



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

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 healthcare 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 Department of Veterans Affairs or 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.

Version 4.0 – 2019

Prepared by:

The Management of Chronic Kidney Disease Work Group

With support from:

The Office of Quality, Safety and Value, VA, Washington, DC

&

Office of Evidence Based Practice, U.S. Army Medical Command

Version 4.0 – 2019

Based on evidence reviewed through November 2018

Table of Contents

I. Introduction.....	6
II. Background.....	6
A. Description of Chronic Kidney Disease	6
B. Epidemiology and Impact in the General Population	7
C. CKD in the Department of Defense and the Department of Veterans Affairs Populations.....	7
III. About this Clinical Practice Guideline	7
A. Methods.....	8
a. Grading Recommendations.....	9
b. Reconciling 2014 Clinical Practice Guideline Recommendations.....	10
c. Peer Review Process	11
B. Summary of Patient Focus Group Methods and Findings.....	11
C. Potential Conflicts of Interest.....	12
D. Scope of this Clinical Practice Guideline	13
E. Highlighted Features of this Clinical Practice Guideline	13
F. Patient-centered Care	14
G. Shared Decision Making	14
H. Co-occurring Conditions	14
I. Implementation	15
IV. Guideline Work Group	16
V. Algorithm	17
A. Module A: Screening for CKD and Initial Assessment	18
B. Module B: Evaluation for AKI or New Decline in Renal Function	20
C. Module C: Evaluation for CKD	22
D. Module D: Management of Patients with CKD Requiring Iodinated Contrast.....	25
VI. Recommendations.....	27
A. Diagnosis Assessment and Lab Monitoring	30
B. General Management Strategies	38
a. Team Management and Education	38
b. Indication for Referral to Nephrology for Renal Replacement Therapy Including Dialysis and Renal Transplant.....	43
C. Non-pharmacologic Management of CKD	47
a. Nutrition.....	47

D.	Pharmacologic Management of CKD and Associated Conditions.....	49
a.	<i>Diabetes Medications</i>	49
b.	<i>Hypertension Medications</i>	53
c.	<i>Anemia Medications</i>	59
d.	<i>Bone Health Medications</i>	63
e.	<i>Other Medications to Slow CKD Progression</i>	65
E.	Contrast-Associated Kidney Injury Management.....	68
VII.	Future Research	75
Appendix A:	Evidence Review Methodology	77
A.	Developing the Key Questions	77
B.	Conducting the Systematic Review.....	85
C.	Convening the Face-to-face Meeting.....	90
D.	Grading Recommendations.....	91
E.	Recommendation Categorization	94
F.	Drafting and Submitting the Final Clinical Practice Guideline.....	96
Appendix B:	Patient Focus Group Methods and Findings	98
A.	Methods.....	98
B.	Findings	98
Appendix C:	Evidence Table	101
Appendix D:	2014 Recommendation Categorization Table	106
Appendix E:	Participant List	112
Appendix F:	Literature Review Search Terms and Strategy	113
A.	Embase.com syntax	113
Appendix G:	Alternative Text Descriptions of Algorithms	123
Module A:	Screening for CKD and Initial Assessment.....	123
Module B:	Evaluation for AKI or New Decline in Renal Function.....	124
Module C:	Evaluation for CKD	125
Module D:	Management of Patients with CKD Requiring Iodinated Contrast.....	126
Appendix H:	Management of CKD Table	128
Appendix I:	Monitoring of CKD Table	130
Appendix J:	Special Considerations When Caring for Older Veterans with CKD	131
A.	Other Considerations.....	132

Appendix K: Nephrotoxic Agents and Medication Dose Adjustments in CKD 133

 A. Background 133

 B. Nephrotoxic Medications 133

 C. Medication dose adjustments in CKD 134

Appendix L: Pain Management in CKD 138

Appendix M: Military occupational exposures and CKD 140

Appendix N: Nephrolithiasis 141

Appendix O: Gadolinium..... 142

Appendix P: Abbreviation List 143

References 147

I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "...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 (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.^[1] This CPG is intended to provide healthcare providers with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients at risk for chronic kidney disease (CKD), thereby leading to improved clinical outcomes.

In 2014, the VA and DoD published an updated CPG for the Primary Care Management of CKD (2014 CKD CPG), which was based on evidence reviewed through January 2013. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of CKD.

Consequently, a recommendation to update the 2014 CKD CPG was initiated in 2018. The updated CPG includes objective, evidence-based information on the management of CKD. It is intended to assist healthcare providers in all aspects of patient care, including, but not limited to, screening, assessment, treatment, and follow-up. The system-wide goal of evidence-based guidelines is to improve the patient's health and well-being by guiding health providers who are taking care of patients with CKD along management pathways that are supported by evidence. The expected outcome of successful implementation of this guideline is to:

- Assess the patient's condition and determine, in collaboration with the patient, the best treatment method
- Optimize each individual's health outcomes and improve quality of life (QoL)
- Minimize preventable complications and morbidity
- Emphasizing the use of patient-centered care (PCC)

II. Background

A. Description of Chronic Kidney Disease

CKD is defined as an abnormal glomerular filtration rate (GFR) or a normal GFR with other markers of kidney disease such as proteinuria, hematuria, or abnormal images of the kidneys. In 2002, the National Kidney Foundation (NKF) published treatment guidelines that delineated five stages of CKD based on declining estimated GFR (eGFR) measurements.^[2] Subsequently, Kidney Disease Improving Global Outcomes (KDIGO) released a CKD guideline in 2012 which further subdivided stage 3 CKD and added subdivisions for albuminuria in each stage.^[3] The stages of CKD are described in [Algorithm: Module C, Sidebars 9a and 9b](#). For any given stage of CKD, the presence of albuminuria, designated as categories A1-A3, is associated with an increased risk of CKD progression. Mortality increases with each higher stage of CKD. Even advanced CKD can be asymptomatic until uremic symptoms develop, at which time renal replacement is required. Interventions described in this CPG can slow the progression of CKD and reduce

mortality. However, as discussed in [Recommendation 1](#), universal screening or even screening of higher risk populations may not always be indicated.

B. Epidemiology and Impact in the General Population

The overall prevalence of CKD (Stages 1-5) in the adult general population in the United States (U.S.) was 14.8% between 2013 and 2016.^[4] Only 9% of patients with CKD are aware of their kidney disease despite efforts to raise community awareness.^[5] The prevalence of CKD increases with age and peaks after the age of 70.^[6] CKD can be caused by several conditions that are more prevalent with advancing age.

C. CKD in the Department of Defense and the Department of Veterans Affairs Populations

There is no published data on the prevalence of CKD in the military. Any data from the military would be biased because the presence of CKD could be an exclusion criterion for continued active service. The Centers for Disease Control and Prevention (CDC) took data from both the National Health and Nutrition Examination Survey (NHANES) and the VA databases to determine the prevalence of CKD in the general population and the VA respectively.^[6] The NHANES dataset covered the years of 1999 to 2016 and included patients with CKD stages 1-4 based on the presence of albuminuria or an eGFR less than 90 mL/min/1.73 m². The prevalence ranged from 13-16%. The VA dataset covered the years of 2005 to 2018 and included Veterans with CKD stages 3-5 based on an eGFR of less than 60 mL/min/1.73 m². Stages 1 and 2 were not included because of the lack of urine albumin measurements.^[6] An abstract by Saran et.al. (2016) reported the prevalence of U.S. Veterans with CKD could range from 16.4% to 36.3% if a restricted or liberal definition is used.^[7] This combined data suggests that CKD is probably more prevalent in the Veteran population. The most important comorbid conditions contributing to CKD are hypertension and diabetes mellitus (DM), both of which can be exacerbated by overweight and obesity. These comorbid conditions are all more prevalent in the Veteran population compared to the general U.S. population, which may explain the increased prevalence of CKD in Veterans.^[8-10] Other contributors to CKD in Veterans could be related to occupational hazards experienced in the military, such as burn pits, Agent Orange, radiation, or other exposures (see [Appendix M](#)).

III. About this Clinical Practice Guideline

This updated guideline represents a significant step toward improving the management of CKD in the VA and DoD. As with other CPGs however, challenges remain, including evidence gaps, the need to develop effective strategies for guideline implementation, and the need to evaluate the effect of guideline adherence on clinical outcomes. This guideline is intended for VA and DoD primary care practitioners, including physicians, physician assistants, and nurse practitioners, as well as nurses, pharmacists, dietitians, CKD educators, social workers, care managers, and others who care for patients with CKD.

As elaborated in the qualifying statement on page one, 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 patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on scientific publications available by November 2018, and is intended to provide a general guide to best practices. For selected topics (i.e., use of sodium-glucose co-transporter 2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists), a limited update of the literature was performed to

capture important evidence published after November 2018. The guideline can assist care providers, but the guidance of a CPG must always be considered within the context of patient values and preferences and a provider's clinical judgment, for the care of an individual patient.

A. Methods

The current document is an update to the 2014 CKD CPG. The methodology used in developing the 2019 CPG follows the *Guideline for Guidelines*, an internal document of the VA and DoD EBPWG that was updated in January 2019.^[11] The *Guideline for Guidelines* can be downloaded from <http://www.healthquality.va.gov/policy/index.asp>. 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 a new or 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 providers within the VA/DoD healthcare systems as well as those within the community who treat individuals within the VA and DoD. Specifically, the Champions and Work Group members for this guideline were responsible for identifying the key questions (KQs) of the most clinical relevance, importance, and interest for the management of CKD. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level and quality of the evidence. The amount of new scientific evidence that had accumulated since the previous version of the CPG was also taken into consideration in the identification of the KQs. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- 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, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified four clinical leaders, Christopher Dyer, MD, FACP, and Jeffrey Penfield, MD, from the VA, and Mai Nguyen, MD, FACP, FASN, and Lt Col Jonathan Sosnov, MD, MSc, from the DoD, as Champions for the 2019 CPG.

The Lewin Team, including The Lewin Group, Duty First 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 first conference call was held in April 2018, with participation from the contracting officer's representative (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, participants discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing and prioritizing specific research questions on which to base a systematic review (SR) about the assessment and management of patients at risk for 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: behavioral health, geriatrics, nephrology, nursing, nutrition, primary care, social work and pharmacology.

The guideline development process for the 2019 CPG update consisted of the following steps:

1. Formulating and prioritizing KQs and defining critical outcomes
2. Convening a patient focus group
3. Conducting the systematic evidence review
4. Convening a face-to-face meeting with the CPG Champions and Work Group members
5. Drafting and submitting a final CPG on the management of CKD to the VA/DoD EBPWG

[Appendix A](#) provides a detailed description of each of these tasks.

a. Grading Recommendations

The Champions and Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[25]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Patient or provider values and preferences
- Other implications, as appropriate, e.g.:
 - ◆ Resource use
 - ◆ Equity
 - ◆ Acceptability
 - ◆ Feasibility
 - ◆ Subgroup considerations

Using these four domains, the Work Group determined the relative strength of each recommendation (“Strong” or “Weak”). A “Strong” recommendation generally indicates a high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient or provider values and preferences, and understood influence of other implications (e.g., resource use, feasibility). If the Work Group has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation, it generally assigns a “Weak” recommendation. It is important to note that the GRADE terminology used to indicate the assessment across the four domains (i.e., “Strong” versus “Weak”) should not be confused with the clinical importance of the recommendation. A “Weak” recommendation may still be important to the clinical care of a patient with CKD.

Occasionally, instances may occur when the Work Group determines that there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

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...”)
- No recommendation for or against (or “There is insufficient evidence...”)
- Weak against (or “We suggest not offering this option...”)
- Strong against (or “We recommend against offering this option...”)

The grade of each recommendation made in the 2019 CPG can be found in the section on [Recommendations](#). Additional information regarding the use of the GRADE system can be found in [Appendix A](#).

b. Reconciling 2014 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous guidelines based on new evidence, or as scheduled and subject to time-based expirations.^[12] For example, the U.S. Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services.^[13]

The CKD CPG Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition to those new and updated recommendations, the Work Group considered, without complete review of the relevant evidence, the current applicability of other recommendations that were included in the 2014 CKD CPG, subject to evolving practice in today’s environment.

A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE).^[14,15] These categories, along with their corresponding definitions, were used to account for the various ways in which older recommendations could have been updated. In brief, the categories took into account whether or not the evidence that related to a recommendation was systematically reviewed, the degree to which a recommendation was modified, and the degree to which a recommendation is relevant in the current care environment and within the scope of the CPG. Additional information regarding these categories and their definitions can be found in [Recommendation Categorization](#). The categories for the recommendations included in the 2019 version of the guideline can be found in the section on [Recommendations](#). The categories for the recommendations carried forward from the 2014 CKD CPG are noted in [Appendix D](#).

The CPG Work Group considered the strength of the evidence cited for each recommendation in the 2014 CKD CPG as well as the intervention’s harms and benefits, values and preferences, and other implications, where possible. The CPG Work Group referred to the available evidence as summarized in the body of the 2014 CKD CPG and did not systematically reassess the evidence. In some instances, relevant peer-reviewed literature published since the 2014 CKD CPG was considered along with the original evidence base for the specific recommendation. Where such newer literature was considered, it is referenced in the discussion that follows the corresponding recommendation, as well as in [Appendix C](#).

The CPG Work Group recognizes that while there are sometimes practical reasons for incorporating findings from a previous SR, previous recommendations,^[16] or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive SR and therefore may introduce bias.

c. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the document. The process for developing the initial draft is described in more detail in [Drafting and Submitting the Final Clinical Practice Guideline](#).

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group members, the draft was sent out for peer review and comment. The draft was posted on a Wiki website for a period of 14 business days. The peer reviewers comprised individuals working within the VA and DoD healthcare systems as well as experts from relevant outside organizations designated by the Work Group members. Organizations designated by the Work Group to participate in the peer review and who provided feedback include the following:

- American Society of Nephrology
- National Kidney Foundation

The VA and DoD Leadership reached out to both the internal and external peer reviewers to solicit their feedback on the CPG. Reviewers were provided a hyperlink to the Wiki website where the draft CPG was posted. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made throughout the CPG development process were made in accordance with the evidence.

B. Summary of Patient Focus Group Methods and Findings

When forming guideline recommendations, consideration should be given to the values of those most affected by the recommendations: patients. Patients bring perspectives, values, and preferences into their healthcare experience that can vary from those of clinicians. These differences can affect decision making in various situations, and should thus be highlighted and made explicit due to their potential to influence a recommendation's implementation.^[17,18] Focus groups can be used as an efficient method to explore ideas and perspectives of a group of individuals and collect qualitative data on a thoughtfully predetermined set of questions.

Therefore, as part of the effort to update this CPG, VA and DoD Leadership, along with the CKD CPG Work Group, held a patient focus group on June 11, 2018, at the Audie L. Murphy Memorial VA Hospital - South Texas Veterans Health Care System in San Antonio, TX. The aim of the focus group was to further understand and incorporate the perspective of patients who are living with CKD and who are covered and/or receiving their care through the VA and/or DoD healthcare systems, as these patients are most affected by the recommendations put forth in the CPG. The focus group delved into the patients' and their families' perspectives on a set of topics related to their CKD management, including their priorities, challenges they have experienced, and the information they received regarding their care, as well as the impacts of their care on their lives.

