100 mEq/day.

Severe hypokalemia, defined as serum potassium level below 3.0 mEq/L, may require intravenous potassium replacement, especially in patients on digoxin or if it is anticipated that potassium losses will continue (e.g., vomiting, diarrhea, etc.) In the patient with kidney disease, replacement should be approached with caution. High potassium chloride doses must be used with more frequent measurements of the serum potassium. Intravenous potassium chloride replacement should be given no faster than 10 mEq per hour. It is preferable to replace potassium as a chloride salt as opposed to potassium-citrate or potassium-bicarbonate; one exception to this may be renal tubular acidosis (the hypokalemic types) and chronic diarrheal states (Rose, 2007).

11.2. Disorders of Bone Mineral Metabolism

BACKGROUND

Patients with CKD often have derangements in calcium, phosphorus, and intact parathyroid hormone (PTH) referred to collectively as secondary hyperparathyroidism. Patients with secondary hyperparathyroidism usually present with low serum calcium, high serum phosphorus, and high serum parathyroid hormone levels. The primary goals of treating these abnormalities and monitoring response to treatment are to avoid complications that may result from serum calcium and phosphorus levels that are outside the normal range and to prevent the bone diseases that may result from PTH levels that are either too high (osteitis fibrosa cystica) or too low (adynamic bone disease).

RECOMMENDATIONS

1. Serum phosphorus, calcium, and intact PTH should be checked at least annually in patients with eGFR < 45 ml/min/1.73 m² and at least every 6 months if abnormal.
2. Goal calcium levels should be within “normal” limits (8.4 - 10.5mg/dL). Phosphorus should be maintained within the range of 2.7 to 4.6 mg/dL, though this goal may not be achievable in patients with very advanced CKD (eGFR < 15 ml/min/1.73 m²).
3. Serum phosphorus above the target should be treated initially with dietary phosphorus restriction and phosphorus binders.
 - a. Calcium carbonate or calcium acetate should be used as first line binders except in patients with a serum calcium level close to the upper limit of normal (e.g., 10.2 mg/dL) or above the normal range.

- b. If hypercalcemia or hypocalcemia occur after correction of hyperphosphatemia, patients should be referred to nephrology.
4. Patients in whom hyperphosphatemia or hypocalcemia cannot be controlled with phosphate binders and those with intact PTH levels greater than twice the normal value should be referred to nephrology.

DISCUSSION

The basic principle in managing phosphorus and calcium is to intervene to keep these parameters within the normal range. The first step in evaluating disorders in calcium, phosphorus and PTH is to determine whether the observed pattern is consistent with secondary hyperparathyroidism. In the earlier stages, patients are able to maintain normal levels of phosphorus and calcium by increasing PTH secretion. Thus an elevated PTH may be the only sign of this disorder initially. Eventually, elevated PTH levels will be accompanied by low serum calcium levels and elevated serum phosphorus levels.

Phosphorus

Phosphorus clearance decreases in patients with CKD and is the primary mechanism by which serum levels of phosphorus become elevated in patients with CKD. There is experimental evidence that lowering serum phosphorus reduces parathyroid hormone production (Portale et al., 1984) and can prevent parathyroid gland hyperplasia (Slatopolsky et al., 1996) in humans and one study in nephrectomized rats demonstrating that phosphate restriction can slow progression of renal disease. A number of different observational studies in dialysis patients have demonstrated an association between elevated serum phosphorus and mortality, cardiovascular events, and hospitalization (Block et al., 1998; Ganesh et al., 2001; Noordzij et al., 2005; Slinin et al., 2005). However, there are no randomized controlled studies demonstrating that lowering serum phosphorus leads to improved clinical outcomes.

Phosphorus levels above the normal range should be treated first with dietary modification. Patients should be instructed to moderate their intake of high phosphorus foods such as colas, dairy products, and processed foods (Uribarri et al., 2003) and should be referred to a renal nutritionist for more specific guidance on optimizing their diet to lower serum phosphorus while at the same time maintaining good nutrition.

Binders

If phosphorus levels remain elevated after dietary modification or if the patient initially presents with phosphorus levels that are very high and thus unlikely to normalize with dietary modification alone (e.g., > 6 mg/dL), then the patient should be started on a phosphate binder. These medications prevent absorption of dietary phosphorus and patients should be specifically instructed to take these medications shortly before or after meals for optimal effect.

Calcium based binders, either calcium carbonate or calcium acetate, are generally the first choice for patients with calcium levels that are low or within the normal range. These agents appear to be at least as effective at lowering serum phosphorus as a newer agent (Chertow et al., 2002) and are cheaper. Calcium acetate contains a lower percentage of elemental calcium compared with calcium carbonate (26% vs. 40%) and has been shown to be a more efficient phosphorus binder than the former (Sheikh et al., 1989). The usual starting dose for calcium carbonate is 500 or 650 mg three times a day with meals and for calcium acetate 667 mg three times daily with meals. Dosage should be titrated to achieve calcium level goals within normal limits (8.4 - 10.5 mg/dL) and phosphorus in the range of 2.7 - 4.6 mg/dL. Most patients with eGFR > 30 ml/min/1.73 m² should be able to be managed with relatively low doses of calcium containing phosphate binders. There are noncalcium containing phosphate binders available (sevelamer and lanthanum), however in most patients with eGFR levels > 30 ml/min/1.73 m², the binders will not be needed to control serum phosphorus and these binders have not been approved by the Food and Drug Administration for use in patients not on dialysis. If there is a question of whether noncalcium binders are needed, referral to nephrology is recommended.

Calcium

Low serum calcium levels (corrected $< 8.4\text{mg/dL}$) will generally respond to interventions to reduce serum phosphorus levels that are described above. If serum calcium levels are lower than normal after improvement in serum phosphorus, patients should be referred to a nutritionist for guidance on how to increase dietary calcium intake and/or calcium carbonate can be recommended between meals (in this setting calcium will be absorbed rather than functioning as a binder for phosphorus). Because calcium carbonate contains a higher percentage of elemental calcium, it is generally preferred over calcium acetate in the treatment of hypocalcemia in patients with CKD. The initial dose should be guided by the severity of the hypocalcemia and the ability of the patient to tolerate additional calcium. If the patient is unable to tolerate additional calcium or serum calcium does not improve on maximally tolerated calcium, refer to or consult with the nephrologist.

Vitamin D Therapy

Vitamin D deficiency is common in the general population and may be even more common in the CKD population. Furthermore, the kidney plays a major role in the metabolism of vitamin D. The kidney is the primary site of 1-hydroxylation which leads to the synthesis of the most active form of vitamin D (1,25 hydroxy vitamin D). This hydroxylation step is impaired with CKD. Therefore, patients with CKD may not only be deficient in the storage form of vitamin D, but also have decreased levels of active vitamin D. Vitamin D not only plays a direct role in the regulation of serum calcium because of its effects on the bone and gut, but it also is important in the regulation of PTH levels, through the presence of vitamin D receptors on the parathyroid gland. The common indications for treatment with vitamin D include the presence of hypocalcemia or secondary hyperparathyroidism. Patients with persistent hypocalcemia after correction of hyperphosphatemia or those with parathyroid hormone levels greater than twice normal should be referred to nephrology.

11.3. Acid Based Abnormalities

BACKGROUND

Metabolic acidosis is a common complication in patients with CKD. It results both from accumulation of organic acids in plasma because of impaired renal excretion and from impaired renal acidification mechanisms. Degree of acidosis approximately correlates with severity of renal failure and usually is more severe at a lower GFR. Acidosis may induce a catabolic state, worsen renal osteodystrophy, and accelerate the progression of kidney disease. Treatment with oral sodium bicarbonate is a simple way to correct the acidosis, but may be complicated by fluid retention.

RECOMMENDATIONS

1. Serum bicarbonate (measured as plasma total CO_2) should be monitored at least annually and should be maintained at or above 22 mEq/L. [C]
2. Oral bicarbonate replacement in the form of sodium bicarbonate tablets is indicated when the serum total CO_2 falls below 22 mEq/L. [C]
3. Caution should be used when administering bicarbonate to patients with uncontrolled hypertension or heart failure. [C]

DISCUSSION

Metabolic acidosis is common in CKD. Early studies documented the development of non-anion gap acidosis in moderate CKD due to impaired renal acidification (Widmer et al., 1979). As kidney disease progresses, an anion gap acidosis develops, due to impaired renal excretion of organic acids. Data from the third annual National Health and Nutrition Examination Survey indicates that a significant decrease in serum bicarbonate is not detectable until the creatinine clearance was ≤ 20 ml/min (Hsu & Chertow,

2002). Typically the serum bicarbonate decreases by 1.7 mEq/L for each increase in serum creatinine of 1 mg/dl and it rarely decreases to < 12 mEq/L (Hakim & Lazarus, 1988). Many patients with a creatinine clearance < 30 ml/min still have a normal serum bicarbonate (Caravaca et al., 1999).

Experimental studies in animals and clinical studies in patients with CKD have identified several potential adverse consequences of acidosis, including muscle wasting (Mitch & Price, 2001), induction of a catabolic state (Kraut & Kurtz, 2005; Verove et al., 2002), exacerbation of renal osteodystrophy (Coen et al., 1996), and accelerating the progression of kidney disease (Kraut & Kurtz, 2005). Correction of metabolic acidosis lessens renal osteodystrophy (Lefebvre et al., 1989) and improves protein metabolism (Kraut & Kurtz, 2005).

The level of bicarbonate at which to initiate treatment and the appropriate degree of correction has not been carefully studied in RCTs (KDOQI, 2002; Kraut & Kurtz, 2005; Roderick et al., 2007). Existing guidelines recommend maintaining the serum bicarbonate \geq 22 mEq/L. Sodium bicarbonate is the preferred replacement therapy and the recommended dose is 0.5 mEq/kg/day in divided doses. Tablets (650 mg) containing 7.7 mEq sodium/7.7 mEq HCO₃⁻ are recommended. Although Shohl's solution (sodium citrate) may also be used and may cause less gastrointestinal distress than sodium bicarbonate, there is a risk of increased intestinal aluminum absorption with the use of sodium citrate, which may result in aluminum intoxication (Walker et al., 1990). It should also be recognized that treatment with sodium bicarbonate or citrate may promote metastatic calcification and result in fluid retention with resultant worsening of hypertension and congestive heart failure. For these reasons, treatment must be individualized and adjustment of diuretic dosages may be necessary.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Serum bicarbonate (measured as plasma total CO ₂) should be maintained above 22 mEq/L	Kraut & Kurtz, 2005 KDOQI, 2002 Lefebvre et al., 1989 Roderick et al., 2007 Verove et al., 2002	III	Poor	C
2	Oral bicarbonate replacement in the form of sodium bicarbonate tablets is indicated when the serum total CO ₂ falls below 22 mEq/L	Kraut & Kurtz, 2005 KDOQI, 2002 Lefebvre et al., 1989 Roderick et al., 2007 Verove et al., 2002	III	Poor	C
3	Caution should be used when administering bicarbonate to patients with uncontrolled hypertension or heart failure	Kraut & Kurtz, 2005	II-3	Fair	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

11.4. Hematologic Abnormalities (Anemia)

BACKGROUND

Anemia is a common complication in patients with CKD. The anemia of CKD is due to erythropoietin deficiency from loss of peritubular fibroblasts in the kidney that produce this growth factor. Recombinant erythropoietic stimulating agents (epoetin and darbepoetin) are available that can successfully correct the anemia. Early recognition and treatment may reduce the need for transfusions and improve the quality of life.

RECOMMENDATIONS

1. Hemoglobin is the preferred test for evaluation of anemia.
2. Hemoglobin should be measured at least annually in patients with CKD.
3. Anemia should be diagnosed when the hemoglobin is < 13.5 g/dL in males and < 12.0 g/dL in females.
4. Evaluation of anemia should consist of measurement of at least the following:
 - a. Hemoglobin
 - b. Complete blood count including white blood cell and platelet count
 - c. Red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin concentration)
 - d. Absolute reticulocyte count
 - e. Iron parameters:
 - Serum iron
 - Total Iron Binding Capacity (TIBC)
 - Percent transferrin saturation (serum iron × 100 divided by TIBC) [TSAT]
 - Serum ferritin
 - Content of hemoglobin in reticulocytes (CHr) if available
 - f. Other tests as indicated by clinical situation (e.g., test for occult blood in stool).
5. Supplemental iron should be provided to anemic CKD patients whose serum ferritin < 100 ng/ml or TSAT < 20 percent or CHr < 29 pg/cell [A]. Hemoglobin and iron parameters should be monitored at least every 6 months in patients receiving supplemental iron. [I]
6. Consider treatment of anemia in patients with CKD with an erythropoietic stimulating agent if the hemoglobin is less than < 10 g/dL and after appropriate evaluation and ruling out other possible causes. Such treatment may require referral to nephrology or hematology and more frequent monitoring of hemoglobin values. [I]
7. For patients receiving erythropoietic stimulating agents, the target hemoglobin should not exceed 12 g/dL. [B]
8. Supplements of Vitamin C, androgens, or carnitine should not be administered as adjuvants to the treatment of anemia of CKD. [D]

Adverse effects of therapy with erythropoietic stimulating agents:

- Hypertension occurs in 20 to 30 percent of patients and is easily treatable
- Vascular access thrombosis
- Hyperkalemia
- Myalgia and flu-like symptoms
- Injection pain and skin irritation around the injection site
- Pure red cell aplasia is very rare and is associated with anti-erythropoietin antibodies.

EVIDENCE STATEMENTS

Anemia is a common consequence of chronic kidney disease, usually caused by erythropoietin deficiency. As kidney function declines, the likelihood of anemia associated with erythropoietin deficiency increases because the diseased kidneys are unable to produce sufficient quantities of erythropoietin. Anemia due to CKD is relatively uncommon until the patient has an eGFR < 30 ml/min/1.73 m². However, there is a wide range of hemoglobin levels for any degree of kidney dysfunction and anemia can develop relatively early in the course of CKD. It has been associated with

only moderate decrements in eGFR, particularly in patients with diabetes (Astor et al., 2002; El-Achkar et al., 2005; Kazmi et al., 2001).

There are only limited data on the natural history of anemia in patients with CKD and most data are cross-sectional. Recommendations on the frequency of anemia assessment are based on the limited prospective data that have been obtained from clinical trials (Gouva et al., 2004; Levin et al., 2005; Roger et al., 2004). In these studies, the decline in hemoglobin was relatively slow. In one study, patients with an eGFR of 26 ml/min/1.73 m² had an average decline in hemoglobin from 11.2 to 11.0 g/dL over the subsequent two years (Roger et al., 2004). Therefore, for most patients annual screening will be sufficient, although more frequent surveillance may be needed for some patients. The NKF recommends that patients with CKD should have their hemoglobin level assayed at least annually. Patients with greater disease burden, unstable clinical course or evidence of previous hemoglobin decline should have their hemoglobin tested more frequently than once a year.

Measurement of hemoglobin concentration is the preferred test for diagnosing anemia. Although, hematocrit is still used by many providers, it is subject to measurement error due to sample storage and differences in analytic instruments (Brittin et al., 1969; Fraser et al., 1989). Expert panels have varied in their definitions of anemia. This guideline has adopted the recommendations of KDOQI, defining anemia as a hemoglobin < 13.5 g/dL in males and < 12.0 g/dL in females (KDOQI, 2007). These values represent the lowest fifth percentile of the sex-specific general adult population. Other guidelines have defined thresholds for diagnosis as low as 12.0 g/dL in men and 11 g/dL in women (Locatelli et al., 2004; WHO, 2001).

The evaluation of the cause of the anemia in patients with CKD should be similar to that in patients without kidney failure. From a cost-effectiveness perspective this evaluation should consist of a complete blood count, including red blood cell indices and absolute reticulocyte count, and assessment of iron status (Hutchinson et al., 1997). Other testing may be indicated based on clinical evaluation, but measurement of erythropoietin level is not indicated for suspected anemia of kidney disease.

Iron deficiency and gastrointestinal blood loss may be more common in patients with CKD because of associated platelet dysfunction. The usual diagnostic indices for iron deficiency may not be applicable in chronic kidney disease. CKD may result in an increase in serum ferritin and fall in transferrin saturation due to the release of inflammatory cytokines. Many patients with CKD who have iron parameters greater than those used to diagnose iron deficiency in the normal population respond to iron supplementation, either oral or parenteral, with an increase in hemoglobin (Panesar et al., 2002; Silverberg et al., 1996; Stoves et al., 2001). Therefore, we recommend determining serum ferritin and transferrin saturation in all patients with CKD with anemia, and treating with oral iron if the serum ferritin is < 100 ng/ml or the transferrin saturation is < 20 percent, as suggested in the KDOQI recommendations (KDOQI, 2007). Many clinical laboratories are now able to report reticulocyte hemoglobin content (CHr) and this test may also be useful in monitoring iron status in patients with CKD (Tsuchiya et al., 2005). Oral iron should be given in a daily dose equivalent to 200 mg elemental iron (typically ferrous sulfate 325 mg three times a day) for six months (Wingard et al., 1995). Although many patients may respond to oral iron, there are some patients who may have a superior response to intravenous iron (Charytan et al., 2005; Stoves et al., 2001; Van Wyck et al., 2005). Parenteral iron may be particularly useful in patients who fail to attain the desired iron parameter targets on oral therapy.

A threshold of less than 11 g/dL of Hb is recommended for the initiation of therapy with an erythropoietic stimulating agent, in most guidelines (KDOQI, 2007; Locatelli et al., 2004). Many of the studies used to establish the recommendations were done in patients on dialysis. [Table 11.2](#) contains a summary of high-quality RCTs studying anemia management in non-dialysis patients with CKD. Each study randomized a minimum of 50 patients and followed them for greater than six months. As can be seen in the first two studies examining effects on left ventricular mass index, there was no difference in outcomes for achieved hemoglobins of 10.8 and 11.4 g/dL compared to 12.1 and 12.7 g/dL. Regarding progression of CKD, initiating treatment with epoetin at hemoglobins of either at 8.9, 9.1 or 10.2 g/dL compared to allowing hemoglobin to fall below 8.6 g/dL slows the progression of CKD. From these

studies it is uncertain whether the threshold for initiating treatment with an erythropoietic stimulating agent might be lower than the guideline recommendation of 11.0 g/dL, but many of the studies used a lower bound for hemoglobin of 10 g/dL. Because of recent clinical trials that have suggested harm from targeting higher hemoglobins (*vide infra*), the FDA has required a black box warning on erythropoietic stimulating agents stating to “use of the lowest dose of that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion.” The prescribing information states that the use of erythropoietic stimulating agents should be considered when the hemoglobin is < 10 g/dL, and in the absence of clinical trial evidence that convincingly demonstrates that there is benefit from starting at higher hemoglobin targets, the Working Group concurs with this recommendation.

In terms of an upper limit for hemoglobin in patients receiving an erythropoietic stimulating agent, the KDOQI guidelines state that the hemoglobin target should not be greater than 13 g/dL and should generally be in the range of 11.0 to 12.0 g/dL (KDOQI, 2007). Two trials in patients with CKD have provided evidence for lack of benefit and possible harm associated with normalization of hemoglobin. In the study of Drueke et al. (2006) there was no evidence of a benefit of correction to a target hemoglobin of 13.0 to 15.0 g/dL compared to one of 10.5 to 11.5 g/dL for the primary endpoint of a composite of eight cardiovascular events. It was noted that the secondary endpoint of progression to dialysis was more common in the high hemoglobin target group. Of greater concern was the finding in the study of Singh et al. (2006) that randomization to a target hemoglobin of 13.5 g/dL compared to target hemoglobin of 11.3 g/dL was associated with a 34 percent higher rate of the composite endpoint of death, myocardial infarction, hospitalization for congestive heart failure, and stroke. The results of these trials prompted the FDA to issue a Public Health Alert recommending that the target hemoglobin not exceed 12 g/dL. Even when including trials in hemodialysis patients, no trial has shown a benefit of achieving hemoglobins greater than 12 g/dL, except perhaps in terms of quality of life (KDOQI, 2007) and the recommendation not to exceed this value seems prudent. Most patients who require erythropoietic stimulating agents (ESA) should be referred to a nephrologist or hematologist to manage this treatment

FDA Alert [3/09/2007]: Regarding safety information for ESAs increased the risk for death and for serious cardiovascular events when dosed to achieve the target hemoglobin of > 12 g/dL.

Several investigators have suggested the use of other agents such as vitamin C, carnitine, androgens, and others to reduce requirements for epoetin. Most of these studies are small and lack adequate controls (KDOQI, 2007). Therefore, they are not recommended at this time.

Table 11.2. Results of randomized trials of anemia management in CKD, not on dialysis (includes only trials of > 6 months duration and with N > 50)

Author, Year	Baseline Hgb (g/dL)	Baseline eGFR (ml/min/1.73 m ²)	Follow-up (mos)	Arms	Mean Hgb Target (Achieved) (g/dL)	Clinical Outcomes
Levin et al., 2005 N=152	11.7	28.8	24	Early ESA Late ESA	12-14 (12.7) 9-10.5 (11.4)	No difference in change in LVMI
Roger et al., 2004 N=152	11.2	26	24	Early ESA Late ESA	12-13 (12.1) 9-10 (10.8)	No differences in change in LVMI, change in eGFR, or change in QOL
Singh et al., 2006 N=1,432	10.1	27.2	16	High Hgb Low Hgb	13.5 (12.6) 11.3 (11.3)	Significant increase in composite outcome of death, myocardial infarction, hospitalization for congestive heart failure, or stroke in the higher Hgb target group
Drueke et al., 2006 N=603	11.6	24.6	36	High Hgb Low Hgb	13-15 (13.5) 10.5-11.5 (11.5)	No difference in composite outcome of eight cardiovascular events including sudden death, myocardial infarction, acute heart failure, stroke, hospitalization for angina, complication of peripheral vascular disease or arrhythmia. Dialysis required in significantly more patients in the high hemoglobin target group.
Roth et al., 1994; Revicki, et al., 1995 N=83	8.9	10.1	11	ESA Control	11.7 (11.5) (8.6)	No difference in time to dialysis, significant improvement in Health Related QOL scores for energy and physical function
Kuriyama, et al., 1997 N=73	9.2	18.1	14-36	ESA Control	11.0-11.7 (11.8) (8.4)	Significant decrease in percentage of patients with doubling of creatinine or need for dialysis in treatment group
Gouva et al., 2004 N=88	10.1	24	22.5	Early ESA – Hgb=9.0-11.6 Late ESA – Hgb <9.0	11.6-13.0 (12.9) 11.6-13.0 (10.3)	Significant decrease with early treatment for end point of doubling of creatinine, renal replacement, or death

Abbreviations: eGFR = estimated glomerular filtration rate; Hgb = hemoglobin; ESA = erythropoietic stimulating agent; LVMI = left ventricular mass index; QOL= quality of life

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Supplemental iron should be provided to anemic CKD patients whose serum ferritin < 100 ng/ml or TSAT < 20 percent or CHr <29 pg/cell	Panesar et al., 2002; Silverberg et al., 1996; Stoves et al., 2001 KDOQI, 2007	I	Good	A
2	Insufficient evidence regarding the lower threshold of erythropoietic stimulating agent	KDOQI, 2007; Locatelli et al., 2004 Levin et al., 2005 Roger et al., 2005	I	Fair	I
3	Hemoglobin greater than 13 g/dL are associated with increased mortality and frequency of cardiovascular events.	Drueke et al. 2006 Singh et al. 2006 KDOQI 2007	I	Fair	B
4	Vitamin C, androgens, or carnitine should not be administered	KDOQI 2007	I	Fair	D

QE = Quality of Evidence; SR = Strength of Recommendations (See Appendix A)

11.5. Volume Overload

BACKGROUND

- Volume overload should be suspected in patients complaining of dyspnea, chest discomfort, orthopnea, paroxysmal nocturnal dyspnea, or progressive decrease in exercise tolerance. It may also be asymptomatic.
- Physical findings could include jugular venous distension, hepatojugular reflux, pulmonary rales, wheezing (in “cardiac asthma”), and S3 or S4, ascites, and peripheral edema.
- Patients with chronic kidney failure may also have significant volume overload even in the absence of the above symptoms and signs.
- Contributors include: excess salt intake, progressive kidney damage (nephrosclerosis), fluid retention from blood pressure medications (calcium channel blockers, minoxidil), and inadequate diuretic therapy.
- In patients with an eGFR > 30 ml/min/1.73m² overload is often due to a cardiac cause (heart failure); in patients with low eGFR (< 30 ml/min/1.73m²), overload may occur primarily as a complication of the kidney disease.
- Chest films may show evidence of pulmonary edema or may be subtle, showing only prominent pulmonary vasculature.
- Although it is sometimes difficult to differentiate fluid overload from cardiac failure from that resulting from CKD, patients with eGFRs of > 30 ml/min/1.73m² will, in general, not suffer from volume overload resulting from CKD.
- Following changes in weight over time is a critical element of the patient’s visit to the primary care clinic. Progressive weight gain may be a sign of salt and water accumulation and may precede the onset of life-threatening pulmonary congestion. Over weeks to months, these patients may lose lean body mass due to malnutrition and can develop fluid overload with relatively little change in weight. Therefore, serial assessment of the patients’ lean body mass is also critical.
- Hyponatremia, developing as a result of decreased free water clearance, may also be a marker for volume overload in the above setting.

