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

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense 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.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

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

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor**.**

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The Management of Chronic Kidney Disease Working Group

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Version 3.0 – 2014

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Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence Based Practice Working Group (EBPWG) was established and first chartered in 2004, with a mission to advise the "…Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration (VHA) and Military Health System," by facilitating the development of clinical practice guidelines for the VA and DoD populations. [1] This Clinical Practice Guideline (CPG) is intended to provide primary care clinicians with a framework by which to evaluate the individual needs and preferences of patients who are experiencing chronic kidney disease (CKD), leading to improved clinical outcomes.

In 2008, the VA and DoD published a CPG for the Management of Chronic Kidney Disease (2008 CKD CPG), which was based on evidence reviewed through 2007. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of CKD. Recognition of the complex nature of this condition has led to the adoption of new strategies to manage and treat patients with CKD, as well as the development and use of new pharmacotherapies.

Consequently, a recommendation to update the 2008 CKD CPG was initiated in August 2013. The updated CPG includes objective, evidence-based information on the patient-centered approach to management of CKD, the benefits and harms of pharmacologic and non-pharmacologic therapies, the management of comorbid conditions, and best practices for care delivery. It is intended to assist health care providers in all aspects of patient care. The system-wide goal of evidence-based guidelines is to improve the patient's health and wellbeing by guiding health providers who are taking care of patients with CKD along the management pathways that are supported by evidence and are thus considered the highest standard of care. The expected outcome of successful implementation of this guideline is to:

- Formulate an efficient and effective assessment of the patient's condition
- Optimize the use of therapy to reduce disease progression, reduce symptoms of CKD, and enhance patient functionality
- Minimize preventable complications and morbidity
- Emphasize the use of personalized, proactive, patient-driven care

Background

Chronic kidney disease is one of the most common serious medical conditions affecting adults in the United States (US). The Centers for Disease Control and Prevention (CDC) estimate that more than 10% of adults in the US—over 20 million people—have CKD, [2] which is defined as having an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2 or albuminuria (albumin excretion rate [AER] of ≥30 mg/24 hours or albumin:creatinine ratio [ACR] of ≥30 mg/g), kidney transplantation, or any of several other less common reasons (e.g., urine sediment abnormalities, electrolytes and other abnormalities due to tubular disorders, histologic abnormalities, structural abnormalities identified by imaging). [3] Patients may suffer from mild illness without symptoms to severe illness associated with increased risk of death or progression to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation. The risk of developing CKD increases among people over 50 years of age and peaks after 70 years of age. [2] In many patients the disease is caused by, or associated with, other conditions including diabetes, hypertension, cardiovascular disease, malnutrition, and anemia. Early intervention and management is important to stabilize or at least slow down progressive kidney damage, which worsens the prognosis of patients with CKD.

The prevalence of CKD in the Veteran population is estimated to be a third higher than in the general population, due to demographic factors and the higher rates of comorbidities associated with CKD, such as diabetes mellitus and hypertension. [4] The Veterans Health Administration (VHA) currently cares for over 200,000 Veterans with moderate to severe kidney disease in their 153 medical treatment facilities or 800 community-based outreach clinics (CBOCs) across the US. [4] In 2002, the National Kidney Foundation published treatment guidelines that identified five stages of CKD based on declining eGFR measurements. [5] Subsequently, the International Society of Nephrology released guidelines in 2013 which further classified stage 3 CKD patients. [6] The stages of CKD are described in Table 1 below. For a given stage of CKD, the categories A1-A3 will increase the risk of CKD progression.

Table 1. Stages of CKD [3,5,6]

Stage		
Stages	eGFR (mL/min/1.73 m^2)	Description
G1	Greater than or equal to 90	Kidney damage with normal or increased GFR
G2	60-89	Kidney damage with mildly decreased GFR
G3a	45-59	Mildly to moderately decreased GFR
G3b	30-44	Moderately to severely decreased GFR
G4	15-29	Severely decreased GFR
G5	Less than 15 or dialysis	Kidney failure
Albuminuria		
Category	Range (mg albumin/g creatinine)	Description
A1	<30 mg/g	Normal to mildly increased
A2	30-300 mg/g	Moderately increased
A3	>300 mg/g	Severely increased

About this Clinical Practice Guideline

This guideline represents a significant step toward improving the treatment and management of patients with CKD in the VA and DoD populations. As with other CPGs, however, challenges remain, including the need to develop effective strategies for guideline implementation and to evaluate the effect of guideline adherence on clinical outcomes. This guideline is directed for VA and DoD primary care physicians involved in the care of Service Members or Veterans who are at risk for or have known CKD. The purpose of this guideline is:

- To enhance clinician awareness of risk factors for CKD;
- To highlight evidence-based approaches that prevent acute kidney injury, which is a contributor to the development of CKD; and
- To identify pharmacologic and treatment strategies that have been shown to delay the progression of CKD to end-stage renal disease.

This CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advances and patterns evolve. This CPG is based on information available at the date of publication, and is intended to provide a general guide to best practices. The guideline can assist care providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment, for the care of an individual patient.

Methods

The methodology used in developing the 2014 CPG follows the *Guideline for Guidelines*, [7] an internal document of the VA and DoD Evidence-Based Practice Working Group (EBPWG). The current document is an update to the 2008 VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the development and submission of an updated CKD CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and writing and publishing a guideline document to be used by primary care providers within the VA/DoD health care system. Specifically, the Champions for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management of patients with CKD. In addition, the Champions assisted in:

1. Providing direction on inclusion and exclusion criteria for the evidence review
2. Assessing the level and quality of the evidence
3. Identifying appropriate disciplines of individuals to be included as part of the Work Group
4. Directing and coordinating the Work Group
5. Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence Based Practice, US Army Medical Command, the proponent for CPGs for the DoD, identified three clinical leaders, Drs.

Susan Crowley and Suzanne Watnick from VA and Dr. Eric Barnes from DoD, as Champions for the 2014 CPG.

The Lewin Team (Team), including DutyFirst Consulting, ECRI Institute and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and conduct the evidence review. The team held the first conference call in August 2013, with participation from the contracting officer's representatives (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence Based Practice, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the management of CKD. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of CKD, from which Work Group members were recruited. The specialties and clinical areas of interest included: Clinical Dietetics, Geriatrics, Family Medicine, Internal Medicine, Nephrology, Nursing (including advance practice nursing), Pharmacy and Social Work.

The guideline development process for the 2014 CPG update consisted of the following steps:

1. Formulating evidence questions (Key Questions)
2. Conducting the systematic review
3. Convening a face-to-face meeting with the CPG Champions and Work Group members
4. Drafting and submitting a final CPG about the management of CKD to the VA/DoD EBPWG

Appendix A provides a detailed description of each of these tasks.

Conflict of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest in the past two years, including verbal affirmations of no conflict of interest at regular meetings. The project team was also subject to random web-based surveillance (e.g., ProPublica). If there was a positive (yes) conflict of interest response (actual or potential), then action was taken by the co-chairs and evidence-based practice program office, based on the level and extent of involvement to mitigate the conflict of interest. Actions ranged from restricting participation and/or voting on sections related to a conflict, to removal from the Work Group. Recusal was determined by the individual, co-chairs, and evidence-based practice office. No member of the final project team had any conflict of interest

Reconciling 2008 CPG Recommendations

Evidence-based CPGs should be current, which typically requires revisions based on new evidence or as scheduled subject to time-based expirations. For example, the US Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services. [8] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed or revised with the past five years.

The CKD Guideline Work Group focused largely on developing new and updated recommendations

based on the evidence review conducted for the priority areas addressed by the Key Questions. In addition to those new and updated recommendations, the Guideline Work Group considered the current applicability of other recommendations that were included in the previous 2008 CKD CPG, subject to evolving practice in today's environment. Subject to Guideline Work Group consensus, recommendations that were no longer relevant to the current practice environment, or were otherwise out of scope for this CPG, were not carried forward to this CPG. Recommendations that were considered to be relevant to the current practice environment and still in scope for this CPG, and that required no substantive (i.e., entailing clinically meaningful) rewording, were carried forward in this CPG. The wording was, however, modified slightly to be best utilized in today's clinical environment and to uphold the GRADE recommendation format. For these modified recommendations, the Guideline Work Group referred to the available evidence as summarized in the body of the 2008 CKD CPG and did not assess the evidence review that was conducted for the 2008 CKD CPG. These "modified carryover" recommendations are noted in the recommendations list.

The Guideline Work Group recognized the need to accommodate the transition in evidence rating systems from the 2008 CKD CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system) the Guideline Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2008 guideline to the GRADE system. As such, the Guideline Work Group considered the strength of the evidence cited for each recommendation in the 2008 CKD CPG as well as harms and benefits, values and preferences, and other implications, where possible. In some instances, peer-reviewed literature published since the 2008 CKD CPG was considered along with the evidence base used for that CPG. Where such newer literature was considered when converting the strength of the recommendation from the USPSTF to GRADE system, it is noted in the discussion that follows the corresponding recommendation.

The guideline Work Group recognizes that, while there are practical reasons for incorporating findings from a previous systematic review or previous recommendations [9] or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and, therefore, may introduce bias.

Scope of this CPG

Regardless of setting or the availability of professional expertise, any patient in the health care system should be offered the interventions that are recommended in this guideline after taking into consideration the patient's specific circumstances.

Guideline recommendations are intended to be patient-centered. Thus, treatment and care should take into account a patient's needs and preferences. Good communication between health care professionals and the patient is essential and should be supported by evidence-based information tailored to the patient's needs. The information that patients are given about treatment and care should be culturally appropriate and also available to people with limited literacy skills. It should also be

accessible to people with additional needs such as physical, sensory or learning disabilities.

This CPG is designed to assist primary care providers in managing or co-managing patients with CKD Stages 1-4. Moreover, the patient population of interest for this CPG is adults (men and women), that are eligible for care in the VHA and DoD health care delivery system. It includes deployed and non-deployed Veterans as well as active duty Service Members. This CPG does not provide recommendations for the management of CKD in children or adolescents.

Highlighted Features of this CPG

The VA/DoD Guideline for the Management of CKD in Primary Care, first published in 2001, was the first such guideline in the US.

The 2014 edition is the third update to the original CPG, specifically targets primary care clinicians, and provides best practice recommendations for the care of populations with CKD stages 1 through 4. A particular strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from the broad spectrum of clinicians engaged in an ideal patient-aligned care team.

The literature review of interventional studies encompassed a seven year period between 2007 and 2013, and targeted 12 key questions focusing on the means by which the delivery of health care by the primary care clinician could be optimized for patients with CKD. Emphasizing prevention and promotion of wellness, the list of recommendations is tightly mapped to the key questions. Importantly, this list is also closely harmonized with those of complementary VA/DoD guidelines for the management of comorbid conditions known to precede or develop from CKD. Furthermore, in recognition of the need for cautious generalization from select randomized controlled trial (RCT) populations to the aging Veteran with competing comorbidities, the framework for recommendations used in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of treatment, equity of resource availability, and the potential for variation in patient values. A straightforward algorithm accompanies the guideline to facilitate its translation into effective primary care practice.

Implementation

This CPG and algorithm are designed to be adapted by individual health care providers with consideration of local needs and resources. The algorithm serves as a guide that providers can use to determine the best interventions and timing of care for their patients in order to optimize quality and improved clinical outcomes.

Although this CPG represents the practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of CPGs may lead to the development of new practice-based evidence.

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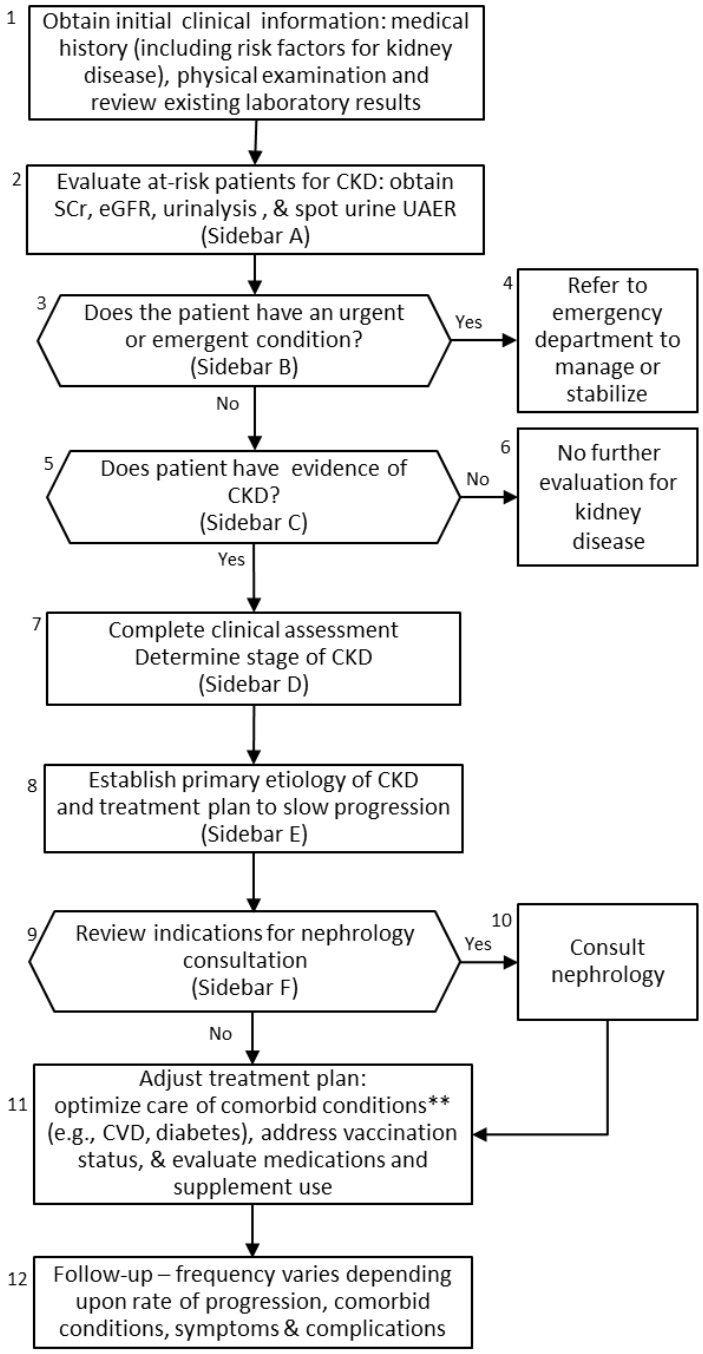
Algorithm

This CPG includes an algorithm which is designed to maximally facilitate clinical decision making for the management of CKD. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format can allow for efficient diagnostic and therapeutic decision making, and has the potential to change patterns of resource use. The algorithm format allows the provider to follow a linear approach in assessing the critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations and examinations
- 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, and arrows connect the numbered boxes indicating the order in which the steps should be followed. [10]

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.



ACEI – angiotensin-converting enzyme inhibitor
ARB – angiotensin II receptor blockers
CHF – chronic heart failure
CVD – cardiovascular disease
DM – diabetes mellitus
eGFR – estimated glomerular filtration rate
RRT – renal replacement therapy
SCr – serum creatinine
UAER – urinary albumin excretion rate

*NB: Referral should be made following shared decision making with patient that ensures the referral focus is consistent with the patient values & preferences
†This list is not exhaustive, consult the discussion of Recommendation 16 for more information
**As appropriate, refer to the following VA/DoD Clinical Practice Guidelines: Chronic Heart Failure, Diabetes, Hypertension, Dyslipidemia, Obesity & Tobacco Cessation

Sidebar A: At-Risk Populations

- Diabetes, hypertension, other end organ disease (e.g., CHF), or a personal or family history of kidney disease
- Systemic illness (e.g., human immunodeficiency virus [HIV], systemic lupus erythematosus, multiple myeloma)
- History of acute kidney injury (AKI) (e.g., acute tubular necrosis, urinary tract obstruction, interstitial nephritis)
- Elderly patients
- Races and ethnicities associated with increased risk (e.g., African Americans, Hispanics, Native Americans)

Sidebar B: Urgent/Emergent Conditions

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

Sidebar C: Criteria for Confirmed CKD

CKD is defined as sustained abnormality for >3 months of

Either:

- eGFR <60 mL/min/1.73m^2

Or any of the following:

- Albuminuria
- Urine sediment abnormality
- Abnormal renal histology
- Structural renal abnormality by imaging
- History of renal transplantation

Sidebar D: Stage of CKD

Stage	eGFR (ml/min/1.73m^2)	Description
G1	≥90	Kidney damage with normal or increased GFR
G2	60-89	Kidney damage with mildly decreased GFR
G3a	45-59	Mildly to moderately decreased GFR
G3b	30-44	Moderately to severely decreased GFR
G4	15-29	Severely decreased GFR
G5	<15 or dialysis	Kidney failure

Albuminuria

Category	Range (mg albumin/ g creatinine)	Description
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased
A3	>300	Severely increased

Sidebar E: Strategies to Slow Progression

- Control of hypertension with preferential use of either an ACEI or an ARB in patients with proteinuria
- Individualized control of hyperglycemia
- Dietary protein restriction in patients with stage 3 and 4 CKD (consider consultation with nephrologist or renal dietitian)
- Correction of metabolic acidosis
- Avoid nephrotoxic agents

Sidebar F: Indications for Nephrology Consultation*†

- eGFR <30 ml/min/1.73m^2
- Rapid decline of eGFR (>5ml/min/1.73m^2 per year)
- Complications of CKD (e.g., anemia, calcium or phosphorus abnormalities)
- Nephrotic range proteinuria (>3.5 grams/24 hours)
- Underlying cause of CKD or proteinuria is unclear
- Patient's level of disease exceeds the level of comfort of the primary care provider

Recommendations

#	Recommendation	Strength
Evaluation for Chronic Kidney Disease (CKD)		
1.	While there is insufficient evidence to associate exposure to depleted uranium and solvents such as hydrocarbons with CKD, we suggest that clinicians take a detailed occupational and non-occupational history.	Weak For
2.	We suggest that periodic evaluation for CKD be considered in patients with the following: a. Diabetes, hypertension, other end organ disease (e.g., chronic heart failure [CHF]), or a personal or family history of kidney disease b. Systemic illness (e.g., human immunodeficiency virus [HIV], systemic lupus erythematosus, multiple myeloma) c. History of acute kidney injury (AKI) (e.g., acute tubular necrosis, urinary tract obstruction, interstitial nephritis) d. Elderly patients e. Races and ethnicities associated with increased risk (e.g., African Americans, Hispanics, Native Americans) *(Carryover modified from the 2008 CPG)***	Weak For
Acute Kidney Injury Avoidance		
Prevention of Contrast-induced Nephropathy (CIN) in Patients with CKD		
3.	We suggest that patients at increased risk for CIN receive volume expansion with intravenous (IV) isotonic crystalloid solutions (saline or sodium bicarbonate) prior to and following iodinated contrast administration.	Weak For
4.	We suggest offering oral hydration to patients in which IV hydration is not feasible for CIN prophylaxis.	Weak For
5.	Given inconsistent evidence, we do not recommend for or against the routine administration of N-acetylcysteine (NAC) for CIN prophylaxis.	Weak For
6.	We recommend against the use of renal replacement therapy (RRT) for CIN prophylaxis.	Strong Against
7.	We suggest not initiating statin therapy for the purpose of CIN prophylaxis in patients undergoing elective angiography.	Weak Against
8.	We suggest not offering theophylline therapy for CIN prophylaxis for patients undergoing elective coronary angiography.	Weak Against
Management of Chronic Kidney Disease		
Self-Management Strategies		
9.	We suggest the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with CKD.	Weak For
10.	In patients with stage 3 and 4 CKD, we suggest a protein diet of 0.6 to 0.8 g/kg/day as it may slow the decline in glomerular filtration rate (GFR) and progression to end-stage renal disease (ESRD). *(Carryover modified from the 2008 CPG)*	Weak For
11.	There is insufficient evidence to recommend for or against weight loss in obese patients as an intervention to reduce proteinuria or to slow progression of CKD. However, we suggest weight loss interventions in obese patients as part of an overall health improvement strategy.	Weak For

#	Recommendation	Strength
12.	There is insufficient evidence to recommend for or against exercise with or without lifestyle intervention to reduce ESRD, mortality, change in GFR, or change in urinary protein. However, we suggest regular exercise as part of an overall health improvement strategy.	Weak For
13.	There is insufficient evidence to recommend for or against health education to reduce time to dialysis initiation or to reduce mortality. However, we suggest CKD health education because it supports the aim of maximizing patient-centered care.	Weak For
14.	There is insufficient evidence to recommend smoking cessation to halt progression of CKD, however, we suggest tobacco cessation for cardiovascular risk reduction in patients with CKD.	Weak For
Clinical Management Strategies		
15.	We suggest offering multidisciplinary care, if available, for patients with CKD to reduce non-fatal stroke, slow progression from micro- to macroalbuminuria, and reduce all-cause mortality.	Weak For
16.	Although there is insufficient evidence to recommend for or against referral to a nephrology specialist for patients with stage 3 CKD for slowing CKD progression, we suggest consultation with a nephrologist to assist in the diagnosis and treatment of patients with any of the following conditions: a. eGFR <30 mL/min/1.73 m^2 to facilitate education and planning for renal replacement therapy (dialysis or kidney transplant) b. Kidney function that is rapidly worsening without obvious cause c. Metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism) d. CKD of unclear etiology after initial work-up, or has a known or suspected kidney condition requiring specialized care e. Nephrotic range proteinuria f. Nephrolithiasis	Weak For
17.	We recommend that treatment with the following vaccinations be considered for patients with CKD as a measure to prevent infections: a. Influenza vaccine* b. Tdap vaccine c. Pneumococcal polysaccharide vaccine (i.e., PCV 13 and PPSV23) d. Hepatitis B vaccine e. Zoster /shingles vaccine* f. Varicella vaccine* g. MMR vaccine* (*Note: Live vaccines, including nasal influenza (LAIV), may be contraindicated in patients with CKD and severe immunodeficiency including treatment with immunosuppressive agents) *(Carryover modified from the 2008 CPG)*	Strong For
18.	We recommend that clinicians avoid or limit the use of nephrotoxic medications for patients with CKD. *(Carryover modified from the 2008 CPG)*	Strong For
19.	In patients with CKD, we suggest that medications should be reviewed and their dosing modified, where appropriate, according to the level of the patient's kidney function. *(Carryover modified from the 2008 CPG)*	Weak For

#	Recommendation	Strength
20.	We suggest the use of bicarbonate supplementation in CKD patients with metabolic acidosis to slow the progression of CKD.	Weak For
21.	In adult patients with stages 1-4 CKD, we recommend that blood pressure targets should be less than 140/90 mmHg. *(Carryover modified from the 2008 CPG)*	Strong For
22.	In patients with non-diabetic CKD, hypertension, and albuminuria, we recommend the use of an angiotensin-converting-enzyme inhibitor (ACEI) to prevent progression of CKD. Angiotensin II receptor blockers (ARBs) may be substituted for patients with an ACEI-induced cough. *(Carryover modified from the 2008 CPG)*	Strong For
23.	In patients with diabetes, hypertension, and albuminuria, we recommend the use of an ACEI or ARB to slow the progression of CKD, unless there is documentation of intolerance. *(Carryover modified from the 2008 CPG)*	Strong For
24.	We recommend against the use of combination renin-angiotensin-aldosterone system (RAAS) blockade (ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor) in patients with CKD.	Strong Against
25.	We recommend that all patients with CKD who are not on dialysis and have no known history of coronary artery disease be assessed for 10-year CVD risk using a validated risk calculator for primary prevention. If at risk (as defined in the VA/DoD Management of Dyslipidemia guideline), we recommend use of at least a low dose statin.	Strong For
26.	We suggest against the use of statins prescribed with the intent of slowing eGFR decline or preserving kidney function.	Weak Against
27.	We recommend against intensive glycemic control to patients with stage 3 or worse CKD due to the lack of benefit on renal or cardiovascular outcomes and potential for significant harm. *(Carryover modified from the 2008 CPG)*	Strong Against
28.	We suggest initiation of oral iron therapy (in preference to parenteral) to support iron requirements in patients with CKD stages 3 and 4.	Weak For
29.	We recommend against offering erythropoiesis-stimulating agents (ESAs) to patients with CKD for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension.	Strong Against
30.	We recommend against initiating ESAs at a hemoglobin level greater than 10 g/dL.	Strong Against
31.	We suggest offering supplemental vitamin D to correct vitamin D deficiency in patients with CKD stages 3 or 4.	Weak For
32.	We suggest not offering active vitamin D analogs or calcitriol to patients with stage 3 and 4 CKD with elevated parathyroid hormone (PTH) levels due to lack of evidence for kidney, bone, or cardiovascular benefit and increased potential of harm from hypercalcemia. (Any use of active vitamin D analogs should be managed by a nephrologist.)	Weak Against
33.	We suggest not offering phosphate binders to patients with stage 3 and 4 CKD with normal serum phosphorous. *(Carryover modified from the 2008 CPG)*	Weak Against
34.	We suggest not offering calcimimetics to patients with stage 3 and 4 CKD due to lack of evidence for kidney or cardiovascular benefit and increased risk of harm from hypocalcemia.	Weak Against

**For additional information, please refer to Reconciling 2008 CPG Recommendations

Evaluation for Chronic Kidney Disease

Background

Chronic kidney disease is common in the US, particularly among high risk groups. Factors that need to be considered prior to screening for an asymptomatic disease include if, a) a simple accurate test is available and b) there are treatments that improve patient outcomes. For CKD, there are currently no randomized controlled trials that demonstrate an improvement in patient outcomes associated with CKD screening. Given the lack of evidence for CKD screening, the Work Group does not encourage screening asymptomatic individuals for the presence of kidney disease. The Work Group recommends periodic evaluation of CKD in patients at high risk for CKD and further evaluation of CKD in those with elements of abnormal kidney tests such as those with albuminuria or abnormal imaging tests.