It is important to note that the focus groups comprised a convenience sample and the Work Group recognizes the lack of generalizability and other limitations inherent in the small sample size. Fewer than 10 people in total were included in the focus group to be consistent with the requirements of the Federal Paperwork Reduction Act, 1980. The Work Group acknowledges that the sample included in the focus group is not representative of all patients within the VA and DoD healthcare systems. Further, time limitations for the focus group prevented exhaustive exploration of all topics related to CKD management in VA and DoD and the patients’ broader experiences with their care. Thus, the Work Group made decisions regarding the priority of topics to discuss at the focus group. These limitations, as well as others, were considered during guideline development as the information collected from the discussion was being used. Recruitment for participation in the focus group was managed by the Champions and VA and DoD Leadership, with assistance from coordinators at the facility at which the focus group took place.

The following concepts are ideas and suggestions about aspects of care that are important to patients who are living with CKD and emerged as recurring themes during the discussions ([Table 1](#)). These concepts were important parts of the participants’ care and added to the Work Group’s understanding of patient values and perspectives. Additional details regarding the patient focus group methods and findings can be found in [Appendix B](#).

Table 1. CKD CPG Focus Group Concepts

CKD CPG Patient Focus Group Concepts	
A.	Recognize the importance of communication and collaboration between care providers, particularly between nephrologists and primary care.
B.	Understand patient-specific goals, priorities, values, and preferences and use shared decision making to develop a patient-centered plan for treatment. Patients greatly value quality of life and the ability to maintain their lifestyle.
C.	Educate patients about their kidney disease. Diagnosis often comes as a shock to patients, and understanding why they have kidney disease is of great importance to them. Patients often fear that exposure to chemicals during their military deployment may have led to their CKD.
D.	Provide nutrition and dietary guidance keeping in mind patient’s individual lifestyle and cultural differences. The patients who had seen a dietitian stated that it helped them adhere to their nutrition plan while those who did not reported difficulty maintaining a healthy diet.
E.	Patients’ biggest fear regarding their kidney disease is having to go on dialysis; they observed others on dialysis and inferred what it would be like for them. Educating patients about the experience of dialysis may alleviate their fears and give them a better understanding of their treatment options.
F.	Create a support group for kidney disease patients. Patients have a number of fears regarding their kidney disease, particularly having to go on dialysis, and may benefit from discussing these issues with other patients at various stages of CKD.
G.	Offer telemedicine and other technology options to augment care, but recognize these options may not align with the preferences of all patients.

Abbreviations: CKD: Chronic Kidney Disease

C. Potential Conflicts 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 (COI) in the past 24 months. Verbal affirmations of no COI were used as necessary during meetings throughout the

guideline development process. The project team was also subject to random web-based surveillance (e.g., Centers for Medicare and Medicaid Services open payments or ProPublica).

If a project team member reported a COI (actual or potential), then it was reported to the Office of Evidence Based Practice. It was also discussed with the CKD CPG Champions in tandem with their review of the evidence and development of recommendations. The Office of Evidence Based Practice and the CKD CPG Champions determined whether or not action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If it was deemed necessary, action to mitigate the COI was taken by the Champions and Office of Evidence Based Practice, based on the level and extent of involvement. No COIs were identified for the CKD CPG Work Group members or Champions. Disclosure forms are on file with the VA Evidence Based Practice Program office and available upon request.

D. Scope of this Clinical Practice Guideline

Regardless of setting, any patient in the healthcare system should ideally have access to 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 healthcare professionals and the patient is essential and should be supported by evidence-based information tailored to the patient's needs. Use of an empathetic and non-judgmental approach facilitates discussions sensitive to gender, cultural, ethnic, and other differences. The information that patients are given about treatment and care should be culturally appropriate and available to people with limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory, or learning disabilities. Family involvement should be considered, if appropriate.

This CPG is designed to assist providers in managing or co-managing patients undergoing treatment for CKD. The patient population of interest for this CPG is patients who are living with CKD and are eligible for care in the VA and DoD healthcare delivery systems. It includes Veterans as well as deployed and non-deployed Active Duty Service, Guard, and Reserve Members and their dependents.

E. Highlighted Features of this Clinical Practice Guideline

The 2019 edition of the VA/DoD CKD CPG is the fourth update to the original CPG. It provides practice recommendations for CKD as well as guidance for specialty referral. A particular strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from the broad spectrum of clinicians engaged in the treatment and management of CKD with and without co-occurring conditions.

The framework for recommendations in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of the intervention, equity of resource availability, the potential for variation in patient values and preferences, and other considerations (e.g., acceptability of the intervention, subgroup considerations) as appropriate. Applicability of the evidence to VA/DoD populations was also taken into consideration. An algorithm accompanies the guideline to provide an overview of the recommendations in the context of the flow of patient care and to assist with training

providers (see the [Algorithm](#)). The algorithm may be used to help facilitate translation of guideline recommendations into effective practice.

F. Patient-centered Care

VA/DoD CPGs encourage clinicians to use a PCC approach that is individualized based on patient needs, characteristics, and preferences. Regardless of setting, all patients in the healthcare system should be able to access evidence-based care appropriate to that patient. When properly executed, PCC may decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.[\[19-21\]](#) Improved patient-clinician communication and a PCC approach conveys openness and supports disclosure of current and future concerns.

As part of the PCC approach, clinicians should ensure that the patient understands their medical condition and the outcomes and experiences of similar patients who are living with CKD. They should elicit the patient's goals of care and explore any concerns, barriers, or outcomes they wish to avoid. They should inform the patient about any decisions that need to be made and involve them in shared decision making (SDM) regarding management of CKD. With the patient's permission, members of the patient's trusted support system should be encouraged to participate in these discussions to ensure they understand the patient's condition, treatment decisions, and their role in supporting the management of CKD. Patients should be allowed time to adjust to serious news about diagnosis and progression of illness before being asked to discuss goals of care and treatment decisions.

G. Shared Decision Making

Throughout this VA/DoD CPG, the authors encourage clinicians to focus on SDM. The SDM model was introduced in *Crossing the Quality Chasm*, an Institute of Medicine (IOM) (now called the National Academy of Medicine [NAM]) report, in 2001.[\[22\]](#) It is readily apparent that patients should make decisions regarding their plan of care and management options together with their clinicians. The unique role of SDM in nephrology care has been previously recognized in CPGs published by the Renal Physicians Association.[\[23\]](#) Clinicians must be adept at presenting information to their patients regarding individual treatments, expected outcomes, and levels and/or settings of care, taking into account the patient's learning needs and information they want to know. Through SDM, treatment plans are individualized based on patient capabilities, needs, goals, and preferences.

H. Co-occurring Conditions

Co-occurring medical and mental health conditions are important to recognize because they can modify the management of CKD, patient or provider treatment priorities, clinical decisions, and the providers with whom management of CKD and ongoing healthcare will be delivered. Providers should expect that many Veterans, Service Members, and their family will have one or more co-occurring health conditions. For example, one analysis of 821,334 Veterans with CKD between January 1, 2005, and December 31, 2008, found that 81% had three or more conditions in addition to CKD.[\[24\]](#) In addition to commonly co-occurring chronic conditions (e.g., DM, hypertension), older Veterans with CKD often have geriatric conditions such as cognitive impairment or are at high risk for falls. For example, in U.S. population-based studies of older adults, cognitive impairment occurred in 15% of those with an eGFR 45-59 mL/minute/1.73 m² and 19% of those with an eGFR <45 mL/minute/1.73 m².[\[25\]](#) Among older Veterans with CKD who had geriatric assessment, more than 25% had cognitive impairment that had not been previously identified.[\[26\]](#)

Because management of CKD usually takes place in parallel with ongoing care for co-occurring conditions, it is generally best to manage CKD in collaboration with the care for other health conditions that are being treated in primary or specialty care.[\[27\]](#)

I. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of patient needs and local resources. The algorithm serves as a tool to prompt providers to consider key decision points in the course of care.

Although this CPG represents the recommended practice on the date of its publication, clinical 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 informing optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new evidence particularly relevant to clinical practice.

IV. Guideline Work Group

Guideline Work Group*	
Department of Veterans Affairs	Christopher Dyer, MD, FACP (Champion)
	Jeffrey Penfield, MD (Champion)
	C. Barrett Bowling, MD, MSPH
	Susan T. Crowley, MD, MBA, FASN
	Elaine Furmaga, PharmD
	Janet Hank, RN, BSN, CNN
	Paul M. Palevsky, MD, FACP, FASN, FNKF
	Michael Shlipak, MD, MPH
	Laura Stubna, MS, RD, LDN, CNSC
	Carol Toms, MSW, LICSW
Department of Defense	Mai Nguyen, MD, FACP, FASN (Champion)
	Lt Col Jonathan Sosnov, MD, MSc (Champion)
	Jennifer Bell, MD
	Maj Sara Koepke, RDN, CSR, CNSC
	David Nick Patterson, PharmD, BCPS
	Evan Steil, MD, MBA, MHA, FAAFP, FACHE
	Lt Col Jesse Wickham, DO, FACP
Office of Quality, Safety and Value Veterans Health Administration	Eric Rodgers, PhD, FNP-BC
	James Sall, PhD, FNP-BC
	Rene Sutton, BS, HCA
Office of Evidence Based Practice U.S. Army Medical Command	Corinne K. B. Devlin, MSN, RN, FNP-BC
	Lisa Jones, BSN, RN, MHA, CPHQ
The Lewin Group	Clifford Goodman, PhD
	Christine Jones, MS, MPH, PMP
	Nicolas Stettler-Davis, MD, MSCE
	Charlie Zachariades, MSc
	Erika Beam, MS
ECRI Institute	James Reston, PhD, MPH
	Jeff Oristaglio, PhD
	Michele Datko, MS
	Linnea Hermanson, MA
	Kariann Hudson, Med
	Constance Martin, BA
	Amber Moran, MA
	Angela Motter, PhD
	Kelley Tipton, MPH
Sigma Health Consulting, LLC	Frances Murphy, MD, MPH
Duty First Consulting	Megan McGovern, BA
	Rachel Piccolino, BA

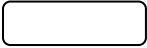

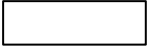

* Additional contributor contact information is available in [Appendix E](#).

V. Algorithm

This CPG follows an algorithm that is designed to facilitate understanding of the clinical pathway and decision-making process used in 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 may promote more efficient diagnostic and therapeutic decision making and has the potential to change patterns of resource use. Although the Work Group recognizes that not all clinical practices are linear, the simplified stepwise approach depicted through the algorithm and its format allows the provider to assess the critical information needed at the major decision points in the clinical process. It includes:

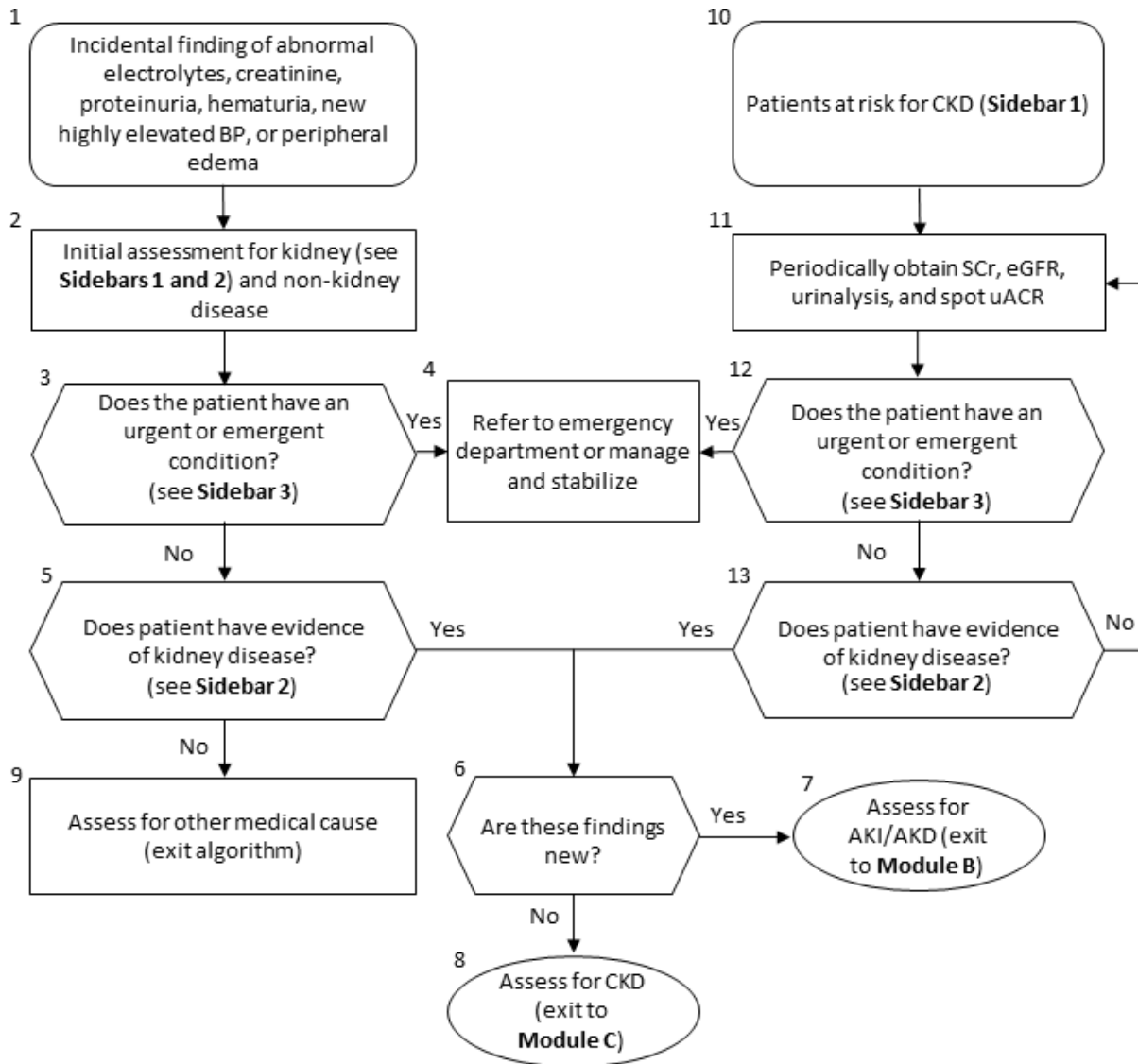
- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

For each guideline, there is a corresponding clinical algorithm that is depicted by 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.[\[28\]](#)

Shape	Description
	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
	Ovals represent a link to another section within the guideline

[Appendix G](#) contains alternative text descriptions of [Module A](#), [Module B](#), [Module C](#), and [Module D](#).