RECOMMENDATIONS

1. Patients with symptoms consistent with volume overload should be evaluated for cardiac causes, and cardiovascular risk should be assessed (see [VA/DoD CPG for Management of Chronic Heart Failure](#)). [I]

2. Patients with CKD and eGFR < 30 ml/min/1.73m² and symptoms consistent with volume overload may be considered as a complication of the kidney disease and managed accordingly. [I]
3. The following interventions should be considered in managing volume overload: [B]
 - a. Obtain weight at every visit
 - b. Restrict dietary sodium to 2 g/day; on occasion, consider measuring urinary sodium concentration to assess compliance with dietary restriction
 - c. Use loop diuretics (divided doses may be preferred); if refractory to twice a day dosing, consider adding thiazide type diuretics with careful follow-up to avoid severe pre-renal azotemia or hypokalemia.
 - d. If volume overload is refractory to therapy, consider referral to nephrology.

DISCUSSION

Volume overload is a frequent complication of CKD, especially in stages 4 and 5, although in patients with severe nephrotic syndrome it may present at an earlier stage. It must be noted that the presence of severe peripheral edema, even anasarca, is not always associated with an expanded intravascular volume, especially when the serum oncotic pressure is low, thus caution must be exercised when using diuretics in nephrotic patients because they will primarily excrete fluid from the intravascular compartment and thus may be associated with hypotension and worsening kidney failure. Periodic adjustments in the dose of diuretics administered may be necessary.

The presence of arterial hypertension, in advanced CKD, is most commonly associated with salt and water retention and may persist despite regimens with multiple antihypertensives. It is important to point out that patients with CKD also have enhanced blood pressure sensitivity to dietary salt (Koomans et al., 1985).

Certain drugs may precipitate or exacerbate salt and fluid retention in patients with CKD. Nonsteroidal anti-inflammatory drugs (NSAIDs) antagonize the natriuretic effects of renal prostaglandins, and promote excessive renal salt and water reabsorption (Whelton et al., 1990). Use of these drugs should be avoided in patients with stages 3 and 4 CKD.

Volume overload should be suspected in patients complaining of dyspnea, chest discomfort, orthopnea, paroxysmal nocturnal dyspnea, or progressive decrease in exercise tolerance. It may also be asymptomatic. Physical findings could include jugular venous distension, hepatojugular reflux, pulmonary rales, wheezing (in “cardiac asthma”), and S3 or S4, ascites, and peripheral edema. Patients with chronic kidney failure may also have significant volume overload even in the absence of the above symptoms and signs. Chest films may show evidence of pulmonary edema or may be subtle, showing only prominent pulmonary vasculature. An increase in weight over time may be a sign of salt and water retention. However, patients with CKD may lose lean body mass due to malnutrition and can develop fluid overload with relatively little change in weight. Therefore, serial assessment of the patients’ lean body mass is also critical.

Contributors include:

- Excess salt intake
- Progressive kidney damage (nephrosclerosis)
- Fluid retention from blood pressure medications
- Inadequate diuretic therapy.

Consider fluid overload for sudden unexplained gains in weight, refractory hypertension, peripheral edema or shortness of breath. These may be secondary to the above causes. Hyponatremia, developing

as a result of water retention in excess of sodium retention, may also be a marker for volume overload in the above setting.

Management:

- Patients should be weighed at every visit
- Dietary sodium restriction to 2 g/day
- Loop diuretics, and if refractory to twice a day dosing, consider adding thiazide-type diuretics
- If advanced kidney failure, consider initiation of dialysis.

11.6. Disorders of Nutrition

BACKGROUND

A dietary assessment of patients with CKD should focus on overall nutrition, including lipids, potassium, phosphate, sodium, protein, and energy. In patients with early or moderate kidney disease, daily energy intake should be 35 kcal/kg body weight and daily protein intake should be 0.8 g/kg body weight. For patients with more severe kidney disease or nephrotic syndrome, severe protein restriction, in conjunction with a dietary supplement and monitoring of caloric intake may be considered to prevent symptoms and reduce proteinuria, although is difficult to implement and maintain (see [Appendix F](#)).

RECOMMENDATIONS

1. Patients may benefit from a dietary evaluation by a medical nutrition therapist and should be advised about a healthy diet and the preferred range of sodium, phosphate, and potassium in their diet (see [Annotation L – Patient Education](#)). [C]
2. Additional assessment and dietary counseling should be initiated if body mass index or other biomarker tests indicate deterioration of nutrition status. [I]
3. Diet modifications may be indicated in patients presenting with metabolic disorders in any of the following: [B]
 - a. Limiting dietary potassium intake between 50 to 70 mEq/day (1950 – 2730 mg/day) in patients with hyperkalemia
 - b. Sodium restrictions in patients with hypertension (< 2 g/day)
 - c. Phosphate restriction is indicated in patients with CKD when:
 - Serum phosphorus levels are above 4.6 mg/dl (1.49 mmol/L)
 - Parathyroid hormone (PTH) levels are above normal
 - d. Limiting dietary protein to < 0.8 g protein/kg/day may be considered in patients with severe CKD (eGFR < 30 ml/min/1.73m²). A restricted protein diet should include at least 50 percent being from high biologic value protein sources and ensure sufficient energy level intake to compensate for restriction and avoid malnutrition. There is insufficient evidence to recommend dietary protein restriction for all patients with CKD (see [Table 11.3. Recommended Intake of Protein, Energy, and Minerals in CKD](#)).

RATIONALE

- If there is an indication for restriction or modification of diet, the assistance of a dietitian may be helpful.
- Inadequate energy intake is considered to be one of the principal reversible factors contributing to malnutrition in the CKD and ESKD populations.

- Individualized diet plan and counseling by a dietitian may increase adherence to dietary limitation and prescription.

EVIDENCE STATEMENTS

Table 11.3. Recommended Intake of Protein, Energy, and Minerals in CKD

	Protein	Energy	Phosphorus	Sodium
Chronic Kidney Disease				
Mild to Moderate (eGFR 25 – 60 ml/min/1.73m ²)	No restriction	No restriction	600 – 800 mg/day	< 2 g/day ^a
Advanced (eGFR < 25 ml/min/1.73m ²)	0.60 – 0.75 g/kg/day ^b	35 kcal/kg/day ^c	600 – 800 mg/day ^d 8 gr/KG	< 2 g/day
a. If hypertensive edema or history of heart failure b. With close supervision and frequent dietary counseling c. 30 kcal/kg/day for individuals 60 years or older d. Along with phosphate binders, as needed				

Hypoalbuminemia (Serum Albumin < 3.5 g/dL)

Malnutrition in patients with kidney failure is common. Early referral to a nutritionist may benefit patients with compromised kidney function. Preferably patients should see a nutritionist at least twice a year and more frequently when they reach pre-ESKD levels of eGFR (< 20 ml/min/1.73m²). Protein intake may be assessed by 24-hour urinary urea nitrogen (UN) excretion (UN g/day).

$\text{Estimated Protein Intake (g)} = [\text{UN} + (.031 \times \text{weight (Kg)})] \times 6.25$
--

Note: Rule-out other coexisting disease, e.g., liver disease, chronic infection, protein-losing enteropathy, or occult malignancy.

Assessment of nutrition: Serum albumin concentration has traditionally been used to measure protein nutrition. However hypoalbuminemia may also reflect an inflammatory response to unknown stimuli (Kaysen, 1999). Therefore, it is advisable to measure other indicators as well, including transthyretin (pre-albumin) (Avram & Mittman, 1994; Tuten et al., 1985) and C-reactive protein (Kaysen, 1999). Anthropometry may also be employed, but its value is limited, especially if data are from a single measurement (Maroni et al., 1998).

Energy intake: The nitrogen balance of uremic patients improves as caloric intake increases, according to some studies (Hyne et al., 1972; Kopple et al., 1986), but not others (Bergstrom, 1999). Based on these conflicting data, it seems prudent to recommend an intake of 35 kcal/kg/day for a patient on a protein-restricted diet who is below ideal body weight. For overweight patients, calories should be restricted. For others, caloric intake may be ad libitum, unless progressive weight loss occurs. If weight is an issue, a consultation with a dietitian is advisable.

11.7. Adjustment of Medication Doses

BACKGROUND

Some medications have the potential to cause an acute decline in GFR (e.g., radiocontrast dye, aminoglycoside antibiotics, NSAIDs) (KDOQI, 2002). In addition, patients with impaired kidney function may require a dose adjustment to minimize adverse events or the potential for drug toxicity, or to ensure optimal efficacy of the drug. Complications may also occur from an increased sensitivity to the medication's effects (e.g., hypoglycemia with insulin or oral hypoglycemic agents excreted by the kidney, such as glyburide).

RECOMMENDATIONS

1. Evaluate the patient's drug therapy for potential dosage modification based on kidney dysfunction (i.e., per CrCl or sCr) at each visit. [I]
2. Avoid medications contraindicated in patients with impaired kidney function. [I]

DISCUSSION

Severe kidney impairment may alter volume of distribution and protein binding, prompting dosage adjustments. Drugs known to be sensitive to changes in renal function such as gabapentin and antibiotics should be closely monitored.

In patients with CKD, medications that are renally excreted may require a lower initial dose or an increase in the interval between doses. In general, nephrotoxic medications should be avoided. Most often, medications will include a recommendation for dosage adjustment based on the patient's CrCl or serum creatinine, or more general recommendations are provided. Recommendations are based on a variety of sources and may not be available for all medications. A list of medications commonly used in patients with CKD (i.e., to manage CKD and/or complications or comorbidities) and recommendations for dosing modifications are included in [Appendix D](#).

11.8. Immunization

BACKGROUND

Adults at increased risk include those who are generally immunocompetent but who have chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease or emphysema), or chronic liver diseases (e.g., cirrhosis). Diabetes Mellitus often is associated with cardiovascular or renal dysfunction, which increases the risk for severe pneumococcal illness. It has been shown that an annual flu vaccine reduces the episodes of influenza in the high risk and elderly populations. There is no evidence for Hepatitis B vaccine in patients with CKD as per the Centers for Disease Control and Prevention (CDC) unless the patients are in a high risk category with multiple sex partners. Vaccination against shingles may help prevent the development of herpes zoster in patients over 60 years regardless of the medical condition.

RECOMMENDATIONS

1. *Influenza* immunization is recommend for adults less than age 50 with chronic illness (i.e., heart, lung or kidney disease; asthma; diabetes; anemia or other blood disorders; HIV/AIDS; patients with weakened immune systems) and all adults age 50 and older. [A]
2. *Pneumococcal* immunization should be administered to all adults age 65 and older, and those less than age 65 with chronic illness that places them at the highest risk for serious pneumococcal infection (HIV/AIDS; sickle cell disease; immunosuppressive treatment with

radiation, chemotherapy or long-term steroids; anatomic or functional asplenia; status post organ or bone marrow transplant; nephrotic syndrome, or renal failure). [B]

3. *Patients with CKD should* receive the pneumococcal vaccine, including previously unvaccinated persons and persons who have not received the vaccine within 5 years (and were less than 65 years of age at the time of vaccination). All persons who have unknown vaccination status should receive one dose of the vaccine. [B]
4. Hepatitis B vaccine should be administered to patients receiving hemodialysis. [C]
5. Adults age 60 years and older should be vaccinated with the zoster/shingles vaccine to reduce the occurrence of herpes zoster (shingles). [C]

EVIDENCE STATEMENTS

Pneumococcal

Adults at increased risk include those who are generally immunocompetent but who have chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease or emphysema), or chronic liver diseases (e.g., cirrhosis). DM often is associated with cardiovascular or renal dysfunction, which increases the risk for severe pneumococcal illness.

Shingles

In persons age 60 years and older, the vaccine reduced the occurrence of herpes zoster (shingles) by about 50 percent. The vaccine effect was highest at 64 percent in people between the ages 60 to 69, but its effectiveness declined with increasing age - to 41 percent for the 70 to 79 age group and 18 percent for those 80 years of age and older.

In those who were vaccinated with the zoster/shingles vaccine, but still developed shingles, the duration of pain was decreased compared to placebo.

At this time, there is not enough information from the studies to determine the risks and benefits of the zoster/shingles vaccine in people younger than 60 years of age.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	Influenza	CDC, 2006	II-1	Good	A
2	Pneumococcal	CDC, 2006	II-2	Fair	B
3	Hepatitis B	CDC, 2006	III	Fair	C
4	Zoster virus	CDC, 2006	III	Fair	C

QE = Quality of Evidence; SR = Strength of Recommendations (See Appendix A)

<i>Annotation J</i>	<i>Prevent and Treat Cardiovascular Disease</i>
---------------------	---

12. THE RISK FOR CARDIOVASCULAR DISEASE

BACKGROUND

Patients with kidney disease and/or proteinuria are at high risk for cardiovascular disease. Modification of risk factors may attenuate these risks. Effective treatment of hypertension and hyperlipidemia, along with smoking cessation and exercise, are essential to improve cardiovascular health in patients with kidney disease, enhance their quality of life, and improve survival rates for patients that progress on to ESKD and dialysis and/or transplantation.

In patients with CKD, the cardiovascular risk is actually much higher than the risk of ESKD. Therefore, many patients with CKD may die from cardiovascular disease before progressing to ESKD. It is important to recognize this elevated cardiovascular risk and aggressively reduce atherosclerosis risk factors.

There is a higher prevalence of hypertriglyceridemia and low HDL-C in patient with CKD.

RECOMMENDATIONS

1. Patients with CKD should be evaluated for risk stratification of cardiovascular disease. Patients with CKD should be assessed for cardiovascular risk including fasting lipid profile, blood pressure, tobacco use (smoking) history, family history of premature cardiovascular disease, obesity, and physical activity level. Strategies to reduce cardiovascular risk factors should be implemented.
 - a. For the treatment of hypertension – see [VA/DoD Guideline for Management of Hypertension](#).
 - b. For control of dyslipidemia – see [VA/DoD Guideline for Management of Dyslipidemia](#). (Dosage adjustment of statins and careful monitoring is required in patients with CKD)
 - c. For the treatment of smoking cessation – see [VA/DoD CPG for Management of Tobacco Use](#).
2. For treatment of ischemic heart disease – see the [VA/DoD CPG for Management of Ischemic Heart Disease](#).
3. For the treatment of congestive heart failure – see the [VA/DoD CPG for Management of Chronic Heart Failure](#).
4. Although the risk of bleeding from anticoagulants/antiplatelet agents is higher in patients with CKD, there is insufficient evidence to recommend a different approach to secondary prevention using aspirin or clopidogrel in patients with CKD. However, there is insufficient evidence to support the use of aspirin for primary prevention of cardiovascular events in all patients with CKD because it is unclear whether the benefits outweigh the risks. [I]

RATIONALE

Individuals with CKD are at high risk for cardiovascular disease (Tonelli et al., 2006). Because many of the intervention trials of primary and secondary prevention of cardiovascular disease excluded patients with CKD, the utility of most therapeutic interventions is extrapolated from the population without CKD. The risk–benefit ratio must be weighed in the individual patients. Nevertheless, because of the high rate of cardiovascular disease in the CKD population, for interventions with low risk, such as aggressive control of blood pressure and smoking cessation, there may be substantial benefit.

EVIDENCE STATEMENTS

Cardiovascular abnormalities start early in kidney failure. Twenty-seven percent of patients with an eGFR ≥ 50 ml/min/1.73m² exhibit left ventricular hypertrophy (Levin et al., 1996). The prevalence of coronary artery disease in patients with kidney failure is not accurately known, but the high death rates in this population suggest that it is quite high.

In the ALLHAT study (2002) (40,514 hypertensive patients), compared with patients with normal or mildly reduced GFR, patients with moderate or severe reductions in GFR were more likely to have had a previous myocardial infarction or stroke (19.2% and 23.4% vs. 28.7% and 26.9%, respectively), have ischemic changes on ECG (16.0% and 18.9% vs. 24.6% and 34.1%, respectively), and have ECG-LVH (3.9% and 4.2% vs. 6.0% and 11.2%, respectively). A decrease in eGFR of 10 ml/min/1.73 m² was independently associated with a 6 percent higher risk for cardiovascular disease and 14 percent higher risk for ECG-LVH. The increase in risk was marked at an eGFR of approximately 60 to 70 ml/min/1.73m² (Rahman et al., 2004).

In a post hoc subgroup analysis of the ALLHAT study, hypertensive patients (aged > 55 years) and > 1 risk factors for coronary heart disease participants with a moderate to severe reduction in GFR had 6-year risk rates higher for coronary heart disease than for ESKD (15.4% vs. 6.0%, respectively). A baseline GFR of less than 53 ml/min/1.73m² (compared with > 104 ml/min·1.73m²) was independently associated with a 32 percent higher risk for coronary heart disease (Shlipak et al., 2005).

Secondary and Primary Prevention - Aspirin

Aspirin is recommended for the prevention of future cardiovascular events among patients with CKD who have already experienced a vascular event (secondary prevention). There is insufficient evidence to support the use of aspirin for primary prevention of cardiovascular events in all patients with CKD because it is unclear whether the benefits outweigh the risks, particularly the potential for increased bleeding events in this population.

In a patient-level meta-analysis of 195 RCTs of anti-platelet therapy that enrolled 135,640 high-risk patients, there was a substantial reduction in risk for serious vascular events across a wide range of high risk groups (Antiplatelet Trialists' Collaboration, 2002). This meta-analysis included 2,632 hemodialysis patients who were enrolled in 14 trials that primarily examined the use of anti-platelet agents other than aspirin to prevent dialysis access thrombosis and most of the studies were less than six months in duration. Overall, patients in the group receiving anti-platelet agents experienced a 41 percent reduction in serious vascular events, although there were only 99 vascular events observed. The authors of the meta-analysis did not feel that they could reliably estimate the bleeding risk from anti-platelet agents in the hemodialysis population. Furthermore, the risks and benefits of aspirin among patients with non-dialysis dependent CKD that were enrolled in these trials have not been reported either in individual trials or in meta-analysis. Thus the recommendation for secondary prevention with aspirin among patients with CKD is based on extrapolation from a large meta-analysis demonstrating risk reduction across a wide range of different high risk groups including hemodialysis patients.

Use of aspirin for primary prevention in the general population is controversial (Patrono et al., 2005) and the risk-benefit-ratio varies depending on each individual's estimated risk of experiencing a vascular event. Benefits exceed risks only among those whose annual risk of experiencing a vascular event is greater than 1 percent based on a meta-analysis of four major primary prevention trials (Hypertension Optimal Treatment (HOT) Study, 1998; Physicians Health Study, 1989; Sanmuganathan et al., 2001; The British Male Doctors Trial [Peto et al., 1988]; Thrombosis Prevention Trial, 1998). Few data exist that specifically pertain to patients with CKD. A secondary analysis of the Hypertension Optimal Treatment (HOT) study showed a non-statistically significant trend toward a protective effect of aspirin 75 mg among those with a serum creatinine > 1.5 mg/dL. Only one trial has assessed the risks and benefits of low dose aspirin among patients with CKD. In the UK HARP I study, patients with CKD received simvastatin 20 mg and aspirin 100 mg in a 2x2 factorial design (Baigent et al., 2005). Allocation to treatment with aspirin was not associated with an increased risk of major bleeding but was associated with a statistically and clinically significantly increased risk of minor bleeding (15% vs. 5%) after one year of follow-up. Larger trials of longer duration in patients with CKD are needed to adequately assess the risks and benefits of low-dose daily aspirin therapy in this population.

13. PATIENT EDUCATION

BACKGROUND

Patient education should begin soon after the diagnosis of CKD. The importance of strategies to delay the progression of kidney disease and avoid further kidney injury must be highlighted. Strategies include education regarding the general definition of CKD, risk factors, tests used to diagnose CKD, steps patients can take to slow the progression (e.g., blood pressure and blood glucose control, smoking cessation, special diet, medications and avoidance of nephrotoxic drugs) and ways to avoid complications (e.g., cardiovascular disease, anemia, hyperkalemia, salt and water retention and bone problems), and their treatment.

RECOMMENDATIONS

1. Patient education should begin soon after the diagnosis of CKD. The importance of strategies to delay the progression of kidney disease and avoid further kidney injury must be highlighted. [I]
2. Assessment of adherence to therapy and strategies to overcome barriers should be discussed with all patients. [I]
3. Patients should be provided with information about: [I]
 - a. The risk factors, natural history, and health consequences of CKD
 - b. Lifestyle changes including smoking cessation, exercise, and dietary modifications needed to prevent progression of kidney disease
 - c. Educate patients about receiving annual vaccinations
 - d. Inform patients with eGFR < 30 ml/min/1.73m² about renal replacement therapy options (hemodialysis, peritoneal dialysis, and transplantation)
 - e. Patients who are considering hemodialysis in the future should be advised about protecting their non-dominant arm for dialysis vascular access placement.

RATIONALE

The success of management of CKD ultimately depends on patient self-management and his or her ability and willingness to change and maintain certain behaviors.

These behaviors may include changes in diet, smoking cessation, limiting alcohol consumption, exercise, adherence to medication regimens, self-monitoring of blood pressure, and adherence to plans for medical follow-up.

EVIDENCE STATEMENTS

An RCT demonstrated the potential of self-management to improve health status and reduce healthcare utilization in patients with chronic diseases. The Chronic Disease Self-Management Program is a 7-week, small-group intervention attended by people with different chronic conditions. It is taught largely by peer instructors from a highly structured manual. The program is based on self-efficacy theory and emphasizes problem-solving, decision-making, and confidence-building (Lorig et al., 2001).

The investigators of a multicenter RCT of predialysis psychoeducational interventions in the mid-1980s collected follow-up data for patients with CKD. Twenty-year survival data from clinical records and databases was gathered. Multiple regression analyses indicated that median survival was 2.25 years longer after patients with CKD received predialysis psychoeducational interventions compared with

usual care. Predialysis psychoeducational intervention is a safe and useful intervention that contributes valuably to multidisciplinary predialysis care (Devins et al., 2005).

Key areas that need to be included in the education program for patients and their families are discussed in [Appendix G](#).

<i>Annotation M</i>	<i>Follow-Up</i>
---------------------	------------------

14. FOLLOW-UP

BACKGROUND

Detect early changes in kidney function, clinical status, and biochemical parameters in order to prevent or to attenuate uremic complications, and possibly, to slow the progression of kidney disease.

RECOMMENDATIONS

1. Patients with CKD and an eGFR > 30 ml/min/1.73m² with no associated co-morbidities should be followed up every 6 to 12 months.
2. Patients with more advanced CKD should be referred to a nephrologist for consultation and/or continued follow-up.

(See [Table 14.1. Classification of CKD and Follow-Up Frequency by Primary Care](#))

DISCUSSION

The frequency of follow-up visits depends on the severity of the kidney disease. It is unlikely that patients with mild kidney disease will develop electrolyte disturbances, anemia, or uremic bone disease. Similarly, patients with normal kidney function and mild proteinuria (< 1.0 g/24 hours), in the absence of DM, are less likely to develop more serious kidney problems. These patients, if they do not have other co-morbidities and if their kidney function has been stable, can be seen about two to three times per year.