Military Occupational Risk of CKD

Military personnel have unique environmental and occupational exposures, some of which have been thought to increase the risk for kidney disease. If confirmed, a change in CKD screening practices for the military/Veteran populations would be in order. We therefore undertook a review of the literature to summarize the evidence for increased risk of CKD following selected exposures.

Recommendation

1. While there is insufficient evidence to associate exposure to depleted uranium and solvents such as hydrocarbons with CKD, we suggest that clinicians take a detailed occupational and non-occupational history. (Weak For)

Discussion

Two potentially nephrotoxic occupational or environmental exposures were considered in the evidence synthesis—depleted uranium and solvents, specifically hydrocarbons. The literature from 2007 forward did not provide sufficient evidence to associate hydrocarbon exposure with CKD. Therefore, patients exposed to these agents do not currently require routine screening for CKD. However, as the evidence base for hydrocarbon exposures may grow in the future, we suggest that providers screen patients newly diagnosed with CKD for hydrocarbon exposure and document its presence or absence. [11] The clinician should take a detailed occupational and non-occupation patient history, which includes but is not limited to: history of diabetes, hypertension, cardiovascular disease, lower urinary tract symptoms suggestive of urinary obstruction, hepatitis B or C, human immunodeficiency virus, 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), genitourinary malignancy, history of abdominal/pelvic surgery or radiation, occupational and other exposure to environmental toxins (including uranium, solvents and hydrocarbons).

Periodic Evaluation

Recommendation

2. We suggest that periodic evaluation for CKD be considered in patients with the following:
    a. Diabetes, hypertension, other end organ disease (e.g., chronic heart failure [CHF]), or a personal or family history of kidney disease
    b. Systemic illness (e.g., human immunodeficiency virus [HIV], systemic lupus erythematosus, multiple myeloma)
    c. History of acute kidney injury (AKI) (e.g., acute tubular necrosis, urinary tract obstruction, interstitial nephritis)
    d. Elderly patients
    e. Races and ethnicities associated with increased risk (e.g., African Americans, Hispanics, Native Americans)

    (Carryover modified from the 2008 CPG) (Weak For)

Discussion

The guideline panel recommends assessing all patients for kidney disease risk factors. In patients with identified risk factors, further evaluation is performed. The goal of identification of high risk patients with CKD is to prevent further progression of disease, evaluate and treat comorbid conditions, aid in drug dosing and prevent exposure to potentially nephrotoxic medications.

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.

A targeted history to detect the presence and possible contribution of conditions present in a patient with new or established CKD includes:

- History of diabetes or kidney disease
- Hypertension
- Cardiovascular disease
- Significant end-organ disease (liver disease)
- Lower urinary tract symptoms suggestive of urinary obstruction
- Systemic illness (e.g., hepatitis B or C, HIV)
- Symptoms suggestive of a systemic vasculitis (e.g., rash, arthritis, serositis)
- Chronic pain syndrome (raising suspicion for analgesic abuse)
- Genito-urinary malignancy
- History of abdominal/pelvic surgery or radiation
- Exposure to environmental toxins or nephrotoxins

To assist in identifying elderly patients at increased risk for CKD, O'Hare et al. presents a mortality risk stratification based on age group for varying levels of Modification of Diet in Renal Disease (MDRD)

glomerular filtration rate (GFR). [12]

In addition, medications should be reviewed to identify those that may be contributing to kidney impairment including: non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, diuretics, lithium, cyclosporine, tacrolimus, antiviral agents, chemotherapeutic agents, antibiotics, allopurinol, and dietary and herbal supplements.

The guideline panel recommends screening for CKD with a serum creatinine measurement for use in GFR estimation and analysis of a random urine sample for albuminuria. Both measurements are needed to exclude the diagnosis of CKD because both conditions can exist independently.

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.

Acute Kidney Injury Avoidance

Background

Acute kidney injury (AKI) is being increasingly recognized as a forerunner of CKD. Additionally, CKD is both a consequence of and a risk factor for AKI. Prevention of AKI may help reduce progression of CKD; thus, AKI avoidance should be a goal of care. Risk factors for AKI are increasingly described; however, the most well-described risk factor of AKI is the parenteral administration of iodinated radiocontrast agents.

Prevention of Contrast-induced Nephropathy (CIN) in Patients with CKD

AKI due to contrast-induced nephropathy (CIN) is an unfortunate complication of diagnostic and interventional procedures that require the intravenous (IV) administration of radiocontrast. There is no standard definition for CIN, however it is broadly described as acute kidney dysfunction following exposure to intravascular contrast media. [13] CIN is associated with unfavorable outcomes and prolonged hospitalizations. While numerous trials have suggested therapies that prevent the rise in creatinine associated with contrast nephropathy, no study has demonstrated an effect on patient-oriented outcomes such as prevention of acute or chronic dialysis. Trials generally look at preventing a small change in creatinine (typically 25% or 0.25 mg/dL) and no trial has ever demonstrated a reduction in hospitalization, dialysis need, or mortality related to CIN prophylaxis. [14,15] Risk factors for developing CIN include:

- Preexisting CKD; serum creatinine >1.5 mg/dL or eGFR <60 mL/min
- Diabetes mellitus
- Heart failure
- Age >75 years
- Volume of contrast >100 mL
- Use of high-osmolality contrast

Patients who are going to receive radiocontrast agents should be made aware of the potential risk for developing CIN. Low-risk patients should maintain adequate hydration orally prior to contrast administration. High-risk patients should be given the standard therapy (defined below) and possibly one or more of the CIN prophylaxis measures discussed below.

There are a variety of medications, techniques and IV fluids that have been examined for CIN prophylaxis. The current standard therapy for CIN prophylaxis is centered on:

- Obtaining a euvolemic state prior to radiocontrast administration through the use of IV and oral fluids
- Avoiding or minimizing the amount of radiocontrast administered
- Using low or iso-osmolar non-ionic radiocontrast

We review below several strategies and interventions to prevent CIN in patients determined to be at high risk of CIN with imaging procedures that require contrast.

Intravenous Isotonic Crystalloid Solutions

Recommendation

3. We suggest that patients at increased risk for CIN receive volume expansion with intravenous (IV) isotonic crystalloid solutions (saline or sodium bicarbonate) prior to and following iodinated contrast administration. (Weak For)

Discussion

A systematic review of the literature identified nine studies of low to very low quality to address the efficacy of sodium bicarbonate volume administration for the prevention of CIN. Two studies evaluated sodium bicarbonate versus sodium chloride infusions in patients with moderate to severe CKD undergoing coronary angiography. There was no significant difference between groups regarding incidence of CIN (4.2% versus 2.7%, p=0.61, [N=145]; [16] and 13.4% versus 14.6%, p=0.82, [N=353]; [17]). One study infused fluids two hours before, during, and after contrast administration, with assessment of outcome via serum creatinine (SCr) at day one or two post-contrast. [16] In the other trial, sodium bicarbonate was administered peri- and post-procedural, while measuring outcomes via eGFR at day one through day four post contrast medium.

Two RCTs evaluated sodium bicarbonate and N-acetylcysteine (NAC) versus sodium chloride and NAC. These trials (n=454) found no significant differences between groups in incidence of CIN (4.5% versus 5.4%, p=.54). In one study by Lee et al. diabetic patients underwent coronary or endovascular intervention or angiography. [18] The other trial by Maoli et al. studied patients with CKD and creatinine clearance (CrCL) below 60 mL/min/1.73m^2 in those undergoing planned angiography or intervention. [19] Another trial by Briguori et al. looked at a similar intervention, and had a third arm with saline plus ascorbic acid and oral NAC. [20] Here, incidence of CIN was significantly lower than the saline group (p=0.019).

Four additional RCTs looked at sodium bicarbonate bolus versus saline. Two of these studies found no significant differences between groups. [21,22] A study by Vasheghani-Farahani et al. found a significant difference between the single-bolus sodium bicarbonate plus saline versus saline solution (1.4% sodium bicarbonate, 12.5% saline, p=0.017) while another study found a significantly lower incidence of CIN in the sodium bicarbonate bolus group (3.3% sodium bicarbonate bolus, 27.5% sodium chloride bolus, risk ratio 0.12, 95% CI 0.016 to 0.91, p=0.01). [23,24]

Due to different results from multiple trials, several meta-analyses and systematic reviews were performed. The results from the meta-analyses showed benefit, but heterogeneity and publication bias makes it difficult to make clear recommendations regarding the utility of sodium bicarbonate over the use of saline infusion. The 2008 CKD CPG commented that providing IV infusions of normal saline or sodium bicarbonate solutions during the peri-procedural period of contrast administration may reduce the incidence of contrast induced nephropathy. [25] Given the heterogeneity of the literature and evidence from our previous guideline, we suggest offering infusion of isotonic or sodium bicarbonate as standard therapy for CIN prophylaxis in patients at appropriate levels of high risk.

Oral versus IV Volume Expansion

Recommendation

4. We suggest offering oral hydration to patients in which IV hydration is not feasible for CIN prophylaxis. (Weak For)

Discussion

Review of the literature for this update identified a single meta-analysis that included 513 patients within six trials who underwent percutaneous coronary intervention. [26] All but one of the trials used normal saline in the IV fluid arm (one used 0.45% saline). The oral fluid arm regimen varied markedly from trial to trial and included mineral water, oral sodium chloride with unrestricted fluid intake, unrestricted fluid intake alone and, finally, 1000 mL of fluid over 10 to 12 hours prior to contrast administration. The radiocontrast administered was predominately low-osmolality non-ionic and the average volume given was 101 mL to 201 mL. After 48-72 hour follow-up, there was no statistically significant difference in the incidence of CIN between the oral and IV groups.

Given the larger body of evidence demonstrating benefit of IV hydration, we suggest offering oral hydration to patients in which IV hydration is not feasible for CIN prophylaxis. While there is no universally accepted oral fluid regimen, patients should be counseled to consume at least 1000 mL of fluid over the 12 hours prior to contrast administration.

Emerging and Alternative Interventions

Automated Induced Diuresis with Matched Hydration

A systematic review of the literature conducted for the update of this guideline identified a single randomized controlled trial that included 170 patients undergoing coronary procedures. [27] One of two groups consisted of 87 patients who underwent furosemide-induced diuresis followed by matched hydration (FMH) prior to undergoing coronary procedures. Matched hydration was achieved using a device which delivers replacement fluid to a patient in an equal amount to the volume of urine the patient makes. The FMH received an initial 250 mL bolus of normal saline delivered over 30 minutes followed by an IV bolus of 0.5 mg/kg furosemide. Further IV hydration was automatically adjusted to precisely replace the patient's urine output. When a urine output rate more than 300 mL/hour was obtained, patients underwent coronary procedures. Matched fluid replacement was maintained during the procedure and for four hours post procedure. A second (control) group of 83 patients received IV hydration with normal saline (1 mL/kg/hour) for at least 12 hours prior to and 12 hours after undergoing coronary procedures. All patients received non-ionic, low-osmolality radiocontrast. After a 72-hour follow-up, there was a statistically significant lower incidence of CIN in the FMH group (4.6% FMH, 18% saline; p=0.005. [27] This and other emerging evidence may lead to a suggestion for furosemide with matched hydration in patients with stage 3 or 4 CKD.

Remote Ischemic Pre-conditioning (RIPC)

Review of the literature for this update identified two randomized controlled trials by Igarashi et al. and Er et al. [28,29] The trials included a total of 160 patients that received standard therapy with normal

saline and RIPC within two hours of undergoing elective angiography. The radiocontrast administered was low-osmolality and non-ionic. The RIPC regimen consisted of five minute inflation of a standard upper-arm blood pressure cuff to 200 mmHg or 50 mmHg above the patient's systolic blood pressure. This was then followed by five minutes of deflation. The inflation and deflation cycle was repeated four times within two hours of the patient undergoing elective angiography. In one of the studies a third arm of patients received standard therapy with normal saline and sham RIPC which consisted of inflation of a standard upper-arm blood pressure cuff to the patient's diastolic blood pressure minus 10 mmHg. After a 24-48 hour follow-up, there was a statistically significant lower incidence of CIN in the RIPC group (eight patients in the control group (26.9%) versus two patients in the RIPC group (7.7%), which could be clinically meaningful. Pending a stronger supporting evidence base, RIPC may be combined with standard therapy in the future for CIN prophylaxis in patients undergoing elective coronary angiography.

Vitamin E

Vitamin E is a fat-soluble antioxidant vitamin available over the counter. The recommended daily allowance of vitamin E as alpha tocopherol is 15 mg. Review of the literature for this update identified two randomized controlled trials that included a total of 325 patients. The larger RCT by Tasanarong et al. studied 305 patients with mild to moderate CKD, comparing α-tocopherol 350 mg/day, γ-tocopherol 300 mg/day, and placebo. [14] All patients received standard therapy, which consisted of 0.9% saline infusion at a rate of 1 mL/kg/hr for 12 hours before and 12 hours after elective coronary procedures, and volume administered 1353 ±320 mL α-tocopherol, 1498 ±300 mL γ-tocopherol, 1520 ±370 mL placebo, depending on the group. Study participants were given their vitamin E or placebo daily for five days pre-procedure and two days post-procedure. The radiocontrast administered was low-osmolality and non-ionic. After 48 hours, there was a statistically significant lower incidence of CIN in the α-tocopherol and γ-tocopherol groups versus placebo treated control group (4.9% and 5.9% versus 14.9%, respectively).

The second RCT by Kitzler et al. [30] had three arms that included vitamin E plus 0.45% saline versus N-acetylcysteine plus 0.45% saline versus 0.45% saline alone. This RCT included only 30 patients, none of which developed CIN. The results indicate that neither vitamin E nor NAC in addition to saline provided additional benefit versus saline alone.

The evidence suggests that there are some benefits to be gained from use of tocopheral. Oral vitamin E could be utilized as an adjunct to standard CIN prophylaxis therapy.

N-acetylcysteine (NAC)

Recommendation

5. Given inconsistent evidence, we do not recommend for or against the routine administration of N-acetylcysteine (NAC) for CIN prophylaxis. (Weak For)

Discussion

Over the past years, NAC has received substantial attention as an intervention to prevent contrast-induced AKI during various types of iodinated contrast administration. Multiple RCTs have shown

conflicting results as to the efficacy of NAC. Meta-analyses have been performed to address this topic but have been inconclusive.

A review of the literature for this update identified one RCT that enrolled cardiac surgery patients receiving IV NAC versus placebo. There was no significant difference between the incidences of AKI in both groups (28% NAC versus 31% placebo). [31]

The 2008 CKD CPG commented that the use of NAC may be effective in reducing the incidence of contrast nephropathy; however, the results were inconsistent. [32-47] Additionally, factors such as cost, history of drug shortages, and patient inconvenience should also be taken into consideration of NAC. At this time there is insufficient evidence to suggest for or against the routine administration of NAC for CIN prophylaxis. However, there is a large ongoing trial sponsored by the Department of Veterans Affairs that compares the effectiveness of IV isotonic sodium bicarbonate with IV isotonic sodium chloride and oral NAC with placebo for the prevention of serious adverse outcomes. This trial is slated to conclude in March 2016. [48]

Renal Replacement Therapy

Recommendation

6. We recommend against the use of renal replacement therapy (RRT) for CIN prophylaxis. (Strong Against)

Discussion

Review of the literature for this update identified a single meta-analysis that included 751 patients within six studies who received radiocontrast. Different types of radiocontrast were used, most of which were low-osmolality. RRT utilized included conventional hemodialysis and continuous renal replacement therapy (CRRT) initiated both before and after contrast administration. All patients appear to have received standard therapy to avoid CIN. After 48-72 hour follow-up, RRT did not significantly reduce the incidence of CIN. [49] RRT is not innocuous as it requires the placement of a large central venous catheter. Furthermore, while the therapy is generally safe, it can cause hemodynamic instability and cardiac arrhythmia. Thus, in the absence of demonstrable benefit, the risks of RRT prohibit its use as a rational strategy for CIN prophylaxis.

Short-Term Statin Therapy

Recommendation

7. We suggest not initiating statin therapy for the purpose of CIN prophylaxis in patients undergoing elective angiography. (Weak Against)

Discussion

Review of the literature since publication of the previous version of the VA/DoD CKD guideline identified three RCTs involving statin therapy for CIN prophylaxis that included a total of 3,458 patients undergoing coronary angiography. Patients were randomized to receive rosuvastatin 10 mg/day for two days before and three days after procedure, or standard hydration therapy, which was administered at the

physician's discretion and included isotonic saline (0.9% sodium chloride, 1 ml/kg/hr) started 12 hours before and continued for 24 hours after contrast medium administration. The radiocontrast administered was low-osmolality and non-ionic. After a 72-hour follow-up, there was a statistically significant lower incidence of CIN in the rosuvastatin group. The interpretation of this study is confounded because the rosuvastatin group did not receive standard hydration therapy. [15]

Toso et al. [50] randomized 304 patients to receive high-dose atorvastatin (80 mg/day) in combination with standard hydration therapy or standard hydration therapy alone. The radiocontrast administered was low-osmolality and non-ionic; all patients were given NAC. There was no statistically significant difference in the incidence of CIN among the groups. [50]

Liu et al. [51] randomized 156 patients to receive atorvastatin (40 mg/day) therapy alone, or atorvastatin (40 mg/day) therapy in combination with alprostadil (20 mcg/day) IV, for seven days starting at one day prior to coronary angiography. All patients received standard therapy. Some patients experienced hypotension and dizziness with alprostadil infusion. There was no statistically significant difference in the incidence of CIN among the groups. [51]

Considered together, the aforementioned studies do not convincingly support the use of statins for the purpose of CIN prevention.

Theophylline Therapy

Recommendation

8. We suggest not offering theophylline therapy for CIN prophylaxis for patients undergoing elective coronary angiography. (Weak Against)

Discussion

Review of the literature during the relevant time period for this update identified a single RCT that included a total of 217 patients. The authors compared the combination of NAC 600 mg twice daily plus theophylline 200 mg twice daily both given the day preceding and the day of elective coronary angiography plus standard therapy versus NAC plus standard therapy versus standard therapy only. The radiocontrast administered was low-osmolality and non-ionic. After 48 hour follow-up, there was a statistically significant lower incidence of CIN in the NAC plus theophylline plus standard therapy group. The authors stated that no arrhythmias were seen with theophylline administration during the study. [52] However, the significant adverse effect profile of theophylline including central nervous system excitement, headache, insomnia, irritability, restlessness, seizures, tachycardia and diarrhea, preclude support for its routine use as a CIN prophylactic measure.

In addition to the literature found and assessed during the 2013 evidence review, the guideline panel recognized that there exists some newer literature to further support the weak recommendation against theophylline therapy. A recently published systematic review found that there is inconsistent evidence of efficacy for theophylline across eight clinical trials for contrast-induced AKI prevention. [53]

Summary

In summary, AKI is a forerunner to CKD and may contribute to CKD progression. CIN is a potentially preventable form of AKI. Beyond standard therapy, additional emerging therapies to prevent CIN in patients at high risk could include vitamin E, RIPC, and automated diuresis.

Self-Management Strategies

Background

The role of the patient in management of CKD is being increasingly emphasized. We reviewed the literature for evidence of self-management strategies that might reduce CKD progression. Strategies identified include participation in multidisciplinary models of hypertension management, dietary sodium intake modification, dietary protein limitation, routine nutritional vitamin D supplementation, weight loss, exercise, health education, over-the-counter medication use, and smoking cessation. More broadly, evidence suggests that patient self-management plays an essential role in the management of any chronic disease. According to the Wagner model of chronic disease management, which has been adopted by many chronic care providers, patient self-management is a critical element. [54]

Dietary Sodium Restriction

Recommendation

9. We suggest the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with CKD. (Weak For)

Discussion

The three RCTs that compared dietary sodium restriction to other interventions (diet or medication) were rated as fair quality for various reasons ranging from baseline imbalances in important patient characteristics to lack of an appropriate control group. [55-57] Blinding of dietary interventions was not feasible.

De Brito-Ashurst et al. [55] compared blood pressure at a six-month follow-up for hypertensive patients with CKD receiving a tailored low-salt diet to a control group receiving only advice on achieving a low-salt diet. This study included 56 patients and reported that changes in eGFR from baseline to follow-up were similar for patients treated with low-salt dietary intervention and those given low-salt dietary advice (decrease of 3.0 ml/min/1.73m^2 [95% CI 0.1 to 6.0] and 3.4 ml/min/1.73m^2, 95% CI 1.0 to 5.7 for intervention and control groups, respectively). The reduction in systolic blood pressure (primary endpoint) was significantly greater (by 8 mm Hg, p=0.0003) in those who received tailored low-salt dietary intervention compared to control group care. [55]

McMahon et al. [56] evaluated the effects of sodium intake on blood pressure, proteinuria, and markers of cardiovascular and kidney disease progression in 25 patients with stage 3 or 4 CKD and hypertension. The study compared change in proteinuria levels between patients following a low-salt diet as compared to those following a high-sodium diet. Significantly lower proteinuria levels were observed for patients on a low-salt diet relative to high-salt diet (835 mg/24hr [95%CI, 185 to 1600] versus 493 mg/24hr [95%CI, 123 to 1300]—a difference of 342 mg/24hr [95%CI, 62 to 300], p<0.01). [56]

Slagman et al. [57] examined the effects of dietary sodium restriction with mono or dual renin-angiotensin aldosterone system (RAAS) inhibition in 52 non-diabetic CKD patients. All patients received a background treatment with ACEIs. The study examined proteinuria reduction with the use of either an

ARB with a regular-sodium diet (target 200 mmol Na^+/day), a low-sodium diet (target 50 mmol Na^+/day), or the combination of a low-sodium diet with an ARB.