A. Module A: Screening for CKD and Initial Assessment



Abbreviations: AKD: acute kidney disease; AKI: acute kidney injury; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SCr: serum creatinine; uACR: urine albumin-to-creatinine ratio

Sidebar 1: At-Risk Populations

- DM, hypertension, cardiac disease/CHF, or vascular disease
- Systemic illness (e.g., HIV, systemic lupus erythematosus, multiple myeloma)
- Urinary tract abnormalities
- History of AKI, proteinuria, or other known kidney disease
- Family history of kidney disease (e.g., ADPKD)
- Patients age 60 and above
- Ethnicities associated with increased risk (e.g., African Americans, Hispanics, Native Americans)

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AKI: acute kidney injury; CHF: chronic heart failure; DM: diabetes mellitus; HIV: human immunodeficiency virus

Sidebar 2: Assessment for Kidney Disease

- History:
 - ◆ Symptoms of volume depletion (lightheadedness, dizziness) or overload (pedal edema, dyspnea)
 - ◆ Cause of volume depletion (diarrhea, vomiting, decreased oral intake, heat exposure)
 - ◆ Medications and supplements (NSAIDs, diuretics, BP medication changes)
 - ◆ Recent illnesses/infections (upper respiratory infection, osteomyelitis)
 - ◆ Urinary changes (hematuria, obstruction)
 - ◆ Rheumatologic symptoms
- Physical: vital signs, peripheral edema, volume status
- Labs: assess for abnormal labs (e.g., electrolytes, creatinine, hematuria, microalbuminuria/proteinuria) and lab trends then repeat labs (as clinically appropriate)

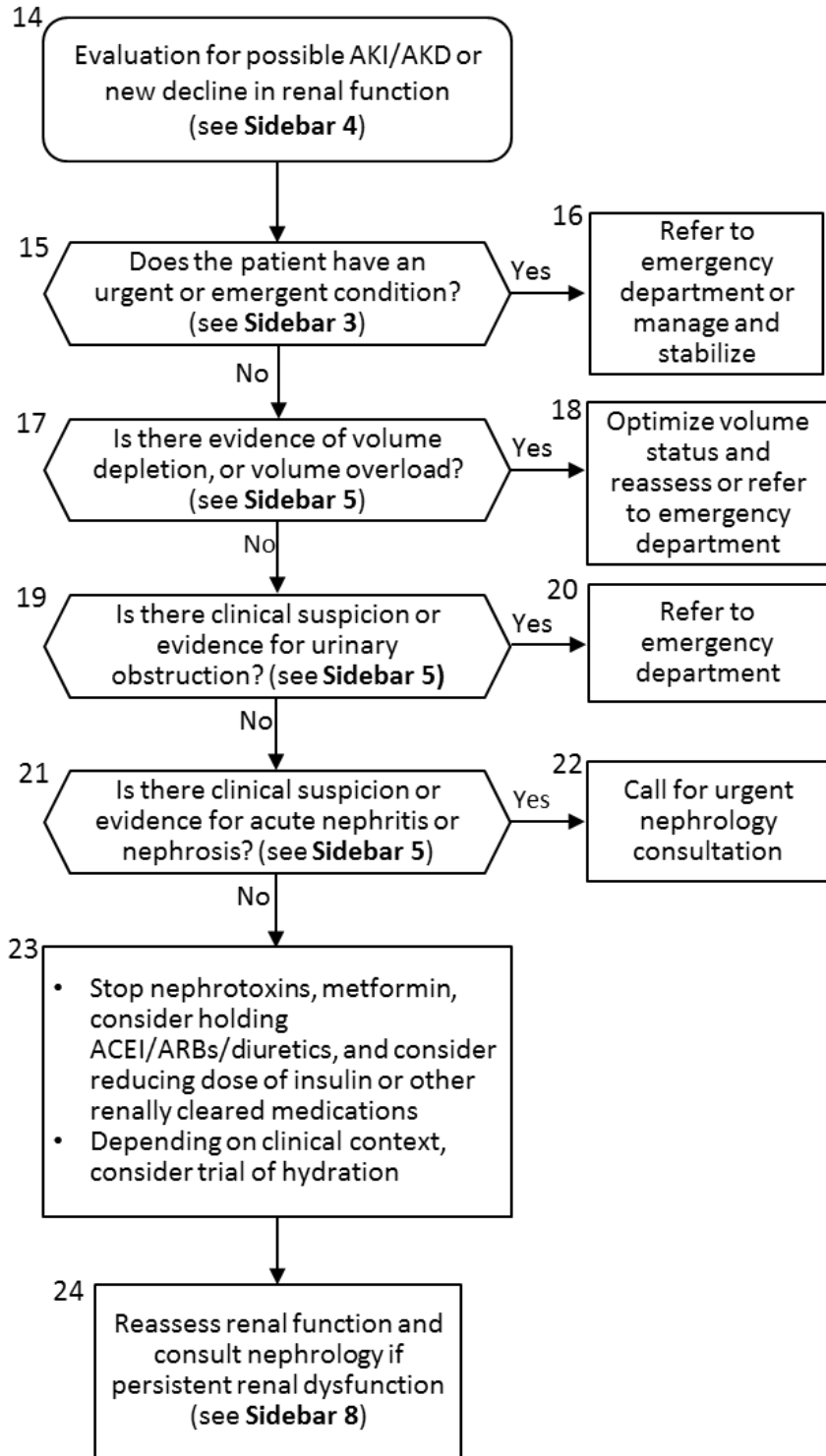
Abbreviations: BP: blood pressure; NSAID: non-steroidal anti-inflammatory drug

Sidebar 3: Urgent/Emergent Conditions

- Clinical signs:
 - ◆ Unstable vital signs
 - ◆ Decompensated heart failure/symptomatic volume overload
 - ◆ Signs or symptoms of uremia
 - ◆ Anuria
- Abnormal labs:
 - ◆ Significantly abnormal potassium (<2.5 mEq/L or ≥6 mEq/L)
 - ◆ Acute unexplained decline in kidney function
 - ◆ Severe acid-base disturbance

Abbreviations: L: liter; mEq: milliequivalent

B. Module B: Evaluation for AKI or New Decline in Renal Function



Abbreviations: ACEI: angiotensin converting enzyme Inhibitor; AKD: acute kidney disorder; AKI: acute kidney injury; ARB: Angiotensin II receptor blocker

Sidebar 4: Definition of AKI and AKD

- Definition of AKI (presence of any of the following):
 - ◆ Increase of SCr of >0.3 mg/dL over not more than 48 hours
 - ◆ Increase in SCr of >50% as compared to baseline, presumed to have occurred over not more than 7 days
 - ◆ Urine output of <0.5 mL/kg/hr over 6 hours
- Definition of AKD (presence of any of the following):
 - ◆ GFR <60 mL/min/1.73 m² for <3 months
 - ◆ Decrease in GFR by >35% or increase in SCr by >50% for <3 months
 - ◆ Kidney damage (structural) for <3 months

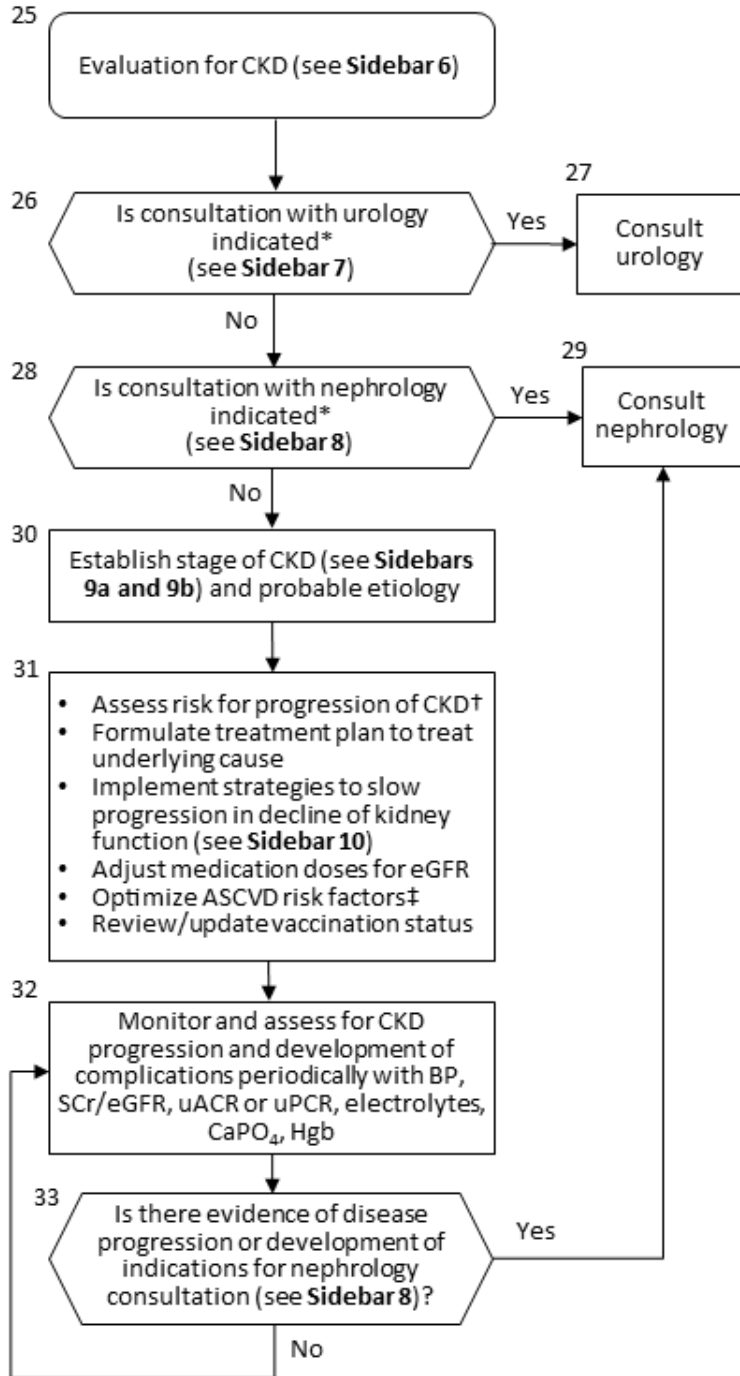
Abbreviations: AKD: acute kidney disorder; AKI: acute kidney injury; dL: deciliter; GFR: glomerular filtration rate; hr: hour; kg: kilogram; m: meter; mg: milligram; min: minute; mL: milliliter; SCr: serum creatinine

Sidebar 5: Assessment for AKD

- For volume depletion, e.g.:
 - ◆ Lightheadedness or dizziness
 - ◆ Hypotension
 - ◆ Orthostasis
- For volume overload, e.g.:
 - ◆ Shortness of breath
 - ◆ Rales
 - ◆ Edema
 - ◆ Jugular vein distension
- For urinary obstruction, e.g.:
 - ◆ Symptoms of voiding dysfunction
 - ◆ Flank pain or hematuria
 - ◆ Elevated post-void bladder volume
 - ◆ Evidence of obstruction on kidney imaging (e.g., hydronephrosis)
- For suspicion of acute nephritis or nephrosis (hematuria, dysmorphic RBCs or RBC casts, new onset proteinuria) with:
 - ◆ Recent illness (e.g., infection)
 - ◆ Constitutional or rheumatologic symptoms
 - ◆ Rash
 - ◆ Edema
 - ◆ Hemoptysis

Abbreviations: AKD: acute kidney disorder; RBC: red blood cell

C. Module C: Evaluation for CKD



Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CaPO₄: calcium orthophosphates; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hgb: hemoglobin; hr: hour; kg: kilogram; mL: milliliter; SCr: serum creatinine; uACR: urine albumin-to-creatinine ratio; uPCR: urine protein-to-creatinine ratio

*Referral should be made following shared decision making with patient that ensures the referral focus is consistent with the patient values and preferences

†See [Table 2: Risk Prediction Equations Developed for Patients with CKD](#)

‡As appropriate, refer to the following VA/DoD Clinical Practice Guidelines: Chronic Heart Failure, Diabetes, Hypertension, Dyslipidemia, Overweight and Obesity, and Tobacco Cessation

Sidebar 6: Criteria for CKD

Sustained abnormality for ≥ 3 months of either:

- eGFR < 60 mL/min/1.73 m²

or any of the following:

- Albuminuria (uACR > 30) or proteinuria (uPCR > 0.2)
- Hematuria or abnormal urinalysis/microscopy
- Structural renal anomalies (e.g. solitary or horseshoe kidney)
- History of abnormal renal histology
- History of renal transplantation

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; m: meter; min: minute; mL: milliliter; uACR: urine albumin-to-creatinine ratio; uPCR: urine protein-to-creatinine ratio

Sidebar 7: Indications for Urology Consultation

- Isolated or gross hematuria
- Renal masses or complex renal cysts
- Symptomatic or obstructing nephrolithiasis
- Hydronephrosis or bladder abnormalities
- Urinary symptoms (e.g., nocturia, hesitancy, urgency, incontinence)

Sidebar 8: Potential Indications for Nephrology Consultation*

- eGFR < 30 mL/min/1.73 m²
- Rapid decline of eGFR (> 5 mL/min/1.73 m² per year)
- Non-diabetics with heavy proteinuria (24 hr urine protein > 500 mg, uPCR > 0.5 , uACR > 300)
- Diabetics with > 3 g proteinuria (uPCR > 3) or hematuria
- Unclear cause of CKD, hematuria, or proteinuria
- Complications of CKD (e.g., anemia, acidosis, hyperphosphatemia, hyperparathyroidism)
- ADPKD
- Renal transplant
- Metabolic management (prevention) of kidney stone disease
- Electrolyte abnormalities (e.g. hyperkalemia, hyponatremia)
- Patient's level of disease exceeds the comfort level of the primary care provider

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; g: gram; hr: hour; m: meter; min: minute; mL: milliliter; uACR: urine albumin-to-creatinine ratio; uPCR: urine protein-to-creatinine ratio

*Referral should be made following shared decision making with patient that ensures the referral focus is consistent with the patient values and preferences

Sidebar 9a: Stage of CKD* – GFR Categories		
Category	eGFR Range (mL/min/1.73 m 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

Sidebar 9b: Stage of CKD* – Albuminuria Categories		
Category	ACR (mg/g)	Description
A1	<30	Normal to mildly increased
A2	30 - <300	Moderately increased
A3	≥300	Severely increased

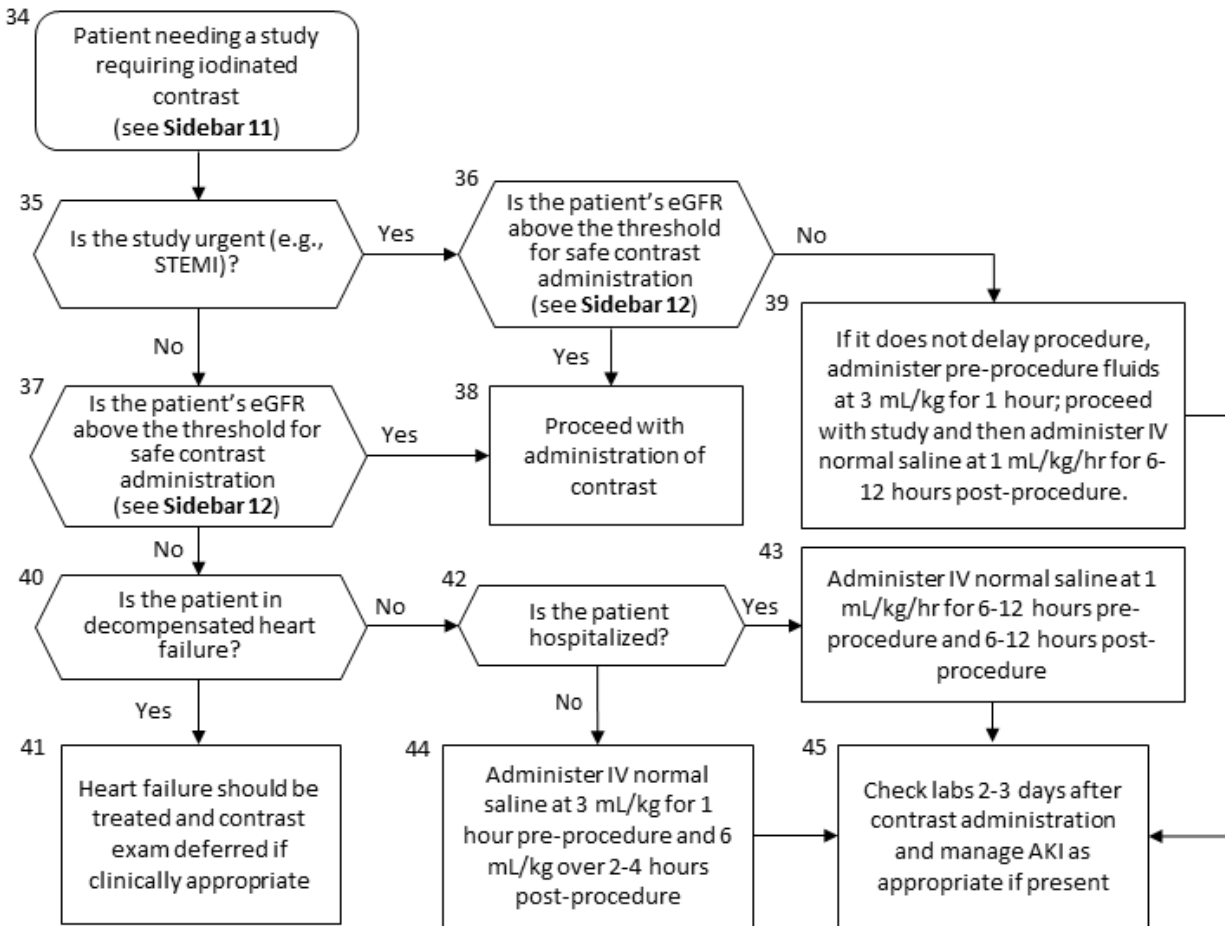
*Consider one-time cystatin C measurement to confirm CKD diagnosis and stage (see [Recommendation 3](#))