It is advisable that a nephrologist be consulted, at least initially, for the care of patients with more advanced kidney disease (eGFR < 45 ml/min/1.73m²) and for patients with larger amount of proteinuria (> 3 g/24 hours) who may need additional work-up that may include kidney biopsy. There is a high possibility that kidney disease will progress to ESKD in patients with eGFR < 45 ml/min/1.73m². Many biochemical abnormalities that will eventually lead to clinical symptoms associated with uremia are already detectable at this level of GFR. Education about ESKD and treatment options should be given to these patients. Dietary protein restriction with amino acid supplementation may be helpful in preventing uremic symptoms and in delaying the progression of kidney disease in patients with severe chronic kidney disease. Low protein diets may also reduce proteinuria in patients with nephrotic syndrome. Attention should be given to overall nutritional status, hyperlipidemia, and electrolyte balance. Patients with an eGFR < 30 ml/min/1.73m² have severe kidney disease and should be referred to a nephrologist. These patients are at high risk of developing uremic complications. They could also progress to ESKD in a relatively short time. By this time the patient should have a good understanding about ESKD and its treatments. If hemodialysis is the treatment option, the patient should receive the instruction not to use the non-dominant arm for blood drawing, since this will be the preferred arm for dialysis access placement. An exercise program to increase the size of the forearm veins should be instituted. A permanent vascular access (preferably an arteriovenous fistula) should be placed when the GFR is approximately 15 ml/min (20 ml/min/1.73m² in patients with diabetes) or at least six months prior to the anticipated need for dialysis. If preemptive kidney allograft transplantation is an option,

work-up for the patient and potential donors must be initiated. Frequent follow-up visits are also indicated in patients with rapid changes in kidney function or in whom there are not enough data to determine the rate of progression of kidney failure. Other groups of kidney patients who need to be seen frequently are patients with poorly controlled blood pressure or blood sugar. Poorly controlled blood pressure (> 130/80 mm Hg) can adversely affect the progression of kidney disease in patients with diabetes as well as in patients with kidney disease from other causes. Poor glycemic control may also adversely affect the progression of diabetic kidney disease. It may be necessary to see these patients and to adjust their medications at least monthly until their blood pressure readings and/or their blood sugar are in the acceptable ranges. If hypertension or DM is difficult to manage, a consultation with a specialist may be appropriate. See the [VA/DoD CPGs for Management of Hypertension and Diabetes Mellitus](#) for more details.

Serum electrolytes and BUN/creatinine should be done routinely at each visit. CBC, calcium, phosphorus, albumin, and PTH should be measured at least annually and more frequently if abnormal. In patients with diabetes who do not have macroalbuminuria, determination of microalbuminuria should be done at least yearly.

Table 14.1. Classification of CKD and Follow-Up Frequency by Primary Care

Stage	Description	eGFR (ml/min/1.73m ²)	Follow-up Frequency by Primary Care
1	Kidney damage with normal or increased GFR	≥ 90	Not more than routine
2	Kidney damage with mildly decreased GFR	60 - 89	12 months *
3	Moderately decreased GFR	30 -59	6 – 12 months *
4	Severely decreased GFR	15 - 29	3 – 6 months * Refer to Nephrology
5	Kidney failure	< 15 or dialysis	Refer to Nephrology

* Patients who are newly diagnosed or in whom kidney disease is progressing rapidly should be seen more frequently.

Kidney function should also be checked during intercurrent illness and peri-operatively in all patients with Stage 2 to 5 CKD.

APPENDICES

Table of Contents

Appendix A: Guideline Development Process

Appendix B: Assessment

B-1: Screening Algorithm for CKD

B-2: Etiologic Evaluation

B-3: Specialized Laboratory Studies for the Diagnosis of Kidney Disease

B-4: Kidney Imaging Studies

Appendix C: Slowing Progression of CKD

C-1: Blood Pressure Control – Summary of Supporting Studies

C-2: Pharmacologic Therapy (ACEI/ARB) – Summary of Supporting Studies

Appendix D: Pharmacotherapy

D-1: Pharmacotherapy Dosing Recommendations for ACEIs and ARBs in Patients with CKD

D-2: Cautions in the Use of Selected Medications in Patients with CKD

Appendix E: Complications of Kidney Disease

Appendix F: Nutrition

F-1: Phosphorus

F-2: Potassium

Appendix G: Patient Education

Appendix H: Follow-up for Chronic Kidney Disease

Appendix I: Acronym List

Appendix J: Participant List

Appendix K: Bibliography

Appendix A: Guideline Development Process

The development update of the VA/DoD Clinical Practice Guideline for Management of CKD followed the steps described in “Guideline for Guidelines,” an internal working document of the VA/DoD Evidence Based Practice Working Group, that requires an ongoing review of the work in progress. The Working Group of the VA/DoD was charged to update the evidence-based action recommendations whenever possible.

The Offices of Quality and Performance and Patient Care Services, in collaboration with the network Clinical Managers, the Deputy Assistant Under Secretary for Health, and the Medical Center Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD that formed the Management of CKD Working Group. Working Group members included representatives of the following specialties: nephrology, internal medicine, primary care, pharmacology, cardiology, and nursing.

The Working Group defined a set of clinical questions within the area of the guideline. This ensured that the guideline development work outside the meeting focused on issues that practitioners considered important and produced criteria for the search and the protocol for systematic review and, where appropriate, meta-analysis.

The Working Group participated in an initial face-to-face meeting to reach consensus about the guideline algorithm and recommendations and to prepare a draft update document. The draft continued to be revised by the Working Group at-large through numerous conference calls and individual contributions to the document. Following the initial effort, an editorial panel of the Working Group convened to further edit the draft document. Recommendations for the performance or inclusion of specific procedures or services were derived through a rigorous methodological approach that included the following:

- Determining appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction
- Reviewing literature to determine the strength of the evidence in relation to these criteria
- Formulating the recommendations and grading the level of evidence supporting the recommendation

Experts from the VA and DoD reviewed the final draft and their feedback was integrated into the final draft document.

This update of the CKD Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, academia, as well as guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The list of participants is included in [Appendix J](#).

Formulation of Questions

The Working Group developed researchable questions and associated key terms after orientation to the scope of the guideline and to goals that had been identified by the Working Group. The questions specified (adapted from the Evidence-Based Medicine toolbox, Center for Evidence-Based Medicine, [<http://www.cebm.net>]):

- **Population** – Characteristics of the target patient population
- **Intervention** – Exposure, diagnostic, or prognosis
- **Comparison** – Intervention, exposure, or control used for comparison
- **Outcome** – Outcomes of interest.

These specifications served as the preliminary criteria for selecting studies. Literature searches were conducted on all topics identified in the algorithm or recommendations of the original guidelines. After reviewing the initial search for systematic reviews and meta-analyses, the Working Group decided to focus the search for individual randomized controlled trials (RCT) on the following questions:

1. Does treatment with ACEIs or ARBs in adult patients with CKD and HTN, compared to placebo, lead to better patients outcome (slow progress to ESKD; slow increase in S_{Cr} , decrease in proteinuria)?
2. In adult patients with CKD (proteinuria), does a high dose of ACEI/ARBs compared to a low dose of ACEI/ARBs lead to better patient health outcomes (slow progress to ESKD; slow increase in S_{Cr} , decrease in proteinuria)?
3. In adult patients with CKD and nephrotic syndrome, does restricted protein nutrition compared to a regular diet (low sodium) lead to better outcomes (slow progress to ESKD; slow increase in S_{Cr} , decrease in proteinuria)?
4. In adult patients with CKD and anemia, does treatment with darbepoetin or erythropoietin increase Hgb and improve quality of life?
5. Does a high hemoglobin target compared to a lower target slow the increase in S_{Cr} , reduce development of cardiovascular disease, or reduce mortality?

Selection of Evidence

The evidence selection was designed to identify the best available evidence to address each key question and ensure maximum coverage of studies at the top of the hierarchy of study types. Published, peer-reviewed RCTs, as well as meta-analyses and systematic reviews that included randomized controlled studies were considered to constitute the strongest level of evidence in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, scientifically sound basis for judging comparative efficacy. The Working Group made this decision recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. When available, the search sought out critical appraisals already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and AHRQ systematic evidence reports.

In addition to Medline/PubMed, the following databases were searched: Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials. For Medline/PubMed searches, limits were set for language (English), and type of research (RCT, systematic reviews and meta-analysis).

As a result of the literature reviews, articles were identified for possible inclusion. These articles formed the basis for formulating the guideline recommendations. The following inclusion criteria were used for studies:

- English language only of studies performed in United States, United Kingdom, Europe, Australia, Japan, New Zealand
- Full articles only
- Study populations age limited to adults greater than 18 years; all races, ethnicities, cultural groups
- Randomized controlled trials or prospective studies
- Key outcomes cited
- Published from July 2000 to the end of 2006.

Admissible evidence (study design and other criteria):

- Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results.
- Randomized controlled trials (RCT); systematic reviews (including EPC and HTA reviews); and meta-analyses.
- Relevant outcomes must be able to be abstracted from data presented in the articles.
- Sample sizes must be appropriate for the study question addressed in the paper. RCTs will be included if they are initiated with 10 or more participants.

Preparation of Evidence Tables (Reports) and Evidence Rating

The results of the search were organized and evidence reports as well as copies of the original studies were provided to the Working Group for further analysis. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal healthcare system. Recommendations were based on consensus of expert opinions and clinical experience only when scientific evidence was unavailable.

A group of research analysts read and coded each article that met inclusion criteria. The articles have been assessed for methodological rigor and clinical importance.

Recommendation and Overall Quality Rating

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group received an orientation and tutorial on the evidence USPSTF 2001 rating process, reviewed the evidence and independently formulated Quality of Evidence ratings (see [Table A-1](#)), a rating of Overall Quality (see [Table A-2](#)), and a Strength of Recommendation (see [Table A-3](#)).

Table A-1: Quality of Evidence (QE)	
I	At least one properly done RCT
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study, preferably from more than one source
II-3	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, descriptive studies, case reports, and expert committees

Table A-2: Overall Quality	
Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; <i>or</i> Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

Table A-3: Net Effect of the Intervention	
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; <i>or</i> A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; <i>or</i> A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; <i>or</i> A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; <i>or</i> No relative impact on either a frequent condition with a substantial burden of suffering; or an infrequent condition with a significant impact on the individual patient level.

Table A-4: Final Grade of Recommendation				
	<i>The net benefit of the intervention</i>			
<i>Quality of Evidence</i>	Substantial	Moderate	Small	Zero or Negative
<i>Good</i>	A	B	C	D
<i>Fair</i>	B	B	C	D
<i>Poor</i>	I	I	I	I

Evidence Rating System

A	A strong recommendation that the clinicians provide the intervention to eligible patients. <i>Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.</i>
B	A recommendation that clinicians provide (the service) to eligible patients. <i>At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.</i>
C	No recommendation for or against the routine provision of the intervention is made. <i>At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.</i>
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. <i>At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</i>
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. <i>Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</i>

Lack of Evidence – Consensus of Experts

Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the Working Group.

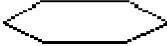
Algorithm Format

The goal in developing the guideline for management of CKD was to incorporate the information into a format which would maximally facilitate clinical decision-making. The use of the algorithm format was chosen because of the evidence that such a format improves data collection, diagnostic and therapeutic decision-making and changes patterns of resource use. However, few guidelines are published in such a format.

The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (Society for Medical Decision-Making Committee, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.

	<p>Rounded rectangles represent a clinical state or condition.</p>
	<p>Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.</p>
	<p>Rectangles represent an action in the process of care.</p>
	<p>Ovals represent a link to another section within the guideline.</p>

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

REFERENCES

Agency for Health Care Policy and Research (AHCPR). Manual for conducting systematic review. Draft. August 1996. Prepared by Steven H. Woolf.

Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Work Group, Third US Preventive Services Task Force. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001 Apr;20(3 Suppl):21-35.

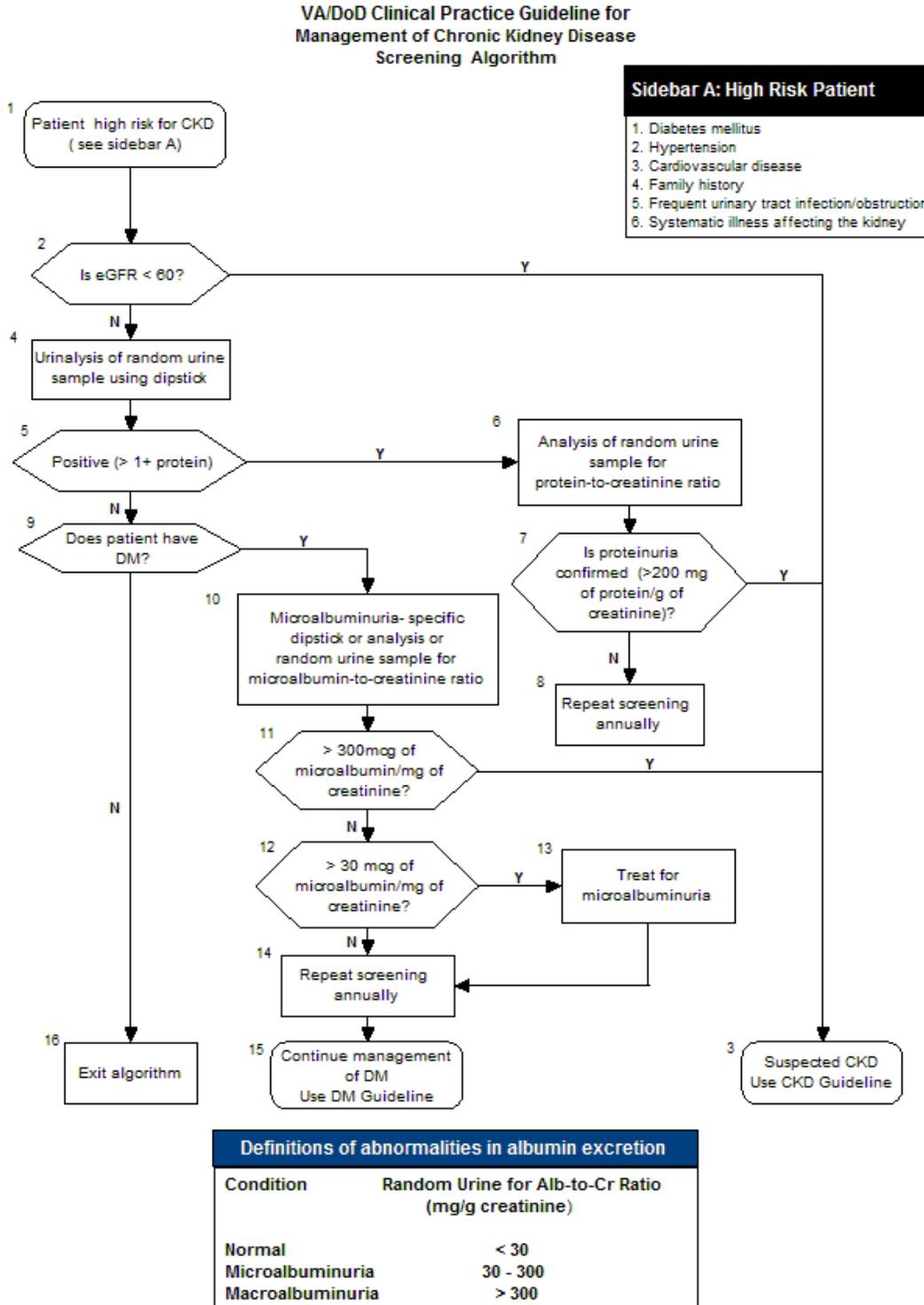
Society for Medical Decision-Making Committee (SMDMC). Proposal for clinical algorithm standards, SMDMC on Standardization of Clinical Algorithms. *Med Decis Making* 1992 Apr-Jun;12(2):149-54.

United States Preventive Service Task Force (USPSTF). Guide to clinical preventive services. 2nd edition. Washington, DC: US Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 1996.

Woolf SH. Practice guidelines, a new reality in medicine II. Methods of developing guidelines. *Arch Intern Med* 1992 May;152(5):946-52.

Appendix B: Assessment

Appendix B-1: Screening Algorithm for CKD



Appendix B-2: Etiologic Evaluation

	CLUES	URINE SEDIMENT	RANGE of PROTEINURIA	SPECIAL TESTS
Essential Hypertension	<ul style="list-style-type: none"> Look for other signs of end organ damage 	No formed elements	Trace→Moderate	N/A
Diabetes Mellitus	<ul style="list-style-type: none"> Frequently associated with retinopathy 	< 25% have microscopic hematuria	Microalbuminuria→Nephrotic	N/A
Glomerulonephritis	<ul style="list-style-type: none"> Use history and physical to focus serological evaluation 	Dysmorphic RBCs or RBC casts	Trace→Nephrotic	C ₃ , C ₄ , ASO, ANCA, HIV, HEP B & C, ANA, RPR, Blood cultures, Cryoglobulin, anti-GBM, SPEP, UPEP
Interstitial Nephritis	<ul style="list-style-type: none"> Medication history, fever, rash, and eosinophilia Classic triad of fever, rash, and eosinophilia is present in a minority only 	Pyuria, WBC casts, eosinophiluria	Trace→Moderate	Galium scanning
Pre-Renal	<ul style="list-style-type: none"> Clinical diagnosis Volume depletion, hypotension Congestive heart failure, sepsis, liver disease 	Hyaline casts may be present	None →Trace	FE _{Na} < 1% FE _{Urea} < 35%
Urinary Tract Obstruction	<ul style="list-style-type: none"> Suggested by history and physical exam May or may not be oliguric 	Benign or may have hematuria	None	Kidney ultrasound, bladder scan, other imaging studies may be necessary
Paraproteinemia	<ul style="list-style-type: none"> Globulin > albumin; constitutional symptoms, anemia out of proportion to kidney failure 	May have hematuria, RBC casts, granular casts	May have false negative dipstick, trace to nephrotic range by spot protein/creatinine	SPEP/UPEP, serum free light chain ratio IEP or immunofixation to confirm, hypercalcemia may be present, ESR
Polycystic Kidney Disease	<ul style="list-style-type: none"> Palpable kidneys +/- family history Flank pain 	May have hematuria	Trace→Moderate	Kidney ultrasound or CT
Renovascular Disease	<ul style="list-style-type: none"> Late onset or refractory hypertension Smoking history Clinical evidence of atherosclerotic disease 	Benign	None →Trace	Asymmetric kidney size on ultrasound; abnormal duplex of kidney arteries; additional investigation (e.g., captopril radionucleotide scan, MRA) may be indicated
Vasculitis	<ul style="list-style-type: none"> Constitutional symptoms, fever, peripheral neuropathy, rash, may have respiratory involvement 	Hematuria; granular casts	Trace →Nephrotic	C ₃ , C ₄ , ANA, ANCA; HepBsurface Ag; HepC Ab; cryoglobulins; ESR, CRP; RF; HIV
Acute Tubular Necrosis	<ul style="list-style-type: none"> Medication history History of hypotension, crush injury, IV contrast 	Muddy brown granular casts; renal tubular epithelial cells; crystalluria	Trace	FE _{Na} > 2%; Uosm < 350 mOsm/l FE _{Urea} > 35% CPK, urine myoglobin
Atheroembolic Disease	<ul style="list-style-type: none"> “Stuttering” GFR loss, stigmata of emboli History of endovascular procedure 	Hematuria and/or eosinophiluria may be present	Trace →Moderate	Eosinophilia; low complements

Appendix B-3. Specialized Laboratory Studies for the Diagnosis of Kidney Disease

Laboratory Test	Significance
Serum complement levels (C ₃ ,C ₄)	May be decreased in: <ul style="list-style-type: none"> ○ Post-streptococcal glomerulonephritis ○ Post-infectious glomerulonephritis ○ Membranoproliferative glomerulonephritis ○ Lupus nephritis ○ Cryoglobulinemia ○ Atheroembolic disease
Anti-nuclear antibody (ANA)	Positive in: <ul style="list-style-type: none"> ○ Lupus nephritis
Anti-neutrophil cytoplasmic antibody (ANCA)	Positive in: <ul style="list-style-type: none"> ○ Wegener’s granulomatosis (C-ANCA) ○ Microscopic polyangiitis (P-ANCA) ○ Pauci-immune rapidly progressive glomerulonephritis (RPGN) (P-ANCA)
Anti-glomerular basement membrane antibodies (anti-GBM)	Positive in: <ul style="list-style-type: none"> ○ Goodpasture’s syndrome ○ Anti-GBM associated RPGN
Serum protein electrophoresis (SPEP) Urine protein electrophoresis (UPEP) Serum free light chain ratio	Positive for monoclonal immunoglobulin in: <ul style="list-style-type: none"> ○ Multiple myeloma ○ Amyloid ○ Light-chain deposition disease
Cryoglobulins	Positive in: <ul style="list-style-type: none"> ○ Cryoglobulinemia
Hepatitis B surface antigen	Associated with: <ul style="list-style-type: none"> ○ Membranous nephropathy ○ Polyarteritis nodosa ○ Membranoproliferative nephritis
Hepatitis C serologies	Associated with: <ul style="list-style-type: none"> ○ Mixed cryoglobulinemia ○ Membranoproliferative glomerulonephritis ○ Membranous nephropathy
HIV serologies	Associated with: <ul style="list-style-type: none"> ○ Focal and segmental glomerulosclerosis (FSGS)
Eosinophiluria	Associated with: <ul style="list-style-type: none"> ○ Acute interstitial nephritis ○ Atheroembolic disease ○ May be positive in any condition with eosinophilia or pyuria

Appendix B-4. Kidney Imaging Studies

Imaging study	Significance
Kidney ultrasound	Diagnosis of: <ul style="list-style-type: none"> ○ Obstructive kidney disease ○ Polycystic kidney disease ○ Assessment of kidney size: <ul style="list-style-type: none"> ▪ Enlarged in diabetic nephropathy, amyloid ▪ Small in chronic kidney disease ▪ Asymmetric in renovascular disease
Kidney Doppler	Diagnosis of: <ul style="list-style-type: none"> ○ Renovascular disease ○ Renal vein thrombosis
Radioisotope kidney scan	Diagnosis of: <ul style="list-style-type: none"> ○ Renovascular disease ○ Obstructive uropathy ○ Assessment of split kidney function
CT scan	Assessment of: <ul style="list-style-type: none"> ○ Kidney masses ○ Atypical kidney cysts ○ Kidney stones
Magnetic resonance angiography	Diagnosis of: <ul style="list-style-type: none"> ○ Renovascular disease
Renal angiography	Diagnosis of: <ul style="list-style-type: none"> ○ Renovascular disease (gold standard) ○ Kidney artery thrombosis/thromboembolism ○ Polyarteritis nodosa
Retrograde ureterogram	Diagnosis of: <ul style="list-style-type: none"> ○ Upper-tract obstruction
Intravenous pyelogram	Not indicated in kidney disease

Appendix C: Slowing Progression of CKD

Appendix C-1: Blood Pressure Control – Summary of Supporting Studies

EVIDENCE STATEMENTS

The MDRD Study (Klahr et al., 1994) consisted of two randomized multicenter trials in two different patient populations, both designed to test two different hypotheses: a reduction in dietary protein and phosphorus intake and the maintenance of blood pressure at a level below that usually recommended retards the progression of renal disease and that these interventions are safe and acceptable. Study 1 (n=585) included patients aged 18 to 70 years with an eGFR 25 to 55 ml/min/1.73m² who were randomized to receive either a usual protein diet or a low protein diet and a usual blood pressure (MAP ≤ 107 (equivalent to 140/90) for patients aged 18 to 60 years and MAP ≤ 113 mm Hg for patients aged ≥ 61 (equivalent to 160/90) or low blood pressure < 92 (125/75) for patients aged 18 to 60 years and MAP ≤ 98 mm Hg (equivalent to 145/75) for patients aged 61 and older. Study 2 (n=255) included patients aged 18 to 70 with an eGFR 13 to 24 ml/min/1.73m² who were randomized to a low protein diet vs. very low protein diet and to the aforementioned age-specific usual vs. low blood pressure arms. The recommended anti-hypertensive regimen was ACE+/- diuretic, calcium channel blocker. The study excluded patients with insulin requiring diabetes. The most common renal diagnoses were glomerular diseases (25 percent) and polycystic kidney disease (24 percent); 3 percent of the patients had non-insulin-dependent diabetes. The primary outcome was rate of change in GFR over time. GFR was assessed using I-125 Iothalamate. Secondary outcome measures were treatment for ESKD and death.

During follow-up there was a 4.7 mm Hg (P<0.001) difference between conventional and low blood pressure arms in achieved blood pressure. There were no differences in either rate of GFR decline or death or ESKD treatment between the conventional and low blood pressure arms. However, results differed in analyses stratified by level of proteinuria, a post hoc analysis. In Study 1, patients with 1 to 3 g and > 3 g proteinuria randomized to low blood pressure arm had a slower rate of GFR decline than patients in the usual blood pressure arm. In study 2, patients with > 3 g proteinuria randomized to the low blood pressure arm had a lower rate of GFR decline compared with patients randomized to the usual blood pressure arm, though rate of GFR decline was similar for patients with 1 to 3 g and < 1 g. In both studies, GFR declined faster in patients with greater degrees of proteinuria. Of note, there were differences in the use of ACE inhibitors across arms with a greater percentage of patients in the low blood pressure arms of both studies using ACE inhibitors. Thus there remains some question, since patients were not randomized based on level of proteinuria, whether lower rates of GFR decline in patients with proteinuria randomized to the low blood pressure arm reflect the benefit of lower blood pressure or use of ACEIs, particularly given the relatively modest difference between arms in achieved blood pressure. The high percentage of patients with polycystic kidney disease included in this study has also raised questions about the generalizability of study results. Finally, use of different targets for younger and older patients also complicates study interpretation. For patients 61 years and older, the target for the low blood pressure arm was 145/75.