The addition of an ARB only (ARB/ACEI and a regular-sodium diet) did not significantly change creatinine clearance, but reduced proteinuria from 1.68 (95% CI, 1.31 to 2.14) g/day to 1.44 (95% CI, 1.07 to 1.93) g/day (p=0.003). A significantly larger (p<0.001) proteinuria reduction was seen with a low-sodium diet/ACEI therapy (-51%, 95% CI, -43% to -58%) than with the ARB/ACEI therapy (-21%, 95% CI, -8% to -32%). Addition of a low-sodium diet only (low-sodium diet/ACEI) reduced proteinuria levels to 0.85 (95% CI 0.66 to 1.10) g/day. Additionally, utilizing the low-sodium diet/ACEI therapy decreased creatinine clearance (from 72 ml/min [62 to 84] to 66 ml/min [57 to 76], p=0.002). Finally, the combined therapy (low-sodium diet + ARB/ACEI) decreased creatinine clearance (from 72 ml/min [62 to 84] to 61 mL/min [53 to 70], p<0.001) and produced the lowest level of proteinuria (0.61, 95% CI, 0.53 to 0.91) g/day, p<0.001). However, reduction of proteinuria by the combined therapy was not significantly larger than the reduction achieved with the low-sodium diet/ACEI therapy alone (-62%, 95% CI, -53% to -70%). [57]

Dietary Protein Restriction

Recommendations

10. In patients with stage 3 and 4 CKD, we suggest a protein diet of 0.6 to 0.8 g/kg/day as it may slow the decline in glomerular filtration rate (GFR) and progression to end-stage renal disease (ESRD). *(Carryover modified from the 2008 CPG)* (Weak For)

Discussion

Several studies over the past 50 years have examined role of dietary protein restriction in reducing CKD progression. Most of these studies have compared low protein diets (LPD) with regular, standard or usual protein diets (RPD) in stages 3 and 4 CKD. Two meta-analyses and one systemic review have been published since 2008. Two reports examined patients with diabetic nephropathy, [58,59] and one report evaluated studies in non-diabetic kidney disease. [60] Most studies in the review by Robertson et al. were included in the recent meta-analysis by Nezu, et al. [58,59]

Nezu, et al. examined 13 randomized controlled trials that included 209 type 1 and 555 type 2 CKD patients with diabetic nephropathy. [58] The LPD group (n=385) was prescribed 0.6-0.8 g/kg/day protein intake, while the RPD group (n=394) was instructed to ingest 1.0-1.6 g/kg protein daily. The study duration was from 4 to 60 months, while the individual studies contained 15 to 112 subjects. Importantly, the authors assessed the dietary compliance by estimating the protein intake in 10 studies using the Maroni's formula [61,62] that uses 24 hour urinary urea nitrogen excretion. The compliance was calculated as actual protein intake ratio (APIR) using fraction of the estimated protein intake of the LPD to the RPD groups. The authors set a cutoff value of 0.9 APIR as optimal indicator of dietary compliance. The review found that the APIR ranged from 0.44 to 1.07, with nine studies showing values less than 0.9. [58]

The primary outcome of the Nezu study was a change in GFR or creatinine clearance. [58] The secondary outcomes were changes in proteinuria, HbA1c and serum albumin values post-treatment. In 11 studies

of 624 patients, the authors reported that the post-treatment GFR in the LPD group was significantly greater (5.82 ml/min/1.73m^2, p <0.001) than the RPD group. In a subgroup analysis, APIR had a significant effect on GFR. Thus, APIR <0.9, indicating fair compliance had better preservation of GFR than higher APIR values (p<0.006). In twelve studies that reported data in 634 patients, no difference was found in proteinuria. HbA1c in 11 studies showed modest improvement with the LPD. Serum albumin was reported by only four studies (179 patients), which showed significant heterogeneity and asymmetry. Due to small sample size and short intervention time noted in these studies, clinical significance of absence of any significant change in serum albumin is uncertain. [58]

Robertson et al. reviewed the role of protein restriction in diabetic kidney disease. [59] Their review included nine RCTs and two before and after intervention studies. Their review showed that relative risk of ESRD or death was 0.23 (95% CI 0.07 to 0.72) in patients assigned to the LPD group. An effect of LPD on GFR was insignificant in both types 1 and 2 diabetes. However, the actual protein intake in the LPD group ranged from 0.7 to 1.0 g/kg daily, indicating potentially poor adherence to the prescribed diet. [59]

Fouque and Laville conducted a systemic review of the LPD in non-diabetic CKD stages 3 to 5 not receiving dialysis therapy. [60] The RDP group was prescribed 0.8 g/kg/day or greater protein intake. The LPD group was assigned 0.6 g/kg/day or a very low protein diet (0.3 g/kg/day) with essential amino acids or ketoacid supplements. They identified 10 RCT that included 1002 patients in the LPD group and 998 in the RPD group. The primary outcome was all-cause mortality or initiation of dialysis therapy. One hundred and thirteen primary outcome events were noted in the restricted protein group compared to 168 in the RPD group (RR 0.68, 95% CI 0.55 to 0.84). The restricted protein diet resulted in a highly significant reduction in relative risk of the primary outcome (32%, p <0.002). The benefit of LPD was seen across the spectrum of causes of kidney disease. The difference in actual protein intake between the two groups was 0.2 to 0.35 g/kg/day. [60]

In conclusion, the data shows that low protein diets, in the range of 0.6 to 0.8 g/kg/day exert a salutary effect in both diabetic and non-diabetic kidney diseases. The benefit was noted both in prevention of kidney failure and preservation of GFR. Two important caveats should be emphasized. First, low protein diets should be prescribed with optimal caloric intake to prevent muscle wasting and malnutrition. Second, careful monitoring of actual protein intake by 24 hour urinary urea nitrogen excretion should be carried out. Nutritional intervention should be a team approach that includes the primary care clinician, dietitian, patient and family members.

Weight Loss

Recommendation

11. There is insufficient evidence to recommend for or against weight loss in obese patients as an intervention to reduce proteinuria or to slow progression of CKD. However, we suggest weight loss interventions in obese patients as part of an overall health improvement strategy. (Weak For)

Discussion

The single relevant systematic review was rated as poor quality because the authors performed a meta-analysis of data to compare pre- and post-diet renal outcomes. [63] The lack of a concurrent control group creates a high potential for bias from confounding factors. The investigators analyzed five studies (two RCTs, three observational) that evaluated the potential benefits of weight loss due to hypocaloric diets in obese patients with non-dialysis dependent CKD. [63] Because the authors only analyzed the pre-post findings in the groups that received the diet, they essentially did an analysis of case series rather than studies with parallel control groups. The systematic review found no significant difference in change in GFR or creatinine clearance (weighted mean difference [WMD] 4.25 ml/min [95% CI -3.30 to 11.81]); the 95% CI indicates very serious imprecision in the estimate of effect. The meta-analysis found significant difference in favoring weight loss in reduction in proteinuria (WMD -1.31 g/24h, 95% CI -2.11 to -0.51, p=0.001); however, the test for heterogeneity in effect sizes indicated serious inconsistency among the individual study results in the meta-analysis. [63]

In the opinion of the Work Group, the benefits of weight loss in obese subjects to reduce renal outcomes are uncertain. However, as overweight and obesity are associated with increased prevalence and worsening of several obesity-associated conditions, including type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome, osteoarthritis, and obstructive sleep apnea, it is recommended that the VA/DoD Clinical Practice Guideline for the Management of Obesity and Overweight (OBE)[1] be reviewed for additional information regarding overweight and obese patients.

Exercise

Recommendation

12. There is insufficient evidence to recommend for or against exercise with or without lifestyle intervention to reduce ESRD, mortality, change in GFR, or change in urinary protein. However, we suggest regular exercise as part of an overall health improvement strategy. (Weak For)

Discussion

Exercise versus no exercise

The only relevant systematic review comparing exercise to no exercise was rated as fair because the author reported that the single small RCT included therein had incomplete reporting of results. [64] This systematic review identified one RCT with 30 patients that compared the benefits of an exercise intervention to no exercise on renal endpoints in patients with CKD. The exercise intervention included at-home bicycle ergometer exercise, walking, running, and swimming, gradually increased in duration

[1] See the VA/DoD Clinical Practice Guideline for Management of Obesity and Overweight. Available at: http://www.healthquality.va.gov/guidelines/cd/obesity/index.asp

(up to 30 minutes) and intensity over time. The results showed no significant difference between groups in ESRD, all-cause mortality, or median change in GFR.

Exercise plus lifestyle intervention versus usual care

Two RCTs evaluated the combined effect on renal outcomes of a combination of exercise and lifestyle interventions in patients with CKD. [65,66] One study was primarily interested in the intervention effect on cardiovascular fitness and risk factors, but also reported on change in eGFR, serum creatinine, and albumin during the course of the study. In addition to exercise training, the patients received lifestyle guidance from a psychologist and dietitian as well as multidisciplinary care focused on cardiovascular risk management. There was no significant between-group difference in change in serum creatinine and serum albumin from baseline to 12 months follow-up. [65] Another trial investigated the combined effect of an exercise program and a nutrition program with counseling and group cooking classes compared with usual dietary counseling on cardiovascular risk factors and CKD-related outcomes (change in eGFR and urinary protein). This trial found no significant between-group difference in mean reduction in urinary protein from baseline to 12 months. Thus, neither investigator found that exercise plus lifestyle intervention significantly affected change in eGFR between treatment and control groups. [66]

Although current evidence does not support the benefits of exercise in CKD patients, physical activity has the potential to provide health benefits and should be encouraged.

Health Education

Recommendation

13. There is insufficient evidence to recommend for or against health education to reduce time to dialysis initiation or to reduce mortality. However, we suggest CKD health education because it supports the aim of maximizing patient-centered care. (Weak For)

Discussion

Education versus usual care

Two systematic reviews evaluated the impact of health education interventions versus usual care in patients with CKD. The systematic review by Clase et al. of three RCTs compared educational interventions to usual care or standard education to an enhanced education program in patients with CKD. [64] Clase et al. identified one RCT that measured the progression to ESRD and found significantly fewer patients progressed to ESRD in the education group (60%) versus the usual care group (72%, p <0.001). [64] The study reported the time to dialysis was significantly shorter in the education group (14 months) than the usual care group (17 months, p <0.001). The study reported no significant between-group difference in reducing mortality prior to dialysis (education 13% versus usual care 7%, p=0.18). Clase et al. also identified one RCT that reported on long-term survival, finding longer median survival in the education group (7.84 years) compared to the usual care group (5.07 years), although the difference was not statistically significant (p=0.053). [64] The third RCT compared enhanced versus standard education and is discussed below.

The systematic review by Li et al. identified one RCT that compared an education program with usual care in patients with diabetic kidney disease. [67] This RCT reported change in self-efficacy at the end of an education intervention (five weeks) and at last follow-up (three months) in patients with diabetes and CKD. The study found a significant between-group difference in self-efficacy favoring the education intervention at the end of treatment, but no significant between-group difference in change from baseline to last follow-up. [67]

An additional prospective controlled study by Choi and Lee [68] was identified that compared a face-to-face self-management educational program to usual care in patients with CKD. Choi and Lee [68] reported no significant between-group difference in change in eGFR from baseline to eight weeks; the effect estimate had very serious imprecision due to the lack of between-group effect size and large variance around the reported change scores. The study also found no change in SCr in either group from baseline to eight weeks follow-up; although the variance was low, the estimate had serious imprecision because it came from a single small study.

Enhanced versus Standard Education

In a systematic review, Clase et al. also identified one RCT that compared enhanced education (i.e., a 75-minute slide presentation along with booklet of presentation contents) versus standard education interventions and found that the enhanced education group had a significantly longer average time before initiating dialysis (an additional 4.6 months) than the standard education group ($p < 0.05$). [64] Although there was demonstrated benefit the effect estimate was methodologically limited. While there is insufficient evidence that renal outcomes are improved by using the self-management strategies of health education in adult CKD patients, the guideline panel emphasizes the importance of education for each patient in order to enhance patient-driven care. Additional studies of longer duration are needed to better gauge the impact of educational interventions on outcomes in patients with CKD.

Smoking Cessation

Recommendations

14. There is insufficient evidence to recommend smoking cessation to halt progression of CKD, however, we suggest tobacco cessation for cardiovascular risk reduction in patients with CKD. (Weak For)

Discussion

Smoking is highly prevalent in the general population. Numerous adverse effects of tobacco use have been described including illness and death. Tobacco use has been associated with over 435,000 deaths annually in the US. Smoking is a known cause of multiple cancers, heart disease, stroke, chronic obstructive pulmonary disease (COPD), and many other diseases (see the VA/DoD CPG for the

Management of Tobacco Use[2]). We were unable to identify any randomized controlled trials or systematic reviews of smoking and adverse renal outcomes. Numerous observational studies have suggested an increased risk of progression of kidney disease to ESRD [69,70] and cardiovascular mortality in patients with CKD. [71] While there is insufficient evidence to recommend smoking cessation for the specific improvement in kidney function, there is compelling evidence to recommend smoking cessation to improve other non-renal outcomes.

The benefits of tobacco cessation have been well documented over the last 30 years. VA/DoD Evidence-Based Clinical Practice Guidelines for Tobacco Use[2], Chronic Obstructive Pulmonary Disease[3] and Chronic Heart Failure[4] provide detailed information on these benefits in improving overall cardiovascular health.

Summary

In summary, given that patient self-management is a critical element of care for CKD, the guideline panel suggests the use of dietary sodium restriction and dietary protein restriction as these interventions may slow CKD progression. The guideline panel also encourages weight loss, exercise, health education and smoking cessation interventions for patients with CKD as these are useful strategies to improve overall patient health.

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[2] See the VA/DoD Clinical Practice Guideline on the Management of Tobacco Use. Available at: http://www.healthquality.va.gov/guidelines/cd/mtu/index.asp

[3] See the VA/DoD Clinical Practice Guideline on the Management of Chronic Obstructive Pulmonary Disease. Available at: http://www.healthquality.va.gov/guidelines/cd/copd/index.asp

[4] See the VA/DoD Clinical Practice Guideline on the Management of Chronic Heart Failure. Available at: http://www.healthquality.va.gov/guidelines/cd/chf/index.asp

Clinical Management Strategies

Background

Patients with CKD are at increased risk of progression of end-stage renal disease, AKI, and mortality due to cardiovascular disease and infection. Clinical management strategies that target these adverse outcomes are discussed below. Strategies to optimize CKD patient care include the implementation of various models of care, preventive immunizations, medication safety initiatives, proteinuria reduction, pharmacologic management initiatives, correction of acidosis, treatment of dyslipidemia, hypertension, anemia, and bone and mineral disorders associated with CKD and appropriate nephrology referral.

Model of Care

Recommendation

15. We suggest offering multidisciplinary care, if available, for patients with CKD to reduce non-fatal stroke, slow progression from micro- to macroalbuminuria, and reduce all-cause mortality. (Weak For)

Discussion

The impact of including a multidisciplinary team in the delivery of nephrology care is not well established. A four-year cohort study and three-year prospective cohort study revealed that specific groups of CKD patients may also benefit from comprehensive multidisciplinary care (MDC). [72,73] Examples of multidisciplinary teams in these two studies consisted of a nephrologist, pharmacy specialist, diabetes educator, dietitian, social worker, and nephrology nurse, or a nephrologist, nephrology nurse educator, renal dietitian, social worker, pharmacy specialist, and surgeon (for vascular access placement, catheter implantation and transplantation). [72] Specific CKD guidelines were used to standardize interventions, with additional focus on lifestyle modification. [73] Multidisciplinary care facilitated within an integrated health care system may lead to a reduction in the decline of kidney function, a postponement of dialysis, and improved health outcomes. [72,73] As compared with usual care, MDC for elderly patients with CKD in particular has been associated with improved survival. [74,75] Contemporary multidisciplinary teams may also include nurse practitioners, physician assistants, and other providers as appropriate.

Recommendation

16. Although there is insufficient evidence to recommend for or against referral to a nephrology specialist for patients with stage 3 CKD for slowing CKD progression, we suggest consultation with a nephrologist to assist in the diagnosis and treatment of patients with any of the following conditions:
    a. eGFR <30 mL/min/1.73 m^2 to facilitate education and planning for renal replacement therapy (dialysis or kidney transplantation)
    b. Kidney function that is rapidly worsening without obvious cause
    c. Metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism, hyperkalemia)

d. CKD of unclear etiology after initial work-up, or has a known or suspected kidney condition requiring specialized care
e. Nephrotic range proteinuria
f. Nephrolithiasis

(Weak For)

Discussion

There is insufficient evidence to recommend for or against routine referral to a nephrologist for stage 3 CKD, however, nephrology referral is always appropriate when the primary care provider (PCP) is not comfortable managing a patient with CKD, or if there are specific indications as listed above. No randomized clinical trials were found during review of the literature in the specified timeframe for this update on nephrology referral or consultation to slow CKD progression or prevent ESRD. Four observational studies have evaluated the impact of nephrology referral on outcomes. While this evidence is limited, the findings suggest that nephrology referral may be associated with slower progression of kidney function decline, lower dialysis-free mortality or the composite outcome of CKD progression or death. Chen et al. reported a significantly lower kidney function decline in stage 3b (-5.5 mL/min/year before versus -2.5 mL/min/year after referral, $p<0.01$), but not stage 3a (-3 mL/min/year before versus -2.3 mL/min/year after referral), one year after nephrology referral. [76] In a large study of Veterans Health Administration clinic users (n=39,031) with concomitant diabetes mellitus and stage 3-4 CKD, Tseng et al. found a lower risk of dialysis-free mortality (in patients with stage 3 or 4 CKD and not receiving dialysis) among those who had a greater number of quarterly visits with a nephrologist. [77] The risk for ESRD was higher among those with a greater number of quarterly visits.

In a study of 1,533 Veterans at the Durham Veteran Affairs Medical Center, nephrology care was shown to be associated with decreased risk of the composite endpoint of death or CKD progression. [78] Nephrology care has also been shown to be associated with improved blood pressure control; however, this study did not report the impact of blood pressure control on CKD outcomes. [79] Patients receiving nephrology care are likely different than those who did not receive nephrology care and this may not be accounted for in these observational studies. For example, nephrology referral may be reserved for those patients considered to be the best candidates for dialysis or interventions to slow CKD progression, therefore overestimating the benefit of nephrology referral. Future research may be necessary to determine the impact of nephrology referral on slowing CKD progression. The use of tools to identify the stage 3 CKD patients at highest risk for progression to ESRD may help discriminate those patients who would most benefit from nephrology referral to improve outcomes. More research is necessary to determine the utility of risk prediction tools in clinical decision making.

Immunization

Recommendation

17. We recommend that treatment with the following vaccinations be considered for patients with CKD as a measure to prevent infections:
    a. Influenza vaccine*
    b. Tdap vaccine
    c. Pneumococcal polysaccharide vaccine (i.e., PCV 13 and PPSV23)
    d. Hepatitis B vaccine
    e. Zoster /shingles vaccine*
    f. Varicella vaccine*
    g. MMR vaccine*

    (*Note: Live vaccines, including nasal influenza (LAIV), may be contraindicated in patients with CKD and severe immunodeficiency including treatment with immunosuppressive agents) *(Carryover modified from the 2008 CPG)* (Strong For)

Discussion

The CDC recommends that the vaccines listed above are administered to patients with health conditions such as kidney disease. [80] 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), chronic liver diseases (e.g., cirrhosis), or diabetes mellitus. [81] Kidney transplant patients receiving immunosuppressive drugs should not be administered live viral vaccines, such as varicella, zoster, (nasal) influenza and MMR. These patients are at risk for developing disseminated viral infection due to immunosuppressive therapy. [82]

Influenza immunization is recommend for adults less than age 50 with chronic illness (e.g., 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. It has been shown that an annual flu vaccine reduces the episodes of influenza in the high risk and elderly populations.

Tdap vaccination to protect against whooping cough and tetanus should be administered to all adult patients. Any adult 19 years of age and older who has not received a dose of Tdap should get one as soon as feasible. When feasible, Boostrix (GSK) should be used for adults 65 years and older; however, either vaccine product administered to a person 65 years or older provides protection and may be considered valid. [83]

Pneumococcal immunization (PCV 13 and PPSV23) 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 kidney failure). Additionally, diabetes mellitus is often associated

with cardiovascular or kidney dysfunction, which increases the risk for severe pneumococcal illness.

If not already administered, hepatitis B vaccine should be given to stage 4 CKD patients who are close to initiation of dialysis therapy (pre-dialysis). The CDC recommends testing pre-dialysis and immunocompromised patients for hepatitis B exposure and offering vaccination to patients who are seronegative for hepatitis B infection. [84] These patients require a higher dose of the vaccine with an additional dose at six months. A consultation with a nephrologist or infectious disease specialist may be obtained. In addition, the CDC also recommends hepatitis B vaccination for patients with type 1 or type 2 diabetes mellitus who are aged 19 through 59 years. The hepatitis B vaccine may be given at the discretion of the providers in diabetics older than 60 years.

Adults age 60 years and older should be vaccinated with the zoster/shingles vaccine to reduce the occurrence of herpes zoster (shingles).Vaccination against shingles may help prevent the development of herpes zoster in patients over 60 years regardless of the medical condition. 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.

All adults without evidence of immunity to varicella should receive two doses of single-antigen varicella vaccine or a second dose if they have received only one dose. [85]

Generally, the CDC recommends that all patients 18 years of age or older who were born after 1956 should get at least one dose of MMR vaccine, unless they can show that they have either been vaccinated or had all three diseases. Patients vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection should be considered for revaccination with two doses of MMR vaccine. [80]

For younger patients, the CDC also recommends the human papillomavirus (HPV) vaccine and the varicella vaccine. [80] The HPV should be administered to women up to age 26 and men up to age 21 to protect against HPV. The varicella/chickenpox vaccine should be administered to patients born in 1980 or after and have not gotten two doses of this vaccine or have immunity to this disease.

Nephrotoxins and Adverse Drug Events Avoidance

Recommendations

18. We recommend that clinicians avoid or limit the use of nephrotoxic medications for patients with CKD.
    (Carryover modified from the 2008 CPG) (Strong For)
19. In patients with CKD, we suggest that medications should be reviewed and their dosing modified, where appropriate, according to the level of the patient's kidney function.
    (Carryover modified from the 2008 CPG) (Weak For)

Discussion

Nephrotoxic medications

Many commonly used medications may be nephrotoxic to patients with CKD. These categories of medications include:

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (non-specific and COX-2)
- Aminoglycosides
- Various chemotherapeutic agents (MTX, mitomycin, cisplatin)
- Lithium
- Some of the bisphosphonates (zoledronic acid)
- Calcineurin inhibitors (e.g., cyclosporine and tacrolimus)

NSAIDs (including cyclooxgenase-2 inhibitors) may cause kidney damage by causing reversible reductions in GFR, as well as idiosyncratic reactions such as acute kidney injury, interstitial nephritis, and nephrotic syndrome. The benefits of utilizing NSAIDs in patients with CKD must be weighed carefully against the possible adverse effects on kidney function. Currently, the appropriate threshold for the use of NSAIDs is not established. Topical NSAIDs such as diclofenac are generally considered to be safe in patients with mild CKD but should be used with caution in patients with advanced CKD.

Several other medications are not nephrotoxic, yet may cause adverse effects that can be harmful in patients with CKD. These effects include hyperkalemia (ACEI, ARB, potassium-sparing diuretics, trimethoprim, digoxin, and heparin) and lactic acidosis (metformin). Oftentimes, the manufacturer's product information can be consulted to determine appropriate dosing based on the patient's kidney function.