Abbreviations: uACR: urine albumin-to-creatinine ratio; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; g: gram; GFR: glomerular filtration rate; hr: hour; m: meter; min: minute; mg: milligram; mL: milliliter

Sidebar 10: Strategies to Slow Progression of CKD
<ul style="list-style-type: none"> • Control of hypertension with preferential use of either ACEI or ARB in patients with albuminuria/proteinuria • Individualized control of diabetes • Use of SGLT2 inhibitors in patients with type 2 DM and an eGFR > 30 mL/min/1.73 m² • Eliminate/avoid nephrotoxic agents whenever possible (e.g., NSAIDs, iodinated contrast) • Refer to dietitian for medical nutrition therapy (e.g., protein intake, sodium restriction, weight loss)

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; m: meter; mg: milligram; mL: milliliter; min: minute; NSAID: non-steroidal anti-inflammatory drug; SGLT2: sodium-glucose co-transporter-2

D. Module D: Management of Patients with CKD Requiring Iodinated Contrast



Abbreviations: AKI: acute kidney injury; eGFR: estimated glomerular filtration rate; hr: hour; IV: intravenous; kg: kilogram; min: minute; mL: milliliter; STEMI: ST-elevation myocardial infarction

Sidebar 11: Considerations for When Studies Requiring Iodinated Contrast are Indicated

- Consider non-contrast studies as alternative
- Use minimum amount of contrast necessary for appropriate testing
- Consider holding metformin due to risk of lactic acidosis (see Recommendation 16)
- Assess for risk factors for CA-AKI:
 - ◆ Decreased kidney function
 - ◆ DM
 - ◆ Proteinuria
 - ◆ Heart failure
 - ◆ Volume depletion
 - ◆ Para-proteinemia

Abbreviations: CA-AKI: contrast associated acute kidney injury; DM: diabetes mellitus

Sidebar 12: eGFR Cutoffs for Contrast

Venous Contrast:

- Patients should have eGFR >30 mL/min/1.73 m²
- Or, if patient has DM, eGFR >45 mL/min/1.73 m²

Arterial Angiography

- Patients should have eGFR >45 mL/min/1.73 m²
- Or, if patient has diabetes, eGFR >60 mL/min/1.73 m²

Abbreviations: DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; m: meters; min: minute; mL: milliliter;

VI. Recommendations

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
Diagnosis Assessment and Lab Monitoring		1.	In the general population, there is insufficient evidence to recommend for or against periodic evaluation for chronic kidney disease.	Neither for nor against	Reviewed, New-replaced
		2.	When screening or stratifying risk for chronic kidney disease, we recommend including urine albumin-to-creatinine ratio testing in addition to estimated glomerular filtration rate to optimize the diagnosis and staging of chronic kidney disease.	Strong for	Reviewed, New-added
		3.	In patients with an estimated glomerular filtration rate <60 mL/minute/1.73 m ² , we suggest one-time cystatin C-based estimated glomerular filtration to confirm diagnosis and/or refine staging of chronic kidney disease.	Weak for	Reviewed, New-added
		4.	We suggest the use of a validated risk prediction model as a clinical decision support aid in the management of patients with chronic kidney disease.	Weak for	Reviewed, New-added
		5.	When assessing the risk of progression to end-stage renal disease, there is insufficient evidence to recommend a specific risk prediction calculator.	Neither for nor against	Reviewed, New-added
General Management Strategies	Team Management and Education	6.	There is currently insufficient evidence to recommend a <i>specific threshold</i> of risk, renal function, or proteinuria to refer patients for a nephrology evaluation and management of chronic kidney disease (see Algorithm: Module C, Sidebar 8 for potential indications for nephrology consultation).	Neither for nor against	Reviewed, New-replaced
		7.	We suggest interdisciplinary care (including dietitians, pharmacists, and social workers in addition to physicians and nurses) for patients with later-stage chronic kidney disease.	Weak for	Reviewed, New-replaced
		8.	When providing patient education, there is insufficient evidence to recommend for or against a particular health education program, mode, or modality to prevent chronic kidney disease progression.	Neither for nor against	Reviewed, New-replaced
		9.	For patients who are at high risk for requiring hemodialysis/renal-replacement and need long-term venous access, we suggest against peripherally inserted central catheter (PICC) lines to optimize future dialysis vascular access options, while considering patient values and preferences.	Weak against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
General Management Strategies (continued)	Indication for Referral to Nephrology for Renal Replacement Therapy Including Dialysis and Renal Transplant	10.	We suggest utilizing shared decision making regarding renal replacement therapy (versus conservative management) in part to improve patient satisfaction.	Weak for	Reviewed, New-added
		11.	In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life is the priority, we suggest evaluation for renal replacement therapy with sufficient time for comprehensive preparation.	Weak for	Reviewed, New-added
		12.	In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom avoiding hospitalization, death in hospitals, or intensive procedures is the priority, we suggest offering conservative management over dialysis.	Weak for	Reviewed, New-added
		13.	In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life may not be the priority, there is insufficient evidence to recommend for or against dialysis to improve quality of life.	Neither for nor against	Reviewed, New-added
Non-pharmacologic Management of CKD	Nutrition	14.	We suggest the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with chronic kidney disease.	Weak for	Not reviewed, Not changed
		15.	In selected patients with stage 3 and 4 chronic kidney disease, we suggest offering a dietary protein intake of 0.6 to 0.8 g/kg/day as it may slow the decline in estimated glomerular filtration rate and progression to end-stage renal disease.	Weak for	Not reviewed, Amended
Pharmacologic Management of CKD and Associated Conditions	Diabetes Medications	16.	We suggest offering metformin as a first-line therapy for the treatment of type 2 diabetes in patients with stage 1 to 3 chronic kidney disease to reduce all-cause mortality.	Weak for	Reviewed, New-added
		17.	We recommend offering sodium-glucose co-transporter 2 inhibitors as an option for add-on therapy for the treatment of type 2 diabetes in patients with stage 1 to 3 chronic kidney disease to reduce chronic kidney disease progression and the risk of cardiovascular events.	Strong for	Reviewed, New-added
		18.	We suggest offering liraglutide or dulaglutide (glucagon-like peptide-1 receptor agonists) as an option for add-on therapy for the treatment of type 2 diabetes in patients with chronic kidney disease to reduce chronic kidney disease progression.	Weak for	Reviewed, New-added
		19.	In patients with chronic kidney disease and type 2 diabetes, there is insufficient evidence to recommend for or against the use of thiazolidinediones or dipeptidyl peptidase-4 inhibitors to decrease progression of chronic kidney disease or mortality.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
Pharmacologic Management of CKD and Associated Conditions (continued)	Hypertension Medications	20.	We suggest intensive blood pressure management (insufficient evidence to recommend a specific target) beyond a target of less than 140/90 mmHg, to reduce mortality in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 m ² .	Weak for	Reviewed, New-added
		21.	In patients with non-diabetic chronic kidney disease, hypertension, and albuminuria, we recommend the use of an angiotensin-converting enzyme inhibitor to prevent progression of chronic kidney disease. Angiotensin II receptor blockers may be substituted for patients with an angiotensin-converting enzyme-inhibitor-induced cough.	Strong for	Not reviewed, Not changed
		22.	In patients with chronic kidney disease, diabetes, hypertension, and albuminuria, we recommend the use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers to slow the progression of chronic kidney disease, unless there is documentation of intolerance.	Strong for	Not reviewed, Amended
		23.	We recommend against the use of combination renin-angiotensin-aldosterone system blockade (an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker, or an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker with a direct renin inhibitor) in patients with chronic kidney disease.	Strong against	Not reviewed, Not changed
	Anemia Medications	24.	We suggest initiation of oral iron therapy to support iron requirements in patients with chronic kidney disease.	Weak for	Not reviewed, Amended
		25.	We recommend against initiating erythropoiesis-stimulating agents in patients with chronic kidney disease for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension.	Strong against	Not reviewed, Amended
		26.	We recommend against initiating erythropoiesis-stimulating agents at a hemoglobin level greater than 10 g/dL.	Strong against	Not reviewed, Not changed
	Bone Health Medications	27.	We suggest against offering calcitriol or active vitamin D analogs to patients with stage 3 and 4 chronic kidney disease and elevated parathyroid hormone levels.	Weak against	Not reviewed, Amended
		28.	We suggest against offering calcimimetics to patients with stage 3 and 4 chronic kidney disease and elevated parathyroid hormone levels.	Weak against	Not reviewed, Amended
		29.	There is insufficient evidence to recommend for or against the use of phosphate binders to reduce mortality, progression of chronic kidney disease, or major cardiovascular outcomes in patients with stage 2 to 5 chronic kidney disease.	Neither for nor against	Reviewed, New-replaced

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
Pharmacologic Mgmt. of CKD (cont.)	Other Medications to Slow CKD Progression	30.	We suggest the use of sodium bicarbonate supplementation in patients with chronic kidney disease and metabolic acidosis to slow the progression of chronic kidney disease.	Weak for	Not reviewed, Amended
		31.	In patients with chronic kidney disease and asymptomatic hyperuricemia, there is insufficient evidence to recommend for or against the use of urate-lowering therapy for the purpose of slowing progression of chronic kidney disease.	Neither for nor against	Reviewed, New-added
		32.	In patients at risk for rapidly progressing autosomal dominant polycystic kidney disease, we suggest offering tolvaptan in consultation with a nephrologist to slow decline in estimated glomerular filtration rate.	Weak for	Reviewed, New-added
Contrast-Associated Kidney Injury Management		33.	For patients at increased risk for iodinated contrast-associated acute kidney injury, we recommend volume expansion with intravenous isotonic saline prior to and following iodinated contrast administration (see Algorithm Module D for additional information).	Strong for	Reviewed, Amended
		34.	We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury.	Strong against	Reviewed, New-replaced
		35.	We recommend against the use of renal replacement therapy for iodinated contrast-associated acute kidney injury prophylaxis.	Strong against	Reviewed, Amended

^a For additional information, please refer to [Grading Recommendations](#).

^b For additional information, please refer to [Recommendation Categorization](#) and [Appendix D](#).

A. Diagnosis Assessment and Lab Monitoring

Recommendation

- In the general population, there is insufficient evidence to recommend for or against periodic evaluation for chronic kidney disease.
(Neither for nor against | Reviewed, New-replaced)

Discussion

There is a rational expectation that screening high-risk populations for kidney disease may be helpful. Optimally, to make a recommendation on screening, there would be evidence such as a randomized controlled trial (RCT) with clinical endpoints that randomly assign patients, providers, or practices to either screening or usual care strategies. No such trial has been conducted. Furthermore, there are three key assumptions for screening which are not clear from observational studies or even analytical models. Key assumptions for the effectiveness of screening include identification of unrecognized/unrecognized CKD, modification of treatment not otherwise used in individuals with occult CKD, and efficacy of treating early CKD states to reduce risk of progression and improve outcomes. The key assumptions for screening to be effective are the presence of undetected/unrecognized disease. Not only is there no data on clinical outcomes of screening, but the impact on patients is also unclear. There are potential benefits and harms of CKD screening, but neither are well defined. Potential benefits include improved identification of patients with CKD with the opportunity to slow CKD progression with treatment. In addition, patients with

CKD have elevated cardiovascular disease (CVD) risk, and prevention efforts could be implemented or intensified. Potential harms include risk of over-diagnosis and “labeling” patients with a diagnosis (at this point not quantified, more intangible), which could include negative impacts on patient finances, employment status, their family members, psychosocial and mental health, and insurance coverage. Information from the patient focus group suggest that patients are often surprised and anguished by the diagnosis of CKD and they want assurance that there is a clear cause of their condition and an action plan. However, there may not be a clear cause or action plan. In the absence of evidence, the conflict over screening becomes evident with proponents decrying the nihilism of doing nothing and the other side repeating the mantra of “first do no harm.” The 2014 CKD CPG used expert opinion to recommend that high-risk populations should benefit from screening; however, screening and treatment strategies have not been evaluated in a rigorous RCT, and there remains insufficient evidence to recommend for or against periodic evaluation to screen for CKD, even in high-risk populations. This current recommendation is based on very low quality evidence on interventions to reduce the risk of CVD events from the 2018 evidence review [29] and evidence carried forward from the 2008 and 2014 versions of the CKD CPG.[30]

Providers have a responsibility to their patients to ensure that screening efforts are accompanied by strong evidence and that there is the opportunity to counsel patients about treatment plans. Although there is an absence of evidence to support widespread screening, clinicians are encouraged to offer CKD screening to high-risk patients, particularly in instances where the recognition of kidney disease may alter therapy or afford opportunity for preventive management (see [Algorithm: Module A](#)). The decision to screen for CKD should be individualized, based on SDM with the patient. There is debate among the Work Group as to which patients might benefit from screening based on interpretations of available information and practice patterns. The Work Group recommends that future research be prioritized to identify the most promising population(s) for potential CKD screening, the optimal method to use for screening, and to evaluate the impact of screening interventions versus usual care on outcomes that are important to patients, providers, and healthcare systems.

A formal recommendation on screening requires evidence with appropriate clinical endpoints for a specific patient population using a specific screening methodology compared to usual care or no screening. However, RCTs have not yet been conducted for CKD and may not be conducted. The impact of screening on patient outcomes and well-being remains unclear, even from observational studies, and may differ between patient groups and individual patients. As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the relevant evidence [29] and considered the assessment of the evidence put forth in the 2008 and 2014 CPGs.[30] The Work Group’s confidence in the quality of the evidence is very low. CKD screening in the general population remains controversial with conflicting statements among professional organizations.[31,32] Although it may appear empirically that early detection of CKD should be beneficial, screening and treatment strategies have not been evaluated in rigorous research. Therefore, while the Work Group concluded that a definitive evidence-based recommendation for or against CKD screening in the general population cannot be made at this time, the Work Group felt CKD screening decisions should be considered on an individual patient basis, taking into account risk factors, implications of the diagnosis, the likelihood of changes in patient management, and patient preferences (see [Algorithm: Module A](#)).