The African American Study of Kidney Disease (AASK)

The AASK study (Wright, 2002) enrolled 1,094 African American patients with hypertension aged 18 to 70 with a GFR between 20 and 65. Patients with diabetes, more than 2.5 g of proteinuria, and CKD due to causes other than hypertension were excluded. The goals of the study were to test the hypothesis that aggressive blood pressure lowering slows the decline in kidney function and whether the type of anti-hypertensive agent influences kidney disease outcomes. Patients were randomized to a usual blood pressure arm (MAP ≤ 107 mm Hg) and a lower MAP of 92 mm Hg. They were also randomized to receive metoprolol, ramipril, or amlodipine. Participants were followed for up to 6.4 years. The primary end point was change in GFR (first 3 months, 3 months onward, and overall) measured using I-125 Iothalamate. Secondary outcomes included the composite endpoint of 50 percent reduction in GFR

or 25 ml/min/1.73m², ESKD or death, and change in urinary protein excretion. There was a mean separation of 10 mm Hg between arms throughout the study (128/78 vs. 149/95 in the low and usual blood pressure arms, respectively). During the first three months, the mean GFR decline was 1.82 ml/min/1.73m² greater in the low blood pressure arm. However, there were no differences between groups in the chronic slope or overall slope of GFR decline. There were also no differences between blood pressure arms in the combined clinical endpoint or in any of the individual clinical endpoints. Baseline proteinuria (> 2.2 protein/creatinine ratio) was a strong predictor of GFR decline. After stratification of baseline proteinuria, the only difference between usual and low blood pressure arms was in the acute slope: with patients with proteinuria < 0.22 randomized to the low blood pressure arm experiencing a faster decline in GFR, although there were trends toward slower decline in the lower blood pressure arm among patients with higher baseline proteinuria, and the opposite in patients with lower levels of baseline proteinuria. Considerations in generalizing these results include the specialized nature of the population (African Americans with hypertensive nephrosclerosis) and the slow mean decline in GFR (2 ml/min/1.73m²) during follow-up which is typical for hypertensive nephrosclerosis but slower than other forms of non-proteinuric kidney disease, and the narrow range of proteinuria among patients enrolled in this study.

A patient-level meta-analysis (Jafar et al., 2003) using data from the **ACI Inhibition in Progressive Renal Disease (AIPRD) Study** Group database (Jafar et al., 2003) examined the relationship of blood pressure, proteinuria and ACE inhibitor use among patients with non-diabetic kidney disease. The study was conducted among 1,860 patients with nondiabetic kidney disease enrolled in 11 RCTs of ACEIs to slow the progression of kidney disease between 1986 and 1996. Criteria for inclusion in the meta-analysis were participation in a randomized trial and presence of at least one year of follow-up. In addition, patients with type II diabetes and patients who were missing baseline blood pressure, creatinine, or protein excretion measurements were excluded. All of these studies used a target blood pressure of <140/90 and included only patients with hypertension and CKD. The mean age of study populations ranged from 47 to 63 years. The primary finding of this meta-analysis was that the adjusted relative risk of kidney disease progression during follow-up was lowest for patients with a systolic blood pressure (SBP) of 110 to 119 and increased both at blood pressure levels lower than this (< 110 mm Hg) and above this, although only at SBP levels 140 to 159 was there a statistically significantly increased risk of progression compared with the referent category. Diastolic blood pressure (DBP) was not associated with kidney disease progression in adjusted analysis. Risk of kidney disease progression also increased above protein excretion levels > 2g/d. After stratification by level of proteinuria, a statistically significant increase in relative risk of kidney disease progression occurred at blood pressure levels of 130 to 139 and higher and at SBP levels < 110. Among patients with less than 1 g/d of proteinuria, there was no statistically significant increase in risk of progression across a wide range of SBP measurements. Results were similar among patients who were receiving and not receiving an ACEI. However, in interpreting these results, it is important to recognize that the trials in which these patients were enrolled were not designed to address the question of whether a lower blood pressure is associated with slower progression of renal disease. Thus, these results demonstrate that among patients with >1 g proteinuria, those with lower blood pressure experienced slower decline in renal function. These observational results cannot be used to infer that lowering blood pressure will result in slower progression of renal disease, even in patients with proteinuria.

REIN-2

The Ramipril Efficacy in Nephropathy (REIN) trial (1997) showed that at comparable levels of blood pressure control, the ACEI ramipril slowed the decline in GFR and reduced progression to ESKD in individuals with non-diabetic CKD. **The REIN-2 Study** (Ruggenti et al., 1998) was a RCT to address the question of whether blood pressure reduction to levels below the REIN Study (DBP < 90 mm Hg) help to further retard or prevent progression of non-diabetic renal disease. This question had been incompletely answered by the MDRD study (Klahr et al., 1994) because of discrepancies in the percentage of patients receiving ACEIs in the normal and low blood pressure arms of this study, and was particularly important given the negative findings of the AASK (2002) which did address this question directly. In REIN-2, 338 patients were randomly assigned to conventional vs. intensified blood pressure control and were followed over a median of 19 months. Patients assigned to

conventional blood pressure received ramipril and additional blood pressure medications to a target blood pressure of < 90 DBP. Patients assigned to the intensive arm were treated with ramipril, felodipine, and additional agents as necessary to reach a blood pressure target of < 130/80. Achieved blood pressures were 130/80 in the intensified group and 134/82 in the conventional group. The rate of decline in creatinine clearance and the incidence of ESKD were no different in the intensified vs. conventional blood pressure arm. There were 25 vs. 37 non-fatal serious adverse events in the conventional and intensive arms. Considerations in interpreting this study are that there was little separation in achieved blood pressure between study arms.

Other Guidelines

KDOQI recommends a target blood pressure of < 130/80 mm Hg in patients with non-diabetic kidney disease, regardless of their level of proteinuria. The rationale is as follows:

“Numerous epidemiological studies show a graded, independent, and strong relationship between the level of arterial blood pressure and cardiovascular disease. Above a SBP of 115 mm Hg, and above a DBP of 75 mm Hg, the risk of cardiovascular disease doubles with each increment of SBP of 20 mm Hg or DBP of 10 mm Hg. In persons over age 50, SBP greater than 140 mm Hg is a critical and more important cardiovascular disease risk factor than DBP.

Controlled trials in essential hypertension conclusively show a beneficial effect of lowering blood pressure to < 140/90 mm Hg. Controlled trials in high-risk individuals with diabetes or heart failure suggest beneficial effects of reduction of blood pressure to even lower values. Based on these studies, and on observational studies, a number of guidelines for patients with either DM or congestive heart failure recommend a goal blood pressure of < 130/80 mm Hg.

There are few studies regarding blood pressure goals for cardiovascular disease risk reduction in patients with CKD. Thus, the Work Group elected to extrapolate the recommendations for high-risk patients to patients with CKD. Based on the summary of other published guidelines, the Work Group recommendations to reduce the risk of cardiovascular disease in CKD are an SBP < 130 mm Hg and a DBP < 80 mm Hg. In certain select cases, it may be appropriate to maintain a blood pressure higher than the recommended goal of < 130/80 mm Hg. These conditions include orthostatic hypotension, postprandial hypotension, autonomic dysfunction, and severe peripheral vascular disease that is exacerbated by a blood pressure less than 130/80 mm Hg. Based on studies of the relationship of SBP and kidney disease outcomes reviewed, the Work Group recommended caution in lowering SBP <110 mm Hg and more frequent monitoring in patients treated with antihypertensive agents and SBP <120 mm Hg.”

Evidence: A SBP goal of < 130 mm Hg is more effective in slowing the progression of nondiabetic kidney disease in patients with proteinuria (Strong). An even lower blood pressure goal may be more effective in patients with proteinuria > 500 to 1,000 mg/g (Weak). The SBP goal recommended for cardiovascular disease risk reduction (< 130/80 mm Hg) corresponds to the achieved SBP in many of the studies reviewed in the summary table. The potential beneficial effect on kidney disease progression of a lower blood pressure goal has been investigated in two large controlled trials. In the Modification of Diet in Renal Disease (MDRD) Study (Klahr et al., 1994) and AASK (2002), patients were randomly assigned to a mean arterial pressure (MAP) goal of < 92 mm Hg (corresponding to < 125/75 mm Hg), compared to a MAP goal of < 107 mm Hg (corresponding to < 140/90 mm Hg). In the MDRD Study, a study of predominantly nondiabetic kidney disease of various causes, mean baseline proteinuria was 2.2 g/d. A beneficial effect of the lower blood pressure goal was observed in patients with higher rates of urinary protein excretion. The threshold level of proteinuria below which there was no substantial benefit was 0.5 to 1.0 g/d. In the AASK Study, participants had a mean baseline proteinuria of less than 1.0 g/d. There was no significant beneficial effect of the lower blood pressure goal. However, there was a trend favoring the lower blood pressure goal in participants with higher baseline proteinuria and an opposite trend in participants with little or no proteinuria.

JNC 7 (2003) recommends a target blood pressure of 130/80 mm Hg in concordance with KDOQI.

CARI (2006) offers the following guidelines:

- a. Lower SBP minimizes the risk of progression to ESKD, especially with proteinuria (Level II evidence).
- b. A target blood pressure of < 125/75 mm Hg (or mean blood pressure of < 92 mm Hg) if proteinuria > 1 g/24-hours, may be beneficial (Level II evidence).
- c. A target blood pressure of < 130/80 mm Hg (or mean blood pressure < 97 mm Hg) if proteinuria is 0.25 to 1 g/24-hours, may be beneficial (Level II evidence).
- d. Target blood pressure should be < 130/85 mm Hg (or mean blood pressure < 100 mm Hg) if proteinuria < 0.25 g/24-hours (Level II evidence). However, there may be other potential benefits of achieving lower blood pressure than a mean of 100 mm Hg with respect to reduced cardiovascular risk.

There is no evidence concerning target blood pressure for pediatric patients with progressive kidney disease.

VA/DoD Guideline (2001)

In patients with CKD, progressive glomerulosclerosis results in a progressive loss of kidney function, even when the initial kidney insult has been removed. Vigorous control of hypertension reduces the glomerular capillary pressure and slows the progression of glomerulosclerosis. The goal blood pressure should be < 125/75 mm Hg or mean arterial pressure less than 92 for patients with proteinuria and 130/85 mm Hg in patients without proteinuria.

Appendix C-2: Pharmacologic Therapy (ACEI/ARB) – Summary of Supporting Studies

EVIDENCE STATEMENT

Patients with Nondiabetic CKD

ACEIs: It is recommended that an ACEI be used in patients with nondiabetic kidney disease (KDOQI, 2004) based on evidence from RCTs reporting that treatment with an ACEI slows the progression of kidney disease in this patient population (AASK, 2002; AIPRI, 1996; Jafar et al., 2003; Jafar et al., 2001; REIN, 1997). Treatment with an ACEI reduces the risk for ESKD by 29 percent, with a 30 percent reduction in the composite outcome of doubling S_{Cr} and ESKD compared to treatment without an ACEI (Jafar et al., 2001). The beneficial effects of the ACEIs appear to be in addition to their antiproteinuric effects and their reductions in blood pressure (Jafar et al., 2001 & 2003; KDOQI, 2004).

ARBs: Treatment with an angiotensin II receptor blocker is recommended in patients with nondiabetic kidney disease who are unable to take an ACEI, based on short-term studies with limited numbers of patients evaluating surrogate endpoints (KDOQI, 2004; Laverman et al., 2002; Luño et al., 2002; Nielsen et al., 1997; Plum et al., 1998; Remuzzi et al., 1999).

Combination ACEI and ARB: The evidence for treatment using an ACEI in combination with an ARB in slowing the progression of nondiabetic kidney disease is also limited, and this treatment requires further study (Campbell et al., 2003; COOPERATE, 2003; KDOQI, 2004; MacKinnon et al., 2006). In the COOPERATE trial, 263 Japanese patients with nondiabetic renal disease were randomized to an ARB, an ACEI, or the combination. The combined primary endpoint of doubling S_{Cr} or ESKD occurred in 11 percent of patients on combination therapy and 23 percent of patients on the ARB (HR 0.40; 95% CI 0.17-0.69; $P=0.016$), and 23 percent of patients on the ACEI (HR 0.38; 95% CI 0.18-0.63; $P=0.018$). Results of a pooled analysis of 16 cross-over trials showed a significant decrease in mean change in proteinuria of 440 mg/24-hours (95% CI 289 to 591). With the addition of an ARB to an ACEI, there was a significant increase in serum potassium (0.1 mEq/L 95% CI 0.05 to 0.17) and nonsignificant decrease in GFR (-1.4 ml/min/1.73 m² 95% CI -2.6 to 0.2). Although combination therapy appeared to be safe and effective, it was noted that additional trials with long-term follow-up are needed to determine whether these findings slow the progression of kidney disease (MacKinnon et al., 2006). Combination of an ACEI and a loop diuretic such as furosemide (AASK, 2002) or a thiazide including chlorthalidone or hydrochlorothiazide (ALLHAT, 2002) may be considered to achieve the target blood pressure or improve cardiovascular outcomes. Combination therapy with an ACEI and nondihydropyridine calcium channel blockers (NCCB) would also be reasonable to reduce proteinuria in patients with hypertension (KDOQI, 2004).

Patients with DM and CKD:

Type 1 DM with microalbuminuria or macroalbuminuria

ACEIs: An ACEI is recommended in patients with type 1 DM, with or without hypertension, with microalbuminuria or macroalbuminuria (ADA, 2003b). The ACEIs have been reported to be beneficial in patients with type 1 DM with macroalbuminuria to decrease the rate of decline in kidney function and to reduce the combined risk of death, dialysis, or transplantation (Lewis et al., 1993); and in type 1 DM with microalbuminuria to decrease the progression of kidney disease (The ACEI/DN Trialists, 2001; Laffel et al., 1995; Viberti et al., 1994).

ARBs: The long-term effects of the ARBs have not been adequately studied in patients with type 1 DM associated with microalbuminuria or macroalbuminuria.

Type 2 DM with microalbuminuria

ACEIs: Treatment with an ACEI in trials of patients with type 2 DM that also included a percentage of patients with microalbuminuria, have demonstrated a reduction in cardiovascular endpoints (CAPPP, 2001; Estacio et al., 1998; FACET, 1998; MICRO-HOPE, 2000; UKPDS, 1998). In trials enrolling patients with type 2 DM and microalbuminuria, treatment with an ACEI has resulted in a decrease in the progression of kidney disease (Ravid et al., 1993; Ravid et al., 1996).

ARBs: As with the ACEIs, treatment with an ARB in patients with type 2 DM and microalbuminuria decreased the progression of kidney disease (IRMA2, 2001). Therefore, an ACEI or ARB can be used in patients with type 2 DM and microalbuminuria to delay progression to macroalbuminuria (ADA, 2003b; KDOQI, 2004).

Type 2 DM with macroalbuminuria

ACEIs: An ACEI is frequently used in the treatment of patients with type 2 DM and macroalbuminuria. The ACEIs have been shown to decrease surrogate endpoints (Bakris et al., 2002), and one long-term trial comparing an ACEI to an ARB reported that the ARB was not inferior to treatment with an ACEI with respect to the primary endpoint of change in GFR rate. The secondary endpoints of annual change in GFR rate, level of S_{Cr} , urinary albumin excretion rate, and blood pressure were not significantly different between the two treatment groups (DETAIL, 2004).

ARBs: An ARB can be considered in patients with type 2 DM and macroalbuminuria (ADA, 2003b; KDOQI, 2004) as per results from two large, long-term, RCTs in patients with type 2 DM and nephropathy plus hypertension or on additional antihypertensive medications. In both trials, the primary endpoint of composite all-cause mortality, doubling of S_{Cr} , and ESKD was reduced by 20 percent (IDNT, 2001) and 16 percent (RENAAL, 2001) with the ARB compared to placebo, and by 23 percent compared to treatment with a dihydropyridine CCB (IDNT, 2001).

For patients with type 1 or type 2 DM and microalbuminuria or macroalbuminuria, if either an ACEI or ARB is not tolerated, the other class should be used (ADA, 2003b; KDOQI, 2004). When an ARB has been compared to an ACEI in trials including patients with type 1 or 2 DM, and microalbuminuria or macroalbuminuria, there have been similar reductions in surrogate endpoints of kidney function (Andersen et al., 2000; DETAIL, 2004; Lacourciere et al., 2000; Muirhead et al., 1999; Nielsen et al., 1997). A meta-analysis of data with the ACEIs and ARBs in patients with diabetic nephropathy showed a significant reduction in all-cause mortality with the ACEIs vs. placebo (RR 0.79; 95% CI 0.63-0.99; P=0.04), a difference that was not statistically significant with the ARBs compared to placebo. The reduction in doubling of S_{Cr} and ESKD were not statistically significant with the ACEIs compared to placebo or no treatment. With the ARBs, there was a significant reduction in doubling of S_{Cr} , ESKD, microalbuminuria to macroalbuminuria, and microalbuminuria to normoalbuminuria compared to placebo or no treatment. The reduction in microalbuminuria to macroalbuminuria, and microalbuminuria to normoalbuminuria were statistically significant with the ACEIs vs. placebo or no treatment. In the three trials comparing an ACEI to an ARB, there was not a statistically significant difference in renal outcomes (i.e., progression from microalbuminuria to macroalbuminuria; regression from microalbuminuria to normoalbuminuria). The meta-analysis concluded that ACEIs should be used as first-line treatment in patients with diabetic nephropathy due their survival benefit, which has yet to be demonstrated with the ARBs (Strippoli et al., 2004).

Combination ACEI and ARB: There have also been studies comparing an ACEI to an ARB, or evaluating their combination, on surrogate endpoints of kidney function (see also results of MacKinnon et al., 2006 in nondiabetic CKD discussion). One study compared the effects of an ARB, an ACEI, or the combination on urinary albumin excretion and blood pressure in 197 patients with hypertension, type 2 DM, and microalbuminuria for 24 weeks. There was a statistically significant reduction in blood pressure in all treatment groups, with the greatest reduction in patients on combination therapy. Urinary albumin-to-creatinine ratio was reduced by 24 percent with the ARB, by 39 percent with the ACEI, and by 50 percent with combination therapy. Combination therapy decreased the urinary albumin-to-creatinine ratio 34 percent compared to patients on an ARB alone; although the difference between combination therapy and the ACEI was not statistically significant (CALM, 2000). There have also

been short-term trials in patients with type 1 or 2 DM and nephropathy, with a greater reduction in albuminuria seen with the combination of an ARB and an ACEI, compared to treatment with an ACEI alone (Jacobsen et al., 2003b; Jacobsen et al., 2003a; Jacobsen et al. 2002). A benefit has also been seen with the combination of an ACEI and NCCB compared to treatment with either agent alone in a long-term trial of patients with type 2 DM and nephropathy (Bakris et al., 1998).

Adverse Effects and Monitoring

Risks associated with the use of the ACEIs and ARBs include dangerous hyperkalemia and acute kidney failure when they are used in situations associated with decreased glomerular filtration pressure such as dehydration or renal artery stenosis (Cronin & Henrich, 2000; Wynckel et al., 1998). Careful monitoring of potassium levels and serum creatinine is warranted (see [Appendix F-2](#)). *In addition, patients should be monitored for other potential adverse effects including hypotension, cough, and angioedema.*

Hyperkalemia

The ARBs, like the ACEIs, decrease release of aldosterone from the adrenal cortex, which can lead to decreased potassium excretion. It is unclear if treatment with an ARB is an appropriate alternative in patients who develop hyperkalemia with an ACEI since they may experience the same adverse effect with an ARB. Hyperkalemia is not a common adverse effect with an ACEI or ARB in patients without risk factors or concomitant use of medications including NSAIDs, potassium-sparing diuretics (e.g., amiloride, triamterene, spironolactone) or immunosuppressive therapy (e.g., cyclosporine, tacrolimus) (Palmer, 2004). The VAL-K Study Group reported that the change in serum potassium was not significantly different in patients on an ACEI compared to ARB with mild renal insufficiency. In patients with moderate renal insufficiency with a GFR ≤ 60 ml/min/1.73 m², there was a significant increase of 0.28 mEq/L (P=0.04) above baseline (4.6 mEq/L) with the ACEI. The increase of 0.12 mEq/L seen with the ARB in this subgroup was not significant (P=0.1) (Bakris & Weir, 2000). After initiating an ACEI or ARB, it is recommended that the patient's potassium be checked within 2 weeks if baseline was > 5.0 mEq/L, at 2 to 4 weeks if baseline potassium was 4.5-5.0 mEq/L, and at 4 to 12 weeks if baseline was ≤ 4.5 mEq/L (KDOQI, 2004). The addition of a diuretic may also be considered to offset the hyperkalemia. If use of a diuretic is contraindicated or is not effective, an ARB may be considered instead of an ACEI, under close monitoring, in patients with moderate renal insufficiency who develop hyperkalemia on an ACEI.

Renal Failure

In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system, treatment with ACEIs and ARBs have been associated with acute renal failure. These drugs are capable of reducing intraglomerular filtration pressure by causing dilation of the efferent renal arterioles. It is unknown if an ARB can be used as an alternative in patients where treatment with an ACEI is limited due to renal dysfunction or in a patient who develops renal dysfunction as a result of treatment with an ACEI (Esmail et al., 1998). As with the ACEIs, similar precautions are recommended for the ARBs in patients with renal artery stenosis.

Hypotension

Hypotension may occur in approximately 2.5 percent of patients on an ACEI or ARB, therefore it is recommended that low to moderate doses be initiated with subsequent follow-up monitoring and titration as tolerated. More frequent monitoring is recommended for patients with a SBP < 120 mm Hg (e.g., at 2-4 weeks if SBP 110-119 mm Hg; ≤ 2 weeks if SBP < 110 mm Hg) (KDOQI, 2004).

ACEI Induced Cough

The incidence of cough with an ACEI is estimated to be anywhere from 0.5 to 39 percent (Pylypchuk, 1998). The cough associated with an ACEI has been described as dry, nonproductive, persistent, beginning with a tickling sensation, and often worse at night. The onset is usually within the first week of ACEI therapy and continues throughout treatment, resolving within a few days to 4 weeks after the ACEI is discontinued. The cough is not usually dose-dependent, although in some instances it may be eliminated with a reduction in dose. Since therapy with an ACEI has proven valuable, it is important to consider alternative diagnoses (e.g., asthma, chronic obstructive pulmonary disease, allergic rhinitis, upper respiratory tract infection, heart failure, gastroesophageal reflux disease) before a diagnosis of ACEI induced cough is made. Patients with a history of cough associated with an ACEI may experience improvement if switched to fosinopril (David et al., 1995; Punzi, 1993; Sharif et al., 1994). Use of an ARB may also be considered in patients who are unable to tolerate an ACEI due to cough.

The incidence of cough associated with the ARBs is similar to placebo (1.6%) (Pylypchuk, 1998). A number of trials evaluating an ARB in patients with previous ACEI induced cough showed that patients treated with an ARB complained of cough similar to that seen with placebo (15.6%-36.7% ARB, 9.7%-31.4% placebo), but statistically significantly less than seen when an ACEI was included (60-97%) (Benz et al., 1997; Chan et al., 1997; Congliaro & Gleason, 1999; David et al., 1995; Lacourciere et al., 1999; Paster et al., 1998; Punzi, 1993; Sharif et al., 1994; Tanser et al., 2000). There is a slight chance that patients who are unable to tolerate treatment with an ACEI due to cough may develop a cough with an ARB (Congliaro & Gleason, 1999).

Angioedema

The incidence of angioedema in patients taking ACEIs is approximately 0.1 to 1.2 percent, and is more common in black patients. The exact mechanism is unknown; although, it is thought to be related to bradykinin accumulation. Angioedema has been reported with the ARBs but to a much lesser degree than the ACEIs. In one trial evaluating an ARB in patients with heart failure and a history of ACEI intolerance, 3 of 1,013 patients randomized to ARB experienced angioedema. One of these patients required discontinuation of the drug (0.1%). All 3 cases occurred out of the 39 patients who previously experienced angioedema or anaphylaxis on an ACEI (7.7%). None of the 1,015 patients who received placebo experienced angioedema (CHARM-Alternative, 2003). There have been a number of published case reports of angioedema in patients treated with an ARB (Abdi et al., 2002; Acker & Greenberg, 1995; Boxer, 1996; Cha & Pearson, 1999; Chiu et al., 2001; Cicardi et al., 2004; Frye & Pettigrew, 1998; Kyrnizakis et al., 2004; Pylypchuk, 1998; Rivera, 1999; Rupprecht et al., 1999; Sharma & Yium, 1997; van Rijnsoever et al., 1998; Warner et al., 2000). In approximately one third of these cases, the patients previously experienced angioedema with an ACEI. Therefore, an ARB should be used with caution in patients who have previously experienced angioedema (Abdi et al., 2002; Kyrnizakis et al., 2004; van Rijnsoever et al., 1998; Warner et al., 2000).