One such medication that warrants caution in patients with CKD is metformin. The product information includes a warning of the risk for lactic acidosis. Although the risk is very low (reported as approximately 0.03 cases/1000 patient-years), the fatality rate is reported to be approximately 50%. Metformin is primarily renally eliminated, and according to the product information, in patients with decreased kidney function (based on measured creatinine clearance), the half-life of metformin is prolonged and the renal clearance is decreased in proportion to the reduction in creatinine clearance (CrCL). As the risk of metformin accumulation and lactic acidosis increases with the degree of kidney dysfunction, it is therefore recommended that patients be treated with the lowest effective dose along with monitoring kidney function. According to the Food and Drug Administration (FDA) approved prescribing information, metformin is contraindicated in men with a SCr greater than 1.5 mg/dL and in women with a SCr greater than 1.4 mg/dL. To further evaluate the risk for lactic acidosis with metformin, pooled data from a systematic review reported no cases of lactic acidosis during 70,490 patient-years of metformin use. [86] It was also noted that nearly half of the trials allowed inclusion of patients with a SCr >1.5 mg/dL. One trial in the review included patients with renal insufficiency (mean plasma creatinine 1.5 to 2.5 mg/dL) and at least one contraindication to metformin, and reported no cases of lactic acidosis. [87] As the SCr alone may not accurately reflect kidney function (e.g., in older patients or those with reduced muscle mass), guidelines outside the US. have established recommendations for dosing metformin based on eGFR. [88] Additionally, temporary discontinuation of metformin at the time of or prior to

intravascular iodinated radio contrast is encouraged and should be withheld for 48 hours after the procedure. Reinstitute only after renal function has been reevaluated and found to be normal. As there continues to be discussion regarding the recommended threshold and parameters for optimal safety of dosing metformin in patients with kidney impairment, at this time, the most recent VA/DoD Clinical Practice Guideline on the Management of Diabetes Mellitus (2010) [5] refers to the current FDA approved prescribing information for the use and discontinuation of metformin based on SCr.

Medication dose adjustments in CKD

Many commonly used medications 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 per the manufacturer's product information. In addition, some medications are potentially nephrotoxic and may precipitate acute kidney deterioration. Reduced kidney function may lead to drug accumulation with toxic effects specific to the drug. Thus, dosage adjustments based upon the level of the patient's kidney function may be required. Table 2 includes a select list of the medications that may require dose adjustment based on kidney function.

[5] See the VA/DoD Clinical Practice Guideline on the Management of Diabetes Mellitus in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/cd/diabetes/index.asp

Table 2. Select Medications Requiring Dose Adjustments or to be Used with Caution in Patients with CKD [89-91]

Select Medications*		
• Most antibiotics (macrolides, clindamycin, and metronidazole are exceptions) and antiviral agents • Multiple anti-cancer therapies (cytotoxic drugs, targeted agents, biologics) • Hypoglycemic agents o Acarbose o Miglitol o Glyburide o Chlorpropamide o Insulin o Metformin o Exenatide o Repaglinide o Alogliptin o Saxagliptin o Sitagliptin o Canagliflozin o Dapagliflozin o Empagliflozin • Cardiovascular agents o Atenolol o Sotalol o Digoxin o Dofetilide o Potassium-sparing diuretics	• RAAS blockers o ACEIs o ARBs o Aliskiren o Eplerenone, spironolactone • Anticoagulants o Apixaban o Dabigatran o Rivaroxaban o Low molecular weight heparins • Opioid analgesics o Codeine o Fentanyl o Hydrocodone o Hydromorphone o Meperidine o Methadone o Morphine o Oxycodone o Oxymorphone o Tapentadol o Tramadol • NSAIDs • Gabapentin • Levetiracetam • Lithium • Memantine • Risperidone, Paliperidone	• Antidepressants o Bupropion o Citalopram o Desipramine o Duloxetine o Mirtazapine o Paroxetine o Venlafaxine • Bisphosphonates • Gout agents o Allopurinol o Colchicine • H2-blockers • PDE5 inhibitors o Sildenafil o Tadalafil • Statins o Fluvastatin o Lovastatin o Pitavastatin o Pravastatin o Rosuvastatin o Simvastatin • Fibric acid derivatives o Gemfibrozil o Fenofibrate

**Note this is not a comprehensive list; consult individual product information or alternate sources such as the American Hospital Formulary Service (AHFS) Drug Information, Lexicomp Online, or UpToDate for dosing information and/or precautions in patients with kidney function impairment.*

When prescribing medications to patients with CKD, start at a lower dose and then gradually titrate the medication upward. When available, monitoring parameters (such as drug levels, blood sugar, and heart rate) should also be utilized. Certain patients with CKD and other comorbid diseases may also be at a higher risk than other patients for drug toxicity. For example, patients with:

- Concurrent diabetes
- Advanced age
- Volume depletion (or states of effective volume depletion)

- Concomitant use of multiple nephrotoxic drugs or medications with the potential for drug interactions
- Repeated and frequent use of higher doses of nephrotoxic drugs may increase risk of kidney damage (however, specific data are lacking)

Currently, there are limited proven data that address measures to improve safety and reduce the risk of adverse drug events due to nephrotoxic or renally cleared medications (to include prescription drugs, over-the-counter medications, and nutritional or herbal supplements) for patients with CKD. Boussadi et al. noted that automated alert systems may assist pharmacists in monitoring for drug prescription safety in patients with CKD. [92] The utility of a pharmacovigilance system to reduce adverse drug events in CKD should be the subject of future research.

Correction of Acidosis

Recommendations

20. We suggest the use of bicarbonate supplementation in CKD patients with metabolic acidosis to slow the progression of CKD. (Weak For)

Discussion

Susantitaphong et al. performed a systematic review of the effects of sodium bicarbonate supplementation on non-dialysis CKD patients. [93] They performed a meta-analysis of six studies with a total of 312 patients. All six trials prescribed sodium bicarbonate in the alkali-treated group. In the long-term studies, alkali therapy was associated with a net decrease in serum creatinine (-0.07 mg/dl, 95% CI -0.09, -0.05; p <0.001), a net improvement in GFR (3.2 ml/min/1.73 m^2, 95% CI 1.6, 4.7; p <0.001), and a lower incidence of dialysis initiation (RR 0.21, 95% CI 0.08, 0.54; p = 0.001). No benefit was observed on the serum creatinine or GFR in short-term studies.

The RCT by de Brito-Ashurst et al. studied sodium bicarbonate supplementation in 134 patients with stage 4 or 5 CKD. [94] The results showed decline in CrCl was slower with bicarbonate supplementation versus the control group (1.88 versus 5.93 ml/min 1.73 m^2; p <0.0001). Patients supplemented with bicarbonate were significantly less likely to experience rapid progression (9 versus 45%; RR 0.15; 95% CI 0.06 to 0.40; p <0.0001). Similarly, fewer patients supplemented with bicarbonate developed ESRD (6.5 versus 33%; RR 0.13; 95% CI 0.04 to 0.40; p <0.001). Taken together, these studies support the use of bicarbonate therapy.

Blood Pressure Targets

Recommendations

21. In adult patients with stages 1-4 CKD, we recommend that blood pressure targets should be less than 140/90 mmHg. *(Carryover modified from the 2008 CPG)* (Strong For)

Discussion

Review of the literature for this update identified only one systematic review that addressed the

question of targeting low versus usual blood pressure goals. This review included three trials that randomized adult CKD patients with or without proteinuria to two blood pressure targets (lower [125/75 mmHg to 130/80 mmHg] versus higher [<140/90 mmHg]). This systematic review included 2,272 non-diabetic patients with CKD stage 3-4. The median follow-up varied from 1.6 years to 3.8 years. [95] The three trials included in the evidence review were the MDRD trial with 840 participants, AASK trial with 1094 participants and the REIN-2 trial with 338 participants. [95] The findings of these trials showed that low blood pressure target of less than 125/75 mmHg to 130/80 mmHg was not significantly associated with reduced kidney function decline compared to a blood pressure (BP) target of less than 140/90 mmHg (p>0.05). This finding was consistent in the review but the authors noted that one study, the MDRD, reported a 23% reduction (95% CI, 18% to 43%) in the hazard for kidney failure in the group assigned to the low target during the long-term post trial follow-up. Regarding cardiovascular mortality**,** a low BP target was not associated with a significant reduction in the risk of cardiovascular mortality compared to usual BP target ([AASK trial HR 0.98, 95% CI (0.48 to 2.01) p=0.96], REIN-2 trial 1% versus 1%). None of the three trials found differences in all-cause mortality between the two levels of blood pressure. However, lower targets were associated with increased risk of adverse events such as the risk for increased pill burden, drug to drug interaction, difficulty with adherence, hypotension, increased risk of falling (particularly in the elderly), pre-renal azotemia and electrolyte disturbances. [95] In addition, there are resource burdens for the patient due to the need for more frequent visits and monitoring. Although two of the trials included in this systematic review signal for a beneficial effect of low blood pressure targets in the groups with proteinuria, these analyses were done as a post-hoc subgroup analyses. Also the cut points for proteinuria varied greatly across groups, ranging from “>320 mg per day” to “>1 mg per day” for the AASK and MDRD studies, respectively. [95] Hence, there remains an important gap in knowledge that needs to be addressed in future research regarding blood pressure targets in patients with proteinuria.

In patients with diabetes and CKD, there is no conclusive evidence that treating to a lower target is beneficial, as there are no RCTs of patient with diabetes mellitus and CKD that randomized to two levels of blood pressure. At this time, the guideline panel suggests against lowering blood pressure to a target of less than 130/80 mmHg in patients with CKD stages 1-4 even in the presence of proteinuria due to increased risk of adverse outcomes. Refer to the VA/DoD Clinical Practice Guideline for Management of Diabetes Mellitus in Primary Care[6] and the VA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care[7] for further discussion of blood pressure targets in patients with diabetes.

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[6] See the VA/DoD Clinical Practice Guideline for Management of Diabetes Mellitus in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/cd/diabetes/index.asp

[7] See the VA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/cd/htn/index.asp

Renin-Angiotensin Aldosterone System (RAAS) Blockade

Recommendations

22. In patients with non-diabetic CKD, hypertension, and albuminuria, we recommend the use of an angiotensin-converting-enzyme inhibitor (ACEI) to prevent progression of CKD. Angiotensin II receptor blockers (ARBs) may be substituted for patients with an ACEI-induced cough. *(Carryover modified from the 2008 CPG)* (Strong For)
23. In patients with diabetes, hypertension, and albuminuria, we recommend the use of an ACEI or ARB to slow the progression of CKD, unless there is documentation of intolerance. *(Carryover modified from the 2008 CPG)* (Strong For)
24. We recommend against the use of combination renin-angiotensin-aldosterone system (RAAS) blockade (ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor) in patients with CKD. (Strong Against)

Discussion

These recommendations are adapted from the previous VA/DoD 2008 CKD CPG with the supporting evidence dated before 2008. The recommendation of ACEIs or ARBs as the initial regimen is based primarily on their beneficial effects on kidney outcomes and significant benefit to slow CKD progression. The data are limited regarding cardiovascular benefits of ACEIs or ARBs compared to other antihypertensive agents in patients with CKD. Two RCTs that support that ACEI therapy slows the progression of CKD in patients with proteinuria are the REIN-2 and the AASK trials. Both trials were reviewed as part of the evidence for blood pressure target recommendations. Results from Nakamura et al. [96] showed that ACEIs or ARBs are equally effective in controlling blood pressure in CKD. There is also good evidence that ARBs or ACEIs slow the progression of CKD in patients with CKD and diabetes, with micro- or macroalbuminuria. The supporting studies for this recommendation were reviewed in the previous CKD guideline. The direct renin inhibitors are not included in this review as there are no studies demonstrating their benefits on kidney or cardiovascular outcomes in patients with CKD. Table 3 highlights the major updates in regard to controlling hypertension and medication selection from the previous 2008 CKD CPG.

Table 3. Comparison of the Recommendations from VA/DoD 2008 CKD CPG for Controlling Hypertension in CKD with Current Recommendations

	VA/DoD CPG for Management of CKD 2008	VA/DoD CPG for Management of CKD 2014
BP target	• Antihypertensive therapy should be adjusted to achieve blood pressure of <130/80 mmHg • If proteinuria is >1 g/day BP <125/75 mmHg	• Antihypertensive therapy should be adjusted to achieve blood pressure of <140/90 mmHg **regardless of the presence of proteinuria**
Drug choice	• 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	• ACEIs or ARBs are the preferred agent for patients with kidney disease and hypertension **with albuminuria** • ARBs may be substituted for patients with an ACEI induced cough
Drug combination	• Combination ACEI and ARB are supported in IgA nephropathy	• There is a strong recommendation **against** the use of ACEI and ARB in combination

Regarding the selection of second or third line agents for additional antihypertensive therapy in patients with CKD, there are limited data available to guide the clinician. Two recent small RCTs showed that a dihydropyridine calcium channel blocker (CCB) was as efficacious as an ACEI in controlling blood pressure [97], as was a loop diuretic compared to an antihypertensive control group. [98] In regard to reaching blood pressure control it seems that other recommended antihypertensive agents such as a thiazide or thiazide-type diuretic (or loop diuretic as indicated) and/or a dihydropyridine CCB are acceptable options. The decision for the use of these or other antihypertensive classes should be considered based on the potential for cardiovascular benefit and the patient's comorbidities and preference. For more detailed information on the diagnosis and management of hypertension, refer to the VA/DoD Clinical Practice Guideline for Management of Hypertension in Primary Care[8] for more complete information on the safety of all antihypertensive agents, and stepwise, sequential, and combination therapy.

Use of ACEIs or ARBs will commonly increase serum creatinine and potassium. An increase up to 30% in SCr within the first two weeks after initiation is acceptable. If potassium becomes elevated, measures to reduce hyperkalemia (e.g., reduction in dose of ACEI or ARB, discontinuation of concomitant medications that may increase potassium, implementation of a low potassium diet, addition of a diuretic, as indicated) should be considered. If therapies to decrease potassium such as a low potassium

[8] See the VA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/cd/htn/index.asp

diet and addition of diuretics are not effective, treatment should be discontinued. Although changes of smaller magnitude in these parameters may not require a dose adjustment, CKD patients on RAAS inhibition require monitoring of potassium and serum creatinine for safety reasons. Patients with cough due to ACEI should be switched to an ARB. It is unknown if an ARB can be safely used as an alternative in patients who have previously developed angioedema on an ACEI. A systematic review found the risk for angioedema to be 9.4% (95% CI 1.6 to 17%) of patients on an ARB who previously experienced angioedema on an ACEI; and 3.5% (95% CI 0 to 9.2%) of patients with previously confirmed angioedema on an ACEI. [99] Another review estimated the risk of cross-reactivity of angioedema with an ARB in patients who previously experienced this adverse event with an ACEI to be from less than 7% up to 17%. [100] Therefore, an ARB should be used with caution in patients who have previously experienced angioedema with an ACEI.

Combination RAAS blockade versus RAAS blockade monotherapy

Although studies evaluating combination therapy with two agents that block the renin-angiotensin-aldosterone system have reported a greater benefit on surrogate endpoints (e.g., decrease in urinary albumin-to-creatinine ratio, reduction in albuminuria) in patients with CKD (trials also included patients with diabetes mellitus) compared to those receiving monotherapy, [101-106] additional information was needed to determine whether combination therapy provided long-term outcome benefit on slowing the progression to ESRD or a reduction in mortality, without an increase in adverse outcomes. More recently, clinical trials have been conducted to determine the long-term outcome benefit and safety of combination RAAS blockade in patients with CKD. [107-109] Results of recent trials are discussed in the text below and displayed in Table 4.

Table 4. Summary of Evidence for Dual RAAS Blockades

Trial Name	Therapy*	Results
VA NEPHRON-D *Fried et al. 2013* [108]	ACEI + ARB versus ARB alone (n = 1,448)	Trial terminated due to a greater number of observed acute kidney injury events (HR 1.7 95% CI 1.3 to 2.2; p<0.001) and hyperkalemia (HR 2.8 95% CI 1.8 to 4.3; p<0.001) in the group receiving combination therapy, without a significant difference in the primary endpoint of first occurrence of a decline in eGFR, ESRD, or death between treatment groups (HR 0.88 95% CI 0.70 to 1.12; p=0.30).
PRONEDI *Fernandez Juarez et al. 2013* [107]	ACEI + ARB versus ACEI or ARB alone (n = 133)	Found no difference in the primary composite endpoint of >50% decrease in SCr, ESRD, or death between an ACEI and combination therapy (HR 0.96 95% CI 0.44 to 2.05; p=0.90) or ARB compared to combination therapy (HR 0.90 95% CI 0.39 to 2.02; p=0.80).

Trial Name	Therapy*	Results
Systematic review *Susantitaphong et al. 2013* [110]	ACEI+ARB; ACEI or ARB+ARA; ACEI+ARB+DRI; ACEI+ARB+ARA versus ACEI or ARB alone (n = 4,975; across 59 studies)	Combined RAAS blockade was associated with a 3.4% higher rate of hyperkalemia (95% CI, 1.7 to 5.1, p <0.001, I2=29.2; 35 study arms) and a 4.6% higher rate of hypotension (4.6%, 95% CI, 2.3 to 6.8, p <0.001, I2=33.1; 24 study arms).
AHRQ Comparative Effectiveness Review *Fink et al. 2012* [111]	ACEI + ARB versus ACEI alone (n = 7,233; across 6 studies) ACEI + ARB versus ARB alone (n =~4,300; across 3 studies) ACEI + ARB versus ACEI or ARB (n = 8,933; across 1 study) ACEI + ARB versus ACEI + ARA (n = 54; across 1 study)	ACEI-ARB combination therapy produced no significant reduction in the risk of doubling creatinine (n=1 study) relative to ACEI monotherapy (HR 0.07, 95%CI, 0.0–1.13); One study reported more serious adverse events for the combination therapy group (9.3%) versus the ARB-only group (2.3%) and another study reported a higher incidence of cough for combination therapy (4.3 versus 0%); Adverse events were more common for the combination therapy group (need for acute dialysis , hyperkalemia (RR 1.65, 95% CI, 1.10 to 1.25), hypotension (RR 1.65, 95% CI, 1.4 to 1.95), cough (RR 1.72, 95% CI, 1.34 to 2.20), and syncope (RR 2.44, 95% CI, 0.75 to 8.0); Reported no significant difference in all-cause mortality or doubling SCr in 53 patients receiving an ACEI who were randomized to either an ARB (losartan) or ARA (spironolactone) for 48 weeks.
Randomized controlled trial *Wang et al. 2013* [112]	ACEI +/or ARB + ARA versus ACEI +/or ARB alone (n = 221)	ARA(spironolactone) group had significantly reduced urine protein levels relative to pre-treatment measures and relative to the control (ACEI plus ARB only) group (both p <0.05). The control group showed no significant reduction in urine protein relative to pretreatment measures. No significant differences in serum creatinine or eGFR.

Trial Name	Therapy*	Results
Chronic Renal Impairment in Birmingham II study (sub-analysis) *Edwards et al. 2012* [113]	ARA or placebo + ACEI +/or ARB (n = 117)	Difference in eGFR between the ARA (spironolactone) and placebo group at week 40 approached significance (46.1 versus 52.3 ml/min/1.72 m^2, p=0.09).
Systematic review *Navaneethan et al. 2009* [114]	ARA + ACEI +/or ARB versus ACEI +/or ARB + placebo (n = 845; across 10 studies)	ARA (spironolactone) plus ACEI and/or ARB significantly reduced 24 hour proteinuria by the end of treatment relative to ACEI and/or ARB alone (mean difference (MD) = -0.80 g/24 hours, 95% CI, -1.27 to -0.33). Combination therapy with ARA plus ACEI or ARB did not significantly affect end of treatment eGFR (MD = 0.70 ml/min, 95% CI, -4.73 to 3.34).
Randomized controlled trial *Guney et al. 2009* [115]	ARA + ACEI +/or ARB versus ACEI +/or ARB alone (n = 30)	Urinary protein/creatinine was significantly reduced relative to baseline in the spironolactone group (from 2.43 ± 4.85 to 1.76 ± 3.39 mg/mgCr), respectively, p=0.028) after 3 months and further reduced after 6 months (1.66 ± 3.51mg/mgCr, p=0.003).
Randomized controlled trial *Furumatsu et al. 2008* [116]	ARA + ACEI + ARB versus ACEI + ARB + diuretic (n = 38)	Proteinuria was significantly decreased at 12 weeks and 1 year follow-ups for the triple-blockade (spironolactone) group (p <0.05 versus baseline at 0 weeks). Estimated GFR did not change throughout the treatment period for either group.
Randomized controlled trial *Ohsawa et al. 2013* [117]	ACEI or DRI + ARB (n = 37)	Baseline measures of urinary albumin/creatinine ratio (UACR) or eGFR were not significantly different between groups. UACR of the aliskiren group, but not the benazepril group, was significantly reduced at 24 weeks. Group eGFR measures were not significantly different.
ALTITUDE *Parving et al. 2012* [109]	DRI or placebo + ACEI or ARB (n = 8,606)	Difference between groups was statistically non-significant (HR 1.08, 95% CI, 0.98 to 1.20; p=0.12) for the composite primary outcome.

**Abbreviations: ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARA: Aldosterone receptor antagonist; DRI: Direct renin inhibitor*

Combination RAAS blockade with an ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor, versus ACEI or ARB monotherapy

When evaluating the individual components of the primary endpoint, there was no significant difference between treatment with combination ACEI and ARB versus ACEI or ARB monotherapy on progression to ESRD, [107,108,111] death, [107,108,110,111] or eGFR decline (as defined in Fried et al. 2013 [108]), >50% increase in SCr [107] or doubling SCr. [110,111] Despite the reduction in proteinuria with combination RAAS blockade compared to monotherapy, there was no significant long-term benefit on reducing kidney disease progression with combination therapy. [108,110] In addition, given the level of evidence that treatment with combination therapy increased the risk for hyperkalemia, [108,110,111] acute kidney injury, [108,111] as well as low level evidence for the risk of hypotension [110,111] compared to monotherapy, the Work Group members felt the harms outweighed the benefit and therefore made a strong recommendation against the use of combination RAAS blockade in patients with CKD.