Recommendation

2. When screening or stratifying risk for chronic kidney disease, we recommend including urine albumin-to-creatinine ratio testing in addition to estimated glomerular filtration rate to optimize the diagnosis and staging of chronic kidney disease.

(Strong for | Reviewed, New-added)

Discussion

The combined impact of eGFR and albuminuria allow for a more complete evaluation of risk for CKD complications. Patient-level meta-analyses that included 105,872 people from 14 studies with measures of urine albumin-to-creatinine (uACR) and 1,128,310 people from seven studies with urine dipstick testing for proteinuria in addition to serum creatinine (SCr) measures demonstrated that albuminuria substantially improved risk prediction for CVD, mortality, and end-stage renal disease (ESRD) at all levels of eGFR.^[3] These findings are based on spot collections of urine and calculated uACRs and are well illustrated in [Figure 7](#) of the KDIGO CKD definition and classification article (not included in our SR and not contributing to the strength of the recommendation).^[3] There appeared to be a steadily increasing risk for adverse outcomes with higher values of the uACR, which emphasizes that the uACR should be reported as a numerical value, if possible, and not as a categorical result. For CKD staging, the clinical categories for uACR that are typically used are <30, 30 to <300, and ≥300 mg/g, although the risk gradient extends below 30 and above 300 mg/g. Associations of uACR with adverse outcomes were present across multiple subgroups, defined by presence or absence of CKD, hypertension, and DM, and across all adult demographic subgroups that were evaluated. Additionally, it is considered standard of care to screen for albuminuria for most patients with hypertension or DM. The predictive strength of albuminuria was much stronger and more progressive across worsening categories than the semi-quantitative measure of proteinuria assessed by dipstick.^[33] Therefore, the Work Group recommends that uACR be measured in all patients with CKD and clinicians should include the uACR for staging and classification of CKD, though there are no studies to guide the frequency of uACR measurement.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant evidence.^[33] The Work Group's confidence in the quality of the evidence is moderate. The body of evidence had some limitations, including the potential for unmeasured confounders in the analyses.^[33] Other considerations regarding this recommendation included the benefits, including improved prognostication of mortality, outweighing the potential harm of adverse events, which was small. Patient values and preferences were consistent with the desire for improved prediction of adverse outcomes. Thus, the Work Group decided upon a "Strong for" recommendation.

Recommendation

3. In patients with an estimated glomerular filtration rate <60 mL/minute/1.73 m², we suggest one-time cystatin C-based estimated glomerular filtration to confirm diagnosis and/or refine staging of chronic kidney disease.

(Weak for | Reviewed, New-added)

Discussion

Many patients are diagnosed, staged, and treated for CKD on the sole basis of an eGFR derived from SCr. Creatinine has many inherent limitations that affect its sensitivity and specificity, resulting in bi-directional misclassification. The primary problem with creatinine is that the serum concentrations in part reflect its production from muscle turnover, and higher creatinine production is a marker of better overall health.[\[34\]](#) In contrast, higher creatinine levels are used to quantify reductions in eGFR, so the bias of creatinine production must be accounted for. Rather than estimating the muscle mass of an individual person, current creatinine based GFR equations derive an estimate of creatinine production based on each individual's age and sex, and whether or not he or she is black. The race adjustment for blacks is particularly controversial. Although blacks overall may have larger muscle mass compared with whites, there is clearly heterogeneity across the population and individuals with the highest risk of kidney disease may also be those with lower than average muscle mass. This can result in delayed diagnosis of CKD, as the GFR estimates in these individuals would be inappropriately adjusted to higher values. Furthermore, at least one population-based study found that the ratio of creatinine production in black people compared to white people is much lower than suggested by the GFR equations.[\[35\]](#) Therefore, an alternative measure of kidney function that is not influenced by muscle mass could be appealing for patients and clinicians.

Cystatin C is an alternative method for estimating kidney function that is less biased by age, sex, race and muscle mass relative to creatinine. In contrast to creatinine, cystatin C does not have bias across race/ethnic groups. Therefore, the GFR estimate based on cystatin C is more reliable across diverse populations.

In a patient-level meta-analysis that included 16 studies and 93,710 individuals that compared CKD staging and prognosis using SCr versus cystatin C,[\[36\]](#) a large proportion were re-classified to different CKD stages by cystatin C, and the re-classification improved risk stratification for clinically relevant outcomes at all multiple eGFR categories. For example, among persons with an eGFR of 45-60 mL/minute/1.73 m² as assessed by SCr, 40% were re-classified as not having CKD by cystatin C while another 25% were re-classified into worse CKD stages. On the basis of this evidence, the Work Group suggests a "one-time" measurement of cystatin C to confirm the diagnosis of CKD and refine the CKD stage. The role of cystatin C for the confirmation of reduced eGFR among the oldest old (80 years and older) is unclear, as it has been shown in a study outside the scope of this evidence review that the percentage of those re-classified as not having CKD is diminished at older ages.[\[37\]](#) Further, it is less certain whether serial measures of cystatin C would have value in comparison with serial measures of SCr, so the Work Group has limited the scope of its recommendation to the use of cystatin C for CKD staging. However, if an individual's health status changes, clinicians may choose to repeat cystatin C beyond the initial test for GFR estimation and staging because the accuracy of SCr may change with health status.

The benefits of using cystatin C include avoidance of over-diagnosing CKD, the provision of more accurate classification of risk for progression and complications, and tailored treatment of comorbid conditions. Avoiding the "false positive" diagnosis of CKD is a high priority based on consensus within the patient focus group that a diagnosis of CKD causes distress. In addition, participants in the focus group indicated that they wanted the most accurate information possible about their disease status and prognosis.

There may be challenges to implementing cystatin C measurement. At some hospitals, including the San Diego and San Francisco VA Health Care System (VAHCS), cystatin C is already available as a routine test; however, it is not offered in all facilities. While there would be up-front costs in implementing cystatin C measurement into local laboratories, including personnel time for local standardization, the per assay cost of cystatin C at the San Francisco VAHCS is less than \$5. As some providers may not be familiar with its use, it is essential that the cystatin C laboratory result be accompanied by an eGFR, and the CKD Epidemiology Collaboration (CKD-EPI) equation for cystatin C is appropriate in these populations.[38]

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant evidence.[36] The Work Group's confidence in the quality of the evidence is low. The body of evidence had some limitations, as the methods for measurement of creatinine and cystatin C varied across the studies included in the Shlipak et al. meta-analysis, as did the efforts to calibrate these measures to reference standards. There is also a risk of residual confounding from observational cohort studies. Other considerations regarding this recommendation included the benefits, including improved outcomes in CVD mortality, outweighing the potential harm of adverse events, which was small. Patient values and preferences were similar. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendations

4. We suggest the use of a validated risk prediction model as a clinical decision support aid in the management of patients with chronic kidney disease.
(Weak for | Reviewed, New-added)
5. When assessing the risk of progression to end-stage renal disease, there is insufficient evidence to recommend a specific risk prediction calculator.
(Neither for nor against | Reviewed, New-added)

Discussion

The utility of CKD progression risk models lies in their promise to cost effectively risk-stratify people. Risk prediction of CKD progression could enable greater tailoring of disease modifying therapies, rational determination of frequency of follow-up, and inform timing of referral to specialty care.[39] In addition, CKD progression risk prediction modelling could enhance SDM surrounding ESRD treatment planning.

A sizeable number of CKD risk prediction calculators have been developed, some focusing on predicting the occurrence of CKD, and others on predicting the risk of CKD progression to ESRD for those with established CKD. (see [Table 2](#)).[39] This discussion is confined to the latter.

The published CKD progression risk equations nearly universally include demographic characteristics, measures of eGFR or SCr, and albuminuria or proteinuria, with some supplemented by other biomarkers (e.g., serum phosphate or bicarbonate) or risk conditions for progression (e.g., hypertension).[39] The most recent SR of CKD progression risk prediction equations identified eight studies describing 11 models of CKD progression.[40,41] Most of the models had not yet been externally validated or suffered from other statistically defined deficiencies.[40]

The Kidney Failure Risk Equation (KFRE) model, developed in 2011, evaluated CKD progression risk for a large group of predominantly Caucasian North American patients with established CKD in stages 3-5.[42]

Both its 4-variable and 8-variable versions have been found to have excellent discrimination, good calibration, and have been externally validated, first in a Dutch cohort, and subsequently in diverse cohorts from North America, Asia, Europe, and Australasia.[\[41,43\]](#)

Grams et al. (2015) compared the 4-variable KFRE ability to predict ESRD incidence by comparing its calculated one-year ESRD risk threshold to an absolute eGFR threshold.[\[44\]](#) Lower variability in time to ESRD was found using the KFRE's one-year ESRD risk threshold of 5% compared with an eGFR threshold alone. Although limited by its observational study design and narrow cohort characteristics (non-diabetic African-American adults under 70 years of age), the study suggests that use of the KFRE prediction tool could be more informative for clinical decision making (e.g., timing for nephrology or transplant referral and vascular access planning) than an arbitrary eGFR threshold.

Additional CKD risk progression models have been proposed following the KRFE. One study explored the benefit of considering a pathology score, derived from a review of diabetic kidney biopsies ("D-Score"), along with the Tangri KFRE to predict renal outcomes.[\[45\]](#) No incremental prognostic value was achieved beyond the use of the KFRE alone. A risk prediction tool for the progression of advanced CKD to ESRD was also developed by investigators in the VA.[\[46\]](#) This study was included in the SR by Tangri et al. (2016).[\[41\]](#) A 6-variable equation predicting one-year ESRD risk was identified using an elderly, male Veteran population with CKD stage 4. The VA equation is more complex, requiring repeated blood pressures (BPs), and the addition of comorbidities into the model as well as demographic and laboratory variables. This equation yielded excellent discrimination in both the development and validation cohorts; however, the KFRE performed nearly as well.[\[46\]](#)

Two additional studies report alternatives to the KRFE, without head-to-head comparisons. A Taiwanese study described the use of a modified clinical diabetic nephropathy score to predict the progression of people with advanced CKD to ESRD.[\[47\]](#) Comprised of five items (age, systolic BP, glycosylated hemoglobin (HbA1c), eGFR, and urine protein-to-creatinine ratio [uPCR]), a score of seven or more out of a maximum of nine points was associated with increased risk of dialysis initiation. While simple to use, confidence in the study findings is tempered by the study's design, sample size, and limited generalizability to the U.S. population.

The slope of eGFR decline has also been compared to two measures of eGFR variability as predictors of progression of CKD stage 3-5 to ESRD.[\[48\]](#) As a predictor of ESRD, the slope of eGFR decline outperformed one eGFR variability equation and underperformed relative to the other. The study suggests that changing renal function using either slope of decline or eGFR variability may enhance prediction of adverse renal outcomes.

While the use of risk prediction equations in other fields has been associated with improved patient outcomes,[\[42\]](#) the impact of estimating progression risk on the processes of ESRD preparation, slope of eGFR decline, and transition to ESRD has not been evaluated.[\[39\]](#) Previously, there has been an absence of recommendations in CKD guidelines for the use of CKD progression risk prediction models, which likely explains the dearth of clinical impact analyses.[\[39\]](#) KDIGO clinical guidelines issued in 2012, not included in this evidence base, suggested use of a risk equation to aid in timing of renal replacement therapy (RRT) referral.[\[3\]](#) More recently, the European Renal Best Practice (ERBP) guideline on management of older

patients with CKD, also not included in this evidence base, endorsed use of the four-variable KFRE because of its performance, broad validation, and simplicity.[\[43\]](#)

The feasibility of using an ESRD risk prediction tool is contingent upon the resources and capabilities of the health system in which it is deployed. Ideally it is used at point of care. The KFRE's availability via online calculator, bedside tablet, or smart phone application make it ideal as a point-of-care decision support aid.[\[40,42\]](#)

As these are *Reviewed, New-added* recommendations, the Work Group systematically reviewed the relevant bodies of evidence.[\[36,39,41,44-48\]](#) Overall, the benefits and harms of using a risk prediction equation were balanced. Participants in the patient focus group indicated that information about kidney disease may be difficult to receive and they expressed difficulty with understanding the complexity of CKD progression. On the other hand, they also expressed a desire for SDM, which necessitates patient understanding of the trajectory of their illness. Use of an ESRD progression tool may aid patients in comprehending the gradual loss of nephron function and could help allay patients' universally expressed fear of starting dialysis, as well as any initial shock concerning the diagnosis. The similarity in expressed values and preferences by patients related to desire for better awareness and understanding of CKD and for SDM suggests that an area of future research is the use of risk prediction equations to aid in forecasting the timeline of CKD progression, changing patient behavior, and possibly changing the rate of progression, to add balance to the unhappy news of CKD.

Although the quality of the evidence pertaining to the relative utility of CKD progression risk prediction tools was low, it should not be construed that ESRD risk prediction equations are not useful. To the contrary, there is strong evidence that the KFRE offers excellent discrimination as a prediction equation for adverse renal outcomes in a broad range of populations. Moreover, there is considerable evidence that its key variables, eGFR and albuminuria, are predictive of renal outcomes.[\[41\]](#)

The use of an ESRD risk prediction tool may be particularly useful to primary care providers in low health resource regions where limited subspecialty care is available, thus enabling the primary care provider to begin patient counseling related to CKD progression using quantitative as well as qualitative discussion points. The choice of ESRD risk prediction tool (e.g., KFRE, slope of eGFR decline, eGFR variability, or modified clinical diabetic nephropathy score) is discretionary according to the provider preferences and patient demographics. Thus, the Work Group decided upon a "Weak for" recommendation and a "Neither for nor against" recommendation regarding the use of a validated risk prediction model as a clinical decision support aid in the management of patients with CKD.