Appendix D: Pharmacotherapy

Appendix D-1. Dosing Recommendations for ACEIs and ARBs in Patients with CKD^{a-c}

DRUG	USUAL DOSE RANGE	COMMENTS/CAUTIONS
Angiotensin Converting Enzyme Inhibitors (ACEIs)		
Benazepril	10 – 40 mg divided once or twice daily	<ul style="list-style-type: none"> ○ Start with lower or less frequent doses in patients with CKD (except fosinopril as partial compensation by hepatobiliary elimination) or in patients currently being treated with a diuretic. ○ Use with caution in patients with renal artery stenosis. ○ Monitor potassium and renal function after initiation. ○ Concomitant therapy with potassium-sparing diuretics and/or potassium supplements may result in hyperkalemia. ○ Due to the potential risk for fetal morbidity and mortality in patients taking ACEIs during pregnancy, it is recommended that therapy be discontinued as soon as a woman becomes pregnant; alternate therapy should be considered. ACEIs should only be prescribed in pregnant women when the benefit clearly outweighs the potential risk for fetal abnormalities. ○ Contraindicated in patients with a history of angioedema on an ACEI
Captopril ^d	25 – 150 mg divided two to three times daily	
Enalapril	5 – 40 mg divided once or twice daily	
Fosinopril	10 – 40 mg once daily	
Lisinopril	10 – 40 mg once daily	
Moexipril ^d	7.5 – 30 mg divided once or twice daily	
Perindopril	4 – 8 mg divided once or twice daily	
Quinapril	10 – 80 mg divided once or twice daily	
Ramipril	2.5 – 20 mg divided once or twice daily	
Trandolapril	1 – 4 mg once daily	
Angiotensin II Receptor Blockers (ARBs)		
Candesartan	8 – 32 mg once daily	<ul style="list-style-type: none"> ○ Alternative to ACEIs in patients unable to tolerate an ACEI. ○ Consider lower doses in patients with intravascular volume depletion (e.g., patients currently being treated with a diuretic). ○ Use with caution in patients with renal artery stenosis. ○ Monitor potassium and renal function after initiation. ○ Concomitant therapy with potassium-sparing diuretics and/or potassium supplements may result in hyperkalemia. ○ Contraindicated in 2nd and 3rd trimesters of pregnancy due to potential neonatal/fetal morbidity and death. ○ Use with caution in patients with a history of angioedema on an ACEI.
Eprosartan	400 – 800 mg divided once or twice daily	
Irbesartan	150 – 300 mg once daily	
Losartan	50 – 100 mg divided once or twice daily	
Olmесartan	20 – 40 mg once daily	
Telimisartan	40 – 80 mg once daily	
Valsartan	80 – 320 mg once daily	

Refer to www.pbm.va.gov or <http://vawww.pbm.va.gov> for a current list of medications on the One VA National Formulary

^a Adapted from KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Guideline 11: Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in CKD at http://www.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm

^b Adapted from McEvoy GK, ed. American Hospital Formulary Service Drug Information, Bethesda, MD: American Society of Health-System Pharmacists, Inc., 2006.

^c Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., May 2006.

^d One hour before meals, on an empty stomach

Appendix D-2: Cautions in the Use of Selected Medications in Patients with CKD

DRUG	COMMENTS
Analgesics/Antipyretics	
NSAIDs	In general, all NSAIDs (including COX-2 inhibitors) should be used with extreme caution, if at all, in patients with kidney disease. Patients with preexisting kidney dysfunction are at increased risk for acute kidney failure, which may occur within several days following administration of NSAIDs. In addition, metabolites are primarily eliminated by the kidneys. If used, monitor kidney function prior to initiating therapy and during chronic administration; use lowest possible dose. May also cause fluid retention or edema, worsening of hypertension, or hyperkalemia.
Opioid Analgesics	Hydromorphone: Accumulation may occur with severe kidney impairment; use with caution. Meperidine: Possible accumulation of meperidine and/or normeperidine in patients with kidney impairment. Oxycodone: Patients with CrCl < 60 ml/min had higher concentrations compared to patients without kidney impairment; monitor for increased sedation. Tramadol: If CrCl < 30 ml/min, increase dosing interval to 12 hours with a maximum dose 200 mg per day.
Anorexiant Medications	
Sibutramine	Do not use in patients with severe kidney impairment as the drug has not been adequately studied in this patient population.
Anticoagulants	
Heparin	Use with caution in patients with kidney impairment as hyperkalemia may develop.
Enoxaparin	Although no dosage adjustment is recommended for patients with mild or moderate kidney impairment, patients should be monitored carefully for signs or symptoms of bleeding. Dose adjustments are recommended for patients with severe kidney impairment (CrCl < 30mL/min).
Antidiabetic Agents	
Alpha-Glucosidase Inhibitors	Acarbose: Increased plasma concentrations of acarbose seen in patients with kidney impairment; not recommended in patients with serum creatinine > 2 gm/dL as has not been studied in this patient population. Miglitol: Safety of using miglitol in patients with CrCl < 25 ml/min unknown.
Exenatide	Not recommended for use in patients with severe kidney impairment (CrCl < 30 ml/min).
Insulin	Half-life may be prolonged in patients with kidney function impairment, decrease insulin dose accordingly.
Repaglinide	Patients with severe kidney impairment should be initiated at a dose of 0.5 mg and carefully titrated; not studied in patients with CrCl < 20 ml/min.
Metformin	Use with caution in patients with decreased GFR due to risk of lactic acidosis (risk increases as kidney function decreases). Metformin is contraindicated in patients with kidney dysfunction as indicated by serum creatinine levels > 1.5 g/dL (males) or 1.4 g/dL (females), or abnormal CrCl. CKD prolongs the half-life and decreases the clearance of metformin.
Sitagliptan	Dosage adjustment recommended for patients with moderate-severe CKD: 50mg once daily if CrCl ≥ 30 to <50 ml/min or serum creatinine > 1.7 to ≤ 3.0 mg/dl for males >1.5 to ≤ 2.5 mg/dl females; 25 mg once daily if CrCl < 30 ml/min or serum creatinine > 3.0 mg/dl for males or > 2.5 mg/dl for females.

Sulfonylureas	Decreased elimination in patients with kidney impairment may lead to hypoglycemia; use with caution and monitor kidney function and glucose levels. Acetohexamide, chlorpropamide, glyburide, tolazamide should be avoided in patients with impaired kidney function as these agents are eliminated unchanged or as active compounds dependent on the kidney for elimination; glipizide or tolbutamide are preferred as these agents are metabolized to inactive or weakly active compounds.
Antigout Agents	
Allopurinol	Decrease dose or adjust regimen based on kidney function due to increased potential for toxicity and rash (suggested doses according to CrCl: 60 ml/min 200 mg daily; 40 ml/min 150 mg daily; 20 ml/min 100 mg daily; 10 ml/min 100 mg every other day; < 10 ml/min 100 mg three times/week). Colchicine should be used with caution in patients with combined kidney and hepatic disease to avoid neutropenia and gastrointestinal side effects.
Anti-infective Agents	
Antibiotics, Antifungals, Antivirals	<p>Dosage adjustments frequently required in kidney disease. Certain infections will require more aggressive dosing (e.g., endocarditis, meningitis, etc.); therefore, consultation with infectious diseases is recommended.</p> <p>Aminoglycosides are nephrotoxic and dose adjustment is required based on CrCl or SCr. Trimethoprim can cause hyperkalemia. Accumulation of the IV vehicle of the parenteral formulation of voriconazole may occur in patients with kidney function impairment; consult package insert for further information. Acyclovir, other antivirals, and sulfa drugs may cause crystaluria. The acyclovir/ganciclovir dose must be decreased to avoid encephalopathy. The dose and/or dosing interval of adefovir and entecavir should be adjusted in patients with kidney function impairment.</p> <p>Consult individual product information or alternate sources on dosing in kidney function impairment.</p>
Bisphosphonates	
Alendronate	Although not adequately studied, it is anticipated that impaired kidney function would result in accumulation of alendronate in bone. No dosage adjustment is required in patients with mild to moderate kidney dysfunction (CrCl 35 to 60 ml/min); not recommended in patients with CrCl < 35 ml/min as the safety and efficacy in this patient population has not been studied.
Etidronate	Only use if potential benefit outweighs risk for worsening kidney function; if used, reduce dose if serum creatinine is 2.5 to 4.9mg/dL.
Ibandronate	Not recommended in patients with CrCl < 30 ml/min.
Pamidronate	If kidney function deteriorates, withhold treatment until the patient's kidney function returns to baseline.
Risedronate	Not recommended in patients with CrCl < 30 ml/min.
Zoledronic acid	Single doses should not exceed 4 mg (and the infusion not less than 15 minutes) due to potential deterioration in kidney function, possibly resulting in kidney failure.
Cardiovascular and Antilipemic Agents	
ACEI/ARB	Refer to Annotation 10.2

Atenolol	Decrease dose or regimen based on kidney function (initiate therapy at 25 mg daily with a maximum dose of 50 mg daily in patients with CrCl 15 to 35 ml/min or 50 mg every other day if CrCl < 15 ml/min). Dosage adjustment in patients with kidney impairment also recommended for bisoprolol, nadolol, and timolol, and for sotalol (used as an antiarrhythmic agent).
Digoxin	Half-life prolonged with impaired kidney function and may take longer to achieve steady state; decrease dose or adjust regimen based on level of kidney function (in general, patients with a CrCl < 50 ml/min will require a reduction in maintenance dose).
Diuretics	Thiazide diuretics may not be effective in patients with advanced kidney disease, although metolazone may be used in addition to a loop diuretic, if required to obtain clinical response. Spironolactone and other potassium sparing diuretics should be used with caution to avoid hyperkalemia.
Fibric Acid Derivatives	Gemfibrozil: has been associated with worsening kidney function in patients with creatinine levels > 2 gm/dL; consider alternative therapy. Fenofibrate: Accumulation of fenofibrate may occur in patients with CrCl < 50 ml/min; minimize dose.
HMG-CoA Reductase Inhibitors (statins)	Kidney impairment may predispose patients to myopathy while on statins. Lovastatin: Lower doses should be considered; doses > 20 mg/day not generally recommended if CrCl < 30 ml/min. Pravastatin: starting dose of 10 mg/day in significant kidney dysfunction. Rosuvastatin: starting dose of 5mg/day with maximum 10mg daily if CrCl < 30 ml/min. Simvastatin: initiate therapy at 5 mg/day and closely monitor patients with severe kidney impairment due to increased plasma concentrations.
Erectile Dysfunction Agents	
PDE Inhibitors	Sildenafil: Initial dose 25 mg if CrCl < 30ml/min. Tadalafil: Initial dose 5 mg if CrCl 31-50 ml/min; maximum dose 10 mg.
Gastrointestinal Drugs	
H2 Antagonists	Adjust dose based on level of kidney function impairment. Cimetidine: 300 mg every 12 hours or lowest possible dose in severe kidney dysfunction. Famotidine: reduce the dose by half or prolong dosing interval to 36 to 48 hours in moderate to severe kidney impairment. Nizatidine: 150 mg/day for acute or 150 mg every other day for maintenance if CrCl is 20 to 50 ml/min or 150 mg every other day for acute or 150 mg every 3 days for maintenance if CrCl < 20 ml/min. Ranitidine: 150 mg every 24 hours if CrCl < 50 ml/min.
Psychotropic and Central Nervous System Agents	

Anticonvulsants	<p>Gabapentin: Decrease dose or adjust regimen based on kidney function (recommended total daily doses according to CrCl: 30 to 59 ml/min 400-1400 mg; 15 to 29 ml/min 200-700 mg; 15 ml/min 100-300 mg).</p> <p>Levetiracetam: Reduce dose depending on level of kidney impairment (CrCl 50-80 ml/min 500 to 1000 mg every 12 hours; CrCl 30-50 ml/min 250 to 750 mg every 12 hours; CrCl < 30 ml/min 250 to 500 mg every 12 hours).</p>
Antidepressants	<p>Paroxetine: Reduce initial dose (10 mg/day immediate-release or 12.5 mg/day controlled-release) in patients with CrCl < 30 ml/min, due to increased plasma concentrations.</p> <p>Citalopram or Escitalopram: Use with caution in patients with severe kidney impairment; no dosage adjustment necessary in mild to moderate impairment.</p> <p>Duloxetine: Not recommended in patients with CrCl < 30 ml/min due to increased plasma concentrations and accumulation of major metabolites.</p> <p>Venlafaxine: Reduce total daily dose of extended-release by 25 to 50% in patients with GFR 10 to 70 ml/min and by 25% for the immediate-release product in patients with mild to moderate kidney impairment due to reduced clearance and prolonged half-life.</p> <p>Bupropion: Use with caution in patients with kidney impairment; consider reduction in dose or frequency of administration due to potential accumulation of the drug and its metabolites.</p>
Antipsychotic Agents	<p>Lithium: Increased risk of toxicity in patients with severe kidney impairment; use with extreme caution, if at all. Risk of toxicity also increased in patients with dehydration or sodium depletion. Nephrogenic diabetes insipidus can occur in up to 30 to 50% of patients and may persist in 10 to 25% of patients after 1 to 2 years of continued therapy.</p> <p>Risperidone: Reduce initial dose in patients with severe kidney disease (oral 0.5 mg twice daily with gradual increases in dose as indicated) due to reduced clearance of the drug and its metabolites.</p> <p>Paliperidone (active metabolite of risperidone): Reduce dose (CrCl \geq 50 to 79 ml/min maximum 6 mg per day; CrCl 10 to < 50 ml/min maximum 3 mg per day).</p>
Memantine	<p>Dosage adjustments may be necessary in patients with a CrCl < 50 ml/min (CrCl 15 to 29 ml/min target dose 5 mg twice daily) due to increased plasma concentrations and half-life.</p>

Appendix E: Complications of Kidney Disease

Parameter	Abnormality	Issues/Needs/Recommendations	Treatment
Potassium	> 6.5 mEq/L	Emergency room treatment	Instruct patient to present to the emergency room
	5.5-6.4 mEq/L	Precipitants: <ul style="list-style-type: none"> Drugs: ACEI, ARBs, potassium-sparing diuretics, NSAIDs, trimethoprim-sulphamethoxazole 	General treatment: <ul style="list-style-type: none"> Sodium polystyrene sulfonate 30 – 60 g qd or qod Loop diuretics to increase potassium secretion Restrict dietary potassium intake Refer if etiology is unknown
			<ul style="list-style-type: none"> Discontinue offending drug
		Other: Volume depletion	Correct dehydration
		<ul style="list-style-type: none"> High intake of potassium-rich foods 	<ul style="list-style-type: none"> Restricted dietary potassium (2 – 3 g/d)
		<ul style="list-style-type: none"> Acidosis/Renal Tubular acidosis 	<ul style="list-style-type: none"> Treat cause, bicarb if < 20
		<ul style="list-style-type: none"> Hyperglycemia or starvation in DM 	<ul style="list-style-type: none"> Control hyperglycemia & ensure adequate nutrition
	<ul style="list-style-type: none"> Urinary tract obstruction 	<ul style="list-style-type: none"> Assess and intervene to relieve 	
	<3.5 mEq/L	Precipitants: <ul style="list-style-type: none"> Diuretics Diarrhea Malnutrition High renin/aldosterone states 	General treatment: <ul style="list-style-type: none"> Supplement potassium only cautiously with close follow-up
			<ul style="list-style-type: none"> Discontinue/reduce dose of diuretics
			<ul style="list-style-type: none"> Treat diarrhea
			<ul style="list-style-type: none"> Provide nutritional counseling
Calcium	< 8 mg/dL	<ul style="list-style-type: none"> Rare in CKD unless the eGFR is < 30 ml/min/1.73m² Results from hyperphosphatemia and decreased production and activity of 1,25-dihydroxyvitamin D₃ If low serum albumin, check ionized calcium 	Serum phosphorous >4.6 mg/dL: <ul style="list-style-type: none"> Dietary phosphorous restriction Calcium acetate or carbonate with meals Serum phosphorous normal: <ul style="list-style-type: none"> Calcium acetate or carbonate between meals Refractory hypocalcemia: <ul style="list-style-type: none"> Consider use 1,25-dihydroxyvitamin D₃ or other active vitamin D
	> 11 mg/dL	<ul style="list-style-type: none"> Usually related to the use of calcium supplements or Vitamin D Consider conditions such as myeloma, granulomas, neoplasms 	<ul style="list-style-type: none"> Reduce calcium supplements, Vitamin D Specific treatment of the underlying condition

Parameter	Abnormality	Issues/Needs/Recommendations	Treatment
Phosphorus	> 4.5 mg/dL	<ul style="list-style-type: none"> ▪ Hyperphosphatemia usually begins to occur when the eGFR is < 30ml/min/1.73 m² 	<ul style="list-style-type: none"> ▪ Restrict dietary phosphorous to 0.6 – 1.2 g/d ▪ Use phosphorous binders (calcium acetate or carbonate) with meals
Albumin	< 3.5 g/dL	<ul style="list-style-type: none"> ▪ Associated with increased mortality ▪ General causes of hypoalbuminemia include abnormal metabolism, chronic inflammation, and liver disease. ▪ Specific causes that could be addressed are: <ul style="list-style-type: none"> ○ Nephrotic syndrome ○ Acidosis ○ Poorly controlled diabetes ○ Reduced intake 	<ul style="list-style-type: none"> ▪ Assess urinary protein, refer if worse ▪ Assess and treat acidosis ▪ Maximize diabetic control ▪ Nutritional assessment & supplementation
Anemia	<p>HCT < 33% Hgb <11g/dL (Pre-menopausal female)</p> <p>HCT < 37% Hgb <12g/dL (Male & post-menopausal female)</p>	<ul style="list-style-type: none"> ▪ Usual causes of anemia must be excluded before attributing to kidney disease ▪ Common causes in CKD: <ul style="list-style-type: none"> ○ Inadequate erythropoiesis ○ Reduced RBC half-life ○ Bleeding 	<ul style="list-style-type: none"> ▪ Erythropoietin levels are not helpful for diagnosis of suspected anemia of kidney disease ▪ Initiate oral iron treatment if the transferrin saturation is < 20% and/or the ferritin is < 100 ng/ml ▪ If the patient is symptomatic, or the Hgb is < 10 g/dL despite iron therapy, refer to nephrology or hematology for consideration of erythropoietin therapy
HCO₃	< 22 mEq/L	<ul style="list-style-type: none"> ▪ Other causes of acidosis must be considered prior to ascribing to kidney disease, especially if the HCO₃ is < 15 mEq/L ▪ Common in CKD. Kidney causes include: <ul style="list-style-type: none"> ○ Impaired kidney acidification ○ Accumulation of organic acids 	<ul style="list-style-type: none"> ▪ NaHCO₃ tablets when the serum bicarbonate falls below 22 mEq/L ▪ Usual starting dose: 0.4 mEq/kg/day in divided doses ▪ One 650 mg NaHCO₃ tablet contains 7.7 mEq sodium/7.7 mEq HCO₃

Key: ACEI-I: Angiotensin-Converting Enzyme-Inhibitor; ARB: Angiotensin Receptor Blockers; CKI: Chronic Kidney Insufficiency; DM: Diabetes Mellitus; eGFR: Estimated Glomerular Filtration Rate; Hgb: Hemoglobin; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; RBC: Red Blood Cell

Appendix F: Nutrition

F-1. Phosphorous

Achieve or Maintain Normal Phosphorus Levels

1. Dietary Phosphorus restriction 800 – 1,000 mg/day (adjusted for dietary protein) should be initiated when serum phosphorus levels are above 4.6 mg/dl (1.49 mmol/L) in CKD stages 3 and 4 and above 5.5 (1.78mmol/L) in CKD stage 5 (KDOQI, 2003).
2. Dietary Phosphorus restriction 800 – 1,000 mg (adjusted for protein needs) should be initiated when parathyroid hormone (PTH) levels are above 70 ng/ml in stage 3 CKD and above 110 ng/ml in CKD stage 5 CKD.

Indications for Dietary Phosphorus restriction

Stage 3 (eGFR < 60 ml/min/1.73m ²)	Stage 4 (eGFR < 30 ml/min/1.73m ²)	Stage 5 (eGFR < 15 ml/min/1.73m ²)
Phosphorus > 4.6 mg/dl PTH > 70 ng/ml	Phosphorus > 4.6 mg/dl PTH > 110 ng/ml	Phosphorus > 5.5 mg/dl

- Hyperphosphatemia is an independent risk factor for death in dialysis patients, exacerbates hyperparathyroidism by promoting gland hyperplasia and plays a major role in the development of vascular calcification.
- Phosphorus excretion becomes impaired when kidney function declines by 20 to 25 percent of normal. Intake can be reduced to 800 mg while maintaining adequate protein intake.
- The precise requirement for dietary phosphorus intake is unknown; 800 mg/day is recommended for adults (except in pregnant or lactating women) and children 11 to 24 years of age.

Phosphorus Content of High Protein Foods

High > 200 mg per serving	Medium 100 - 199 mg serving	Low < 100 mg per serving
<ul style="list-style-type: none"> • Meat or fish 3oz • Milk evaporated , skim, or buttermilk 1 cup • Soybeans ½ cup • Sunflower seeds 1 oz • Combination Foods: <ul style="list-style-type: none"> ○ Pizza 1 slice ○ Cheeseburger 1 ○ Sub sandwich 1 ○ Pancakes 	<ul style="list-style-type: none"> • Poultry 3oz • Meat or fish 2 oz • Milk evaporated , skim, or buttermilk ½ cup • Nuts 1 oz • Yogurt 4 oz • Cheese 1 oz • Cottage cheese ½ cup • Peanut butter 2 Tbsp • Milk chocolate 1 miniature 	<ul style="list-style-type: none"> • Egg 1 large • Tofu 3 oz

REFERENCES

- Almaden Y, Hernandez A, Torregrosa V, Canalejo A, Sabate L, Fernandez Cruz L, Campistol JM, Torres A, Rodriguez M. High phosphate level directly stimulates parathyroid hormone secretion and synthesis by human parathyroid tissue in vitro. *J Am Soc Nephrol* 1998 Oct;9(10):1845-52.
- Goodman WG. Calcium and phosphorus metabolism in patients who have chronic kidney disease. *Med Clin North Am* 2005;89:631-647.
- Hsu CY, Chertow GM. Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. *Nephrol Dial Transplant* 2002 Aug;17(8):1419-25.
- Massry SG, Smogorzewski M. Management of vascular calcification in CKD patients. *Semin Nephrol* 2006 Jan;26(1):38-41.
- National Kidney Foundation KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Disease. *Am J Kidney Dis* 2003 Oct;42(4Suppl 3):S1-202.
- Ribeiro S, Ramos A, Brandao A, Rebelo JR, Guerra A, Resina C, Vila-Lobos A, Carvalho F, Remedio F, Ribeiro F. Cardiac valve calcification in haemodialysis patients: role of calcium-phosphate metabolism. *Nephrol Dial Transplant* 1998 Aug;13(8):2037-40.
- Slatopolsky E, Dusso A, Brown AJ. The role of phosphorus in the development of secondary hyperparathyroidism and parathyroid cell proliferation in chronic renal failure. *Am J Med Sci* 1999 Jun;317(6):370-6.
- Winkelmayer WC, Levin R, Avorn J. The nephrologists' role in the management of calcium-phosphorus metabolism in patients with chronic kidney disease. *Kidney Int* 2003 May;63(5):1836-42.

F-2. POTASSIUM

Potassium Levels Should Be Monitored Regularly

In patients with CKD, dietary potassium is usually not restricted unless there is a history of hyperkalemia. Cardiac arrhythmias have greater chance of occurring when the potassium is greater than 6.5 mEq/L, but levels over 6.0 mEq/L should be treated and may require referral to the Emergency Department. Potassium should be monitored in patients with Stage 4 and Stage 5 chronic kidney disease taking certain medications (i.e., ACEI, ARB, aldosterone antagonists) to catch and treat hyperkalemia.

1. Serum potassium should be kept in a normal range.
2. Patients with hyperkalemia should be referred to a dietitian for counseling.
3. Patients with potassium disorders should receive nutrition education about dietary sources of potassium and consider modifying their diet to maintain dietary potassium intake between 50 - 70 mEq/day (1950 – 2730 mg/day) to prevent future hyperkalemia.
4. Dietary potassium intake should be restricted in patients with hyperkalemia.

It is important to evaluate dietary causes of hyperkalemia. This will allow patients to avoid recurrence. The following chart lists some of the high potassium foods that should be restricted in patients with a history of hyperkalemia.