Results from the VA Cooperative Study, Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D), support the recommendation against the use of combination therapy with an ACEI and ARB in patients with CKD. [108] In this trial, 724 patients were randomized to treatment with combination of an ARB (losartan) and ACEI (lisinopril) and 724 patients to an ARB plus placebo. The trial was terminated at a median follow-up of 2.2 years due to a greater number of observed acute kidney injury events and hyperkalemia in the group receiving combination therapy, without a significant difference in the primary endpoint of first occurrence of a decline in eGFR, ESRD, or death between treatment groups. There was a greater decline in the urinary albumin-to-creatinine ratio (tertiary endpoint) with combination therapy compared to monotherapy ($p<0.001$). [108]

Another trial, PRONEDI, with a median follow-up of 32 months, randomized 133 patients with diabetic nephropathy to an ACEI (lisinopril), an ARB (irbesartan), or the combination, and found no difference in the primary composite endpoint of >50% decrease in SCr, ESRD, or death between an ACEI and combination therapy or an ARB compared to combination therapy. There was no significant difference in the decrease in proteinuria (secondary endpoint) between treatment groups. There was a significant increase in serum potassium in all treatment groups, which was reported not to be statistically significantly different between the treatment groups. [107]

This strong recommendation against use of combination RAAS blockade also includes combination with a direct renin inhibitor and an ACEI or ARB. Evidence for this recommendation includes data from the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) that evaluated patients with type 2 diabetes mellitus and CKD, cardiovascular disease, or both treated with combination of a direct renin inhibitor (aliskiren) and an ACEI or ARB versus monotherapy with an ACEI or ARB. This trial was terminated early with a median follow-up of 32.9 months. [109] There was no significant difference between combination and monotherapy for the primary composite outcome (time to cardiovascular death or first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; ESRD, death attributable to kidney failure, or the

need for renal-replacement therapy with no dialysis or transplantation available or initiated; or doubling of the baseline SCr level). There was a significant increase in discontinuations due to an adverse event (13.2% versus 10.2%; p<0.001), rates of hyperkalemia (39.1% versus 29.0%; p<0.001) and hypotension (12.1% versus 8.3%; p<0.001) in patients treated with combination therapy versus monotherapy, respectively. [109] A significantly increased risk (3.4%) for hyperkalemia with combination therapy compared to monotherapy was also found in several studies (95% CI, 1.7 to 5.1, p <0.001, 35 study arms) included in one systematic review. [110]

Mineralocorticoid receptor antagonist in combination with RAAS blockade versus RAAS blockade monotherapy

Data was not available to adequately determine the impact on long-term outcomes such as progression to ESRD or death with a mineralocorticoid receptor antagonist in combination with additional RAAS blockade compared to monotherapy in patients with CKD. The suggestion against use of combination with a mineralocorticoid receptor antagonist and additional RAAS blockade is based on the following data: one trial [118] included in one systematic review [111] reported no significant difference in all-cause mortality or doubling SCr in 53 patients receiving an ACEI who were randomized to either an ARB (losartan) or aldosterone antagonist (spironolactone) for 48 weeks; and results from one systematic review, [114] one 16-week trial of 221 patients, [112] and a one-year study of 32 patients (comparing triple RAAS blockade including a mineralocorticoid receptor antagonist versus dual RAAS blockade with an ACEI and ARB), [116] that reported additional RAAS blockade with a mineralocorticoid receptor antagonist further reduced proteinuria versus the comparator group.

One systematic review evaluating the addition of a mineralocorticoid receptor antagonist to RAAS blockade reported an increased risk for hyperkalemia in patients receiving a mineralocorticoid receptor antagonist plus an ACEI and/or ARB compared to an ACEI and/or ARB alone (RR 2.23; 05% CI 1.19 to 41.0; p=0.01). [114] In a trial of 115 patients, serum potassium levels were significantly higher (p<0.05) in patients treated with a mineralocorticoid receptor antagonist (spironolactone) in addition to an ACEI and/or ARB (1% of patients on ACEI plus ARB) compared to placebo plus an ACEI and/or ARB (2% of patients on ACEI plus ARB), with two patients in each group experiencing an increase in serum potassium ≥5.5 mEq/L. There was also an increased risk for developing hyperkalemia if the baseline potassium was ≥5.0 mEq/L (p<0.01) or baseline eGFR ≤45 mL/min/1.73 m^2 (p=0.04). [113] Two of 15 patients treated with a mineralocorticoid receptor antagonist (spironolactone) in addition to an ACEI and ARB experienced an increase in serum potassium (>5.0 mEq/L) requiring intervention with a potassium binder. [116] In another trial of 221 patients, no significant difference in potassium levels was found between treatment with a mineralocorticoid receptor antagonist (spironolactone) in addition to an ACEI and/or ARB compared to patients continuing treatment on an ACEI and/or ARB. [112]

The mineralocorticoid receptor antagonists, ACEIs, ARBs, and direct renin inhibitors have all been associated with an increase in serum potassium and/or risk for hyperkalemia. As noted above, when multiple RAAS blockades are used, the risk for hyperkalemia is further increased. [108,110,111,114] Most trials evaluating combination RAAS blockade in patients with CKD excluded patients with a serum potassium >5.0 mEq/L [109,112,116] or >5.5 mEq/L. [107,108,111,113] Patients with CKD receiving RAAS

blockers require close monitoring of serum potassium, as well as kidney function. Although combination RAAS blockade is not recommended in patients with CKD in general, if the combination is used (e.g., use of an ACEI or ARB in combination with a mineralocorticoid receptor antagonist in patients with heart failure), increased diligence is recommended to monitor for hyperkalemia (i.e., within three days and at one week after initiation of a mineralocorticoid receptor antagonist and at least monthly for the first three months, and every three months thereafter) [119] as well as for acute kidney injury. Clinical trials evaluating combination RAAS compared to monotherapy in patients with CKD varied in their protocols for follow-up, with the most conservative monitoring at one and two weeks after initiation of therapy [113] or at 10 to 14 days after initiation or increase in dose, [108] then monthly (e.g., for the study duration of 16 weeks [112]) to every three months. [108] Frequency of monitoring should take into account additional factors including baseline serum potassium or SCr, medications that may increase the risk for hyperkalemia, or conditions that may contribute to volume depletion. [119,120] (See Appendix B: Pharmacotherapy with ACEIs or ARBs.)

Given the minimal data on the benefit of combining a mineralocorticoid receptor antagonist with an additional RAAS blockade, the limited data suggesting an increased incidence of hyperkalemia, and the harms demonstrated for combinations with other drugs using this mechanism of action (renin blockers and combination RAAS blockers), the Work Group suggests against the use of a mineralocorticoid receptor antagonist with additional RAAS blockade. Furthermore, the Work Group identified that additional studies are needed to determine the impact on long-term clinical outcomes and safety of RAAS blockade in combination with a mineralocorticoid receptor antagonist in patients with CKD.

Statins for Cardiovascular Risk Reduction

Recommendations

25. We recommend that all patients with CKD who are not on dialysis and have no known history of coronary artery disease be assessed for 10-year CVD risk using a validated risk calculator for primary prevention. If at risk (as defined in the VA/DoD Management of Dyslipidemia guideline), we recommend use of at least a low dose statin. (Strong For)
26. We suggest against the use of statins prescribed with the intent of slowing eGFR decline or preserving kidney function. (Weak Against)

Discussion

Risk calculators

Population-based observational studies provide the basis to calculate the estimated 10-year risk for CVD, using demographic (age, sex, race) and clinical (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], blood pressure [BP]) variables. Several calculators exist and are based on different (though sometimes overlapping) populations and a different combination of variables. Below are some examples of calculators that clinicians may want to consider using to calculate the 10-year risk, depending on the characteristics (e.g., age) of their patient population:

- Framingham (cohort age range 40-74): http://cvdrisk.nhlbi.nih.gov/
- ASCVD Pooled Risk Calculator from the 2013 American College of Cardiology (ACC)/American

Heart Association (AHA) Lipid Guideline (cohort age range 40-79): http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

- Cardiovascular Risk/Benefit Calculator (combines Framingham and ACC/AHA cohorts): http://bestsciencemedicine.com/chd/calc2.html
- Mayo Statin Decision Aid: http://statindecisionaid.mayoclinic.org/index.php/site/index

While the Framingham risk calculator was developed based on a primarily white population, some observational studies have shown that it performs fairly well in other populations, including those with CKD. The more recently developed ACC/AHA calculator is based on a more diverse population that include a large enough number of African American subjects to calculate separately risk for white and for African American patients. Additionally, the ACC/AHA calculator includes ischemic stroke as an outcome. The Cardiovascular Risk/Benefit Calculator uses the same prediction models as the previous two calculators, but displays the results in an interactive visual format that facilitates shared decision making with patients and can illustrate the potential effect of medications. The Mayo Statin Decision Aid also provides a patient-friendly illustration of risk.

All of these risk calculators have limitations and their use has not been rigorously shown to improve outcomes. However, their wide acceptance may render such studies difficult to perform. Risk calculators have been criticized for overestimating the risk. One of the reasons may be that they are based on data that were collected before the recent significant improvement in clinical care and prevention for CVD, when the overall population was at higher risk of events or death from CVD causes.

Another limitation of risk calculators is that they provide an average risk or probability and cannot precisely predict whether an individual patient will develop a CVD event or benefit from medications. They can, however, be useful to discuss CVD risks and potentials for harm or benefit from medications in the process of shared decision making. Based on these calculations, patients at low 10-year risk for CVD events are unlikely to benefit from medications in the near future, but could experience some of the side effects. On the other hand, patients at high risk may benefit from a significantly decreased risk of an acute event in the following 10 years. Therefore, the use of risk calculators to aide in medication decision making is currently recommended by most medical societies.

Once the 10-year risk has been calculated, shared decision making is recommended to decide whether the potential benefits of medications outweigh the potential harms. For high-risk patients with a 10-year risk of 12% or more, it is estimated that risk of cardiovascular events can be decreased by 20-30% with use of medication for five years. The rationale for a threshold of 12% may appear arbitrary, but it reflects a threshold that most closely resembles the populations in the clinical trials for which the benefits clearly outweighed the risks, including the SHARP trial whose mean 10-year risk exceeded 15%. A similar rationale is used for the threshold of 6%. There are no clinical trials that specifically address this <6% ten-year risk category. The mean 10-year risk of the few primary preventions trials that included patients in what is considered an intermediate risk group (6-12%) was approximately 8%. However, these trials are few in number and had idiosyncratic inclusion criteria (e.g., Jupiter, MEGA). Also, 6% has been used by the ACC/AHA as a conventional threshold for defining the transition from low

to intermediate risk. Admittedly, these are arbitrary thresholds, but they also represent thresholds that rationally define inflection points of increasing risk and increasing congruency with the populations included in clinical trials that showed benefit from statin therapy. Additional information regarding risk calculation can be found in the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia.[9]

Statins to reduce cardiovascular events

Literature prior to 2007 suggests benefit from use of statins as a means of secondary prevention of cardiovascular events in patients with CKD. [121,122] A review of the literature since 2007 identified four RCTs which expand the examined scope of statin therapy in non-dialysis CKD patients to reduce renal outcomes or primary or secondary prevention of cardiovascular endpoints. [123-126] One trial examined the role of statins to reduce renal endpoints. [123] Two of the RCTs [124,125] were large trials initially constructed to assess prevention of secondary or primary prevention of non-renal end points with secondary analyses of statin efficacy to reduce lipid levels. The fourth RCT was a secondary analysis of patients with stage 2-4 CKD enrolled in a primary prevention study evaluating statin efficacy compared to placebo to reduce cardiovascular events or mortality. [126] In addition, the SHARP trial examined the efficacy and safety of the combination of simvastatin plus ezetimibe in patients with moderate-to-severe kidney disease in the primary prevention of atherosclerotic events and mortality. [127]

One secondary and one post-hoc analysis of moderate quality RCTs support the recommendation for use of statins to reduce cardiovascular events in patients with stage 3 or 4 CKD. [125,126] In the secondary analysis, Ridker et al. studied 3,267 patients with CKD who were on rosuvastatin (20 mg/d) or placebo (the JUPITER trial). [126] Cardiovascular events, including composite myocardial infarction (MI), stroke or confirmed cardiovascular death, were reduced by 41% in those patients receiving the statin, regardless of Framingham risk score of > or ≤10% . All-cause mortality was also reduced in those treated with statin (HR 0.56; 95% CI 0.37-0.85). In the post-hoc analysis, Kendrick et al. studied 304 patients with stage 3 CKD receiving either lovastatin (20 mg/d) or placebo. [125] Lovastatin was associated with reduced rates of fatal and nonfatal cardiovascular events (adjusted RR, 0.39; 95% CI of 0.16 to 0.93, p=0.03), fatal and nonfatal coronary events (adjusted RR, 0.35; 95% CI 0.13-0.93), and coronary revascularizations (adjusted RR 0.23; 95% CI 0.07-0.77), and while not associated with a significant decrease in cardiovascular or coronary heart disease mortality, the study had a low frequency of these endpoints and was not powered to detect treatment differences in this frequency range. [126]

The SHARP trial, conducted by Baigent et al., included 9,270 patients and evaluated the efficacy simvastatin in combination with ezetimibe to reduce atherosclerotic events and mortality. [127] Although the trial examined statin therapy in combination with ezetimibe, it offered support for the

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[9] See the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia. Available at: http://www.healthquality.va.gov/guidelines/cd/lipids/index.asp

reduction of the incidence of major atherosclerotic events in patients with advanced CKD. Compared to the placebo group, the simvastatin plus ezetimibe group experienced a 17% proportional reduction in major atherosclerotic events (526 [11.3%] simvastatin plus ezetimibe versus 619 [13.4%] placebo; RR 0.83, 95% CI 0.74-0.94, p=0.0021) over a range of kidney function and degree of proteinuria. [127]

Taken together, the three studies that examined the effect of statin therapy on the primary prevention of cardiovascular outcomes, all demonstrate benefit in their cohorts of patients with CKD, and while each of these cohorts was free of manifest CVD, each population had a predisposing CV risk factor to qualify them for treatment (e.g., dyslipidemia, elevated C-reactive protein [CRP], or diabetes, respectively). [123,125,126] In the opinion of the working group, the comprehensive risk for arteriosclerotic cardiovascular disease in those with CKD should be considered. Those with CKD may not have diabetes and may not have a low-density lipoprotein (LDL) high enough to indicate statin treatment, but they may still benefit from use of statin therapy to modify the independent increased risk of cardiovascular disease in CKD. A risk prediction equation has been validated for use in the CKD population and may be useful in guiding decisions about initiation of statin therapy. [128]

While patients with CKD may be at increased risk of drug-induced myopathy, [129] none of the studies included in the evidence base found a statistically significant difference in adverse events for any of the statins investigated. However, providers are nonetheless encouraged to engage in shared decision making discussions with patients so that the risks and benefits are adequately communicated, and are in line with patient values and preferences. Providers should also consider the individual patient, to include presence of comorbidities and cardiovascular disease risk, life expectancy and the time needed to treat with a statin to see benefits in morbidity and mortality, and the individual risk for adverse events related to statin therapy (e.g., rhabdomyolysis). Providers are also encouraged to consult the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia.[10]

Statins to slow CKD progression

The literature was also reviewed for reports concerning the impact of statins on decline of kidney function. The decline in kidney function is defined by change in mean eGFR. Ridker et al. reported a marginal improvement in eGFR at 12 months between those assigned to rosuvastatin versus placebo (66.8 versus 66.6 m/min/1.73m^2, p = 0.02). [126] In the study by Huskey et al., [124] kidney function loss (defined as a ≥ 25% decrease in eGFR from baseline) was significantly decreased in the simvastatin group versus placebo (adjusted OR: 0.21, 95% CI 0.05 to 0.94, p = 0.04). However, using the same definition of kidney function loss, Kendrick et al. [125] found no difference between lovastatin versus placebo. Fassett el al. [123] used the rate of Modification of Diet in Renal Disease (MDRD) equation to estimate GFR from creatinine. The results of the study found no statistically significant different in eGFR

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[10] See the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia. Available at: http://www.healthquality.va.gov/guidelines/cd/lipids/index.asp

between atorvastatin and placebo but was underpowered to detect a meaningful difference. Due to the inconsistencies in study findings, the Work Group suggests against use of statins to slow CKD progression until further evidence is available.

Glycemic Control

Recommendations

27. We recommend against intensive glycemic control to patients with stage 3 or worse CKD due to the lack of benefit on renal or cardiovascular outcomes and potential for significant harm. *(Carryover modified from the 2008 CPG)* (Strong Against)

Discussion

Recommendations regarding the treatment of diabetes were also discussed in the 2008 CKD CPG. The Work Group noted the importance of the recommendation and decided to modify the recommendation in this update to be consistent with the VA/DoD CPG for Management of Diabetes Mellitus.[11] We suggest patients with CKD and diabetes be targeted to an HbA1c consistent with that recommended for the general diabetes population as outlined in the VA/DoD Clinical Practice Guideline for Management of Diabetes Mellitus.[11] Generally, the target range for glycemic control should be individualized based on the provider's appraisal of the risk-benefit ratio and discussion of the target with the patient. Table 5 summarizes the target glycemic control in the current VA/DoD Clinical Practice Guideline for Management of Diabetes Mellitus.[11]

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[11] See the VA/DoD Clinical Practice Guideline for Management of Diabetes Mellitus in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/cd/diabetes/index.asp

Table 5. Determination of Target HbA1c Level [(1) (2)]

Major Comorbidity (d) or Physiologic Age	Microvascular Complications		
	Absent or Mild (a)	Moderate (b)	Advanced (c)
Absent >10 years of life expectancy	<7%	<8%	8-9% *
Present (e) 5 to 10 years of life expectancy	<8 %	<8%	8-9% *
Marked (f) <5 years of life expectancy	8-9% *	8-9% *	8-9% *

(1) Based upon the Diabetes Control and Complications trial referent standard. Clinicians need to evaluate the methodology used at their site.
(2) Reflects a "goal" over time. Intensification of therapy should be undertaken based upon individual clinical circumstances and treatment option.
(a) Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria, and/or mild neuropathy.
(b) Moderate microvascular disease is defined by pre-proliferative (without severe hemorrhage, intra-retinal microvascular anomalies [IRMA], or venous bleeding) retinopathy or persistent, fixed proteinuria (macroalbuminuria) and/or demonstrable peripheral neuropathy (sensory loss).
(c) Advanced microvascular disease is defined by severe non-proliferative (with severe hemorrhage, IRMA, or venous bleeding), or proliferative retinopathy and/or renal insufficiency (serum creatinine level >2.0 mg/dL), and/or insensate extremities or autonomic neuropathy (e.g., gastroparesis, impaired sweating, or orthostatic hypotension).
(d) Major comorbidity includes, but is not limited to, any or several of the following active conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent stroke, and life-threatening malignancy.
(e) Major comorbidity is present, but is not end-stage and management achievable.
(f) Major comorbidity is present and is either end-stage or management is significantly challenging.
* Further reductions may be appropriate, balancing safety and tolerability of therapy.

Intensive versus conventional glycemic control therapy

Diabetes mellitus is the leading cause of ESRD in the United States. [130] We identified two randomized controlled studies comparing intensive to conventional glycemic control in our target population of patients with CKD. [131,132] The first study included 70 patients with microalbuminuria who were randomized to intensive glycemic management (≤7.5%) versus conventional control (no defined control level, but insulin was adjusted based only on symptoms). At six months post randomization those in the intensive group achieved a glycosylated hemoglobin concentration of 8.9% versus 10.3% in the control group. This difference became smaller over time and was abolished after 36 months. Progression to clinical albuminuria was the same in both groups. [131] The larger VA Cooperative Study by Duckworth et al. comparing intensive versus conventional glycemic control involved 1791 patients not selected on the basis of kidney function. [132] Patients were randomized to intensive therapy (defined as an absolute reduction in glycosylated hemoglobin of 1.5%) versus standard therapy (achieved glycosylated hemoglobin at six months 6.9% versus 8.4%, intensive versus control, respectively). The study duration was 5.6 years. In the overall population, there was no difference in any component of the primary outcomes (major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene), death, or microvascular complications with the

exception of albuminuria. Among the subgroup of patients with microalbuminuria at baseline there was no difference in the incidence of macroalbuminuria (p=0.10). [132] But patients in the more intensive therapy group had a greater incidence of hypoglycemia (24.1%) compared to the conventional therapy group (17.6%).

A meta-analysis of these two studies by Fink et al. [111] showed that intensive glycemic control therapies resulted in a non-significant 3.1% decrease in the risk of progression from micro- to macroalbuminuria (8.7% versus 12.8% for intensive and conventional therapies, respectively, risk ratio 0.69 [95% CI, 0.42 to 1.12], n=561 patients). [111]

Thus the current evidence does not support intensive glycemic control for the purpose of reducing adverse renal or cardiovascular outcomes in patients with CKD.

Iron Therapy

Recommendation

28. We suggest initiation of oral iron therapy (in preference to parenteral) to support iron requirements in patients with CKD stages 3 and 4. (Weak For)

Discussion

Use of iron therapy for treatment of iron deficient anemia has been a mainstay of management in patients with CKD. Iron deficiency is common in patients with CKD due to reasons such as non-renal factors (i.e., menstrual bleeding) and iron depletion as a result of gastrointestinal (GI) loss or surgical blood loss. In patients with CKD, medications and drug interactions such as gastric acid reducers or phosphate binders may cause poor intestinal absorption of iron. Also, patients with CKD not on dialysis are at an increased risk of inflammation with elevated C-reactive protein (CRP) and hepcidin levels, which causes poor iron absorption. [133]

Based upon current evidence, route of administration of iron therapy in patients with CKD did not make a significant difference in the ability to reduce the dose of or discontinue erythropoietin-stimulating agents (ESAs). Albaramki, et al. performed a comprehensive systematic review on IV iron therapy versus oral iron therapy. [134] For the purpose of this guideline, nine studies that evaluated outcomes in adult non-dialysis patients were reviewed. This systematic review reported that IV iron therapy was associated with a small but significant increase in hemoglobin, ferritin and transferrin saturation levels compared to oral iron therapy. Use of ESAs was varied. Adverse effects were reported in 50% of included studies. The most common side effects reported for oral iron therapy were GI-related; for IV iron therapy hypotensive and allergic reaction were the most common side effects. There was limited data on mortality, cardiovascular mortality and quality of life. One study reported patient-centered outcomes; however there was no significant difference between IV iron therapy and oral iron therapy. [134]

There is limited evidence to support recommendation for specific ferritin and transferrin saturation levels to start iron therapy, or as targets. The 2008 CKD CPG suggested ferritin levels be maintained

above 100 ng/mL and transferrin saturation more than 20% in patients with CKD not on dialysis. The Work Group concurred with these parameters, recognizing these are largely based on expert opinion.

The Work Group also assessed other potential burdens of IV iron therapy and oral iron therapy for the patient and provider. Some of the burdens for patients prescribed oral iron therapy would be potential GI side effects, pill burden, possible drug-drug interactions, and drug-diet interactions. For patients receiving IV iron therapy, some of the burdens would be increased costs; inconvenience of travel and time to an infusion center or clinic for treatment; risks associated with any IV therapy, such as venous infiltration; and potential serious adverse effects, such as anaphylaxis. Resource implications present challenges for IV iron therapy, such as need for IV iron infusion centers, additional cost of IV iron, and increased nursing time. Burdens to the provider are increased provider time to monitor response, order surveillance laboratory tests and availability to respond to potential severe adverse drug events.

It is the expert opinion of the Work Group that oral iron therapy is as effective as IV iron therapy in most cases. Patient preferences due to side effects, added patient costs and burdens and response to treatment should take priority in the treatment decision. If IV iron therapy is required, the Work Group suggests referral to nephrology, if not already done, for management of therapy. Future research is needed to explore oral iron therapy options in CKD patients, maximize the most effective dose regimens and assess long-term clinical benefits or adverse events associated with chronic use.

Safety and Efficacy of Erythropoiesis-Stimulating Agents

Recommendation

29. We recommend against offering erythropoietin-stimulating agents (ESAs) to patients with CKD for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension. (Strong Against)
30. We recommend against initiating ESAs at a hemoglobin level greater than 10 g/dL. (Strong Against)

Discussion

Anemia is a common complication that develops in patients with CKD, usually most prevalent when eGFR is consistently below 30 mL/min. Common factors for anemia in CKD include lack of effective erythropoietin (EPO) production by diseased kidneys, shortened life of red blood cells in uremic state, and the chronic inflammatory state seen in uremia. While its incidence and prevalence tends to increase as CKD progresses, anemia can occur at any CKD stage. Anemia with patients with CKD is normochromic and normocytic and has been associated with adverse effects on cardiac function, mental and cognitive decline, fatigue and dyspnea.

The 2008 CKD CPG recommended the use of hemoglobin to define anemia and to start an anemia work-up when hemoglobin falls below 13.0 g/dL in males and below 12.0 g/dL in females. Due to wide variability, the usage of hematocrit to define anemia is not recommended. There are other complete blood count (CBC) indices that are used in the differential diagnosis of anemia and to assess adequacy of bone marrow function. Evaluation of anemia in CKD should screen for all causes of anemia except for

EPO deficiency. Serum EPO levels in persons with CKD are usually inappropriately low and generally not helpful in establishing the differential diagnosis of anemia. The regular surveillance of hemoglobin for CKD patients is recommended. The frequency of monitoring should be influenced by the level of hemoglobin and the rate of decline.