Table 2. Risk Prediction Equations Developed for Patients with CKD

	Name	Variables/ Formula	Population of Interest	Outcome Predicted	Reference & Link
CKD Progression to ESRD	Kidney Failure Risk Prediction Equation	Albuminuria, sex, age, eGFR	Stage G3+ CKD	2 and 5 year probability of progression to ESRD	Tangri et al. (2011) [42] Tangri et al. (2016) [41] https://kidneyfailurerisk.com/
Competing Events and Patterns of Events in Patients with Late Stage CKD	CKD-PC Model	Albuminuria, sex, age, eGFR, race, history of CVD, current smoking status, systolic BP, DM	Stage G 4+ CKD	2 and 4 year probability & timing of: <ul style="list-style-type: none"> • kidney failure requiring kidney replacement therapy • non-fatal CVD event • death 	Grams et al. (2015) [44] http://ckdpcrisk.org/lowgfrevents/
Alternatives to KFRE for Progression to ESRD	Veterans Risk Prediction Equation	Demographics, BP, comorbidities, labs	<ul style="list-style-type: none"> • Elderly, male • Stage G4+ CKD 	1 year probability of progression to ESRD	Drawz et al. (2013) [46]
	Slope of eGFR decline or eGFR variability	eGFR over time	Stage G3+ CKD	Progression to ESRD	Chen et al. (2014) [48]
	Absolute eGFR Threshold	Age, sex, uPCR ratio ≥ 1 g/g, <i>APOL1</i> high-risk status, and 3-year antecedent eGFR decline	Non DM, African-American adults under 70 years of age	1 year probability of progression to ESRD	Grams et al. (2015) [44]
	Modified clinical diabetic nephropathy score	Age, systolic BP, HbA1c, eGFR, uPCR ratio	Taiwanese Stage G3b+ CKD	Progression to ESRD	Chen et al. (2017) [47]
	KPNW Model	Age, sex, eGFR, Hgb, proteinuria/albuminuria, systolic BP, anti-hypertension medications, DM	Stage G3+ CKD	5 year probability of progression to ESRD	Schroeder et al. (2017) [49]
	Renal Path Score	KFRE + Pathology Score	Stage G3+ diabetic CKD	Progression to ESRD	Yamanouchi et al. (2018) [45]

Abbreviations: *APOL1*: apolipoprotein L1; BP: blood pressure, CKD: chronic kidney disease, CVD: cardiovascular disease, DM: diabetes mellitus, ESRD: end stage renal disease, Hgb: hemoglobin, HbA1c: hemoglobin A1c, KFRE: kidney failure risk equation, PC: Prognosis Consortium, KPNW: Kaiser-Permanente Northwest, uPCR: urine protein-to-creatinine ratio

B. General Management Strategies

a. Team Management and Education

Recommendation

6. There is currently insufficient evidence to recommend a specific threshold of risk, renal function, or proteinuria to refer patients for a nephrology evaluation and management of chronic kidney disease (see [Algorithm: Module C, Sidebar 8](#) for potential indications for nephrology consultation).
(Neither for nor against | Reviewed, New-replaced)

Discussion

One SR [50] and five observational studies [51-55] were identified which evaluate the impact of nephrology referral on outcomes. The findings suggest that nephrology referral may be associated with slower progression of kidney function decline, decreased mortality, and improved BP control. In a study of 1,533 Veterans by Orlando et al. (2007), nephrology care was associated with decreased risk of the composite endpoint of death or CKD progression.[54] Chen et al. (2008) reported a significantly lower kidney function decline in CKD stage 3b (-5.5mL/min/year before versus -2.5mL/min/year after referral, $p < 0.01$), but not stage 3a (-3mL/min/year before versus -2.3mL/min/year after referral), one year after nephrology referral.[55] In a retrospective cohort study of 42,048 patients, Lonnemann et al. (2017) demonstrated that nephrology referral at stage 3 was associated with stabilizing of renal function (75.1% versus 63%, $p < 0.037$) but not in stage 4 (57.2% versus 46.6%, $p = 0.1$). Additionally, there was improved mortality with nephrology referral at both CKD stage 3 and 4.[53] A meta-analysis of 40 longitudinal studies by Smart et al. (2014) showed lower mortality with early referral (defined as referral more than 1-6 months before dialysis initiation) compared to late referral (defined as referral less than 1-6 months prior to starting dialysis).[50] In a large study of VHA clinic users ($n = 39,031$) with concomitant DM and stage 3-4 CKD, Tseng et al. (2008) found a lower risk of dialysis-free mortality in patients with stage 3 or 4 CKD among those who had a greater number of quarterly visits with a nephrologist.[51] Nephrology care has also been shown to be associated with improved BP control; however, Minutolo et al. (2005) did not report the impact of BP control on CKD outcomes.[52]

Although a pre-specified eGFR level for referral would potentially reduce late referral of patients, no RCTs have been performed to assess the clinical impact of nephrology care at a pre-specified CKD stage or eGFR. The rate of decline of renal function is variable, so the impact of timing of nephrology referral may be difficult to ascertain. Additionally, differences in healthcare system resources related to availability of nephrology specialty care, as well as feasibility of accessing that care, make a singular referral point an unreasonable universal expectation. Finally, participants in the focus group emphasized importance of understanding patient-specific goals, priorities, values and preferences, and the use of SDM in developing treatment plans. Some patients may desire preservation of QoL over aggressive treatment or may specifically object to RRT and the increasing complexity of multiple provider care. In those instances, it may be more patient-centered to delay referral beyond an arbitrary cutoff point to align care with a well-informed patient's values and preferences.

There is currently insufficient evidence to recommend a specific threshold of risk, renal function, or proteinuria to refer patients for nephrology evaluation and management of CKD. However, the Work Group concurs with the 2014 CKD CPG that consultation with a nephrologist to assist in the diagnosis and

treatment of patients could be considered for the following conditions (see [Algorithm: Module C, Sidebar 8](#)):

- a. eGFR <30 mL/min/1.73 m² to facilitate education and planning for RRT (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 known or suspected kidney condition requiring specialized care (e.g., autosomal dominant polycystic kidney disease [ADPKD], renal vasculitis)
- e. Non-diabetics with heavy proteinuria (24 hr urine protein >500 mg, uPCR >0.5, uACR >300)
- f. Diabetics with >3 g proteinuria (uPCR >3) or hematuria

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the relevant evidence [50,53] and considered the assessment of the evidence put forth in the 2008 and 2014 CPGs.[51,52,54,55] The Work Group’s confidence in the quality of the evidence is low due to the heterogeneity in the definitions of “early” and “late” referral and the observational nature of the studies found. Defining the ideal timing of nephrology referral that improves patient outcomes while optimizing resource utilization and healthcare value is an important knowledge gap to fill and should be the focus of future studies. Thus, the Work Group decided upon a “Neither for nor against” recommendation.

Recommendation

7. We suggest interdisciplinary care (including dietitians, pharmacists, and social workers in addition to physicians and nurses) for patients with later-stage chronic kidney disease.
(Weak for | Reviewed, New-replaced)

Discussion

The outcomes of utilizing an interdisciplinary team (IDT) to provide care to patients with CKD are not well established, and the studies identified in the evidence review had serious limitations and inconsistency with mixed results.[56-59] An SR and meta-analysis of 21 studies with a mix of cohort and RCT designs by Shi et al. (2018) indicated that IDTs may reduce all-cause mortality, hospitalization rates, need for dialysis initiation with a catheter, and eGFR decline.[57] IDTs demonstrated the greatest benefit in patients with late stage 4 or stage 5 CKD.[57] However, a second SR by Valentijn et al. (2018) did not reveal difference in all-cause mortality, eGFR decline, or rate of RRT with IDT care, but did demonstrate that IDTs – including dietitians, pharmacists, and social workers in addition to physicians and nurses – were associated with decreased rates of hospitalizations and improved BP control.[58] An RCT by Foglefeld et al. (2017) showed that IDT appointments with coordinated care focused on tight control of BP, glycemia, lipid control, and albuminuria in diabetic patients with CKD stage 3-4 may slow progression to ESRD compared with usual care, but the study was not blinded, only enrolled 120 subjects, and had a high attrition rate.[56,57,59]

Participants in the patient focus group also noted that SDM and open communication helped with adherence to treatment goals and that having assistance from an IDT in the development of individualized treatment plans, along with education about why the interventions were beneficial and augmented support in making lifestyle changes, increased their ability to adhere to their individual plans.

Implications for resource use, equity with regard to availability and feasibility of IDT care, and time commitment from both patients and providers associated with IDT care must also be considered. While mixed preferences regarding the use of mobile or telehealth technology were noted within the focus group, younger populations may be more open to use of these modalities; all patients felt that having these options available would be beneficial to those open to using them. Availability of these resources may help to overcome the barriers of time, distance, and feasibility of IDT care.

Additionally, the terms “multidisciplinary” versus “interdisciplinary” teams are not clearly defined in the literature; further clarification about which healthcare professionals should comprise an IDT, for which purpose or outcome an IDT is needed, and which components of IDT are most beneficial to patients (e.g., education, case management) is needed. Future research could also focus on assessing the use of IDTs via telehealth and/or mobile technology in urban and rural areas to improve lifestyle, medication adherence, patient satisfaction, and overall comprehension. The impact of these interventions in eliminating barriers to care, such as distance, limited access to transportation, low socioeconomic resources, age, and health literacy should also be evaluated, particularly since participants expressed interest in expansion of telehealth services.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the relevant evidence.[\[56-59\]](#) The Work Group’s confidence in the quality of the evidence is very low. The body of evidence had very serious limitations and serious inconsistency with mixed results. Other considerations regarding this recommendation included the benefits, including improved mortality outweighing the risk of complications with aggressive treatment. There is large variation in patients’ values and preferences due to the time commitment associated with treatment. Thus, the Work Group decided upon a “Weak for” recommendation.

Recommendation

8. When providing patient education, there is insufficient evidence to recommend for or against a particular health education program, mode, or modality to prevent chronic kidney disease progression.

(Neither for nor against | Reviewed, New-replaced)

Discussion

CKD health education supports the aim of maximizing PCC and SDM, consistent with the patient focus group findings. While the benefits of patient education and self-care are often informally recognized by both patients and clinicians, the benefits of these specific interventions can be difficult to demonstrate in a study setting. Since most clinical care will include some component of informal patient education, the Work Group reviewed studies that included formalized self-management education, e-learning, behavior modification, and nutritional education compared to usual care.[\[60-63\]](#)

In 2018, Zimbudzi et al. performed an SR of eight RCTs on the effects of self-management interventions on patients with DM and CKD.[\[60\]](#) The primary outcomes assessed included: systolic BP, diastolic BP, eGFR and HbA1c. Secondary outcomes reviewed included self-management activity, health service utilization, QoL, medication adherence, and death. The review found that self-management interventions may improve self-care activities, systolic BP, and HbA1c. There were inconclusive results on markers of CKD

progression, QoL, mortality, and hospitalization. It was also not possible to determine which self-management strategies were more effective. The authors concluded that further evidence from high quality studies is needed to better understand these impacts.

An RCT by Joboshi and Oka (2017) compared a unique education program (Encourage Autonomous Self-Enrichment [EASE]) to a control group that received standardized patient education where nurses distributed leaflets and answered patients' questions over a 12-week period to determine effects on psychological outcomes (perceived self-efficacy and self-management) and physiologic outcomes (systolic BP and renal function).[\[61\]](#) While the study was of good quality, the effects on CKD progression and BP control were inconclusive. Significant improvement in the psychological aspects were demonstrated; however, the trial period of 12 weeks was very short.

A non-randomized controlled clinical trial published by Barahimi et al. (2017) evaluated the impact of using self-care education through computer-based e-learning (virtual training) on kidney function in diabetics with eGFR <60 mL/minute/1.73 m² in Iran.[\[62\]](#) The intervention group (n=39) received e-learning developed using the ADDIE (analysis, design, development, implementation, and evaluation) model with content identified using KDIGO in addition to usual care, while the controls (n=92) received only usual care, which consisted of face-to-face education and therapeutic interventions. The mean eGFR improved from 51.1 mL/minute to 57.8 mL/minute in the intervention group compared with a decline of 2.3 mL/minute in the control group. Thus e-learning in addition to usual care appeared to modestly improve, or at least prevent a decline in, eGFR compared with usual care over a six-month period. There was also a trend towards improved mean HbA1c in the intervention group with a decline from 6.7% to 6.1%, versus an increase of 0.2% in the control group. There were no statistically significant impacts on BP control, weight, waist circumference, lipid measurements, or body mass index (BMI). Of note, though the educational content was available online, the intervention group received face-to-face verbal instruction in utilization of the materials. Furthermore, the e-learning population was statistically younger (mean age of 58.1 years versus 67.5 years) and better educated (53% versus 30% having completed grade 12 and higher) compared with the control group, which may also affect health literacy.

An open clustered randomized trial published by Yamagata et al. (2016) studied the effects of behavior modification in addition to standard treatment on CKD progression.[\[63\]](#) The study group (n=1,184) received education about lifestyle modifications at their medical appointments every three months and CKD status letters to remind them about ideal lifestyle choices and medical appointments to prevent withdrawal from treatment. Additionally, their general practitioners received patient data sheets and recommendations regarding treatment and nephrology referral. Improvement in adherence to medical appointments (rate of discontinuous clinical visits 11.5% in study group versus 16.2% in controls, p=0.01) as well as significantly higher referral and co-treatment rates (p<0.01) were seen in the intervention group. The difference in rate of CKD progression between the two groups was not statistically significant. The Work Group did not infer that these results represented behavior modification within the patient population. However, the study highlights changes to healthcare professional practice patterns that the patient focus group deemed important, specifically the importance of communication and collaboration between care providers.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the relevant evidence.[\[60-63\]](#) The Work Group's confidence in the quality of the evidence is very low due to

study design limitations and imprecision. After considering the available evidence and risk versus benefit, the Work Group's recommendation was "neither for nor against" intensive education programs or a specific education modality to prevent CKD progression. Although the evidence for patient education programs to improve CKD progression is not strong, there is evidence, outside of the scope of this literature review, to support the use of self-management strategies in other health conditions. Future studies should focus on the impact of patient education on CKD outcomes, feasibility, and effect of resource utilization on various healthcare systems and the most effective modality for formalized patient education.

Recommendation

9. For patients who are at high risk for requiring hemodialysis/renal-replacement and need long-term venous access, we suggest against peripherally inserted central catheter (PICC) lines to optimize future dialysis vascular access options, while considering patient values and preferences.

(Weak against | Reviewed, New-added)

Discussion

Mature arteriovenous fistulas (AVF) are associated with superior survival compared with arteriovenous grafts or catheters in patients on hemodialysis, and are considered the gold standard for hemodialysis vascular access.^[64] Two observational studies were identified that found that peripherally inserted central catheter (PICC) lines were associated with increased risk of failure to achieve a working AVF or graft.^[65,66] One of these studies was a retrospective cohort of 33,918 incident hemodialysis patients in the United States Renal Data System (USRDS) registry who started hemodialysis with a central venous catheter.^[66] They found prior PICC placement was associated with lower likelihood of a successful AVF. A second study used a case-control design with 120 patients who had no functioning AVF and 162 controls with functioning AVF.^[65] Prior PICC use was associated with higher odds of inability to achieve a functioning AVF. The Work Group rated these studies as moderate quality evidence with the limitations being the observational study designs and the potential for bias and confounding.

PICC lines (including PICC lines and midline catheters) are used for long-term intravenous (IV) access and may alleviate the pain of repeated venipuncture and peripheral intravenous (PIV) replacements, resulting in shorter hospitalization and potential cost savings. PICC lines may be complicated by infection and venous thromboembolism, which may lead to increased resource use and additional care following PICC line placement. Further, clinicians should consider the patient's risk of requiring future hemodialysis prior to inserting a PICC line. Estimates of ESRD risk can be made through either the proper CKD staging or through a risk equation (see [Recommendations 4 and 5](#)). The potential risk of failing to achieve adequate vascular access for hemodialysis must be balanced against the benefits of IV access with PICC lines. The Work Group recognizes that a patient may need long-term vascular access, and there may be instances in which no practical alternatives to a PICC line exist. However, in patients at high risk for ESRD, small-bore tunneled internal jugular catheters or ultrasound-guided PIV placement are acceptable options to avoid the risks a PICC line could pose on the success of future dialysis access.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the evidence.^[65,66] The Work Group identified two large observational studies that found that PICC lines were associated with increased risk of failure to achieve a working AVF or graft.^[65,66] The Work Group's

confidence in the quality of evidence is moderate due to the limitations of the observational study designs and potential for bias and confounding. Other considerations regarding this recommendation included the harms of failure to achieve adequate hemodialysis access outweighing the benefits of vascular access with PICC lines, especially with the availability of alternative methods (e.g., small-bore tunneled internal jugular catheters, ultrasound-guided PIV placement). Patient values were somewhat varied, as discussed above. Thus, the Work Group decided upon a “Weak against” recommendation.

b. Indication for Referral to Nephrology for Renal Replacement Therapy Including Dialysis and Renal Transplant

Recommendation

10. We suggest utilizing shared decision making regarding renal replacement therapy (versus conservative management) in part to improve patient satisfaction.