Food group	High Potassium Foods to Restrict
Dairy	Condensed milk, evaporated milk, plain yogurt
Cooked dry beans and peas	Baked beans, black-eye peas, kidney beans, lentils, lima beans, navy beans, pinto beans, soybeans, split peas
Vegetables	Artichoke, avocado, beet greens, Chinese cabbage, kohlrabi, okra, parsnips, French fries, white/sweet potatoes, potato chips, yams, pumpkin, rutabagas, dried seaweed, spinach, tomato products (sauce, paste, puree), tomatoes, tomato sauce/puree, vegetable juice, winter squash
Fruit/Juice	Bananas, cantaloupe, dried fruit (i.e., apricots, dates, figs), kiwi, nectarine, passion fruit (purple), passion fruit juice (purple/yellow), honeydew melon, Japanese persimmon, mango, orange, orange juice, plantain (cooked), pomegranate, pomegranate juice, prunes (dried), prune juice, raisins, watermelon
Cereals	Raisin bran®, All bran®, bran cereals, granola
Miscellaneous	Chili w/ beans; Cocoa mix, sugar-free, made with water; chocolate; fruitcake; molasses; nuts and seeds; peanut butter; salt substitute; soups, made with water - chicken vegetable, clam chowder, minestrone, tomato; tacos; tropical or regular trail mix; wheat germ

Moderate intake of foods is important to prevent hyperkalemia. As few foods are completely potassium free, it is possible to consume large quantities of low potassium foods and develop hyperkalemia. Portion control should be emphasized.

**Glycyrrhetic acid (found in licorice and chewing tobacco) inhibits the enzyme involved in the conversion of cortisol resulting in renal potassium wasting and in some cases hypokalemia (Merck Manuel Section 2, Chapter 12 Water, Electrolyte and Acid-Base Metabolism).*

REFERENCES

- ADA. A Clinical Guide to Nutrition Care in ESRD, 2nd edition. 1994;21.
- Beto J. Hyperkalemia: evaluating dietary and nondietary etiology. J Ren Nutr 1992;2(1):28-29.
- Dietary Guidelines for Americans 2005, pg. ix. Available from: www.healthierus.gov/dietaryguidelines/
- European Dialysis and Transplant Nurse Association/European Renal Care Association (taken from CARI 12/05).
- Gennari FJ. New Eng J Med 1998 August;339:451-458.
- Merck Manuel Section 2, Chapter 12 Water, Electrolyte and Acid-Base Metabolism.
- National Kidney Foundation. Pocket Guide to Nutrition Assessment of the Patient with Chronic Kidney Disease, 3rd edition. NKF 2002:3.
- U.S. Food and Drug Administration. www.fda.gov (accessed Sept 18, 2006).

Appendix G: Patient Education

Patient education is a field in itself that includes such complex issues as compliance, resistance to change, motivation, and the communication skills of the health provider.

- a. Teaching must start early and must include the most basic information regarding kidney function and its relation to the patient's condition. Early education, while the patient feels relatively well, can reduce anxiety through preparation. It allows choices, assures informed consent, encourages independence, and promotes a sense of control (Hayslip & Suttle, 1995).
- b. Conveying the information to the patient is a major challenge. Although the healthcare provider may be convinced that instructions are understood, the message frequently is misunderstood or not understood at all. Often, a patient's learning style and readiness to learn are not considered.
- c. Common barriers to learning include anger, denial, language differences, physical disabilities, pain, fear, anxiety, cognitive limitations, cultural variables, health beliefs and religious practices. Other factors are age, co-morbid conditions, financial resources, distance to the treatment center, and support systems. Readiness to learn needs to be determined at each step since it has a profound effect on the patient's comprehension. An environment conducive to learning—free of interruptions such as beepers, phone calls, and foot traffic—is the responsibility of the educator.
- d. Do not assume the patient can read or comprehend your printed materials. One out of every five adults reads at the 5th grade level or below. For older Americans (65 and over) and for inner city minorities, almost 2 out of 5 read below the 5th grade level. The average reading level of adults in this country is 8th to 9th grade. Half of the population read at the 9th grade level or lower (Doak et al., 1996). Materials should be culturally appropriate at a level of reading commensurate with the patient's educational background.
- e. Healthcare professionals tend to overestimate the literacy skills of their patients. It is common to assume that a patient reads at the level of the last grade completed in school. Generally, however, adult reading levels are approximately 3 to 5 grades lower than their last grade completed. A recent study of VA patients over the age of 50 in Shreveport found the reading level to be at the 5th grade level. However, general VA guidelines require written instructions to patients to be at the 8th grade level.
- f. Videos, audios, and flip charts are useful for instructions. Tell the patient what the instruction is aimed at and get to the point quickly. Avoid a patronizing tone and fear provoking messages. Also, avoid the use of the word "you" as in "you need to start taking your blood pressure pills everyday or you are going to have a stroke."
- g. When assessing patient comprehension ask open-ended questions rather than questions that can be answered with a yes or no. An example of an open-ended question is "Tell me what medications you are taking for your blood pressure?" rather than "Are you taking your blood pressures medications?" Speak slowly and use simple words (Szczepanik, 1995). Be aware that healthcare providers tend to give too much information at one time. Instructions must be simple, focused, consistent and repetitive.

Key Areas in the CKD Education Program

1. **General overview:** Patients should be informed that chronic kidney disease (CKD) involves the permanent loss of kidney function. CKD may be the result of physical injury or a disease that damages the kidneys, such as diabetes or high blood pressure. Patients need to understand that CKD is asymptomatic since it often develops so slowly that many people do not realize they are sick until the disease is advanced. Teaching should include information about risk factors such as diabetes, hypertension and family history. Diabetes is the leading cause of kidney failure. Family history is important since CKD runs in families and some racial groups are also at increased risk.
2. **Anatomy and normal function of the kidneys:** altered kidney function and the patient's disease process need to be explored. Since CKD has no symptoms, blood pressure, laboratory tests (blood and urine) and results need to be evaluated. Medications should be reviewed. This can be done in small groups. Groups may be inappropriate, however, for patients who have low literacy skills or learning problems.
3. **Control of blood pressure:** High blood pressure can lead to kidney damage. It can also be a sign that kidney damage has already occurred. Keeping the blood pressure below 130/80 is important to protect the kidneys. Patients should also limit the amount of sodium in their diet. Adherence to recommended medications as well as dietary and lifestyle changes may reduce blood pressure and as result reduce the rate of progression of kidney disease, and reduce cardiovascular disease risk.
4. **Blood glucose control:** Diabetes worsens renal damage in patients with CKD. Glycemic control is important to minimize progression of CKD. See the [VA/DoD Clinical Guidelines for the Management of Diabetes Mellitus, Module G](#).
5. **Angiotensin converting enzyme inhibitors (ACEI):** ACEIs delay the progression of diabetic and non-diabetic kidney disease, even in the absence of hypertension. Thus, initiation of this treatment must be done with close follow-up to monitor potassium and creatinine, and continuation may require dietary potassium restriction. Patients on ACEI must be advised of the increased risk of acute renal failure in the setting of volume depletion, such as may be seen with protracted vomiting, diarrhea or high fevers. In such instances, patients must be instructed to seek evaluation. Address alternatives to ACE for patient who cannot tolerate ACEI.
6. **Avoidance of NSAIDs and other nephrotoxic drugs, including illicit drugs:** Patients should be counseled about the possible adverse consequences of NSAIDs, which are in many over-the-counter cold and pain preparations. They need to understand that the kidney is a frequent target for toxic injury because it is a major route of excretion for a variety of drugs. It is also important to obtain a history of any alternative medical therapies the patient may be using. Occupational and environmental exposures as well as the use of cocaine, heroin, and amphetamines (Ecstasy) need to be explored as well.
7. **Lifestyle changes:** Patients may need to make lifestyle changes in such areas as: smoking cessation, weight control, other dietary changes, drug and alcohol treatment, increased physical activity, stress management, social issues, vocational rehabilitation, family issues, and issues of sexuality.

These changes may take a concerted team effort and may require on-going support groups. Repetitive contact, monitoring, and encouragement are all methods to reinforce behavior change. See the [VA/DoD Clinical Guidelines for the Management of Diabetes Mellitus, Module R, Kidney Disease](#). Also see [Module M](#) for suggestions on smoking cessation, exercise, and stress management.

AVOIDING COMPLICATIONS

Abnormal calcium and phosphate metabolism: Patients should be advised about the importance of the control of calcium and phosphate for the prevention of bone and cardiovascular disease. Educate the patient about phosphorus content in different food. For patients who may need supplemental calcium, the importance of taking it with their meals should be emphasized.

Anemia secondary to relative erythropoietin deficiency: Patients with CKD are at increased risk for anemia. Anemia is associated with the development of left ventricular hypertrophy and congestive heart failure, both of which increase cardiovascular mortality among patients with kidney failure. Anemia may be treated with iron or erythropoietin if indicated.

Hyperkalemia related to reduced clearance: Hyperkalemia usually does not develop until late in the course of kidney disease, once the GFR falls below 20 ml/min/1.73m² or oliguria has developed. However, earlier development of hyperkalemia may occur among patients with diabetic nephropathy (or other conditions associated with hyporeninemic hypoaldosteronism, such as chronic interstitial nephritis), and patients on ACEI/ARBs, NSAIDs or potassium-sparing diuretics. Formal dietary counseling is recommended for potassium restriction for hyperkalemia that does not resolve with discontinuation of possible culprit medications. Potassium-binding resins may be necessary, along with close monitoring as kidney failure progresses. Patients must be told that significant hyperkalemia predisposes to cardiac dysrhythmias and death.

Preparation for kidney replacement therapy: Once there is evidence of progression of CKD, or at the latest when the creatinine is ≥ 3 mg/dL or the eGFR is ≤ 40 to 50 ml/min/1.73m², the patient must be instructed to 'save' the non-dominant arm for hemodialysis access (no venipuncture or IV), and physicians must avoid central lines (in particular subclavian, but also internal jugular (IJ) given the risk of IJ or superior vena cava (SVC) stenosis).

The various modalities of kidney replacement therapy, including hemodialysis, peritoneal dialysis and preemptive transplantation, should be introduced when there is clear evidence of progression of CKD. There are currently no age restrictions on the initiation of dialysis. The patient should be referred to a nephrologist for discussion of renal replacement therapy and/or transplantation.

REFERENCES

- Doak DG, Mulvey D, Kawaguchi K, Villalain J, Campbell ID. Structural studies of synthetic peptides dissected from the voltage-gated sodium channel. *J Mol Biol* 1996 May 17;258(4):672-87.
- Hayslip DM, Suttle CD. Pre-ESRD patient education: a review of the literature. *Adv Ren Replace Ther* 1995 Jul;2(3):217-26.
- Szczepanik ME. Assessment and selection considerations: ESRD patient and family education materials and media. *Adv Ren Replace Ther* 1995 Jul;2(3):207-16.

RESOURCES FOR PATIENT EDUCATION

Education materials are available through a number of resources. Below is a listing of organizations that provide information including videos, pamphlets, fact sheets, and books.

Resource	Contact
American Association of Kidney Patients	800-749-AAKP www.aakp.org
National Kidney Foundation (Series of patient education booklets are free online)	800-622-9010 http://www.kidney.org/patients/
American Kidney Fund	800-638-8299 http://www.akfinc.org
Baxter Healthcare Renal Division	http://www.kidneydirections.com/
Fresenius Medical Care North America	http://www.fmcna.com
National Kidney and Urologic Disease Information Clearinghouse <ul style="list-style-type: none"> • “Kidney Disease Dictionary” • “ESRD & Choosing a Treatment that is Right for You” • “Your Kidneys and How They Work “ • “Vascular Access for Hemodialysis” • “Eat Right to Feel Right on Hemodialysis” 	http://kidney.niddk.nih.gov/
The Nephron Information Center <ul style="list-style-type: none"> • “How the Kidney Works” • “Early Renal Insufficiency” • ESRD diet books and brochures 	http://www.nephron.com
R &D Laboratories	http://www.ikidney.com/
Renalnet	http://www.renalnet.org/
Kidney School: tailored, interactive self-management learning center with 16 modules. Provided by Life Options. Supported by an unrestricted educational grant from Amgen Inc ®: The Medical Education Institute, Inc.	http://www.kidneyschool.org/pdfs/KSIdeaGuide.pdf

The above list of sites is not all-inclusive. Some of the sites have links to other sites as well.

Appendix H: Follow-up for Chronic Kidney Disease

Category	Issue		When
History	Nephrotoxic medications	Ask about use of medications such as NSAIDs, aminoglycoside, contrast agents	Each visit
	Fluid overload	Ask about ankle swelling, dyspnea, orthopnea	
	Uremia	Ask about anorexia, nausea, vomiting (More likely to be apparent when GFR < 30 ml/min/1.73m ²)	
	Malnutrition	Ask about weight, dietary history, food recall records for protein and energy intake; do subjective global assessment	
	Neuropathy	Ask about paresthesias, mental-status abnormalities, sleep disturbances, restless legs	
Physical exam	Fluid overload	Look for jugular venous distension, rales, S3 gallop, ankle edema	Each visit
	Uremia	Look for asterixis, pericardial rub	Each visit for eGFR < 30 ml/min/1.73m ²
Labs	Renal function eGFR	Use the Modification of Diet in Renal Disease (MDRD) equation to estimate GFR	Each CKD visit
	Anemia	Hemoglobin	Each year and as clinically indicated
	Iron deficiency	Serum iron, total iron binding capacity (TIBC), and ferritin	Each year and as clinically indicated
	Proteinuria	Spot urine for protein and creatinine	Each year and as clinically indicated
	Metabolic abnormalities	Electrolytes	Each CKD visit
	Bone disease	Calcium, phosphorus, parathyroid hormone (PTH)	Each year, if abnormal every 6 months and as clinically indicated
	Malnutrition	24-hour urine for urea nitrogen excretion	As clinically indicated
	Obstruction	Renal ultrasound	At initial evaluation and for acute decline in GFR
Non-drug therapy	Dietary modification	Advise about diet, protein, salt restriction Aim for weight to be within 30% of ideal through diet and exercise	Each visit
Drug therapy	Blood pressure	Antihypertensive drug therapy	Each visit
	Glycemic control	Oral hypoglycemic agents or insulin	
	Anemia and other metabolic consequences of CKD	Erythropoietin, iron, if iron deficient, or both	
	Hyperkalemia	Sodium polystyrene sulfonate and bicarbonate as needed	
	Fluid overload	Diuretics	
	Calcium and phosphorus metabolism	Phosphate binders and Vitamin D	
Patient education	Overall management	Patient education about complexity of management, minimizing risk factors, importance of adherence to medical regimen and follow-up, preparation for possible future need for dialysis	Ongoing

Appendix I: Acronym List

ACEI	Angiotensin-Converting Enzyme Inhibitor
ANA	Anti-Nuclear Antibody
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ARB	Angiotensin II Receptor Blocker
BUN	Blood Urea Nitrogen
CDC	Centers for Disease Control and Prevention
CHr	Content of Hemoglobin in Reticulocytes
CKD	Chronic Kidney Disease
CPG	Clinical Practice Guideline
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage-Kidney Disease
GBM	Glomerular Basement Membrane
GFR	Glomerular Filtration Rate
GN	Glomerulonephritis
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-AN	HIV-Associated Nephropathy
HTN	Hypertension
HR-QOL	Health-Related Quality of Life
HUS	Hemolytic Uremic Syndrome
IEP	Immuno-Electrophoresis
IGA	Immunoglobulin A
MDRD	Modification of Diet in Renal Disease
MPGN	Membranoproliferative Glomerulonephritis
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PCKD	Polycystic Kidney Disease
PTH	Parathyroid Hormone
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
ROC	Receiver Operator Characteristic
RPGN	Rapidly Progressive Glomerulonephritis
RVD	Renovascular Disease
SBP	Systolic Blood Pressure
S_{Cr}	Serum Creatinine Concentration
SPEP	Serum Protein Electrophoresis
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
TTP	Thrombotic Thrombocytopenic Purpura
UPEP	Urine Protein Electrophoresis
UN	Urea Nitrogen
UTI	Urinary Tract Infection
UTO	Urinary Tract Obstruction
WBC	White Blood Cell

Appendix J: Participants

Guideline Development Team

Management of Chronic Kidney Disease – Update

Kevin Abbott, MD

COL, MC, USA

Nephrology Consultant to the Surgeon General of the Army

Medical Director

Walter Reed Army Medical Center

6900 Georgia Avenue

Washington, DC 20307

Phone: (202) 782-6463

Fax: (202) 782-0185

Email: kevin.abbott@na.amedd.army.mil

Arianna M. Aoun MS, RD, CSR

Clinical Dietitian, Renal

Louis Stokes Cleveland VA Medical Center

Nutrition & Food Service 120(w)

10701 East Boulevard

Cleveland, OH 44106

Phone: (216) 791-3800 ext. 5179

Fax: (216) 421-3014

Email: Arianna.aoun@med.va.gov

Erin M. Bohlen, MD

Col, MC, USA

Assistant Chief, Neurology Service

Program Director, NCC Nephrology Fellowship

Walter Reed Army Medical Center

6900 Georgia Avenue

Washington, DC 20307

Phone: (202) 782-6463

Fax: (202) 782-0185

Email: erin.bohlen@na.amedd.army.mil

Magna Brito, RD

Supervisory Dietitian

Salem VA Medical Center

Nutrition & Food Service 120(w)

1790 Roanoke Boulevard

Salem, VA 24153

Phone: (540) 982 2463 ext 2365

Fax: (540) 983-1059

Email: magna.brito@va.gov

Peter G. Carson, MD

Chief CCU
Washington DC VA Medical Center
50 Irving Street, NW
Washington DC 20422
Phone: (202) 745-8428
Fax: (202) 745-8172
Email: Peter.carson@med.va.gov

Carla Cassidy, CRNP, MSN

Director, Evidence-based Practice Guideline Program
Department of Veterans Affairs
810 Vermont Avenue
Washington, DC 20420
Phone: (202) 273-6954
Fax: (202) 273-9097
Email: Carla.cassidy@va.gov

Martha D'Erasmus, MPH

Independent Consultant
4550 North Park Avenue, Apt. 505
Chevy Chase, MD 20815
Phone: (301) 654-3152
Email: Marty@hqiinc.com

John A. Dooley, MD

Primary Care Clinics
Washington VA Medical Center
50 Irving Street NW
Washington, DC 20422
Phone: (202) 745-8377
Fax: (202) 745-2209
Email: John.Dooley2@med.va.gov

Rosalie Fishman, RN, MSN, CPHQ

President
Healthcare Quality Informatics, Inc.
15200 Shady Grove Road, Suite 350
Rockville, MD 20850
Phone: (301) 296-4542
Fax: (301) 296-4476
Email: Rosalie@hqiinc.com

Elaine M. Furmaga, PharmD

Clinical Pharmacy Specialist
Pharmacy Benefits Management Service
1st Avenue; Building 37; Room 139
Hines, IL 60141
Phone: (708) 786-7862
Fax: (708) 786-78914
Email: Elaine.Furmaga@va.gov

Margaret A. Hawthorne, RN, MSN
COL, AN, USA
Chief, Evidence-Based Practice, USAMEDCOM
2050 Worth Road, Suite 26
Fort Sam Houston, TX 78234-6026
Phone: (210) 221-8297 ext. 6527
Fax: (210) 221-8478
Email: Margaret.Hawthorne@amedd.army.mil

James S. Kaufman, MD
Staff Physician
VA Boston Healthcare System
150 S. Huntington Avenue
Boston, MA 02130
Phone: (857) 364-5613
Fax: (857) 364-4424
Email: james.kaufman@va.gov

Angela V. Klar, MSN, RN, ANP-CS
Clinical Practice Guideline Coordinator
US Army MEDCOM Quality Management
2050 Worth Road, Building 2792, Suite 26
FT. Sam Houston, TX 78234
Phone: (210) 221-8740 (DSN 471)
Fax: (210) 221-8478
Email: Angela.Klar@cen.amedd.army.mil

Joanne Marko, MS, SLP
Independent Consultant
Olney, MD 20832
Phone: (301) 774-5812
Email: Joanne@hqiinc.com

Parnell C. Mattison, DO
Major, MC, USA
Chief Pediatric Service
DeWitt Army Community Hospital
9501 Farrell Road
Fort Belvoir, VA 22060
Phone: (703) 805-0531
Fax: (703) 805-9024
Parnell.mattison@na.amedd.army.mil

Mary Ellen Nugent, RN, MSN
Nurse Manager
Dialysis Unit/Infusion Center
VA Greater Los Angeles Healthcare System
Phone: (310) 478-3711 x41314
Email: MaryEllen.Nugent@va.gov

Ann M. O'Hare, MA, MD

Staff Physician
VA Medical Center, San Francisco
4150 Clement Street
San Francisco CA 94121
Phone: (415) 221-4810x4953
Fax: (415) 750-6949
Email: Ann.oHare@va.gov

Carlos E. Palant, MD

Chief, Renal Section
Washington DC VA Medical Center
50 Irving Street, NW
Washington DC 20422
Phone: (202) 745-8105
Fax: (202) 518-4326
Email: carlos.palant2@med.va.gov

Christine Pasquariello, MD

Medical Center BK-111
VA New York Harbor Healthcare System-Brooklyn
800 Poly Place
Brooklyn, New York 11209
Phone: (718) 836-6600X 3198
Email: christine.pasquariello@va.gov

Thakor G. Patel, MD, MACP

Program Chief, Oncology and Kidney Diseases
Veterans Health Administration
810 Vermont Avenue, NW
Washington, DC 20420
Phone: (202) 273-8490
Fax: (202) 273-9140
Email: tgpatel@va.gov

Eric Sawyers, MD, LCDR USN

Chief of Nephrology
National Naval Medical Center
Phone: (301) 295-4330
Fax: (301) 295-6081
Email: ESSawyers@bethesda.med.navy.mil

Mark Stephens, MD, MS, FAAFP

CDR
Associate Professor, Department of Family Medicine
Uniformed Services University of the Health Science
4301 Jones Bridge Road
Bethesda, MD 20814-4799
Phone: (301) 295-3632
Fax: (301) 295-3100
Email: mstepens@usuhs.mil

Kevin T. Stroupe, PhD

Research Scientist
Hines VA Hospital
Hines, IL 60141
Phone: (708) 202-3557
Fax: (708) 202-2316
Email: kevin.stroupe@va.gov

Oded Susskind, MPH

Medical Education Consultant
Brookline, MA 02446
Phone: (617) 232-3558
Fax: (775) 370-3470
Email: Oded@tiac.net

Fred Yeo, MD

LCDR, MC, USN
Chief, NNMC Nephrology Division
National Naval Medical Center
8901 Wisconsin Ave.
Bethesda, MD 20889
Phone: (301) 295-4331
Fax: (301) 295-6081
Email: FEYeo@Bethesda.med.navy.mil

Appendix K: Bibliography

- AASK study – see Wright, 2002.
- ABCD – see Estacio et al, 2000.
- Abdi R, Dong VM, Lee CJ, Ntoso KA. Angiotensin II receptor blocker-associated angioedema: on the heels of ACE inhibitor angioedema. *Pharmacotherapy* 2002 Sep;22(9):1173-5.
- ACE Inhibitors in Diabetic Nephropathy Trialists Group (ACEI/DN Trialists). Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001 Mar 6;134(5):370-9.
- Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan (letter). *N Engl J Med* 1995 Dec 7;333(23):1572.
- ADA, 2003a – See Treatment of hypertension, Arauz-Pacheco et al, 2003.
- ADA, 2003b – See Diabetic nephropathy, Molitch et al, 2003.
- AIPRD Study – see Jafar et al, 2003.
- AIPRI – see Maschio et al., 1996.
- Akbari A, Swedko PJ, Clark HD, Hogg W, Lemelin J, Magner P, Moore L, Ooi D. Detection of chronic kidney disease with laboratory reporting of estimated glomerular filtration rate and an educational program. *Arch Intern Med* 2004 Sep 13;164(16):1788-92.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002 Dec 18;288(23):2981-97.
- Allon M. Hyperkalemia in end-stage renal disease: mechanisms and management. *J Am Soc Nephrol* 1995 Oct;6(4): 1134-42.
- Andersen S, Tarnow L, Rossing P, Hansen BV, Parving HH. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *Kidney Int* 2000 Feb;57(2):601-6.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002 Jan; 324(7329):71-86.
- Appel GB. Aminoglycoside nephrotoxicity. *Am J Med* 1990 Mar 23;88(3C):16S-20S; discussion 38S-42S.
- Aranda P, Segura J, Ruilope LM, Aranda FJ, Frutos MA, Lopez V, Lopez de Novales E. Long-term renoprotective effects of standard versus high doses of telmisartan in hypertensive nondiabetic nephropathies. *Am J Kidney Dis* 2005 Dec;46 (6): 1074-9.
- Arauz-Pacheco C, Parrott MA, Raskin P; American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care* 2003a Jan;26(suppl 1):S80-2.
- Arias E, Anderson RN, Kung HC, Murphy SL, Kochanek KD. Deaths: final data for 2001. *Natl Vital Stat Rep* 2003 Sept 18;52(3):1-115.
- Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ; Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003 Feb 6;348(6):491-9.