Recognizing there are multiple etiologies for anemia, the objective of the evaluation is to determine the cause and to assess the potential reversibility of anemia with treatment. For the primary care provider, early awareness of anemia in patients with CKD, prompt diagnosis, and referral to nephrology are the cornerstones of clinical management.

Safety and efficacy of ESAs in CKD

The literature search included five systematic reviews, 13 RCTs and one case study which evaluated the safety and/or efficacy of ESA treatment in CKD patients with anemia. Outcomes of interest were all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, worsening hypertension, progression to ESRD, mean decrease in GFR, and quality of life.

In the evidence reviewed, the ESA treatment was effective in raising the mean hemoglobin. Recent data suggest that an ESA (darbepoetin alfa) effectively reduces the need for blood transfusions in patients with stage 3 to 5 CKD. [135-138] However, there was insufficient evidence to recommend specific thresholds for starting treatment or for maintaining hemoglobin within a certain target range to decrease the need for blood transfusions.

Treatment with ESAs is associated with risks and benefits and these should be discussed by a nephrologist or anemia management clinic with the patient. In weighing the potential harms versus benefits of ESA treatment, there was moderate evidence that treatment to higher hemoglobin targets was associated with increased risk of hypertension and cerebral vascular accident compared to lower hemoglobin targets. [138,139] There were no significant differences in all-cause mortality, [140,141] cardiovascular mortality or reducing progression to ESRD. [137,142] The TREAT study [138] was a large trial looking at the use of ESAs in patients with CKD, type 2 diabetes, and anemia that randomized patients to an ESA to achieve a hemoglobin of 13 g/dL or rescue ESA when the hemoglobin was less than 9 g/dL. The primary end-points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or ESRD. The use of an ESA did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event, or death or a renal event) and was associated with an increased risk of stroke. In patients with history of malignancy, ESA use was associated with increased adverse events, including increased mortality from cancer, tumor progression and thrombotic events. [138,143,144] In the 2008 VA/DoD CKD Clinical Practice Guideline review of other controlled trials on ESA treatment in patients with CKD and anemia (CHOIR and CREATE trials [145,146]), patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11.5 g/dL.

The FDA released its guidance on the usage of ESAs in 2011. [147] The Agency stated that the providers should individualize the dosing to use the lowest dose of ESA sufficient to reduce the need for red blood

cell transfusions and to adjust the dose as indicated. The FDA did not recommend a specific target range but did advise to initiate ESA treatment when the hemoglobin level falls below 10 g/dL. Other situations to consider use of ESA include the rate of decline suggesting the need for red blood cell transfusion; and the reduction of risks of alloimmunization and/or other risks related to red blood cell transfusion. If the hemoglobin level rises above 10 g/dL in patients with CKD not on dialysis, the FDA recommended lowering or stopping the ESA.

ESA use should be individualized based upon the rate of hemoglobin decline, prior response to iron therapy, and weighing the risks related to blood transfusion versus ESA therapy with the benefits of alleviation of symptoms. It advised not to start ESAs when hemoglobin is above 10 g/dL or to maintain hemoglobin above 11.5 g/dL. The harms outweigh the benefits of normalization of hemoglobin above 13 g/dL in patients with CKD. Recognizing there may be patients who may need higher hemoglobin due to symptom alleviation, other comorbidities, such as heart failure or pulmonary disease, and geography, such as living in high altitude. Providers need to discuss with the patient the risks of ESA use versus the benefits for these special circumstances.

Quality of life

There was incomplete reporting of full domains for assessment of quality of life, which did not support consistent data interpretation across all domains. The mean difference in the quality of life among those with the higher hemoglobin level was not statistically significant. [137-139] Similarly, in the 2014 Cochrane review, use of darbepoetin had little or no effect on quality of life. [139]

Comparisons of ESA products

None of the drug-specific studies included in the recent literature search were relevant, due to the drugs not being available on the U.S. market. Therefore, the Work Group was not able to compare specific ESA drugs against each other or different dosing strategies based on the recent literature review.

The Work Group considered other burdens associated with ESA use for patients with CKD not on dialysis, such as the cost of the drug, frequency of clinic visits for ESA injections and need for laboratory monitoring. There are also burdens to the provider for ESA management which include increase in resource allocations for the provider, laboratory, clinic staff and pharmacy. Additional burdens would include monthly laboratory monitoring, on-going surveillance of patient condition changes and prompt identification of critical findings requiring cessation of ESA treatment. Due to the ability to promptly identify risks associated with ESA use for patients with CKD and follow resource burdens, the Work Group encourages referral to a nephrology clinic or specialized clinic for ESA management.

Correction of Vitamin D Deficiency

Recommendations

31. We suggest offering supplemental vitamin D to correct vitamin D deficiency in patients with CKD stages 3 or 4. (Weak For)

Discussion

As noted in the previous VA/DOD CKD guideline (2008), vitamin D deficiency is common in the general population and may be even more common in patients with CKD. The Institute of Medicine (IOM) recommends a Recommended Dietary Allowance (RDA) of 600 IU/day (800 IU/day in those >70 years of age) vitamin D for bone health. In addition, the IOM concluded that intake of vitamin D above 4,000 IU/day increases the risk for harm. [148] It has been suggested that doses of 800 IU to 1000 IU per day are necessary for those individuals with inadequate sun exposure, and daily supplementation of 400 IU to 2,000 IU of cholecalciferol for the prevention of vitamin D deficiency in those at high risk. [149]

Three studies identified for this review examined the effects of oral cholecalciferol supplementation on biochemical parameters in CKD patients. [150-152] The average baseline serum calcidiol levels in two studies were indicative of vitamin D deficiency, [150,151] while the third study included patients with normal serum levels. [152] All three studies, varying in duration (one to six months) and dose (normalized monthly dose ranging from 200,000-300,000 IU), reported a significant improvement in serum calcidiol levels. Serum parathyroid hormone (PTH) levels improved significantly in one study, [151] tended to decline in another [150]and did not change in the third. [152] No changes were observed in serum calcium or phosphate levels. No incidence of hypercalcemia or hyperphosphatemia was reported in these studies. None of the three studies reported mortality or morbidity outcomes.

Although none of these studies reported convincing changes in biochemical parameters or other outcomes, the Work Group suggests that supplemental vitamin D (cholecalciferol or ergocalciferol) to correct vitamin D deficiency may be offered to CKD patients as recommended for the general population after six months of treatment.

Active Vitamin D Use

Recommendation

32. We suggest not offering active vitamin D analogs or calcitriol to patients with stage 3 and 4 CKD with elevated parathyroid hormone (PTH) levels due to lack of evidence for kidney, bone, or cardiovascular benefit and increased potential of harm from hypercalcemia. (Any use of active vitamin D analogs should be managed by a nephrologist.) (Weak Against)

Discussion

In CKD patients, the updated literature review identified studies with two orally active vitamin D compounds, paricalcitol [153-155] and doxercalciferol, [156] both compared with placebo. Kovesdy et al. [157] compared paricalcitol to ergocalciferol. All studies demonstrated a significant decline in PTH levels during 8 to 48 weeks of study duration. Thadhani et al. also noted a significant decline in bone-specific serum alkaline phosphatase levels. [154] Whereas Kovesdy et al. reported a significant increase in serum calcidiol levels in both paricalcitol and ergocalciferol groups, de Boer et al. found a significant decline in serum calcidiol levels with paricalcitol compared to placebo. The study also reported a significant elevation in serum fibroblast growth factor 23 (FGF23) levels in the paricalcitol treated group versus placebo. [153,157]

The study by Thadhani et al. [154] was designed to examine changes in left ventricular mass index by cardiac magnetic resonance imaging (MRI) and echocardiography in patients with left ventricular hypertrophy during paricalcitol therapy in a randomized, placebo controlled trial. They did not report a significant improvement in left ventricular mass index or left ventricular end-diastolic volume index after 48 weeks of therapy. The hospitalization rates from all causes did not differ between the two groups, although hospital admissions due to congestive heart failure were greater in the placebo group. [154]

Fishbane et al. [155] evaluated the effects of paricalcitol on proteinuria and eGFR in a randomized, placebo-controlled trial. Although a significant decrease in proteinuria was observed by these authors, the eGFR did not significantly change. [155]

The effects of active vitamin D compounds on changes in serum calcium and phosphate levels were variable. Thadhani et al. and de Boer et al. reported a significant increase in serum calcium levels and incidences of hypercalcemia with paricalcitol therapy. [153,154] The Thadhani et al. study also reported significantly higher serum phosphate levels in the treatment group compared to placebo. Fishbane et al., Patel et al. and Kovesdy et al. noted no differences in serum calcium or phosphate values. These disparate findings may be explained by varying sample size, dose and duration of treatment apparent in these clinical trials. [154-157]

Of note, Thadhani et al. found that the paricalcitol group experienced significantly higher serum creatinine levels and lower creatinine-based eGFR values when compared to placebo. This difference in eGFR was not observed with cystatin-C based eGFR measurements. The authors attributed the discrepancy in eGFR outcomes by serum creatinine and cystatin-C to reported increase in creatinine production by active vitamin D drugs. [154]

In a systemic review, Palmer et al. reported on studies that described bone histomorphomatric changes, bone density and fractures in CKD patients treated with active vitamin D compounds. [158] In one study, no significant differences were found in bone mineral density at femoral neck or lumber spine after 12 months of oral calcitriol therapy in 25 patients. In the same analysis, studies reporting changes in bone histomorphometry included small number of patients. These studies suggested that oral calcitriol may slightly improve osteitis fibrosa, but may increase the risk of developing osteomalacia. In another study reported in the same systemic review, calcitriol did not improve fracture rates with oral calcitriol in 38 patients.

In summary, in the absence of consistent evidence pointing toward kidney, bone or cardiovascular benefit (other than parathyroid hormone reduction) and because of the potential for harm of causing hypercalcemia, the Work Group suggests not offering active vitamin D analogs or calcitriol to patients with stage 3 and 4 CKD.

Phosphate Binders

Recommendation

33. We suggest not offering phosphate binders to patients with stage 3 and 4 CKD with normal serum phosphorous. *(Carryover modified from the 2008 CPG)* (Weak Against)

Discussion

In CKD patients, hyperphosphatemia occurs when GFR is reduced to less than 30-35 mL/min/1.73m^2. Serum phosphate levels are dependent on dietary phosphorus intake, intestinal absorption and renal excretion. The hormonal regulation by parathyroid hormone, vitamin D and FGF23 play a crucial role in the physiology of phosphorus homeostasis. Hyperphosphatemia in stage 4 CKD patients occurs due to ingestion of phosphorus containing foods, including additives and preservatives. The common metabolic consequences of hyperphosphatemia include changes in serum calcium and phosphorus levels, secondary hyperparathyroidism and vascular calcification. Changes in phosphaturic hormones, such as FGF23 and serum fetuin-A, an inhibitor of vascular calcification, are also reported.

The initial approach to manage hyperphosphatemia is dietary restriction of phosphorus-containing foods. Phosphate binders are currently approved by the FDA for the control of serum phosphate levels in end-stage renal disease patients receiving renal replacement therapy.

Oral phosphate binders are classified as calcium based (calcium carbonate or acetate) or non-calcium based (sevelamer, lanthanum salts, or iron-based, magnesium-based, or aluminum-based binders). Use of these agents in CKD patients have been evaluated in placebo-controlled and comparator clinical studies.

Five RCTs identified in patients with CKD not on dialysis were placebo-controlled studies, four of the five RCTs used a single agent, calcium acetate, [159] sevelamer [160] or lanthanum. [161,162] One study compared three drugs with placebo. [163] Two studies reported comparison of sevelamer with calcium carbonate [164] or calcium acetate. [165] Also of note, three of the seven studies were conducted in patients who had normal serum phosphorus levels, with a mean baseline < 4.6 mg/dL. [160,161,163]

The outcome parameters included changes in serum calcium, phosphate and parathyroid hormone (PTH) levels. Some studies measured serum calcitriol levels. [160,162,163] Few authors reported measurements of bone mineral density [160,161,163] or vascular calcification. [161,163] Only one study reported mortality data. [164]

Changes in serum PTH levels showed conflicting results. Using lanthanum carbonate versus placebo, Seifert et al. found no significant change in serum PTH or serum phosphate levels at 12 months in patients with normal baseline serum phosphorus (mean < 3.5 mg/dL), while Sprague et al. reported a significant decline in serum PTH and serum phosphate values after eight weeks of the same drug therapy. [161,162] Chue et al. examined sevelamer therapy with a placebo control in patients with normal serum phosphorus levels (mean baseline approximately 3.2 mg/dL) for 40 weeks. [160] They reported no significant differences in serum phosphorus, PTH, calcitriol or calcidiol levels or bone

mineral density between the two groups. Qunibi et al. evaluated calcium acetate versus placebo in nondialysis CKD patients with hyperphosphatemia (baseline phosphorous 5.1 mg/dL) and reported greater than 50% reduction in serum PTH levels associated with a significant decline in serum phosphate levels. [159] However, the drug therapy resulted in significant incidence of hypercalcemia. In a preliminary study, Block et al. conducted a 1:1:1 RCT using calcium acetate, sevelamer and lanthanum versus placebo in 148 patients with stage 3 and 4 CKD and normal serum phosphorus (mean baseline 4.2 mg/dL). [163] The authors reported no significant change in serum PTH levels with active therapy, while the placebo group showed 21% increase in serum PTH. Serum phosphate was significantly lower in the lanthanum group. The calcium acetate group showed improvement in annualized bone density. In a subgroup of patients, active phosphate binder therapy showed significant increase in calcification of coronary arteries and abdominal aorta. Using Hokanson criterion, 38% of patients in the phosphate-binder group had progression of coronary calcification compared with 17% in the placebo group ($p = 0.03$). Caglar et al. confirmed salutary effects of sevelamer and calcium acetate on serum phosphorus levels in stage 4 CKD patients with hyperphosphatemia (mean baseline 7.8 mg/dL). [165] However, both groups exhibited a significant increase in serum PTH levels at the end of eight weeks.

The evidence reviewed yielded conflicting and inconsistent results. Based on inadequate data and possible increased risk of vascular calcification, we do not recommend use of phosphate binders in patients with normal serum phosphorous levels. However, oral phosphate binders may be considered in patients with stage 3 or 4 CKD with elevated serum phosphorous levels that do not normalize with dietary interventions alone.

Calcimimetics

Recommendation

34. We suggest not offering calcimimetics to patients with stage 3 and 4 CKD due to lack of evidence for kidney or cardiovascular benefit and increased risk of harm from hypocalcemia. (Weak Against)

Discussion

Calcimimetic agents are approved for the control of secondary hyperparathyroidism in end-stage renal disease patients. Rated as a fair quality study, Chonchol et al. examined the effects of cinacalcet versus placebo in a 32 week study of patients with CKD stages 3 and 4. [166] The cinacalcet group showed a significant decline in serum parathyroid hormone levels, and a greater proportion of patients on therapy showed more than 30% fall in serum PTH values compared with the placebo group. However, approximately two thirds of patients treated with cinacalcet developed hypocalcemia. Importantly, cinacalcet therapy led to a 20% increase in serum phosphorus levels at the end of the study. The clinical significance of these biochemical changes in PTH is uncertain. No studies have documented any bone/mineral or cardiovascular benefit of calcimimetic treatment in CKD population. Due to substantial risk of developing hypocalcemia and a moderate possibility of developing hyperphosphatemia with cinacalcet therapy, we do not recommend this class of drugs to manage hyperparathyroidism in stage 3 and 4 CKD patients.

Summary

Complementing patient self-management strategies, there are numerous effective clinical management strategies that may be employed to reduce the adverse outcomes of CKD. Blood pressure control, appropriately tailored to patient tolerance, and preferential use of ACEI/ARBs in patients with hypertension and CKD with albuminuria are essential to limit progression of CKD to ESRD. Monitored dietary interventions including sodium and protein restriction in patients with CKD, and bicarbonate supplementation in patients with metabolic acidosis may also be useful in limiting progression to kidney failure. For patients with diabetes and CKD, the risks and benefits of intensive glycemic control need to be discussed with the patient and balanced to achieve patient-centered goals of care.

Prevention of cardiovascular disease and infection is paramount in this at-risk population, thus the directed use of statins and administration of prophylactic immunizations should be built into the routine care of patients with CKD.

In light of the increased possibility for adverse drug events in patients with CKD, vigilance is required to appropriately dose-adjust all medications for the patient's level of kidney function, avoid potentially hazardous combinations of medications, and limit the patient's exposure to potentially nephrotoxic agents.

Patient safety must also be considered and prudence applied when using medications to treat the complications of progressive kidney disease (e.g., ESAs to treat anemia, and oral phosphate binders, vitamin D analogs, and calcimimetics in the management of CKD bone and mineral disorders).

Lastly, the use of a multidisciplinary model of care and timely engagement of nephrology specialty care is suggested to more effectively meet the myriad needs of patients with CKD.

Knowledge Gaps and Recommended Research

The availability of high quality CKD research is limited due to the stipulation of CKD as a common exclusion criterion in non-kidney related trials. This has resulted in frequent reliance on either observational studies of CKD populations or secondary cohort analyses of RCTs involving non-CKD subjects rather than on primary CKD population health studies for insight into effective health care strategies in kidney disease. During the course of the literature review for this guideline, the Work Group identified a need for additional research to close the knowledge gap in the optimal primary and secondary prevention and treatment of patients with CKD.

The need for clinical trials and comparative effectiveness research was identified in key areas. First, there is a need for studies evaluating patient activation strategies such as patient education, in order to quantify the impact that patient education and self-management may have on clinical outcomes, and to determine the relative efficacy of tools and methodologies employed in the education process.

Second, the impact of alternative health care models and practitioners on clinical outcomes in CKD deserves attention. Particularly, with the VA/DoD investment in virtual care, there is a growing need to define the role and health care value of electronically facilitated access to care as compared to the traditional face-to-face model, especially in patients with complex disease such as CKD. There is also a need to better understand the optimal deployment of non-nephrologists and of primary care versus patient-aligned care teams to meet the needs of patients with CKD.

Third, the sparseness of literature on the effective dissemination and implementation of evidence-based CKD management strategies warrants further research. Literature investigating tools to translate evidence for optimal CKD care into clinical practice (e.g., virtual care models, smartphone apps, checklists, etc.) should be conducted.

An important gap in knowledge remains for the target blood pressure and the best antihypertensive choice for the older patient with CKD, where a careful balance of risks and benefits needs to be taken into consideration. Another gap in knowledge remains regarding the appropriate blood pressure target in patients with proteinuria. Additionally, future studies need to address the use of self-monitoring of blood pressure using the VA/DoD created tools, such as MyhealthyVET, health promotion mobile apps, and home telehealth.

Other recommendations for research include studies to gain an improved understanding of predictors of CKD progression to enable high risk population management. Confirming a benefit of targeted reduction of proteinuria on CKD outcomes is overdue. Also, strategies and tools to reduce the harm of treatments used in the CKD population need to be developed.

Newer forms of clinical trial design such as point of care/pragmatic research may be particularly cost effective and valuable in studying the care of CKD patients where there is clinical equipoise between competing management strategies**.**

A dearth of new literature exists about optimal nutrition prescriptions, but additional research

examining phosphate and micronutrients balance is necessary. Other recommended research includes mortality in CKD and CKD progression in high risk population management.

Further epidemiologic study of the impact of military occupational exposures on the development and progression of CKD is also warranted.

Finally, because of the substantial data assets of the VA health care system, including one of the world's largest genetic data bases, and its comprehensive, national, and longitudinal EHR, the VA is uniquely poised to offer insights into the drivers of health disparities in kidney disease and into the kidney health of the Veteran population.

Appendix A: Evidence Review Methodology

The Clinical Practice Guideline (CPG) Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on Chronic Kidney Disease (CKD). These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the Veterans Affairs (VA) and Department of Defense (DoD) populations. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [167]

P	Patients, Population or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, comorbidities, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 contains the final set of key questions used to guide the systematic review for this CPG.

Population(s)

The key questions are specific to adults 18 years or older with CKD In this review, CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health outcomes. [3] Patients with CKD stage 5 (end-stage renal disease), patients who have received a kidney transplant, and pediatric patients with CKD are not covered in this guideline.

Interventions

The therapeutic interventions considered under Key Question 1 and 2 of the review were the measures designed to prevent acute kidney injury. The reviews also addressed the association of occupational/

environmental exposure and acute kidney injury or CKD.

Treatments covered in Key Questions 3 through 7 of the review include the following: pharmacologic treatments such as renin-angiotensin blockade (ACEIs and ARBs), mineralocorticoid antagonists, direct renin inhibitors (e.g., aliskiren), statin therapy, diuretics, and erythropoiesis-stimulating agents (ESAs).

Management approaches considered in Key Questions 7 through 9, 11 and 12 included integrated models of patient care, consulting referral for nephrologist, impact of glycemic control and measures designed to improve safety and reduce risk of adverse drug events.

Self-management approaches considered in Key Question 10, which included strategies such as exercise, smoking cessation, nutrition, weight loss, health education, and lowering blood pressure.

Outcomes

For some Key Questions the outcomes of interest were measures of disease progression, including rate of progress to ESRD, increase in serum creatinine, proteinuria, and development of cardiovascular disease. For other key questions the outcomes of interest were patient-oriented clinical outcomes, including disease-related morbidity (e.g., stroke), treatment-related adverse events, hospitalization, quality of life and mortality. For Key Question 1 the outcome of interest was development of acute kidney injury. For Key Question 2 (occupational exposures), the outcome of interest was the degree of association with acute kidney disease or CKD. For Key Question 5 the outcomes of interest include change in blood markers such as vitamin D level, parathyroid hormone levels, and phosphate levels; DEXA scans; decrease in bone fractures; and mortality.

Conducting the Systematic Review

The methods guiding this systematic review are described below. In part, these methods follow the guidelines for conducting a systematic review set forth by the Agency for Healthcare Research and Quality (AHRQ) in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. [168] The methods also follow the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document. [7]

Extensive literature searches identified 7,172 citations potentially addressing the key questions of interest to this evidence review. Of those, 2,857 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 4,315 abstracts were reviewed with 3,050 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a Key Question of interest to this review, did not enroll population of interest, or published prior to January 2007. A total of 1,265 full-length articles were reviewed. Of those, 884 were excluded at a first pass review for the following: not addressing a key question of interest (42%), not enrolling the population of interest (26%), not meeting the inclusion criteria for clinical study or systematic review (21%), or being a duplicate (11%). A total of 381 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 262 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below.