(Weak for | Reviewed, New-added)

Discussion

As noted in the 2010 Renal Physicians Association’s CPG, the clinical management and care of patients with CKD poses complex decisions for the patients, their families, and medical providers.^[23] Several publications reviewed in this VA/DoD CPG also acknowledge the importance and challenges of SDM in this population. SDM places patients at the center of their care process and ensures that their values and preferences are paramount in their treatment decisions. For these reasons, SDM is the ethical foundation on which ESRD management decisions are built and is accepted as the standard of care. In this VA/DoD evidence-based CPG, the Work Group sought to identify specific impacts of SDM in the care of patients with progressive CKD as reported in literature.

Only two studies with very low quality evidence were identified regarding such impacts in the medical management of patients with CKD.^[67,68] Both studies identified increased patient satisfaction with modality selection when patients were actively involved in the planning and decision making of their treatment options.

The first study, the German Choice of Renal Replacement therapy (CORETH) project, focused on the psychosocial aspects that contribute to increased patient satisfaction in treatment choices for ESRD. The study population consisted of 780 dialysis patients across Germany who had been on either peritoneal dialysis or hemodialysis for 6 to 24 months. Although a primary objective of this study was to evaluate the difference in patient satisfaction between peritoneal dialysis and in-center hemodialysis, there was also a statistically significant increase in patient satisfaction for those who were included in the process of modality choice.^[67]

The second study, by the European Kidney Patients’ Federation (CEAPIR), retrospectively reviewed patients’ perceptions of information and education for their RRT. Approximately 4,000 patients from 36 countries, who were either on hemodialysis or had a functioning transplanted kidney, were surveyed. The review found that a large majority of those surveyed considered that they had been part of the decision-making process for selecting their treatment modality, which appeared to be associated with higher levels of satisfaction with their selected treatment.^[68]

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant evidence.[\[67,68\]](#) The confidence in quality of the evidence was very low due to participant recall limitations in the retrospective collection of data in the CEAPIR study [\[68\]](#) and a limited focus on hemodialysis versus peritoneal dialysis and lack of randomization in the CORETH study.[\[67\]](#) However, the Work Group considered that the potential benefits of SDM in the care of patients with progressive kidney disease outweighed the harms/burdens. SDM with regard to CKD treatment includes ongoing communication and collaboration between patients, their primary care physician (PCP) and their nephrologists, which was emphasized by the patient focus group. Some barriers to this process include the varying levels of comfort among PCPs with RRT discussions and the difficulty of maintaining ongoing communication between PCPs and nephrologists. With the normal progression of CKD, timely education in patients with progressive CKD is essential so that patients can make an informed decision about the direction of their treatment. Early referral also allows time for patients to formulate and articulate their goals of care, evaluate their options, and adequately prepare for whichever treatment option they choose (i.e., vascular access placement, transplant referral, or palliative care referral). Therefore, based on the available evidence, the Work Group decided upon a “Weak for” recommendation, suggesting the utilization of SDM on modality selection involving the patient, the PCP, and the nephrologist for optimal management of RRT (versus conservative management) to improve patient satisfaction and achieve patient-centered goals for treatment, while noting that all benefits of SDM may not be captured in peer-reviewed literature.

Recommendations

11. In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life is the priority, we suggest evaluation for renal replacement therapy with sufficient time for comprehensive preparation.
(Weak for | Reviewed, New-added)
12. In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom avoiding hospitalization, death in hospitals, or intensive procedures is the priority, we suggest offering conservative management over dialysis.
(Weak for | Reviewed, New-added)
13. In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life may not be the priority, there is insufficient evidence to recommend for or against dialysis to improve quality of life.
(Neither for nor against | Reviewed, New-added)

Discussion

The decision to pursue renal replacement in the very elderly, frail, or medically complex CKD population is challenging for patients and providers alike. Because of the complexity of the patient population, the role of patient preferences in treatment decisions, and ethical issues, optimally designed clinical trials comparing renal replacement versus conservative (non-renal replacement) management are not possible. The above recommendations are constructed based on review of data from one comprehensive SR,[\[69\]](#) two retrospective studies,[\[70,71\]](#) and one prospective cohort observational study.[\[72\]](#) Evidence from these studies demonstrated a strong survival advantage for patients electing to pursue dialysis versus

supportive care.[\[70-72\]](#) However, these benefits attenuate on covariate analyses when comorbid features and advanced age are considered.[\[69,72,73\]](#)

Foote et al. (2016) performed a meta-analysis of 89 studies which included 294,921 patients with ESRD ranging in age from 60.5 to 92 years of age, examining a primary outcome of survival/mortality.[\[69\]](#) There was significant heterogeneity in study design and outcomes within the data pool, and no RCTs comparing dialysis versus supportive care could be identified in this population. Time intervals of one year (84.2% versus 72.7%), two years (62.2% versus 44.4%), and five years (34.5% versus 8.5%) all identified a strong survival benefit for dialysis over supportive care. However, p-values were not reported, and the data remain inconclusive. Several studies in this meta-analysis examined factors associated with benefit from dialysis, noting that high comorbidity, impaired functional status, and age over 80 years were associated with loss of survival benefit.[\[69\]](#) Based on this evidence, persistent uncertainty regarding survival benefit in this population, and the need for individualized management, the Work Group suggests that patients in this population, whose first priority is duration of life, be referred to nephrology for evaluation for dialysis. Recognizing the complexity, nuances, and logistics of preparing this patient population for dialysis, patients should optimally be referred with adequate time for clinical evaluation, patient education, SDM, and dialysis preparation. Dialysis preparation typically includes modality selection, access planning, placement and maturation, and hepatitis B vaccination. Initial nephrology referral at the time of dialysis initiation is associated with poorer clinical outcomes.[\[50,53\]](#) In the experience of the Work Group, up to a year may be required to adequately address these issues, recognizing that it is not possible to accurately predict when patients are likely to require dialysis. When consistent with the patient's goals of care, nephrology consultation for eGFR below 30 mL/minute/1.73 m², as discussed elsewhere in this guideline (see [Algorithm: Module C, Sidebar 8](#)), supports this process and allows for co-management of CKD complications that may also postpone the need for dialysis.[\[69\]](#)

Comparative analyses for hospital utilization and end-of-life care outcomes are available for elderly patients electing to pursue dialysis. Tam-Tham et al. (2018) conducted a retrospective cohort study of 838 ESRD patients in Canada between 2002 and 2012.[\[71\]](#) Patients aged 65 or over with an eGFR below 10 mL/minute were divided into dialysis treatment versus no dialysis treatment cohorts. A survival benefit of up to three years was identified in the dialysis population. However these patients also experienced a 40% increased risk of hospitalization (hazard ratio [HR]: 1.40; 95% confidence interval [CI]: 1.16-1.69). Within the U.S. Veteran population, Wong et al. (2018) conducted a retrospective cohort study of end-of-life care characteristics in 14,701 VA patients with an eGFR below 15 mL/min/1.73 m², identified between 2000 and 2009, and who died during that same time period.[\[70\]](#) Patients who elected not to pursue dialysis had significantly lower rates of hospital admission (odds ratio [OR]: 0.4; 95% CI: 0.34-0.46), intensive procedures defined as cardiopulmonary resuscitation (CPR), mechanical ventilation (MV), and total parenteral nutrition (TPN) (OR: 0.15; 95% CI: 0.10-0.22), and death occurring in the hospital (OR: 0.78; 95% CI: 0.74-0.82). The use of palliative care and hospice services were significantly increased in the non-dialysis population (OR: 4.19; 95% CI: 3.58-4.90 and OR: 3.32; 95% CI 2.83-3.89, respectively). Significantly fewer hospital days, and longer duration of hospice and palliative care services were also noted in this cohort. Based on this evidence, a conservative or symptom-driven approach to ESRD management may better match the goals of care for patients who prioritize the avoidance of aggressive medical treatment when compared with dialysis. This retrospective study

examined the utilization of medical services at the end of life in this relevant population. However, specific QoL indicators were not included or available for study.

There is a paucity of published data comparing formal QoL indicators between elderly populations who choose to pursue non-dialytic supportive care and those on dialysis. A prospective observational study of 467 patients compared QoL as assessed by 36-Item Short Form Survey (SF-36) between patients with CKD 4 and 5 attending a pre-dialysis clinic versus those enrolled in a renal supportive care clinic.[72] At time of enrollment, patients in the renal supportive care clinic were significantly older compared with the pre-dialysis clinic patients and reported lower SF-36 physical composite scores. While there was statistically significant survival in the pre-dialysis clinic cohort, there was no significant difference in the changes in QoL and symptoms indices between these two groups, with response rates to the voluntary QoL instruments of around 50% in each group.

The Work Group found the evidence on this topic had significant limitations. Limited-to-no ability to randomize patients, as well as difficulty with balancing cohorts in treatment arms, present challenges to conducting randomized and/or other controlled trials. Further, the body of evidence is limited by variability between comparator groups, observational data, lead time bias (i.e., apparent survival advantage related to early treatment, rather than true benefit of treatment), as well as cultural and socioeconomic factors. Differences in baseline characteristics between patients electing to pursue dialysis versus supportive care (i.e., confounding by indication in which survival benefit of dialysis versus conservative management arises due to healthier patients choosing dialysis over supportive care) may also limit applicability across study populations.

There is significant variability in patient and provider preferences regarding RRT in the frail and elderly populations. Other considerations regarding these recommendations included respect for patient autonomy in the decision to pursue or decline life-sustaining treatment with dialysis, the potential harms to patient independence and QoL with pursuit of dialysis, and the wide variation in patient values and preferences. Potential survival benefits of dialysis must be balanced against risks for more intensive medical care [69-71] death in hospital,[70] and loss of functional capability and independence, all of which may impact patient QoL.[74] One study suggested that 61% of patients in one study regretted the initiation of dialysis, particularly when decisions were made according to provider and family preferences rather than their own, highlighting the importance of SDM to this setting.[70] Provider understanding of patient-specific goals, priorities, values, preferences, and the value of SDM were also recognized as themes from the focus group, which included several participants over the age of 80. The Work Group suggests utilizing SDM regarding RRT (versus conservative management) to improve patient satisfaction (see [Recommendation 10](#) for further discussion of evidence). Particularly in frail and elderly patients, where survival benefit is less clear, the decision to pursue dialytic therapy should not be assumed to be a foregone conclusion; instead, goals of care must be individualized to the preferences, values, and capabilities of the patient and their caregivers.[23] Referring providers and nephrologists should also thoughtfully consider the patient's frame of mind, mood, and capability to make complex decisions (including extent of any cognitive impairment), when pursuing goals of care discussions.[67,68] In situations where providers, patients, and caregivers are undecided regarding whether or not dialysis will be beneficial, a time-limited trial of RRT followed by re-engagement of the patient and caregivers in an SDM discussion may be appropriate.

There is emerging interest in the concept of “palliative dialysis,” that is the provision of dialytic therapy with the intention of easing symptoms of ESRD while prioritizing QoL over longevity and traditional treatment benchmarks. When commensurate with the patient’s goals of care, this approach can include reducing the treatment time or frequency of dialysis, as well as relaxation of targets for dialysis adequacy and metabolic control of metabolic derangements. While this approach demonstrates high respect for patient autonomy, specific indications, benefits, the infrastructure to support its use, and its advantages have not yet been developed in the U.S.[75] For example, there is currently no mechanism to separate quality and outcomes data from palliative dialysis patients from standard care in the assessment of dialysis unit quality benchmarks. Consequently, this approach to therapy is not universally available at this time and may benefit from further study and development of policy to support it.

As these are *Reviewed, New-added* recommendations, the Work Group systematically reviewed the relevant evidence.[50,53,67-74] The Work Group’s confidence in the quality of the evidence is low to very low. The body of evidence is limited by variability across comparator groups, observational data, lead time bias, as well as cultural and socioeconomic factors. Thus, the Work Group decided upon two “Weak for” recommendations and one “Neither for nor against” recommendation.

For additional considerations in the management of elderly patients with CKD, see [Appendix J](#).

C. Non-pharmacologic Management of CKD

a. Nutrition

Recommendation

14. We suggest the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with chronic kidney disease.
(Weak for | Not reviewed, Not-changed)

Discussion

Dietary sodium restriction has been found to reduce proteinuria and improve BP control in patients with CKD.[76-78] McMahon et al. (2013) found significantly lower proteinuria levels and reductions in BP in patients with CKD on a low sodium diet (60-80 mmol/day or 1380-1840 mg/day) versus a higher sodium diet.[77] de Brito-Ashurst et al. (2013) found that patients with CKD receiving a tailored low sodium diet had a significantly greater reduction in systolic BP than those receiving low sodium diet advice alone.[76] Slagman et al. (2011) found significantly larger proteinuria reductions in patients on a low sodium diet (50 mmol/day or 1150 mg/day) plus angiotensin-converting enzyme inhibitor (ACEI) therapy compared with combination angiotensin receptor blocker (ARB)/ACEI therapy and a regular sodium diet (200 mmol/day or 4600 mg/day). Additionally, a greater level of proteinuria reduction was seen in patients on a low sodium diet plus combination ARB/ACEI; however, this was not significantly larger than the reduction achieved with the low sodium diet plus ACEI therapy alone.[78]

Despite general consistency in the evidence supporting a dietary sodium restriction for patients, the degree of sodium restriction required is controversial. While Slagman et al. (2011) studied patients who restricted their sodium to 50 mmol/day (1150 mg/day) and McMahon et al. (2013) examined 60-80 mmol/day (1380-1840 mg/day), it is likely that a more liberal restriction would be just as beneficial and more realistic for patients to follow.[77,78] A sodium intake of 90-100 mmol (2070-2300 mg/day) is

generally accepted and consistent with the NKF's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.^[2]

Patient acceptance of and compliance with a low sodium diet varies. Providers should consider referring patients to registered dietitians (RD) for further dietary counseling, as patients in the focus group who had seen an RD perceived that it helped them adhere to their nutrition plan. A patient's mental health, socioeconomic status, and access to food should also be considered when gauging their ability to adhere to dietary recommendations. It may be beneficial to have a mental health professional and/or social worker involved if concerns in these areas are identified.

As this is a *Not reviewed, Not changed* recommendation, the Work Group did not conduct an updated evidence review, but reviewed the evidence identified in the 2014 CPG.^[76-78] The Work Group's confidence in the quality of the evidence is moderate. The three RCTs that compared dietary sodium restriction to other interventions (diet or medication) were limited by baseline imbalances in important patient characteristics and lack of an appropriate control group.^[76-78] Blinding of dietary interventions was not feasible. Other considerations regarding this recommendation included the benefits, such as reduction in proteinuria and improvement in BP control, outweighing the potential harms, which were small. Thus, the Work Group decided to carry forward a "Weak for" recommendation.

Recommendation

15. In selected patients with stage 3 and 4 chronic kidney disease, we suggest offering a dietary protein intake of 0.6 to 0.8 g/kg/day as it may slow the decline in estimated glomerular filtration rate and progression to end-stage renal disease.