- Astor BC, Eustace JA, Powe NR, Klag MJ, Sadler JH, Fink NE, Coresh J. Timing of nephrologist referral and arteriovenous access use: the CHOICE Study. *Am J Kidney Dis* 2001 Sep;38(3):494-501.
- Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 2002 Jun 24;162(12):1401-8.
- Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Elisaf M. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 2004 Jul;57(7): 728-34.
- Avorn J, Bohn RL, Levy E, Levin R, Owen WF Jr, Winkelmayer WC, Glynn RJ. Nephrologist care and mortality in patients with chronic renal insufficiency. *Arch Intern Med* 2002 Sep 23;162(17):2002-6.
- Avram, MM, Mittman N. Malnutrition in uremia. *Semin Nephrol* 1994 May;14(3):238-44.
- Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, Cairns HS, Collins R, Foley RN, Frighi V, Kourellias K. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis* 2005 Mar;45(3):473-84.
- Bakris GL, Siomos M, Richardson D, Janssen I, Bolton WK, Hebert L, Aqarwal R, Catanzaro D. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. *Kidney Int* 2000 Nov;58(5):2084-92.
- Bakris GL, Weir M. ACE inhibitors and protection against kidney disease progression in type 2 diabetes: What's the evidence. *J Clin Hypertens (Greenwich)* 2002 Nov-Dec;4(6):420-3.
- Bakris GL, Weir MR, DeQuattro V, McMahon FG. Effects of an ACEI inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int* 1998 Oct;54(4):1283-9.
- Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000 Mar 13;160(5): 685-93.
- Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy *N Engl J Med* 2004 Nov 4;351(19):1952-61.
- Barrett AJ. The cystatins: small protein inhibitors of cysteine proteinases. *Prog Clin Biol Res* 1985;180:105-16.
- Benz J, Oshrain C, Henry D, Avery C, Chiang YT, Gatlin M. Valsartan, a new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. *J Clin Pharmacol* 1997 Feb;37(2):101-7.
- Bergstrom J. Topical Questions in Nutritional Therapy in Nephrology and Gastroenterology: in Canzler (ed.). Stuttgart: Georg Thieme Verlag 1999, pp1-16.
- Bianchi S, Bigazzi R, Caiazza A, Camprese VM. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kidney Dis* 2003 Mar;41(3):565-70.
- Biesenbach G, Grafinger P, Janko O, Zazgornik J. Influence of cigarette-smoking on the progression of clinical diabetic nephropathy in type 2 diabetic patients. *Clin Nephrol* 1997 Sep;48(3):146-50.
- Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998;31:607-17.
- Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost effectiveness analysis. *JAMA* 2003 Dec 17;(290)290:3101-14.
- Boxer M. Accupril- and Cozaar-induced angioedema in the same patient (letter). *J Allergy Clin Immunol* 1996 Aug;98(2):471.

- Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001 Sep 20;345(12): 861–9.
- Briganti EM, Branley P, Chadban SJ, Shaw JE, McNeil JJ, Welborn TA, Atkins RC. Smoking is associated with renal impairment and proteinuria in the normal population: the AusDiab kidney study. *Australian Diabetes, Obesity and Lifestyle Study. Am J Kidney Dis.* 2002 Oct;40(4):704-12.
- Briguori C, Colombo A, Airoidi F, Melzi G, Michev I, Carlino M, Montorfano M, Chieffo A, Bellanca R, Ricciardelli B. Gadolinium-based contrast agents and nephrotoxicity in patients undergoing coronary artery procedures. *Catheter Cardiovasc Interv.* 2006 Feb;67(2):175-80.
- Briguori C, Colombo A, Airoidi F, Morici N, Sangiorgi GM, Violante A, Focaccio A, Montorfano M, Carlino M, Condorelli G, Ricciardelli B. Nephrotoxicity of low-osmolality versus is-osmolality contrast agents: impact of N-acetylcysteine. *Kidney Int.* 2005 Nov;68(5):2250-5.
- Briguori C, Colombo A, Airoidi F, Violante A, Castelli A, Balestrieri P, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Librera M, Focaccio A, Ricciardelli B. N-Acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. *J Am Coll Cardiol* 2004a;44(4):762-5.
- Briguori C, Colombo A, Violante A, Balestrieri P, Manganelli F, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Focaccio A, Librera M, Bonizzoni E, Ricciardelli B. Standard vs. double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J* 2004b;25(3):206-11.
- Briguori C, Manganelli F, Scarpato P, Elia PP, Golia B, Riviezzo G, Lepore S, Librera M, Villari B, Colombo A, Ricciardelli B. Acetylcysteine and contrast agent-associated nephrotoxicity. *J Am Coll Cardiol* 2002;40(2):298-303.
- Briguori C, Tavano D, Colombo A. Contrast agent--associated nephrotoxicity. *Prog Cardiovasc Dis* 2003;45(6):493-503.
- Brittin G, Brecher G, Johnson C, Elashoff R. Stability of blood in commonly used anticoagulants. Use of refrigerated blood for quality control of the Coulter Counter Model S. *Am J Clin Pathol* 1969 Dec;52(6):690-4.
- CALM study – see Mogensen et al., 2000.
- Campbell R, Sangalli F, Perticucci E, Aros C, Viscarra C, Perna A, Remuzzi A, Bertocchi F, Remuzzi G, Ruggenenti P. Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies. *Kidney Int* 2003 Mar;63(3):1094-103.
- CAPPP – see Niskanen et al., 2001.
- Caravaca F, Arrobas M, Pizarro JL, Esparrago JF. Metabolic acidosis in advanced renal failure: Differences between diabetic and nondiabetic patients. *Am J Kidney Dis* 1999;33:892-898.
- CARE study – see Lewis et al, 1998.
- CARI Guidelines – see Elder et al., 2006; Harris et al., 2006; Johnson, 2005 & 2006; Pollock et al., 2005; Walker et al., 2005.
- Cha YJ, Pearson VE. Angioedema due to losartan. *Ann Pharmacother* 1999 Sep;33(9):936-8.
- Chan P, Tomlinson B, Huang TY, Ko JT, Lin TS, Lee YS. Double-blind comparison of losartan, lisinopril, and metolazone in elderly hypertensive patients with previous angiotensin-converting enzyme inhibitor-induced cough. *J Clin Pharmacol* 1997 Mar;37(3):253-7.
- CHARM – see Granger et al, 2003.
- Charytan C, Qunibi W, Bailie G. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract* 2005;100(3):c55-c62.
- Chase HP, Garg SK, Marshall G, berg CL, Harris S, Jackson WE, Hamman RE. Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA* 1991 Feb 6;265(5): 614–7.

- Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002;62:245-52.
- Chiu AG, Krowiak EJ, Deeb ZE. Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology. *Laryngoscope* 2001 Oct;111:1729-31.
- Chobanian AV, Bakris G, Black HR, Cushman WC, Green LA, Izzo JL, Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Rocella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003 Dec;42(6):1206-52.
- Chronic Kidney Disease in Adults: UK Guidelines- see Joint Specialty Committee on Renal Medicine.
- Chuahirun T, Simoni J, Hudson C, Seipel T, Khanna A, Harrist RB, Wesson DE. Cigarette smoking exacerbates and its cessation ameliorates renal injury in type 2 diabetes. *Am J Med Sci* 2004 Feb;327(2):57-67.
- Chuahirun T, Wesson DE. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. *Am J Kidney Dis* 2002 Feb;39(2):376-82.
- Ciavarella A, Gianfranco MI, Stefoni S, Borgnino LC, Bannini P. Reduced albuminuria after dietary protein restrictions in insulin dependent diabetic patients with clinical nephropathy. *Diabetes Care* 1987 Nov-Dec;10(6):407-13.
- Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. *Arch Intern Med* 2004 Apr 26;164(8):910-3.
- Cigarroa, RG, Lange, RA, Williams, RH, Hillis, LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 1989 Jun;86(6 Pt 1):649-52.
- Cleveland DR, Jindal KK, Hirsch DJ, Kiberd BA. Quality of prereferral care in patients with chronic renal insufficiency. *Am J Kidney Dis* 2002 July;40(1):30-6.
- Coen G, Mazzaferro S, Ballanti P, Sardella D, Chicca S, Manni M, Bonucci E, Taggi F: Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: A cross-sectional study. *Nephrol Dial Transplant* 1996 May;11(5):813-819.
- Conigliaro RL, Gleason PP. Losartan-induced cough after lisinopril therapy. *Am J Health-Syst Pharm* 1999 May 1;56(9):914-5.
- COOPERATE, 2003 – See Nakao 2003
- Crepaldi G, Carta Q, Deferrari G, Mangili R, Navalesi R, Santeusano F, Spalluto A, Vanasis A, Villa GM, Nosadini R. Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. The Italian Microalbuminuria Study Group in IDDM. *Diabetes Care* 1998 Jan; 2(1):104–10.
- Cronin RE, Henrich WL. Toxic Nephropathies; in Brenner BM (ed.). *The Kidney* ed 6. Philadelphia, Saunders. 2000, pp.563-1596.
- CSG Captopril Trial, 1993 –See Lewis 1993
- D’Amico G, Gentile MG, Fellin G, Manna G, Cofano F. Effect of dietary protein restriction on the progression of renal failure: a prospective randomized trial. *Nephrol Dial Transplant* 1994;9(11):1590-4.
- David D, Jallad N, Germino FW, Willett MS, de Silva J, Weidner SM, Mills DJ. A Comparison of the Cough Profile of Fosinopril and Enalapril in Hypertensive Patients with a History of ACE Inhibitor-Associated Cough. *Am J Ther* 1995 2(10):806-13.
- Davidson, CJ, Hlatky, M, Morris, KG, Pieper K, Skelton TN, Schwab SJ, Bashore TM. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. *Ann Intern Med* 1989 Jan 15;110(2):119-24.

- Dean RH, Tribble RW, Hansen K.J, O'Neil E, Craven TE, Redding JF. Evolution of renal insufficiency in ischemic nephropathy. *Ann Surg* 1991 May;213(5):446-56.
- DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Inter* 1980 Jan;17(1):118-34.
- Del Vecchio L, Pozzi M, Salvetti A, Maschio G, Fusaroli M, Rovati C, Antonucci F, Cascone C, Scanferla F, Panichi V, Sturani A, Locatelli F. Efficacy and tolerability of manidipine in the treatment of hypertension in patients with non-diabetic chronic kidney disease without glomerular disease. Prospective, randomized, double-blind study of parallel groups in comparison with enalapril. *J Nephrol* 2004 Mar-Apr;17(2):261-9.
- DETAIL – see Barnett et al., 2004.
- Devins GM, Mendelssohn DC, Barre PE, Taub K, Binik YM. Predialysis psychoeducational intervention extends survival in CKD: a 20-year follow-up. *Am J Kidney Dis* 2005;46:1088-98.
- Douglas K, O'Malley P, Jackson L. Meta-Analysis: The Effect of statins on albuminuria. *Ann Intern Med* 2006 July 18;145(2):117-24.
- Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006 Nov 16;355(20):2071-84.
- Dullaart RP, Beusekamp BJ, Meijer S, van Doormaal JJ, Sluiter WJ. Long term effects of protein-restricted diet on albuminuria and renal function in IDDM patients without clinical nephropathy and hypertension. *Diabetes Care* 1993 Feb;16(2):483-92.
- El-Achkar TM, Ohmit SE, McCullough PA, Crook ED, Brown WW, Grimm R, Bakris GL, Keane WF, Flack JM; Kidney Early Evaluation Program. Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. *Kidney Int* 2005 Apr;67(4):1483-8.
- Elder G, Faull R, Branley P, Hawley C; Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. *Nephrology (Carlton)*. 2006 Apr;11 Suppl 1:S230-61.
- Esmail ZN, Loewen PS. Losartan as an alternative to ACE inhibitors in patients with renal dysfunction. *Ann Pharmacother* 1998 Oct;32(10):1096-8.
- Esnault VL, Ekhlas A, Delcroix C, Moutel MG, Nguyen JM. Diuretic and enhanced sodium restriction results in improved antiproteinuric response to RAS blocking agents. *J Am Soc Nephrol* 2005 Feb;16(2):474-81.
- Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000 Apr;23 Suppl 2: B54-64.
- Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998 Mar;338(10):645-52.
- FACET – see Tatti, 1998.
- Fischer MJ, Stroupe KT, Browning M, Hynes DM, Kaufman JS. Chronic Kidney Disease is highly prevalent among VA healthcare users. Poster Presentation: American Society of Nephrology National Meeting. Philadelphia, PA, Nov 1-8, 2005.
- Fouque D., Laville M. and Boissel J. P. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev* 2006 Apr 19;(2):CD001892.
- Fraser C, Wilkinson S, Neville R, Knox J, King J, MacWalter R. Biologic variation of common hematologic laboratory quantiles in the elderly. *Am J Clin Pathol* 1989 Oct;92(4):465-70.
- Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001;59(1):260-9.
- Frye CB, Pettigrew TJ. Angioedema and photosensitive rash induced by valsartan. *Pharmacotherapy* 1998;18:866-8.

- Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 1997 Mar 15;314(7083):783-8.
- Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO₄, Ca x PO₄ product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001;12:2131-38.
- Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. *Kidney Int* 2002 Jun;61(6):2165-75.
- Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin- Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Ann Intern Med* 1997; 127: 337-45.
- Gouva C, Nikolopoulos P, Ioannidis JA, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: A randomized controlled trial. *Kidney Int* 2004 Aug;66(2):753-60.
- Graham A, Reaich D, Channon S.M, Downie S, Goodship TH. Correction of acidosis in hemodialysis decreases whole-body protein degradation. *J Am Soc of Nephrol* 1977 Apr;8(4), 632-7.
- Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003 Sep 6;362(0386):772-6.
- Grobner T, Prischl FC. Gadolinium and nephrogenic systemic fibrosis. *Kidney Int* 2007 Aug;72(3):260-4.
- Grubb A, Simonsen O, Sturfelt G, Truedsson L, Thysell H. Serum concentration of cystatin C, factor D and beta 2-microglobulin as a measure of glomerular filtration rate. *Acta Med Scan* 1985;218(5):499-503.
- Hakim RM, Lazarus JM. Biochemical parameters in chronic renal failure. *Am J Kidney Dis* 1988 Mar; 11:238-47.
- Halimi JM, Giraudeau B, Vol S, Caces E, Nivet H, Lebranchu Y, Tichet J. Effects of current smoking and smoking discontinuation on renal function and proteinuria in the general population. *Kidney Int* 2000 Sep;58(3):1285-92.
- Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 2002 Jul;62(1):220-8.
- Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998 Jun 13;351(9118):1755-62.
- Harris D, Thomas M, Johnson D, Nicholls K, Gillin A; Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Prevention of progression of kidney disease. *Nephrology (Carlton)*. 2006 Apr;11 Suppl 1:S2-197.
- Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000 Jan 22;355(9200):253-9.
- Hebert LA, Kusek JW, Greene T, Agodoa LY, Jones CA, Levey AS, Breyer JA, Faubert P, Rolin HA, Wang SR. Effects of blood pressure control on progressive renal disease in blacks and whites. Modification of Diet in Renal Disease Study Group. *Hypertension* 1997 Sep 30;30(3 Pt 1):428-35.
- Hoitsma AJ, Wetzels JF, Koene RA. Drug-induced nephrotoxicity. Aetiology, clinical features and management. *Drug Saf* 1991;6(2):131-47.
- HOT Study – see Hansson et al., 1998.

- Hricik DE, Browning PJ, Kopelman R, Goorno WE, Madias NE, Dzau VJ. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. *NEJM* 1983 Feb 17;308(7):374-6.
- Hsu CY, Chertow GM. Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. *Nephrol Dial Transplant* 2002 Aug 17;(8):1419-25.
- Huisman RM. The deadly risk of late referral. *Nephrol Dial Transplant* 2004 September;19(9):2175-80.
- Hutchinson FN, Jones WJ. A cost-effectiveness analysis of anemia screening before erythropoietin in patients with end-stage renal disease. *Am J Kidney Dis* 1997;29(5):651-7.
- Hyne BE, Fowell E, Lee HA. The effect of caloric intake on nitrogen balance in chronic renal failure. *Clin Sci* 1972 Nov;43(5):679-88.
- IDNT, 2001 – see Lewis, 2001.
- Ihle BU, Becker GJ, Whitworth JA, Charlwood RA, Kincaid Smith PS. The effect of protein restriction on the progression of renal insufficiency. *N Engl J Med* 1989 Dec 28;321(26):1773-7.
- Iino Y, Hayashi M, Kawamura T, Shiigai T, Tomino Y, Yamada K, Kitajima T, Ideura T, Koyama A, Sugisaki T, Suzuki H, Umemura S, Kawaguchi Y, Uchida S, Kuwahara M, Yamazaki T; Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) Study Investigators. Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension—a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. *Hypertens Res* 2004 Jan;27(1):21-30.
- Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM. Spontaneous dietary protein intake during progression of chronic renal failure. *J Am Soc Nephrol* 1995 Nov; 6(5):1386-91.
- Imai Y, Suzuki H, Saito T, Tsuji I, Abe K, Saruta T. The effect of pravastatin on renal function and lipid metabolism in patients with renal dysfunction with hypertension and hyperlipidemia. Pravastatin and Renal Function Research Group. *Clin Exp Hypertens* 1999 Nov;21(8):1345-55.
- IRMA-2, 2001 – see Parving, 2001.
- Ishimitsu T, Kobayashi T, Honda T, Takahashi M, Minami J, Ohta S, Inada H, Yoshii M, Ono H, Matsuoka H. Protective effects of an angiotensin II receptor blocker and a long-acting calcium channel blocker against cardiovascular organ injuries in hypertensive patients. *Hypertens Res* 2005 Apr;28(4):351-9.
- Jacobsen P, Andersen S, Jensen BR, Parving HH. Additive effect of ACE inhibition and angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *J Am Soc Nephrol* 2003a;14:992-9.
- Jacobsen P, Andersen S, Rossing K, Hansen BV, Parving HH. Dual blockade of the renin-angiotensin system in type 1 patients with diabetic nephropathy. *Nephrol Dial Transplant* 2002;17:1019-24.
- Jacobsen P, Andersen S, Rossing K, Jensen BR, Parving HH. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. *Kidney Int* 2003b;63:1874-80.
- Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, Maschio G, Brenner BM, Kamper A, Zucchelli P, Becker G, Himmelman A, Bannister K, Landais P, Shahinfar S, de Jong PE, de Zeeuw D, Lau J, Levey AS. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001 Jul 17;135(2):73-87.
- Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS; AIPRD Study Group. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003 Aug 19;139(4):244-52.
- JNC 7 – see Chobanian et al., 2003
- Jo SH, Youn TJ, Koo BK, Park JS, Kang HJ, Cho YS, Chung WY, Joo GW, Chae IH, Choi DJ, Oh BH, Lee MM, Park YB, Kim HS. Renal toxicity evaluation and comparison between visipaque (iodixanol) and

- hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. *J Am Coll Cardiol* 2006;48(5):924-30.
- Johnson D. W. Dietary protein restriction as a treatment for slowing chronic kidney disease progression: the case against. *Nephrology (Carlton)* 2006;11(1):58-62.
- Johnson DW. Caring for Australians with Renal Impairment (CARI). The CARI guidelines. Evaluation of renal function. *Nephrology (Carlton)*. 2005 Oct;10 Suppl 4:S133-76.
- Johnson R.J, Willson R, Yarnabe H, Couser, W, Alpers CE, Wener MH, Davis C, Gretch DR. Renal manifestations of hepatitis C virus infection. *Kidney Int* 1994 Nov;46(5):1255-63.
- Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association, and the Royal College of General Practitioners. Chronic kidney disease in adults: UK guidelines for identification, management and referral. London: Royal College of Physicians, 2006. Available from: <http://www.renal.org/CKDguide/full/CKDprintedfullguide.pdf>
- Jungers P, Chauveau P, Poyard F, Lebkim B, Ciancioni C, Man NK. Comparison of ketoacids and low protein diet on advanced chronic renal failure progression. *Kidney Int Suppl*. 1987 Oct;22:S67-71.
- Kappel J, Calissi P. Safe drug prescribing for patients with renal insufficiency. *CMAJ* 2002 Feb 19; 166(4):473-7.
- Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993 Jan 15;118(2):129–38.
- Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998 Jun;31(6) 954–61.
- Kaysen GA. Inflammation nutritional state and outcome in end stage renal disease. *Miner Electrolyte Metab*. 1999 Jul-Dec;25(4-6):242-50.
- Kazmi WH, Kausz AT, Khan S, Abichandani R, Ruthazer R, Obrador GT, Perira BJ. Anemia: An early complication of chronic renal insufficiency. *Am J Kidney Dis* 2001 Oct;38(4):803-12.
- KDOQI Clinical Practice Guidelines and Clinical Practice for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis* 2007 Feb;49(2 Suppl 2):S12-154.
- KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Vascular Access, Update 2006. *Am J Kidney Dis* July 2006 supplement. Development Sponsors: Amgen, Inc, Baxter Healthcare Corporation, Fresenius, USA, Inc., Genentech, Inc., and Watson Pharmaceuticals, Inc.
- KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis* May 2006;47(Suppl 3):S1-S146.
- KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 2003 Oct;42(4 Suppl 3):S1-201.
- KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. *Am J Kidney Dis* April 2005;45(Suppl 3):S1-S153.
- KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation Classification and Stratification. *Am J Kidney Dis* 2002 Feb;39(2 Suppl 1):S1-266.
- KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *Am J Kidney Dis* April 2003;41(Suppl 3):S1-S91.
- KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. *Am J Kidney Dis* 2000 Jun;35(6 Suppl 2):S1-140.
- KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. *Am J Kidney Dis* 2004 May;43(5 Suppl 1):S1-290.
- Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kidney Dis* 1999 May;33(5):1004-10.

KEEP, 2003 – see National Kidney Foundation.

Khamidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002 August;40(2):221-6.

Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, Steinman TI, Wang SR, Yamamoto ME. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. *J Am Soc Nephrol* 1995 Jun;5(12):2037-47.

Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994 Mar 31;330(13) 877-84.

Koomans HA, Roos JC, Dorout Mees EJ, Delawi IMK. Sodium balance in renal failure: a comparison of patients with normal subjects under extremes of sodium intake. *Hypertension* 1985;7:714-721.

Kopple JD, Monteon FJ, Shaib JK. Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. *Kidney Int* 1986;29(3):734-42.

Kraut JA, Kurtz I. Metabolic acidosis of CKD: Diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis* 2005 Jul;45(6):978-93.

Krolewski AS, Warram JH, Christlieb AR. Hypercholesterolemia--a determinant of renal function loss and deaths in IDDM patients with nephropathy. *Kidney Int Suppl* 1994 Feb;45:S125-31.

Kuo P, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology* 2007 Mar;242(3):644-9.

Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Yoshindo K, Sakai O. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 1997;77:176-85.

Kyrmizakis DE, Papadakis CE, Liolios AD, Karatzanis AD, Malandrakis S, Skoulakis CE, Bizakis JG, Velegrakis GA. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists. *Arch Otolaryngol Head Neck Surg* 2004 Dec;130(12):1416-9.

Lacourciere Y, Belanger A, Godin C, Halle JP, Ross S, Wright N, Marion J. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetes with early nephropathy. *Kidney Int* 2000 Aug;58(2):762-9.

Lacourciere Y. The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. *Telmisartan Cough Study Group. Int J Clin Pract* 1999 Mar;53(2):99-103.

Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria: North American Microalbuminuria Study Group. *Am J Med* 1995;99:497-504.

Lam KS, Cheng IK, Janus ED, Pang RW. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. *Diabetologia* 1995 May;38(5):604-9.

Lameier NH. Contrast-induced nephropathy--prevention and risk reduction. *Nephrol Dial Transplant* 2006;21(6):i11-23.

Lautin, EM, Freeman, NJ, Schoenfeld, AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish EG, et al. Radiocontrast-associated renal dysfunction: Incidence and risk factors. *AJR Am J Roentgenol* 1991;157:49.

Laverman GD, Navis G, Henning RH, de Jong PE, de Zeeuw D. Dual renin-angiotensin system blockade at optimal doses for proteinuria. *Kidney Int* 2002;62:1020-5.

Lefebvre A, de Vernejoul MC, Gueris J, Goldfarb B, Graulet AM, Morieux C. Optimal correction of acidosis changes progression of dialysis osteodystrophy. *Kidney Int* 1989;36(6):1112-8.

Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT Jr. Controlling the epidemic of

- cardiovascular disease in chronic renal disease: What do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 1998 Nov;32(5):853-906.
- Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003 Jul 15;139(2):137-47.
- Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006 Aug 15;145(4):247-54.
- Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, Carlisle E, Barre P, Magner P, Muirhead N, Tobe S, Tam P, Wadgymar JA, Kappel J, Holland D, Pichette V, Shoker A, Soltys G, Verrelli M, Singer J, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis* 2005 Nov;46(5):799-811.
- Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. *Am J Kidney Dis* 1996 Mar;27(3):347-54.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993 Nov 11;329(20):1456-62.
- Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001 Sep 20;345(12):851-60.
- Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. *Am J Kidney Dis* 1999 Nov;34(5):809-17.
- Lewis SJ, Moye LA, Sacks FM, Johnstone DE, Timmis G, Mitchell J, Limacher M, Kell S, Glasser SP, Grant J, Davis BR, Pfeffer MA, Braunwald E. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med* 1998 Nov 1;129(9):681-9.
- Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A. Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet* 1991 Jun 1;337(8753):1299-304.
- Locatelli F, Aljama P, Barany P, Canaud B, Carrera F, Eckardt KU, Horl WH, Macdougall IC, Macleod A, Wiecek A, Cameron S; European Best Practice Guidelines Working Group. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 2004 May;19 Suppl 2:ii1-47.
- Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract* 2001 Nov-Dec;4(6):256-62.
- Lovell HG. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria. *Cochrane Database Syst Rev* 2001;(1):CD002183.
- Luno J, Barrio V, Goicoechea MA, De Vinuesa SG, Gomez F, Bernis C, Espinosa M, Ahijado F, Gomez J, Escalada P. Effects of dual blockade of the renin-angiotensin system in primary proteinuric nephropathies. *Kidney Inter* 2002 Dec;62 Suppl 82:47-52.
- MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006 Jul;48(1):8-20.
- Maki DD, Ma JZ, Louis TA, Kasiske BL. Long-term effects of antihypertensive agents on proteinuria and renal function. *Arch Intern Med* 1995 May 22;155(10):1073-80.
- Management of Chronic Kidney Disease and Pre-ESRD in the Primary Care Setting. Washington, DC: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department

- of Veterans Affairs, and Health Affairs, Department of Defense, November 2000. Office of Quality and Performance publication 10Q-CPG/ESRD-00. Available from: <http://www.oqp.med.va.gov/cpg>:
- Management of Diabetes Mellitus. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, December 1999 (Update 2003). Office of Quality and Performance publication 10Q-CPG/DM-03. Available from: <http://www.oqp.med.va.gov/cpg>
- Management of Dyslipidemia in the Primary Care Setting. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, October 2001.(Update 2006) Office of Quality and Performance publication 10Q-CPG/Lipids-05. Available from: <http://www.oqp.med.va.gov/cpg>
- Management of Hypertension in the Primary Care Setting. Washington, DC: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, November 1999. Office of Quality and Performance publication 10Q-CPG/HTN-99. (Update 2004). Office of Quality and Performance publication 10Q-CPG/HTN-04. Available from: <http://www.oqp.med.va.gov/cpg>
- Management of Ischemic Heart Disease. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, October 2001. Update November 2003. Office of Quality and Performance publication 10Q-CPG/IHD-03. Available from: <http://www.oqp.med.va.gov/cpg>
- Management of Overweight and Obesity. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, December 2006. Office of Quality and Performance publication 10Q-CPG/Obesity-06. Available from: <http://www.oqp.med.va.gov/cpg>
- Management of Tobacco Use. Washington D.C.: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, Dec 1999 (update 2004). Office of Quality and Performance Publication 10Q-CPG/TUC-04. Available from: <http://www.oqp.med.va.gov/cpg>
- Marenzi G, Bartorelli AL. Recent advances in the prevention of radiocontrast nephropathy. *Curr Opin Crit Care* 2004 Dec;10(6):505-9.
- Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'Agati VD. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. *J Am Soc Nephrol* 2000;11(8):1439-48.
- Maroni BJ; in Mitch, WE, Klahr, S. (eds). *Nutrition and the Kidney* (3rd ed). Philadelphia: Lippincott-Raven 1998, pp. 144-165.
- Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, Ponticelli C, Ritz E, Zucchelli P. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996 Apr 11;334(15):939-45.
- Matsuda H, Hayashi K, Saruta T. Distinct time courses of renal protective action of angiotensin receptor antagonists and ACE inhibitors in chronic renal disease. *J Hum Hypertens* 2003 April;17(4):271-6.
- McClellan WM, Ramirez SP, Jurkowitz C. Screening for chronic kidney disease: unresolved issues. *J Am Soc Nephrol* 2003;14(7 suppl 2):S81-7.
- MDRD Study – see Klahr, 1994.
- Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; Oct 6;44(7):1393-9.
- Meloni C, Morosetti M, Suraci C, Pennafina MG, Tozzo C, Taccone-Gallucci M, Casciani CU. Severe dietary protein restriction in overt diabetic nephropathy: benefits or risks? *J Ren Nutr* 2002 Apr;12(2):96-101

- Menon V, Shlipak MG, Wang X, Coresh J, Greene T, Stevens L, Kusek JW, Beck GJ, Collins AJ, Levey AS, Sarnak MJ. Cystatin C as a risk factor for outcomes in chronic kidney disease. *Ann Intern Med.* 2007 Jul 3;147(1):19-27.
- MICRO-HOPE – see Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000.
- Mitch WE, Price SR: Mechanisms activated by kidney disease and the loss of muscle mass. *Am J Kidney Dis* 2001 Dec;38(6):1337-42.
- MMWR. 2007;56:161-165 Prevalence of Chronic Kidney Disease and Associated Risk Factors—United States, 1999-2004. *JAMA* 2007;297:1767-1768.
- Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper ME. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000 Dec 9;321(7274):1440-4.
- Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Morgensen CE, Parving HH, American Diabetes Association. Diabetic nephropathy. *Diabetes Care* 2003 Jan;26(Suppl 1):S94-8.
- Morimoto T, Gandhi TK, Fiskio JM, Seger AC, So JW, Cook EF, Fukui T, Bates DW. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. *J Eval Clin Pract* 2004 Nov;10(4):499-509.
- Muirhead N, Feagan BF, Mahon J, Lewanczuk RZ, Rodger NW, Botteri F, Oddou-Stock P, Pecher E, Cheung R. The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: a placebo-controlled trial. *Curr Ther Res* 1999;60(12):650-60.
- Mulec H, Johnson SA, Bjorck S. Relation between serum cholesterol and diabetic nephropathy. *Lancet* 1990 Jun 23;335(8704):1537-8.
- Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial. *Lancet* 2003 Jan 11;361(9352):117-24.
- National Kidney Foundation. KEEP: Kidney Early Evaluation Program. Annual data report. Program introduction. *Am J Kidney Dis* 2003;42(5 suppl 4):S5-15. Accessed online February 15, 2006, at: http://www.kidney.org/news/keep/pdf/KEEP2003AJKD_ADR.pdf
- NHANES III – see Coresh et al., 2003.
- Nielsen S, Dollerup J, Nielsen B, Jensen HA, Mogensen CE. Losartan reduces albuminuria in patients with essential hypertension. An enalapril controlled 3 months study. *Nephrol Dial Transplant* 1997;12(Suppl 2):19-23.
- Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A; CAPPP Study Group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care* 2001Dec;24(12):2091-6.
- Noordzij M, Korevaar JC, Boeschoten EW, Dekker FW, Bos WJ, Krediet RT. The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline for Bone Metabolism and Disease in CKD: association with mortality in dialysis patients. *Am J Kidney Dis* 2005;46:925-32.
- Odoni G, Ogata H, Viedt C, Amann K, Ritz E, Orth SR. Cigarette smoke condensate aggravates renal injury in the renal ablation model. *Kidney Int.* 2002 Jun;61(6):2090-8.
- Orth SR, Viedt C, Ritz E. Adverse effects of smoking in the renal patient. *Tohoku J Exp Med* 2001 May;194(1):1-15.
- Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med.* 2004 Aug 5;351(6):585-92.

- Panesar A, Agarwal R. Safety and efficacy of sodium ferric gluconate complex in patients with chronic kidney disease. *Am J Kidney Dis* 2002;40(5):924-31.
- Parfrey, PS, Griffiths, SM, Barrett, BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med* 1989 Jan 19;320(3):143-9.
- Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with Type 2 diabetes. *N Engl J Med* 2001 Sep 20;345(12): 870–8.
- Paster RZ, Snavely DB, Sweet AR, Draper RA, Goldberg AI, Soffer BA, Sweet CS. Use of losartan in the treatment of hypertensive patients with a history of cough induced by angiotensin-converting enzyme inhibitors. *Clin Ther* 1998 Sep-Oct;20(5):978-89.
- Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005 Dec 1;353(22):2373-83.
- Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med* 1996 Apr 1;124(7): 627–32.
- Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamorzik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J* 1988; 296(6618):313-16.
- Pharmacologic Management of Chronic Heart Failure. Washington, D.C.: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration Department of Veterans Affairs: Feb 2001 PRM-SHG Publication #00-0015.
- Physicians' Health Study. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989;321(3):129-35.
- Pijls LT, de Vries H, van Eijk JT, Donker AJ. Protein restriction, glomerular filtration rate and albuminuria in patients with type 2 diabetes mellitus: a randomized trial. *Eur J Clin Nutr* 2002 Dec;56(12):1200-7.
- Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, deZeeuw D, de Jong PF. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med* 2000 Oct 17;133(8):585–91.
- Plum J, Buntzen B, Nemeth R, Grabensee B. Effects of the angiotensin II antagonist valsartan on blood pressure, proteinuria, and renal hemodynamics in patients with chronic renal failure and hypertension. *J Am Soc Nephrol* 1998 Dec;9(12):2223-34.
- Pollock C, Voss D, Hodson E, Crompton C; Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Nutrition and growth in kidney disease. *Nephrology (Carlton)* 2005 Dec;10 Suppl 5:S177-230.
- Portale AA, Booth BE, Halloran BP, Morris RC, Jr. Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. *J Clin Invest* 1984;73:1580-1589.
- Punzi HA. Safety update: focus on cough. *Am J Cardiol* 1993 Dec 30;72(20):45H-8H.
- Pylypchuk GB. ACE inhibitor- versus angiotensin II blocker-induced cough and angioedema. *Ann Pharmacother* 1998 Oct;32(10):1060-6.
- Raal FJ, Kalk WJ, Lawson M, Esser JD, Buys R, Fourie L. Effect of moderate dietary protein restriction on the progression of overt diabetic nephropathy: a 6-month prospective study. *Am J Clin Nutr* 1994 Oct;60(4):579-85.
- Rahman M, Brown CD, Coresh J, Davis BR, Eckfeldt JH, Kopyt N, Levey AS, Nwachuku C, Reisin E, Walworth; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. The prevalence of reduced glomerular filtration rate in older hypertensive patients and its

- association with cardiovascular disease: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Arch Intern Med* 2004 May 10;164(9):969-76.
- Raml A, Schmekal B, Grafinger P, Biesenbach G. Risk for hyperkalemia during long-term treatment with angiotensin-converting enzyme inhibitors in insulin-dependent type 2 diabetics in relation to the glomerular filtration rate. *Dtsch Med Wochenschr* 2001 Nov 23;126(47):1327-30.
- Ravid M, Lang R, Rachmani R, Lishner M. Long term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996 Feb 12;126(3):286-9.
- Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long term stabilizing effect of angiotensin-converting enzyme inhibitors on plasma creatinine and proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993 Apr 15;118(8):577-81.
- Regalado M, Yang S, Wesson DE. Cigarette smoking is associated with augmented progression of renal insufficiency in severe essential hypertension. *Am J Kidney Dis.* 2000 Apr;35(4):687-94.
- REIN – see The GISEN Group, 1997.
- REIN-2 – see Ruggenenti et al., 1998.
- Remuzzi A, Perico N, Sangalli F, Vendramin G, Moriggi M, Ruggenenti P, Remuzzi G. ACE inhibition and ANG II receptor blockade improve glomerular size-selectivity in IgA nephropathy. *Am J Physiol* 1999 Mar;276(3 Pt 2):F457-66.
- RENAAL – see Brenner et al., 2001.
- Rihal, CS, Textor, SC, Grill, DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002 May 14;105(19):2259-64.
- Ritz E, Benck U, Franek E, Keller C, Seyfarth M, Clorius J. Effects of smoking on renal hemodynamics in healthy volunteers and in patients with glomerular disease. *Am Soc Nephrol* 1998 Oct;9(10):1798-804.
- Rivera JO. Losartan-induced angioedema. *Ann Pharmacother* 1999 Sep;33(9):933-5.
- Rodby RA, Rohde R, Evans J, Bain RP, Mulcahy WS, Lewis EJ. The urine protein to creatinine ratio as a predictor of 24-hour urine protein excretion in type 1 diabetic patients with nephropathy. The Collaborative Study Group. *Am J Kidney Dis.* 1995 Dec;26(6):904-9.
- Roderick P, Jones C, Drey N, Blakeley S, Webster P, Goddard J, Garland S, Bourton L, Tomson C. Late referral for end-stage renal disease: a region-wide survey in the south west of England. *Nephrol Dial Transplant* 2002a July;17(7):1252-9.
- Roderick P, Jones C, Tomson C, Mason J. Late referral for dialysis: improving the management of chronic renal disease. *QJM* 2002b June;95(6):363-70.
- Roderick P, Willis N, Blakeley S, Jones C, Tomson C. Correction of chronic metabolic acidosis for chronic kidney disease patients. *Cochrane Database Syst Rev* 2007 Jan 24;(1):CD01890.
- Roger SD, McMahon LP, Clarkson A, Disney A, Harris D, Hawley C, Healy H, Kerr P, Lynn K, Parnham A, Pascie R, Voss D, Walker R, Levin A. Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): Results of a randomized clinical trial. *J Am Soc Nephrol* 2004 Jan;15(1):148-56.
- Rose BD. Clinical manifestations and treatment of hyperkalemia. *Up to Date in Medicine.* Wellesley, MA 2007.
- Rosman JB, Langer K, Brandl M, Piers-Becht TP, van der Hem GK, ter Wee PM, Donker AJ. Protein-restricted diets in chronic renal failure: a four year follow-up shows limited indications. *Kidney Int Suppl.* 1989 Nov;27:S96-102.
- Rosman JB, ter Wee PM, Meijer S, Piers-Becht TP, Sluiter WJ, Donker AJ. Prospective randomised trial of early dietary protein restriction in chronic renal failure. *Lancet* 1984 Dec 8;2(8415):1291-6.

- Roth D, Smith RD, Schulman G, Schulman G, Steinman TI, Hatch FE, Rudnick MR, Sloand JA, Freedman BI, Williams WW Jr, Shadur, et al. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am J Kidney Dis* 1994;24(5):777-84.
- Rudnick, MR, Goldfarb, S, Wexler, L, Ludbrook PA, Murphy MJ, Halpern EF, Hill JA, Winniford M, Cohen MB, VanFossen. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial. *Kidney Int* 1995 Jan;47(1):254-61.
- Ruggenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial year? Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). *Lancet* 1998 Oct 17;352(9136):1252-6.
- Rupprecht R, Vente C, Grafe A, Fuchs T. Angioedema due to losartan. *Allergy* 1999;54:81-2.
- Sandhu C, Belli AM, Oliveira DB. The role of N-acetylcysteine in the prevention of contrast-induced nephrotoxicity. *Cardiovasc Intervent Radiol* 2006;29(3):344-7.
- Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001;85(3):265-71.
- Sawicki PT, Didjurgeit U, Muhlhauser I, Bender R, Heinemann L, Berger M. Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 1994 Feb;17(2):126-31.
- Schiff H, Lang SM, Fischer R. Stopping smoking slows accelerated progression of renal failure in primary renal disease. *J Nephrol* 2002 May-Jun;15(3):270-4.
- Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. *Am J Epidemiol* 2006;164(9):881-9.
- Schwab SJ, Hlatky, MA, Pieper, KS, Davidson CJ, Morris KG, Skelton TN, Bashore TM. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med* 1989 Jan 19;320(3):149-53.
- Sharif MN, Evans BL, Pylypchuk GB. Cough induced by quinapril with resolution after changing to fosinopril. *Ann Pharmacother* 1994 Jun;28(6):720-1.
- Sharma PK, Yium JJ. Angioedema associated with angiotensin II receptor antagonist losartan. *South Med J* 1997 May;90(5):552-3.
- Sheikh MS, Maguire JA, Emmett M, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS. Reduction of dietary phosphorus absorption by phosphorus binders. A theoretical, in vitro, and in vivo study. *J Clin Invest* 1989 Jan;83(1):66-73.
- Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 2005 Apr 13;293(14):1737-45.
- Silverberg DS, Iaina A, Peer G, et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kidney Dis* 1996;27(2):234-8.
- Simonsen O, Grubb A, Thysell H. The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate. *Scand J Clin Lab Invest* 1985 April;45(2):97-101.
- Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355(20):2085-98.
- Slatopolsky EA, Burke SK, Dillon MA. RenaGel, a nonabsorbed calcium-and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. *Kidney Int* 1999 Jan;55(1):299-307.
- Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol* 2005;16:1788-93.

- Stacul F. Reducing the risks for contrast-induced nephropathy. *Cardiovasc Intervent Radiol* 2005;28 Suppl 2:S12-8.
- Stevens LA, Coresh J, Feldman HI, Greene T, Lash JP, Nelson RG, Rahman M, Deysher AE, Zhang YL, Schmid CH, Levey AS. Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol* 2007 Oct;18(10):2749-57.
- Stoves J, Inglis H, Newstead CG. A randomized study of oral vs. intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 2001 May;16(5):967-74.
- Strippoli GF, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004 Oct 9;329(7470):828.
- Tanser PH, Campbell LM, Carranza J, Karrash J, Toutouzas P, Watts R. Candesartan cilexetil is not associated with cough in hypertensive patients with enalapril-induced cough. Multicentre Cough Study Group. *Am J Hypertens* 2000 Feb;13(2):214-8.
- Tatti P, Pahor M, Byington RP, DiMauro P, Guarisco R, Strollo G, Strollo F. Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998 Apr;21(4):597-603.
- The CARI guidelines. Caring for Australians with Renal Impairment. Chronic Kidney Disease Prevention of Progression of Kidney Disease. Published April 2006. http://www.cari.org.au/ckd_prevent_list_published.php.
- The CARI guidelines. Caring for Australians with Renal Impairment. Chronic Kidney Disease Nutrition and Growth in Kidney Disease. Published December 2005. http://www.cari.org.au/ckd_nutrition_list_published.php.
- The CARI guidelines. Caring for Australians with Renal Impairment. Urine protein as diagnostic test: evaluation of proteinuria in children. *Nephrology (Carlton)* 2004 Oct;9 Suppl 3:S15-9.
- The CARI guidelines. Caring for Australians with Renal Impairment. Chronic Kidney Disease Cardiovascular Risk Factors. Published December 2005. http://www.cari.org.au/ckd_cardio_list_published.php.
- The CARI guidelines. Caring for Australians with Renal Impairment. Chronic Kidney Disease Vitamin D, Calcimimetics and Phosphate Binders. Published April 2006. http://www.cari.org.au/ckd_bone_list_published.php.
- The GISEN Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997 Jun 28;349(9069):1857-63.
- The Pharmacologic Management of Chronic Heart Failure. Washington, DC: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs; February, 2001. PRM-SHG Publication No. 00-0015. Available from: <http://www.oqp.med.va.gov/cpg>
- Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998; 351(9098):233-41.
- Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, Craven T, West M. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2004 Sep 21;110 (12):1557-63.
- Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC; Cholesterol and Recurrent Events Trial Investigators. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol* 2003 Jun;14 (6):1605-13.

- Tonelli M, Moye L, Sacks FM, Kiberd B, Curhan G; Cholesterol and Recurrent Events (CARE) Trial Investigators. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med* 2003 Jan 21;138(2):98-104.
- Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006 Jul;17(7) 2034-47.
- Tsuchiya K, Saito M, Okano-Sugiyama H, Nihei H, Ando M, Teramura M, Iwamoto YS, Shimada K, Akiba T. Monitoring the content of reticulocyte hemoglobin (CHr) as the progression of anemia in nondialysis chronic renal failure patients. *Renal Failure* 2005;27(1):59-65.
- Tuten MB, Wogt S, Dasse F, Leider Z. Utilization of prealbumin as a nutritional parameter. *JPen J Parenter Enteral Nutr* 1985;9(6):709-11.
- U.S. Renal Data System, USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2006. Available from: <http://www.usrds.org/adr.htm>
- UK Guideline – See chronic kidney disease in adults.
- UK Prospective Diabetes Study Group (UKPDS). Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998 Sep 12;317(7160):713-20.
- Uribarri J, Calvo MS. Hidden sources of phosphorus in the typical American diet: Does it matter in nephrology. *Semin Dial* 2003;16(3):186-188.
- Van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. *Arch Intern Med* 1998 Oct 12;158(18):2063-5.
- Van Wyck D, Roppolo M, Martinez C, Mazey R, McMurray S; for the United States Iron Sucrose (Venofer) Clinical Trial Groups A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005;68:2846-56.
- Vanherweghem JL, Depierreux M, Tielemans C, Abramowicz D, Dratwa M, Jadoul M, Richard C, Vandervelde D, Verbeelen D, Vanhaelen-Fastre R, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet*. 1993 Feb 13;341(8842):387-91.
- Verove C, Maisonneuve N, El Azouzi A, Boldron A, Azar R: Effect of the correction of metabolic acidosis on nutritional status in elderly patient with chronic renal failure. *J Ren Nutr* 2002 Oct;12(4):224-8.
- Viberti G, Morgensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *JAMA* 1994 Jan 26;271(4):275-9.
- von Moos R. Bisphosphonate treatment recommendations for oncologists. *Oncologist* 2005;10 Suppl 1:19-24.
- Walker JA, Sherman RA, Cody RF. The effect of oral bases on enteral aluminum absorption. *Arch Int Med* 1990 Oct;150(10):2037-9.
- Walker R; Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Cardiovascular risk factors. Lipid-lowering therapy in patients with chronic kidney disease. *Nephrology (Carlton)* 2005 Dec;10 Suppl5:S231-4.
- Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000 Apr;34(4):526-8.
- Warner C, Krane V, Maerz W., Oschewski M, Mann JF, Ruf G, Ritz E., German Diabetes and Dizlysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoin hemodialysis. *N Engl J Med* 2005 Jul 21;353(3):238-48. Erratum in: *N Engl J Med* 2005 Oct 13;353(15):1640.
- Weidmann P, Schneider M, Bohlen L. Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy: an updated meta-analysis. *Nephrol Dial Transplant* 1995 Oct;10 Suppl 9:39–45.

- Weisbord SD, Hartwig KC, Sonel AF, Fine MJ, Palevsky P. The incidence of clinically significant contrast-induced nephropathy following non-emergent coronary angiography. *Catheter Cardiovasc Interv* 2008 Apr 15; [Epub ahead of print].
- Whelton A, Stout RL, Spilman PS, Klassen DK. Renal effects of Ibuprofen, Piroxicam, and Sulindac in patients with asymptomatic renal failure. *Ann Int Med* 1990;112:568-576.
- WHO. Iron deficiency anaemia: Assessment, prevention and control. A guide for programme managers. Geneva, Switzerland: World Health Organization; 2001. Available from: http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf
- Widmer B, Gerhardt RE, Harrington JT, Cohen JJ: Serum electrolyte and acid base composition. The influence of graded degrees of chronic renal failure. *Arch Intern Med* 1979 Oct;139(10):1099-102
- Williams PS, Stevens ME, Fass G, Irons L, Bone JM. Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *Q J Med* 1991 Oct;81(294):837-55.
- Wingard RL, Parker RA, Ismail N, Hakim RM. Efficacy of oral iron therapy in patients receiving recombinant human erythropoietin. *Am J Kidney Dis* 1995;25(3):433-9.
- Winkelmayer WC, Glynn RJ, Levin R, Mittleman MA, Pliskin JS, Avorn J. Late nephrologist referral and access to renal transplantation. *Transplantation* 2002 June 27;73(12):1918-23.
- Winkelmayer WC, Owen WF, Jr., Levin R, Avorn J. A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 2003 Feb;14(2):486-92.
- Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glasscock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002 Nov 20;288(19):2421-31.
- Wynckel A, Ebikili B, Melin JP, Randoux C, Lavaud S, Chanard J. Long-term follow-up of acute renal failure caused by angiotensin converting enzyme inhibitors. *Am J Hypertens*. 1998 Sep;11(9):1080-6.
- Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1991 Jan 10;324(2):78-84.