Overall, 115 studies addressed one or more of the Key Questions and were considered as evidence in this review. Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. PRISMA Diagram of Literature Search Results

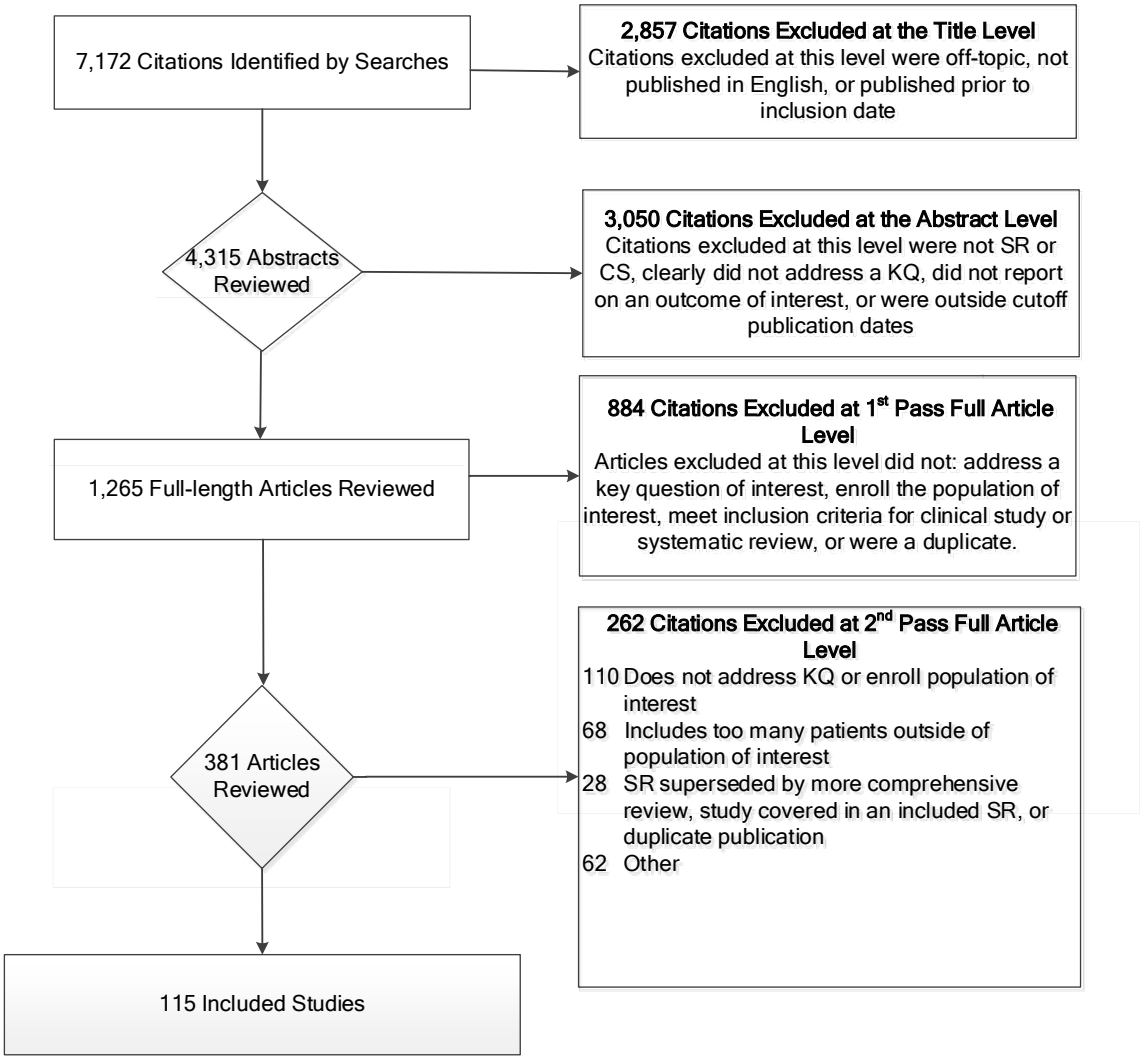

Table A-2. Evidence Base for Key Questions

Number of Question	Question	Number of Studies and Type of Studies
Screening/Prevention/Risk Factors		
1	In adult patients with CKD, what are the causes of and effective measures to prevent acute kidney injury?	2 systematic reviews, 19 randomized controlled trials (RCTs) and 1 non-randomized controlled study
2	In Veterans and military Service Members, what occupational exposures are nephrotoxic or increase the risk of CKD and therefore should prompt screening for CKD?	3 systematic reviews, 6 observational cohort studies and 1 cross-sectional study
Pharmacologic Treatments		
3	In adult patients with chronic kidney disease (CKD), is combined renin-angiotensin aldosterone (RAAS) blockade (ACEIs and ARBs), or spironolactone or eplerenone, or direct renin inhibitors in conjunction with RAAS inhibitor, safe and effective for slowing progress to end-stage renal disease (ESRD), slowing increase in serum creatinine (SCr), and decreasing proteinuria?	3 systematic reviews and 8 RCTs
4	In adult non-diabetic patients with CKD and dyslipidemia (LDL-C>100), what is the evidence that pharmacologic therapy is safe and effective as an adjunct to lifestyle changes in improving morbidity (such as decreased CVD, stroke) and mortality?	3 secondary analyses of RCTs and 1 primary RCT
5	In adult patients with CKD 3 and 4, what therapies are effective for treatment of CKD-mineral and bone disorder (MBD)?	2 systematic reviews and 10 RCTs
6	In adult patients with CKD and anemia, are ESAs safe and effective in increasing hemoglobin, improving QoL and slowing the progression of CKD and if so, how should iron be supplemented to optimize ESA effectiveness?	6 systematic reviews, 13 RCTs, and 1 case-control study
7	In adult hypertensive patients with CKD with and without proteinuria, what medication (ACEI, ARB, diuretics) should be used for controlling blood pressure? In adult patients with CKD, what is the evidence for a blood pressure target and what is the evidence that outcomes are differentially improved based on targets? Do those targets vary by age?	3 systematic reviews and 11 RCTs

Number of Question	Question	Number of Studies and Type of Studies
Management Strategies		
8	In patients with CKD and diabetes, what is the impact of glycemic control on slowing progression to ESRD, proteinuria, SCr, and decreased hospitalization? What is the optimal range of glycemic control to achieve the measures above and decrease morbidity?	1 systematic review, 2 RCTs and 2 retrospective cohort studies
9	In adult patients with stage 3 CKD, with and without diabetes, is consultation with a nephrology specialist associated with slowing progress to ESRD, slowing increase in serum creatinine, decreasing proteinuria, reducing development of cardiovascular disease (CVD), preparing and transitioning to renal replacement therapy and addressing advanced care planning?	4 observational study designs
10	In adults with CKD, what is the evidence that outcomes are improved by self- management strategies addressing:	8 systematic reviews and 4 individual studies (see below for breakdown according to specific self-management category)
	a. Blood pressure interventions	1 RCT
	b. Nutrition (protein restriction, micronutrients)	5 systematic reviews
	c. Weight loss management, maintenance of healthy body weight	1 systematic review
	d. Exercise	1 systematic review and 2 RCTs
	e. Smoking cessation	No studies identified
	f. Health education	2 systematic reviews and 1 prospective non-randomized controlled study
11	In adult patients with CKD, what measures (e.g., dose adjustment for eGFR, periodic laboratory monitoring, clinical reminders, informed consent, clinical pharmacist surveillance, education) have been proven to improve safety and reduce the risk of adverse drug events due to nephrotoxic or renally-cleared medications, including prescription drugs, OTCs, and nutritional supplements?	1 diagnostic performance study

Number of Question	Question	Number of Studies and Type of Studies
12	In adult patients with CKD, what integrated models of CKD patient care have been shown to improve outcomes? (Outcomes: proteinuria, SCr, slow progression to ESRD, decreased hospitalization, functional status, quality of life)	1 systematic review, 2 RCTs, and 5 non-randomized controlled studies
Total Evidence Base		**115 studies**

Criteria for Study Inclusion/Exclusion

General Criteria

- Clinical studies or systematic reviews published on or after January 1, 2007 (eliminated via filtered search)
- Studies must have been published in English (eliminated via filtered search)
- Publication must have been a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies were not accepted as evidence (partially eliminated via filtered search)
- Studies must have enrolled a patient population in which at least 85% of patients had CKD (stage 1, 2, 3, or 4) or associated condition or symptoms
- Studies enrolled adults 18 years or older; in studies that mixed adults and children, at least 85% of the enrolled patients had to be 18 years or older

Prevention, Pharmacologic Treatment, and Management Strategies

- Studies must have evaluated a treatment or management strategy for CKD
- Studies must have been a randomized controlled trial (RCT), prospective controlled clinical trial (CCT) or a systematic review of RCTs and/or CCTs. If no studies meet this criterion for all or part of a given key question, large observational studies (n ≥500 patients) will be considered for inclusion
- Crossover trials were considered only if data from the first treatment period were reported separately
- Studies must have enrolled ≥ 10 patients per treatment arm
- Studies must report data on at least one of the included outcomes
- Studies must have followed patients for at least 4 weeks; the exception is studies addressing Key Questions with acute kidney injury as an outcome (Key Question 1 and 2), which have no minimum follow-up time requirement
- All subjective outcomes (e.g., quality of life) must be measured using validated instruments

CKD Risk Factor Awareness Studies (Key Question 2)

- Studies must have been a case controlled or a comparative cohort study that assesses presence versus absence of occupational exposure (e.g., development of CKD in occupational exposure cohort versus cohort without exposure, or history of occupational exposure in patients with CKD versus comparison group without CKD)
- Studies must have investigated occupational exposures that may increase the risk of CKD. Expert

opinion papers were not considered as evidence addressing this question

Literature Search Strategy

Name	Date Limits	Platform/Provider
Agency for Healthcare Research and Quality (AHRQ)	2007 through December 12, 2013	U.S. Department of Health & Human Services
Cochrane Library	2007 through December 4, 2013	John Wiley and Sons, Ltd.
EMBASE	2007 through December 2, 2013	OVID Technologies, Inc.
MEDLINE	2007 through December 2, 2013	OVID Technologies, Inc.
National Institute of Health and Care Excellence (NICE)	2007 through December 4, 2013	National Institute for Health and Care Excellence
PubMed (In-process, Publisher, and PubMedNotMedline records)	2007 through December 4, 2013	National Library of Medicine (NLM)

EMBASE and Medline

The strategies below are presented in OVID syntax; the searches were simultaneously conducted across EMBASE and Medline.

OVID Conventions:

$ or * = truncation character (wildcard)

ADJn = search terms within a specified number (*n*) of words from each other in any order

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

Key Question 1

	Concepts	Search Statement
1	Acute kidney injury prevention	*acute kidney injury/et,pc
2	Acute kidney injury	*acute kidney injury/ or AKI.ti. or (acute adj (renal or kidney$) adj (injur$ or insufficienc$ or fail$)).ti.
3	Prevention and etiology	*primary prevention/ or *accident prevention/ or *biomarkers, pharmaceutical/ or (prevent$ or protect$ or caus$ or etiolog$).ti,ab.
4	Combine	1 or (2 and 3)
5	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
6	Combine	4 and 5

	Concepts	Search Statement
7	Limit by study type	6 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)
8	Limit by study type	6 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
9	Combine	7 or 8
10	Limit	9 to “all adult (19 plus years)” and English language and humans and yr=
11	Deduplicate	Remove duplicates from 10

Key Question 2

	Concepts	Search Statement
1	Chronic kidney disease	exp renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) adj (failure or disease)).ti,ab.
2	Acute kidney injury	exp acute kidney injury/ci or exp kidney diseases/ci
3	Nephrotoxicity	nephrotox$.mp.
4	Combine	1 or 2 or 3
5	Service Members	exp veterans/ or exp veterans health/ or exp military personnel/ or (veteran$ or military or army or navy or naval or marine$ or soldier$ or armed force$ or air force or coast guard$).mp.
6	Occupational exposures	exp occupational exposure/ or (OSHA or environment$ or work$ or vocation$ or occupation$).mp.
7	Combine	4 and 5 and 6
8	Deduplicate	remove duplicates from 7
9	Limit	8 to English and yr="2007 -Current"

Key Question 3

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.

	Concepts	Search Statement
2	Combined renin-angiotensin blockade (ACEIs and ARBs)	(exp *angiotensin-converting enzyme inhibitors/ or ACE inhibitor$.ti,ab. or ACE-I.ti,ab. or ACEI.ti,ab. or ACE-inhibitor$.ti,ab. OR (angiotensin ADJ3 inhibitor$).ti,ab.) and (exp *angiotensin receptor antagonists/ or ARB.ti,ab. or ARBs.ti,ab. or ((angiotensin or angiotensin-receptor) ADJ3 (block$ or antagonist$)).ti,ab.) OR renin-angiotensin blockade.ti,ab. or RAS blockade.ti,ab. or renin-angiotensin inhibitor.ti,ab. or RAS inhibitor.ti,ab.
3	Spironolactone	spironolactone/ or spironolactone.ti,ab.
4	Direct renin inhibitor	DRI.ti,ab. or (direct adj renin adj inhibitor$).ti,ab.
5	Combine	2 or 3 or 4
6	Treatment outcome	"outcome assessment (health care)"/ or treatment outcome/ or outcome$.ti,ab. or disease progression/ or progress$.ti,ab. or efficac$.ti,ab. or effective$.ti,ab.
7	Combine	1 and 5 and 6
8	Limit by study type	7 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)
9	Limit by study type	7 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
10	Combine	8 or 9
11	Limit	10 to English language and humans and "all adult (19 plus years)" and yr="2007 -Current"
12	Deduplicate	Remove duplicates from 11

Key Question 4

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Dyslipidemia	dyslipidemias/ or (dyslipid$ or dyslipoproteinemia$).ti,ab.
3	Pharmacologic therapy	drug therapy/ or (drug$ or medicat$ or pharma$).ti,ab.
4	Lifestyle changes	life style/ or health behavior/ or diet/ or exercise/ or weight loss/ or (lifestyle$ or life style$ or life-style$ or diet$ or exercis$ or nutrit$ or weigh$ or health$ or cessation$ or smok$).ti,ab.

	Concepts	Search Statement
5	Combine	1 and 2 and 3 and 4
6	Limit	5 to "all adult (19 plus years)" and humans and English language and yr="2007 -Current"
7	Deduplicate	Remove duplicates from 6

Key Question 5

	Concepts	Search Statement
1	Chronic kidney disease	exp renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Mineral and bone disorders	exp hyperparathyroidism, secondary/ or exp osteomalacia/ or exp bone diseases, metabolic/ or exp renal osteodystrophy/ or (hyperparathyroid$ or osteomalac$ or adynamic bone or (bone adj2 disease$) or mixed bone disease$ or renal osteodystroph$ or renal ricket$).ti,ab.
3	Mineral and bone disorder	((mineral$ ADJ3 bone$ ADJ3 disorder$) or MBD OR CKD-MBD or MBD-CKD or CKD-mineral bone disorder OR chronic kidney disease-mineral bone disorder).ti,ab.
4	Combine	(1 and 2) or 3
5	Stages 3 and 4	((advanced adj stage) or (stage adj (three or III or "3" or four or IV or "4" or 3?4))).ti,ab.
6	Combine	4 and 5
7	Limit	6 to "all adult (19 plus years)"
8	Limit	7 to English and yr="2007 -Current"
9	Deduplicate	remove duplicates from 8

Key Question 6

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Anemia	*anemia/ or anemi$.ti,ab.
3	Erythropoiesis-stimulating agents (ESAs)	*erythropoietin/ or (erythropoie$ or ESA OR ESAs).ti,ab.
4	Combine	1 and 2 and 3

	Concepts	Search Statement
5	Limit by study type	4 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)
6	Limit by study type	4 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
7	Combine	5 or 6
8	Limit	7 to "all adult (19 plus years)" and English and human and yr="2007 - Current"
9	Deduplicate	Remove duplicates from 8

Key Question 7

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Hypertension	*hypertension/ or hypertens$.ti,ab. or (blood ADJ pressure).ti,ab.
3	Antihypertensive agents	*antihypertensive agents/ or *diuretics/ or *angiotensin-converting enzyme inhibitors/ or *angiotensin receptor antagonists/ or (anti-hypertensive$ or antihypertensive$ or anti hypertensive$ or diuretic$ or ACE inhibitor$ or ACE-I or ACEI or ACE-inhibitor$ or ARB or ARBs).ti. or (angiotensin adj2 inhibitor$).ti. or ((angiotensin or angiotensin-receptor) adj2 (block$ or antagonist$)).ti.
4	Combine	1 and 2 and 3
5	Limit by study type	4 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)

	Concepts	Search Statement
6	Limit by study type	4 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
7	Combine	5 or 6
8	Limit	7 to English and human and yr="2007 -Current" and "all adult (19 plus years)"
9	Deduplicate	remove duplicates from 8

Key Question 8

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Diabetes	diabetes mellitus/ or diabet$.ti,ab.
3	Glucose	blood glucose/ or (glucose or glycemi$ or sugar$).ti,ab.
4	Control	(control$ or regulat$ or monitor$ or self-monitor$).ti,ab.
5	Blood glucose self-monitoring	blood glucose self-monitoring/
6	Combine	(3 and 4) or 5
7	Combine	1 and 2 and 6
8	Limit by study type	7 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)
9	Limit by study type	7 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
10	Combine	8 or 9
11	Limit	Limit 10 to English language and humans and "all adult (19 plus years)" and yr="2007 -Current"
12	Deduplicate	Remove duplicates from 11

Key Question 9

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Stage 3	(stage adj (three or III or "3")).ti,ab.
3	Nephrology specialist	nephrology/ OR nephrolog$.ti,ab. or specialization/ or special$.ti,ab. or consult$.ti,ab. or refer$.ti,ab.
4	Combine	1 and 2 and 3
5	Limit by study type	4 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)
6	Limit by study type	4 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
7	Combine	5 or 6
8	Limit	7 to English and humans and"all adult (19 plus years)" and yr="2007 - Current"
9	Deduplicate	remove duplicates from 8

Key Question 10

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Self-care	*self care/ or *risk reduction behavior/ or *health behavior/ or self-care.ti,ab. or self-management.ti,ab. or (behave$ and (risk$ or health$)).ti,ab. or (self ADJ (care$ or caring or manag$)).ti,ab.
3	Combine	1 and 2

	Concepts	Search Statement
4	Limit by study type	3 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)
5	Limit by study type	3 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
6	Combine	4 or 5
7	Limit	6 to "all adult (19 plus years)" and English language and humans and yr="2007 -Current"
8	Deduplicate	remove duplicates from 7

Key Question 11

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Safety/risk reduction	patient safety/ or biomarkers, pharmacological/ or risk reduction behavior/ or (safe$ or risk$).ti,ab.
3	Nephrotoxins	kidney/de or kidney/me or nephrotox$.ti,ab.
4	Renally cleared medication	(clear$ adj2 (renal or kidney)).ti,ab.
5	Combine	3 or 4
6	Combine	1 and 2 and 5
7	Limit by study type	6 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)

	Concepts	Search Statement
8	Limit by study type	6 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
9	Combine	7 or 8
10	Limit	9 to "all adult (19 plus years)" and English language and humans and yr="2007 -Current"
11	Deduplicate	remove duplicates from 10

Key Question 12

	Concepts	Search Statement
1	Chronic kidney disease	*renal insufficiency, chronic/ or CKD.ti,ab. or ((kidney OR renal) ADJ (failure or disease)).ti,ab.
2	Integrated health care	delivery of health care, integrated/ or (integrated adj (health or care or medicine$ or deliver$ or system$ or treatment$ or therap$ or model$)).ti,ab.
3	Integrative medicine	integrative medicine/ or complementary therapies/ or ((integrative or complementary or alternative) adj (health or care or medicine$ or medicat$ or drug$ or deliver$ or system$ or treatment$ or therap$ or model$)).ti,ab.
4	Combine	2 or 3
5	Combine	1 and 4
6	Limit by study type	5 and (randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp.)
7	Limit by study type	5 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt.)))
8	Combine	6 or 7
9	Limit	8 to "all adult (19 plus years)" and English and yr="2007 -Current"
10	Deduplicate	remove duplicates from 9

PubMed

The strategies below are presented in MeSH syntax; the searches were conducted in PubMed.

*	=	truncation character (wildcard)
[tiab]	=	limit to title or abstract

Key Question 1

	Concepts	Search Statement
1	Acute kidney injury	AKI OR (acute AND (renal OR kidney*) AND (injur* OR insufficienc*))
2	Prevention	caus* OR etiolog* OR prevent* OR protect*
3	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
4	Combine	1 AND 2 AND 3
5	Combine	4 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
6	Limit	5 to yr="2007 -Current"

Key Question 2

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Acute kidney injury	acute kidney injur*
3	Nephrotoxicity	Nephrotox*
4	Combine	1 OR 2 OR 3
5	Service Members	Veteran* OR military OR army OR navy OR naval OR marine* OR soldier* OR armed force* OR air force OR coast guard
6	Occupational exposures	OSHA OR environment* OR work* OR vocation* OR occupation*
7	Combine	4 AND 5 AND 6
8	Limit	7 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
9	Limit	8 to yr="2007 -Current"

Key Question 3

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure or disease))
2	Combined renin-angiotensin blockade (ACEIs and ARBs)	((renin-angiotensin blockade* OR RAS blockade* OR renin-angiotensin inhibitor* OR RAS inhibitor*)) OR (((ACE inhibitor* OR ACE-I OR ACEI OR ACE-inhibitor* OR (angiotensin AND inhibitor*))) AND (ARB OR ARBs OR ((angiotensin OR angiotensin-receptor*) AND (block* OR antagonist*))))
3	Spironolactone	spironolactone
4	Direct renin inhibitor	DRI OR (direct AND renin AND inhibitor*)
5	Combine	2 OR 3 OR 4
6	Treatment outcome	Outcome* OR progress* OR efficac* OR effective*
7	Combine	1 and 5 and 6
8	Limit by publication type	7 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
9	Limit	8 to yr="2007 -Current"

Key Question 4

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Dyslipidemia	Dyslipid* OR dyslipoproteinemia*
3	Pharmacologic therapy	Drug* OR medicat* OR pharma*
4	Lifestyle changes	Lifestyle* OR life style* OR life-style* OR diet* OR exercis* OR nutrit* OR weigh* OR health* OR cessation* OR smok*
5	Combine	1 AND 2 AND 3 AND 4
6	Limit	5 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
7	Limit	6 to yr="2007 -Current"

Key Question 5

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Mineral and bone disorders	Hyperparathyroid* OR osteomalac* OR adynamic bone OR (bone AND disease*) OR osteodystroph* OR renal ricket*
3	Mineral and bone disorder	MBD OR CKD-MBD OR MBD-CKD OR CKD-mineral bone disorder* OR chronic kidney disease-mineral bone disorder*
4	Combine	(1 AND 2) OR 3
5	Stages 3 and 4	(advanced AND stage) OR (stage AND (three OR III OR "3" OR four OR IV OR "4" OR 3?4))
6	Combine	4 AND 5
7	Limit	6 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
8	Limit	7 to yr="2007 -Current"

Key Question 6

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Anemia	Anemi*
3	Erythropoiesis-stimulating agents (ESAs)	Erythropoie* OR ESA OR ESAs
4	Combine	1 AND 2 AND 3
5	Limit	4 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
6	Limit	5 to yr="2007 -Current"

Key Question 7

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Hypertension	Hypertens* OR (blood AND pressure)

	Concepts	Search Statement
3	Antihypertensive agents	anti-hypertensive* OR antihypertensive* OR anti hypertensive* OR diuretic* OR ACE inhibitor* OR ACE-I OR ACEI OR ACE-inhibitor* OR ARB OR ARBs OR (angiotensin AND inhibitor*) OR ((angiotensin OR angiotensin-receptor) AND (block* OR antagonist*))
4	Combine	1 AND 2 AND 3
5	Limit	4 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
6	Limit	5 to yr="2007 -Current"

Key Question 8

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure or disease))
2	Diabetes	diabet*
3	Glucose	glucose OR glycemic* OR sugar*
4	Control	control* OR regulat* OR monitor* OR self-monitor*
5	Combine	1 AND 2 AND 3 AND 4
6	Limit	5 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
7	Limit	6 to yr="2007 -Current"

Key Question 9

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure or disease))
2	Stage 3	stage AND (three OR III OR "3")
3	Nephrology specialist	Nephrolog* OR special* OR consult* OR refer*
4	Combine	1 AND 2 AND 3
5	Limit	4 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
6	Limit	5 to yr="2007 -Current"

Key Question 10

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Self-care	self-care* OR self-management OR (behave* AND (risk* OR health*)) OR (self AND (care* OR caring OR manag*))
3	Combine	1 AND 2
4	Limit	3 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
5	Limit	4 to yr="2007 -Current"

Key Question 11

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))

	Concepts	Search Statement
2	Safety/risk reduction	safe* OR risk*
3	Nephrotoxins	nephrotox*
4	Renally cleared medication	clear* AND (renal OR kidney*)
5	Combine	3 OR 4
6	Combine	1 AND 2 AND 5
7	Limit	6 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
8	Limit	7 to yr="2007 -Current"

Key Question 12

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Integrated health care	integrated AND (health OR care OR medicine* OR deliver* OR system* OR treatment* OR therap* OR model*)
3	Integrative medicine	(integrative OR complementary OR alternative) AND (health OR care OR medicine* OR medicat* OR drug* OR deliver* OR system* OR treatment* OR therap* OR model*)
4	Combine	2 OR 3
5	Combine	1 AND 4
6	Combine	5 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
7	Limit	6 to yr="2007 -Current"

Cochrane

The strategies below were conducted in Cochrane.

* = truncation character (wildcard)

Key Question 1

	Concepts	Search Statement
1	Acute kidney injury	AKI OR (acute AND (renal OR kidney*) AND (injur* OR insufficienc* OR fail*))
2	Prevention	prevent* OR protect* OR caus* OR etiol*
3	Combine	1 AND 2
4	Limit by publication dates	3 from 2007 to 2013

Key Question 2

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR “chronic kidney disease” OR ((kidney OR renal) AND (failure OR disease))
2	Acute kidney injury	acute kidney injury
3	Nephrotoxicity	nephrotox*

	Concepts	Search Statement
4	Combine	1 OR 2 OR 3
5	Service Members	Veteran* OR military OR army OR navy OR naval OR marine* OR soldier* OR armed force* OR air force OR coast guard*
6	Occupational exposures	OSHA OR environment* OR work* OR vocation* OR occupation*
7	Combine	4 AND 5 AND 6
8	Limit by publication dates	7 from 2007 to 2013

Key Question 3

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR "chronic kidney disease" OR ((kidney OR renal) AND (failure or disease))
2	Combined renin-angiotensin blockade	((angiotensin-converting enzyme inhibitor* OR ACE inhibitor* OR angiotensin inhibitor* OR ACEI OR ACE-I) AND (angiotensin receptor antagonist* OR angiotensin blocker* OR ARB OR ARBs)) OR renin-angiotensin blockade* OR RAS blockade* OR renin-angiotensin inhibitor* OR RAS inhibitor*
3	Spironolactone	spironolactone
4	Direct renin inhibitor	DRI OR (direct AND renin AND inhibitor*)
5	Combine	2 OR 3 OR 4
6	Treatment outcome	outcome* OR progress* OR efficac* OR effective*
7	Combine	1 AND 5 AND 6
8	Limit by publication dates	7 from 2007 to 2013

Key Question 4

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR "chronic kidney disease" OR ((kidney OR renal) AND (failure OR disease))
2	Dyslipidemia	dyslipid* OR dyslipoproteinemia*
3	Pharmacologic therapy	drug* OR medicat* OR pharma*
4	Lifestyle changes	lifestyle* OR life style* OR life-style* OR diet* OR exercise* OR nutrit* OR weigh* OR health* OR cessation* OR smok*
5	Combine	1 AND 2 AND 3 AND 4
6	Limit by publication dates	5 from 2007 to 2013

Key Question 5

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR "chronic kidney disease" OR ((kidney OR renal) AND (failure OR disease))
2	Mineral and bone disorders	hyperparathyroid* OR osteomalac* OR renal osteodystroph* OR adynamic bone* OR bone disease* OR renal ricket*

	Concepts	Search Statement
3	Mineral and bone disorder	MBD OR CKD-MBD OR MBD-CKD OR (mineral AND bone AND disorder*)
4	Combine	(1 AND 2) OR 3
5	Stages 3 and 4	advanced stage* OR (stage AND (three OR III OR 3 OR four OR IV OR 4 OR 3-4 OR 3&4))
6	Combine	4 AND 5
7	Limit by publication dates	6 from 2007 to 2013

Key Question 6

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR "chronic kidney disease" OR ((kidney OR renal) AND (failure OR disease))
2	Anemia	anemi*
3	Erythropoiesis-stimulating agents (ESAs)	erythropoie* OR ESA OR ESAs
4	Combine	1 AND 2 AND 3
5	Limit by publication dates	4 from 2007 to 2013

Key Question 7

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR "chronic kidney disease" OR ((kidney OR renal) AND (failure OR disease))
2	Hypertension	hypertens* OR (blood AND pressure)
3	Antihypertensive agents	anti-hypertensive* OR antihypertensive* OR anti hypertensive* OR diuretic* OR ACE inhibitor* OR ACE-I or ACEI OR ACE-inhibitor* OR ARB OR ARBs OR ((angiotensin OR angiotensin-receptor) AND (block* OR antagonist*))
4	Combine	1 AND 2 AND 3
5	Limit by publication dates	4 from 2007 to 2013

Key Question 8

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR ((kidney OR renal) AND (failure OR disease))
2	Diabetes	diabet*
3	Glucose	glucose OR glycemic* OR sugar*
4	Control	control* OR regulat* OR monitor* OR self-monitor*
5	Combine	1 AND 2 AND 3 AND 4
6	Limit by publication dates	5 from 2007 to 2013

Key Question 9

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR “chronic kidney disease” OR ((kidney OR renal) AND (failure OR disease))
2	Stage 3	stage AND (three OR III OR 3)
3	Nephrology specialist	nephrolog* OR special* OR consult* OR refer*
4	Combine	1 AND 2 AND 3
5	Limit by publication dates	4 from 2007 to 2013

Key Question 10

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR “chronic kidney disease” OR ((kidney OR renal) AND (failure OR disease))
2	Self-care	(behave* AND (risk* OR health*)) OR (self AND (care* OR caring OR manag*))
3	Combine	1 AND 2
4	Limit by publication dates	3 from 2007 to 2013

Key Question 11

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR “chronic kidney disease” OR ((kidney OR renal) AND (failure OR disease))
2	Safety/risk reduction	safe* OR risk*
3	Nephrotoxins	nephrotox*
4	Renally cleared medication	(clear* AND (renal* OR kidney*))
5	Combine	3 OR 4
6	Combine	1 AND 2 AND 5
7	Limit by publication dates	6 from 2007 to 2013

Key Question 12

	Concepts	Search Statement
1	Chronic kidney disease	CKD OR “chronic kidney disease” OR ((kidney OR renal) AND (failure OR disease))
2	Integrated health care	integrated AND (health OR care OR medicine* OR deliver* OR system* OR treatment* OR therap* OR model*)
3	Integrative medicine	(integrative OR complementary OR alternative) AND (health OR care OR medicine* OR medicat* OR drug* OR deliver* OR system* OR treatment* OR therap* OR model*)
4	Combine	2 OR 3
5	Combine	AND
6	Limit by publication dates	5 from 2007 to 2013

Convening the Face-to-Face Meeting

In consultation with the Contracting Officer Representative (COR), the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on March 17-20, 2014. These experts were gathered to develop and draft the clinical recommendations for an update to the 2008 CKD CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to retain, revise, or reject each recommendation from the 2008 CKD CPG. The members also developed new clinical practice recommendations, not presented in the 2008 CKD CPG, based on the 2014 evidence review. The subject matter experts were divided into two smaller subgroups at this meeting.

Following the drafting of clinical practice recommendations, the Work Group assigned a grade for each recommendation based on a modified GRADE and US Preventative Service Task Force (USPSTF) methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [169]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource Use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life (QoL), decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects.

The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for CKD, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rate of "High", "Moderate", "Low" or "Very Low".

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values", "some variation", or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly

and others with multiple comorbidities may not be effective and depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility and subgroup considerations require similar judgments around the practically of the recommendation.

The framework below was used by the Work Group to guide discussions on each domain.

Table A-3. Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? Are the desirable anticipated effects large? Are the undesirable anticipated effects small? Are the desirable effects large relative to undesirable effects?	Benefits outweigh harms/burden Benefits slightly outweigh harms/burden Benefits and harms/burden are balanced Harms/burden slightly outweigh benefits Harms/burden outweigh benefits
Confidence in the quality of the evidence	
Is there high or moderate quality evidence that answers this question? What is the overall certainty of this evidence?	High Moderate Low Very low
Values and preferences	
Are you confident about the typical values and preferences and are they similar across the target population? What are the patient's values and preferences? Are the assumed or identified relative values similar across the target population?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	
Are the resources worth the expected net benefit from the recommendation? What are the costs per resource unit? Is this intervention generally available? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions Is there lots of variability in resource requirements across settings?	Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains. [169] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is

low. [170] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified". Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Drafting and Submitting the Final CPG

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2008 CKD CPG that would form the narrative text for the 2014 CKD CPG. During this time, the Champions also revised the 2008 algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the Evidence-Based Practice Working Group (EBPWG) following the publication of the 2014 CPG. The algorithms will be included as part of this CPG so as to provide a clear description of the flow of patient care. The final 2014 CKD CPG was submitted to the EBPWG in December 2014.

Appendix B: Pharmacotherapy with ACEIs or ARBs

Table B-1. Dosing Recommendations for ACEIs and ARBs in Patients with CKD[a,b]

DRUG	USUAL DOSE RANGE	COMMENTS/CAUTIONS
Angiotensin-Converting Enzyme Inhibitors (ACEIs)		
Benazepril	10 – 40 mg divided once or twice daily	o 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. o Use with caution in patients with renal artery stenosis. o Monitor potassium and kidney function (e.g., one-to-two weeks after initiation or dose adjustment) o Concomitant therapy with potassium-sparing diuretics, potassium supplements, and/or additional RAAS blockers may result in hyperkalemia. o Boxed Warning: due to the potential risk for fetal morbidity and mortality in patients taking an ACEI during pregnancy, it is recommended that therapy be discontinued as soon as a woman becomes pregnant; alternate therapy should be considered. o Contraindicated in patients with a history of angioedema on an ACEI.
Captopril[c]	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[c]	7.5 – 30 mg divided once or twice daily	
Perindopril	4 – 8 mg divided once or twice daily	
Quinapril	10 – 40 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)		
Azilsartan	80 mg once daily	o Consider lower doses in patients with intravascular volume depletion (e.g., patients currently being treated with a diuretic). o Use with caution in patients with renal artery stenosis. o Monitor potassium and renal function after initiation. o Concomitant therapy with potassium-sparing diuretics, potassium supplements, and/or additional RAAS blockers may result in hyperkalemia. o Boxed Warning: due to the potential risk for fetal morbidity and mortality in patients taking an ARB during pregnancy, it is recommended that therapy be discontinued as soon as a woman becomes pregnant; alternate therapy should be considered. o Use with caution in patients with a history of angioedema on an ACEI. o An ARB may be considered in patients unable to tolerate an ACEI due to cough.
Candesartan	8 – 32 mg once daily	
Eprosartan	400 – 800 mg divided once or twice daily	
Irbesartan	150 – 300 mg once daily	
Losartan	25 – 100 mg divided once or twice daily	
Olmesartan	20 – 40 mg once daily	
Telimisartan	20 – 80 mg once daily	
Valsartan	80 – 320 mg once daily	

Refer to www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx for a current list of medications on the VA National Formulary

[a] Adapted from VA/DoD Clinical practice guideline for management of chronic kidney disease in primary care. Washington DC: Department of Veteran Affairs and Department of Defense; Version 2.0 - 2007.
[b] Facts & Comparisons® eAnswers http://efactsonline.com/ Accessed 2014 Apr 25.
[c] One hour before meals, on an empty stomach.

Appendix C: Evidence Table

	2008	2014		
Recommendation	**Grade[12]**	**Evidence[13]**	**Strength of Evidence[14]**	**Strength of Recommendation[15]**
Evaluation for Chronic Kidney Disease				
1. While there is insufficient evidence to associate exposure to depleted uranium and solvents such as hydrocarbons with CKD, we suggest that clinicians take a detailed occupational and non-occupational history.	-		Very Low	Weak For
2. We suggest that periodic evaluation for CKD be considered in patients with the following: a. Diabetes, hypertension, other end organ disease (e.g., chronic heart failure [CHF]), or a personal or family history of kidney disease b. Systemic illness (e.g., human immunodeficiency virus [HIV], systemic lupus erythematosus, multiple myeloma) c. History of acute kidney injury (AKI) (e.g., acute tubular necrosis, urinary tract obstruction, interstitial nephritis) d. Elderly patients e. Races and ethnicities associated with increased risk (e.g., African Americans,	C →			Weak For

[12] The 2008 VA/DoD CKD CPG used the U.S. Preventive Services Task Force (USPSTF) evidence grading system. http://www.uspreventiveservicestaskforce.org.
[13] The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2014 guideline Work Group, the literature cited corresponds directly to the 2013 evidence review. For recommendations that have been carried over from the 2008 VA/DoD CKD CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to either 1) studies that support the recommendation and which were identified through the 2014 evidence review, or 2) relevant studies that support the recommendation, but which were not systematically identified through a literature review.
[14] The strength of evidence is only one of four domains in the GRADE system that factor into the strength of recommendation. See the Grading Recommendations section for more information.
[15] Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

Recommendation	2008 Grade[12]	2014 Evidence[13]	2014 Strength of Evidence[14]	2014 Strength of Recommendation[15]
Hispanics, Native Americans)				
Acute Kidney Injury Avoidance				
3. We suggest that patients at increased risk for CIN receive volume expansion with intravenous (IV) isotonic crystalloid solutions (saline or sodium bicarbonate) prior to and following iodinated contrast administration.	-	[16] [17] [18] [19] [20] [21] [22] [23] [24]	Very Low	Weak For
4. We suggest offering oral hydration to patients in which IV hydration is not feasible for CIN prophylaxis.	-	[26]	Low	Weak For
5. Given inconsistent evidence, we do not recommend for or against the routine administration of N-acetylcysteine (NAC) for CIN prophylaxis.	-	[31]	Low	Weak For
6. We recommend against the use of renal replacement therapy (RRT) for CIN prophylaxis.	-	[49]	Very Low	Strong Against
7. We suggest not initiating statin therapy for the purpose of CIN prophylaxis in patients undergoing elective angiography.	-	[15] [50] [51]	Moderate	Weak Against
8. We suggest not offering theophylline therapy for CIN prophylaxis for patients undergoing elective coronary angiography.	-	[52] [53]	Low	Weak Against
Management of Chronic Kidney Disease				
Self-Management Strategies				
9. We suggest the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with CKD.	-	[55] [171] [57]	Low	Weak For
10. In patients with stage 3 and 4 CKD, we suggest a protein diet of 0.6 to 0.8 g/kg/day as it may slow the decline in glomerular filtration rate (GFR) and	B →	**Additional Evidence:**	Low	→ Weak For

Recommendation	2008	2014		
	Grade[12]	Evidence[13]	Strength of Evidence[14]	Strength of Recommendation[15]
progression to end-stage renal disease (ESRD).		[58] [59] [60]		
11. There is insufficient evidence to recommend for or against weight loss in obese patients as an intervention to reduce proteinuria or to slow progression of CKD. However, we suggest weight loss interventions in obese patients as part of an overall health improvement strategy.	-	[63]	Very Low	Weak For
12. There is insufficient evidence to recommend for or against exercise with or without lifestyle intervention to reduce ESRD, mortality, change in GFR, or change in urinary protein. However, we suggest regular exercise as part of an overall health improvement strategy.	-	[64] [65] [66]	Very Low	Weak For
13. There is insufficient evidence to recommend for or against health education to reduce time to dialysis initiation or to reduce mortality. However, we suggest CKD health education because it supports the aim of maximizing patient-centered care.	-	[64] [67] [68]	Very Low	Weak For
14. There is insufficient evidence to recommend smoking cessation to halt progression of CKD, however, we suggest tobacco cessation for cardiovascular risk reduction in patients with CKD.	-		Very Low	Weak For
Clinical Management Strategies				
15. We suggest offering multidisciplinary care, if available, for patients with CKD to reduce non-fatal stroke, slow progression from micro- to macroalbuminuria, and reduce all-cause mortality.	-	[72] [73] [64] [74] [75]	Low	Weak For
16. Although there is insufficient evidence to recommend for or against referral to a nephrology specialist for patients with stage 3 CKD for slowing CKD progression, we suggest consultation with a nephrologist to assist in the diagnosis and treatment of patients with any of the following conditions: a. eGFR <30 mL/min/1.73 m^2 to facilitate education and planning for renal	-	[76] [77] [78] [79]	Low	Weak For

Recommendation	2008 Grade[12]	2014 Evidence[13]	2014 Strength of Evidence[14]	2014 Strength of Recommendation[15]
replacement therapy (dialysis or kidney transplant) b. Kidney function that is rapidly worsening without obvious cause c. Metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism) d. CKD of unclear etiology after initial work-up, or has a known or suspected kidney condition requiring specialized care e. Nephrotic range proteinuria f. Nephrolithiasis				
17. We recommend that treatment with the following vaccinations be considered for patients with CKD as a measure to prevent infections: a. Influenza vaccine* b. Tdap vaccine c. Pneumococcal polysaccharide vaccine (i.e., PCV 13 and PPSV23) d. Hepatitis B vaccine e. Zoster /shingles vaccine* f. Varicella vaccine* g. MMR vaccine* (*Note: Live vaccines, including nasal influenza (LAIV), may be contraindicated in those patients with CKD and severe immunodeficiency including treatment with immunosuppressive agents)	A-C →	**Additional Evidence:** [80] [82] [83] [84] [85]		Strong For
18. We recommend that clinicians avoid or limit the use of nephrotoxic medications for patients with CKD.	D →	**Additional Evidence:** [86] [87] [88]		Strong For
19. In patients with CKD, we suggest that medications should be reviewed and their dosing modified, where appropriate, according to the level of the patient's kidney function.	C →	**Additional Evidence:** [90] [89]		Weak For

Recommendation	2008 Grade[12]	2014 Evidence[13]	2014 Strength of Evidence[14]	2014 Strength of Recommendation[15]
		[91]		
20. We suggest the use of bicarbonate supplementation in CKD patients with metabolic acidosis to slow the progression of CKD.	-	[93] [94]	Very Low	Weak For
21. In adult patients with stages 1-4 CKD, we recommend that blood pressure targets should be less than 140/90 mmHg.	C →	**Additional Evidence:** [95]	Low	→ Strong For
22. In patients with non-diabetic CKD, hypertension, and albuminuria, we recommend the use of an angiotensin-converting-enzyme inhibitor (ACEI) to prevent progression of CKD. Angiotensin II receptor blockers (ARBs) may be substituted for patients with an ACEI-induced cough.	A →	**Additional Evidence:** [96]	Moderate	→ Strong For
23. In patients with diabetes, hypertension, and albuminuria, we recommend the use of an ACEI or ARB to slow the progression of CKD, unless there is documentation of intolerance.	A →	**Additional Evidence:** [96]	Moderate	→ Strong For
24. We recommend against the use of combination renin-angiotensin-aldosterone system (RAAS) blockade (ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor) in patients with CKD.	-	[108] [107] [110] [111] [109] [112] [113] [114] [115] [116] [117]	Moderate	Strong Against
25. We recommend that all patients with CKD who are not on dialysis and have no known history of coronary artery disease be assessed for 10-year CVD risk using a validated risk calculator for primary prevention. If at risk (as defined in the	-	[121] [122] [123] [124]	Low	Strong For

Recommendation	2008 Grade[12]	2014 Evidence[13]	2014 Strength of Evidence[14]	2014 Strength of Recommendation[15]
VA/DoD Management of Dyslipidemia guideline), we recommend use of at least a low dose statin.		[125] [126] [127]		
26. We suggest against the use of statins prescribed with the intent of slowing eGFR decline or preserving kidney function.	-	[123] [124] [125] [126]	Low	Weak Against
27. We recommend against intensive glycemic control to patients with stage 3 or worse CKD due to the lack of benefit on renal or cardiovascular outcomes and potential for significant harm.	N/A →	**Additional Evidence:** [131] [132]		Strong Against
28. We suggest initiation of oral iron therapy (in preference to parenteral) to support iron requirements in patients with CKD stages 3 and 4.	-	[134]	Moderate	Weak For
29. We recommend against offering erythropoietin-stimulating agents (ESAs) to patients with CKD for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension.	-	[135] [136] [137] [138] [139] [141] [140] [142] [143] [144] [145] [146]	Moderate	Strong Against
30. We recommend against initiating ESAs at a hemoglobin level greater than 10 g/dL.	-	[135] [136] [137] [138] [139]	Moderate	Strong Against

Recommendation	2008	2014		
	Grade[12]	Evidence[13]	Strength of Evidence[14]	Strength of Recommendation[15]
		[141] [140] [142] [143] [144] [145] [146]		
31. We suggest offering supplemental vitamin D to correct vitamin D deficiency in patients with CKD stages 3 or 4.	-	[150] [151] [152]	Low	Weak For
32. We suggest not offering active vitamin D analogs or calcitriol to patients with stage 3 and 4 CKD with elevated parathyroid hormone (PTH) levels due to lack of evidence for kidney, bone, or cardiovascular benefit and increased potential of harm from hypercalcemia. (Any use of active vitamin D analogs should be managed by a nephrologist.)	-	[153] [154] [155] [156] [157] [158]	Moderate	Weak Against
33. We suggest not offering phosphate binders to patients with stage 3 and 4 CKD with normal serum phosphorous.	N/A →	**Additional Evidence:** [159] [160] [161] [162] [163] [164] [165]	Low	→ Weak Against
34. We suggest not offering calcimimetics to patients with stage 3 and 4 CKD due to lack of evidence for kidney or cardiovascular benefit and increased risk of harm from hypocalcemia.	-	[166]	Low	Weak Against

Appendix D: Participant List

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Appendix E: Acronyms List

Abbreviation	Definition
ACC	American College of Cardiology
ACEI	angiotensin-converting enzyme inhibitor
AER	albumin excretion rate
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AKI	acute kidney injury
APIR	actual protein intake ratio
ARA	aldosterone receptor antagonist
ARB	angiotensin II receptor blockers
BP	blood pressure
CBC	complete blood count
CBOC	community-based outreach clinics
CCB	calcium channel blocker
CCT	controlled clinical trial
CDC	Centers for Disease Control and Prevention
CHF	chronic heart failure
CI	confidence interval
CIN	contrast-induced nephropathy
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
COR	Contracting Officer Representative
CPG	clinical practice guideline
CrCL	creatinine clearance
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CV	cardiovascular
CVD	cardiovascular disease
DM	diabetes mellitus
DoD	Department of Defense
DRI	direct renin inhibitor
EBPWG	Evidence-Based Practice Working Group
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
ESA	erythropoietin-stimulating agents
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
FMH	furosemide with matched hydration
GFR	glomerular filtration rate
GI	gastrointestinal
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
HPV	human papillomavirus

Abbreviation	Definition
HR	hazard ratio
HTN	hypertension
IV	intravenous
LPD	low protein diets
MBD	mineral and bone disorder
MDC	multidisciplinary care
MDRD	modification of diet in renal disease
MI	myocardial infarction
MRI	magnetic resonance imaging
NAC	N-acetylcysteine
NSAID	non-steroidal anti-inflammatory drug
PCP	primary care provider
PTH	parathyroid hormone
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RIPC	remote ischemic pre-conditioning
RPD	regular protein diets
RR	relative risk
RRT	renal replacement therapy
SCr	serum creatinine
TC	total cholesterol
UAER	urinary albumin excretion rate
USPSTF	US Preventative Service Task Force
VA	Department of Veteran Affairs
VHA	Veterans Health Administration
WMD	weighted mean difference

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