(Weak for | Not reviewed, Amended)

Discussion

Dietary protein restriction has been shown to slow the decline in GFR and the progression to ESRD, potentially by reducing intraglomerular pressure and reducing metabolic acidosis.^[79,80] Nezu et al. (2013) found that patients who limited their protein intake to 0.6-0.8 g protein/kg body weight had significantly higher GFRs than patients consuming higher amounts of protein.^[79] This was consistent among patients with CKD, both with and without diabetic nephropathy. Additionally, Fouque and Laville (2009) found that a low protein diet of 0.6 g/kg/day resulted in a significant reduction of all-cause mortality and longer time to initiation of dialysis.^[80] This was consistent among patients with CKD both with and without diabetic nephropathy.

Despite evidence supporting a dietary protein restriction to slow the progression of kidney disease, this intervention may increase the risk for calorie malnutrition if patients are not educated and monitored appropriately. Patients with CKD are at risk for malnutrition and protein restriction without adequate calorie intake can exacerbate this.^[80] These risks may be compounded in patients with significant proteinuria. Patients may vary greatly in their willingness to follow a dietary protein restriction, as well as their ability to maintain it. Patients in the focus group who had seen an RD reported that dietary counseling helped them adhere to their nutrition plan; however, others did not understand how to limit protein intake, so referral to an RD for dietary counseling should be considered. The RD should consider fluid status and weight status when determining protein needs. Patients from backgrounds where large

protein intake is part of the culture as well as individuals with food insecurity and restricted dietary choices may find it difficult to restrict their protein intake. These patients may particularly benefit from referral to psychologists, social workers, and RDs to assist with behavior modification, access to resources to assist with food security, as well as education on healthier dietary options, respectively. Future research should explore the benefits of plant-based versus animal-based proteins in patients with CKD.

As this is a *Not reviewed, Amended* recommendation, the Work Group did not systematically review evidence related to this recommendation, but reviewed evidence from the 2014 CPG.^[79,80] The Work Group's confidence in the quality of the evidence is low due to lack of information regarding blinding and unclear allocation concealment and intention-to-treat (ITT) analyses. The Work Group judged that the potential benefits of a modestly slower decline in GFR and longer time to initiate dialysis may slightly outweigh the potential harms, including malnutrition. Thus, the Work Group decided upon a "Weak for" recommendation.

D. Pharmacologic Management of CKD and Associated Conditions

a. Diabetes Medications

Recommendation

16. We suggest offering metformin as a first-line therapy for the treatment of type 2 diabetes in patients with stage 1 to 3 chronic kidney disease to reduce all-cause mortality.

(Weak for | Reviewed, New-added)

Discussion

Metformin is recommended in the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care (VA/DoD DM CPG)^a as a first-line agent. In the 2014 version of this guideline, CKD, based on the level of SCr, was documented as a contraindication for use of metformin due to concern about metformin-associated lactic acidosis. However, the U.S. Food and Drug Administration (FDA) revised its warnings on the use of metformin in mild-to-moderate renal impairment based on eGFR in April 2016 after a review of the medical literature on the safety of metformin in patients with CKD.^[81] The evidence review conducted for the update of this guideline identified a single meta-analysis that included 17 observational studies, only six of which assessed the use of metformin in patients with CKD and type 2 DM. Although the quality of the evidence was low, metformin use was associated with a statistically significant decrease in all-cause mortality compared to treatment regimens that did not include metformin.^[82] According to one observational study in the meta-analysis, there was a statistically significant reduction in hypoglycemic episodes in patients treated with metformin monotherapy compared to insulin monotherapy. Since metformin is an oral agent available as a generic, it is more acceptable to patients and providers to initiate or continue due to cost, convenience, and ease of use, compared to injectable insulin. The Work Group determined that the benefits of treatment with metformin outweigh the potential harms in patients with CKD and an eGFR >30 mL/minute/1.73 m². Though lactic acidosis is a worrying side effect for patients and providers, the most common side effects associated with metformin use are gastrointestinal (GI) discomfort and diarrhea.

^a See the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/cd/diabetes/index.asp>

There are no specific recommendations in this CPG for adjusting dosages based on the eGFR, but the FDA provided the following guidance.^[83] Metformin is contraindicated in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m²) and metformin initiation is not recommended in patients with eGFR between 30 and 45 mL/minute/1.73 m². However, metformin use may be used at standard doses in patients with eGFR >45 mL/minute/1.73 m², and may be continued at eGFR between 30 and 45 mL/minute/1.73 m² after consideration of the individual patient's risks and the benefits of treatment. In addition, the FDA recommends holding metformin at the time of or prior to iodinated contrast imaging procedures in patients with an eGFR between 30 and 60 mL/minute/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast, because a contrast-associated acute kidney injury (CA-AKI) may increase the risk of a lactic acidosis with metformin use. Metformin can then be resumed if renal function is stable 48 hours after the imaging procedure or when renal function has recovered.^[83]

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant evidence.^[82] The Work Group's confidence in the quality of the evidence is low due to the observational study design. Additional considerations include the availability of metformin as a generic and as an oral agent, both of which are preferred by patients and providers. Given the available evidence demonstrating decrease in mortality, the Work Group suggests offering metformin as a first-line therapy for the treatment of type 2 DM in patients with stage 1 to 3 CKD. The change in FDA guidance regarding metformin use in patients with CKD supports this recommendation. Additional research is needed to determine appropriate dosages of metformin, specifically looking at the incidence of adverse events in those with increasing renal impairment.

See [Appendix K](#) for additional information on the potential concerns of metformin in patients with CKD.

Recommendation

17. We recommend offering sodium-glucose co-transporter 2 inhibitors as an option for add-on therapy for the treatment of type 2 diabetes in patients with stage 1 to 3 chronic kidney disease to reduce chronic kidney disease progression and the risk of cardiovascular events.

(Strong for | Reviewed, New-added)

Discussion

For the purposes of this CPG, "add-on therapy" refers to the use of all other DM medications in addition to the use of metformin (in patients for whom metformin is not contraindicated) for the treatment of type 2 DM in patients with stage 1 to 3 CKD. While metformin should be considered a first-line therapy for the treatment of type 2 DM in patients with stage 1 to 3 CKD (see [Recommendation 16](#)), there are no data that metformin has any salutary benefit regarding the progression of CKD, whereas sodium-glucose cotransporter 2 (SGLT2) inhibitors do slow the progression of CKD.^[84] There are no studies comparing outcomes with metformin to those with SGLT2 inhibitors alone. The evidence review identified two SRs evaluating SGLT2 inhibitors in patients with both CKD and DM.^[84,85] A meta-analysis of three randomized, placebo-controlled trials (n=34,322) performed by Zelniker et al. (2019) showed that SGLT2 inhibitors were associated with decreased risk of CKD progression (composite of worsening renal function, ESRD, and renal death) in all groups stratified by CKD stage, but the effect was higher at increasing levels of renal function (33% risk reduction with baseline eGFR <60 mL/minute/1.73 m², 44% risk reduction in group

with eGFR 60-90 mL/minute/1.73 m², and 56% risk reduction for those with eGFR >90 mL/minute/1.73 m²).^[84] This decreasing effectiveness in more advanced disease may support consideration of SGLT2 inhibitor use earlier in disease. Furthermore, SGLT2 inhibitors were associated with decreased hospitalization for heart failure regardless of prior history of atherosclerotic CVD (ASCVD) or heart failure in all subgroups. However, the effect also appeared to correlate with decreasing renal function (40% reduction if baseline eGFR <60 mL/minute/1.73 m², 31% in group with eGFR 60-90 mL/minute/1.73 m², and a nonsignificant 12% risk reduction for those with eGFR >90 mL/minute/1.73 m²). The authors hypothesized that natriuresis induced by the SGLT2 inhibitors might explain the effect on heart failure. The SGLT2 inhibitors' risk reduction for major cardiovascular (CV) events was statistically significant in patients with eGFR <60 mL/minute/1.73 m², but not in patients with eGFR >60 mL/minute/1.73 m², and risk reduction was only noted in those with known ASCVD. Although SGLT2 inhibitors also decreased all-cause mortality by 15%, there was significant heterogeneity between groups.^[84]

The earlier and smaller SR by Lo et al. (2018) included nine studies comparing SGLT2 inhibitors with placebo (n=1,092).^[85] In their analysis, SGLT2 inhibitors showed improvement in uACR, heart failure and BP. SGLT2 inhibitors were associated with an increase in SCr. However, closer review of data revealed that the average increase in SCr was 0.04 mg/dL, which the Work Group judged to be not clinically significant. Additionally, the follow-up period for the included studies was weeks, and change in renal function may be explained by mild volume depletion induced by osmotic diuresis. There was no significant difference in mortality and other major adverse CV events (MACE). There was also no difference in discontinuation due to adverse events in SGLT2 inhibitors, which were associated with a 2.5-fold increase in genital infections compared to placebo.^[85]

Further data from the Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial, published after the end of the SR, demonstrated participants with a uACR > 300 and an eGFR of 30-90 mL/minute/1.73 m², randomly assigned to canagliflozin experienced a 30% reduction in a composite outcome of the risk of ESRD, doubling of SCr, or renal or CVD mortality, compared with participants assigned to placebo.^[86]

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant studies identified in the evidence review.^[84,85] The strength of this recommendation is based primarily on moderate-to-high quality evidence presented by the Zelniker et al. SR and meta-analysis. Compared to the low-quality evidence found by Lo et al., Zelniker et al. included a larger number of patients (tens of thousands versus hundreds), a longer study period (years versus weeks to months), and more complete outcome data.^[84,85] Due to the SR and meta-analysis by Zelniker et al. and the significant risk reduction for the critical outcome of decreased CKD progression and CV morbidity markedly outweighing the harms, including risk of side effects (e.g., genital infections), the Work Group decided upon a "Strong for" recommendation.

Recommendation

18. We suggest offering liraglutide or dulaglutide (glucagon-like peptide-1 receptor agonists) as an option for add-on therapy for the treatment of type 2 diabetes in patients with chronic kidney disease to reduce chronic kidney disease progression.

(Weak for | Reviewed, New-added)

Discussion

Evidence on the use of GLP-1 receptor agonists was limited to two studies with moderate-to-high quality evidence.[\[87,88\]](#) In a post hoc subgroup analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, liraglutide was found to reduce the risk of all-cause mortality and MACE compared to placebo in patients with eGFR <60 mL/minute/1.73 m².[\[87\]](#) In addition, liraglutide reduced the risk of MACE in patients with albuminuria (uACR >30 mg/g). In the Dulaglutide Versus Insulin Glargine in Patients with Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease (AWARD-7) trial, dulaglutide was found to significantly reduce the decline of eGFR in patients with stage 3 and 4 CKD, but had no significant effect on ESRD or kidney transplant.[\[88\]](#) There was also no significant difference in all-cause or CV mortality, but this study was not designed to assess mortality and MACE outcomes. Both of these studies showed no significant difference in adverse events in comparison with the control groups.[\[87,88\]](#)

In weighing the options for management of DM in the CKD population, GLP-1 agonists would not be considered first line. As noted above (see [Recommendation 16](#)), there is strong evidence for the reduction of all-cause mortality with metformin and emerging evidence for the renoprotective benefit of SGLT2 inhibitors. Thus, the Work Group suggests offering liraglutide or dulaglutide as adjuncts to metformin or as alternatives to SGLT2 inhibitors. Some GLP-1 agonists (e.g., dulaglutide) may be dosed weekly, which may be of value for patients. However, the cost and need for injection to administer could decrease the desirability for some patients. GLP-1 agonists are contraindicated in patients at increased risk for thyroid tumors, but the low overall risk of adverse effects and the potential for weight loss make GLP-1 agonists an attractive option.

In regards to semaglutide, two articles, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) [\[89\]](#) and Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (PIONEER-6) [\[90\]](#) did not meet the criteria for inclusion. These studies showed favorable trends with the use of a GLP-1 agonist, but the target population was patients with DM. With no subgroup analysis and less than a quarter of the patients having CKD, these could not be used in supporting this recommendation.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant studies identified in the evidence review.[\[87,88\]](#) The systematic evidence review did not identify studies using other GLP-1 agonists that met the criteria for inclusion, so it is uncertain whether other GLP-1 agonists would have the observed benefits. The Work Group's confidence in the quality of the evidence is moderate for the outcome of mortality and high for the outcomes of myocardial infarction (MI), stroke, change in eGFR, and serious adverse events. Other considerations include the benefits of improved mortality and eGFR, outweighing the potential harm of adverse events, which were small. Patient values and preferences were somewhat varied as GLP-1s are delivered subcutaneously. Thus, the Work Group decided upon a "Weak for" recommendation. Future research should examine other GLP-1 agonists in order to assess potential class effects, and assess the long-term effects on renal function and kidney outcomes in patients with CKD.

Recommendation

19. In patients with chronic kidney disease and type 2 diabetes, there is insufficient evidence to recommend for or against the use of thiazolidinediones or dipeptidyl peptidase-4 inhibitors to decrease progression of chronic kidney disease or mortality.

(Neither for nor against | Reviewed, New-added)

Discussion

The systematic evidence review for this CPG update identified two SRs related to the use of dipeptidyl peptidase 4 (DPP-4) inhibitors (also known as “gliptins”) [91,92] and one retrospective cohort study on the use of thiazolidinediones (TZD). [93] In a pooled analysis by Perl et al. (2016) of nine RCTs comparing saxagliptin to placebo, there was no statistically significant change in eGFR or hypoglycemia based on very low quality evidence. [92] A second SR by McGill et al. (2015) examined another DPP-4 inhibitor, linagliptin, versus placebo in a post hoc subgroup analysis of two RCTs and found no significant difference in cardiac failure, congestive heart failure, left ventricular failure, or other serious adverse events based on low quality evidence. [91] A retrospective cohort study by Chen et al. (2015) on TZD use showed lower mortality and decreased need for long-term dialysis with TZDs. However, the study was of very low quality due to lack of randomization and blinding in the study design. [93]

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant evidence. [91-93] Given the low to very low quality of available literature, there was insufficient evidence for the Work Group to recommend for or against the use of either DPP-4 inhibitors or TZD in patients with DM and CKD to improve long-term kidney outcomes or mortality benefit. Additional research is needed in these areas.

b. Hypertension Medications

Recommendation

20. We suggest intensive blood pressure management (insufficient evidence to recommend a specific target) beyond a target of less than 140/90 mmHg, to reduce mortality in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 m².

(Weak for | Reviewed, New-added)

Discussion

Based on the evidence review for the 2019 CKD CPG, treatment to a more intensive BP target has been reported to reduce mortality in patients with CKD, a critical outcome for this CPG update. [94-96] Additional evidence is available since the 2014 CKD CPG regarding patients with hypertension, as well as those with CKD. The evidence review for this CKD CPG update focused on the question of optimal BP goals in patients with CKD and consisted of two SRs, [94,97] one subgroup analysis of a multicenter RCT (Systolic Blood Pressure Intervention Trial [SPRINT]), [95] and extensions of two prospective cohort studies (African American Study of Kidney Disease [AASK] with a follow-up of 14.4 years [98] and Modification of Diet in Renal Disease [MDRD] trials with a follow-up of 19.3 years [96]), that compared treatment to more intensive or lower BP goals versus standard or usual BP targets.

The literature review for the 2014 CKD CPG included one SR that addressed the question of targeting low versus usual or standard BP goals.[\[99\]](#) The three trials included in the SR were the MDRD trial (n=840), the AASK trial (n=1,094), and the Blood-Pressure Control for Renoprotection in Patients with Non-Diabetic Chronic Renal Disease (REIN-2) trial (n=338), which randomized non-diabetic adults with stage 3 to 4 CKD with or without proteinuria to two BP targets (lower [125/75 mmHg to 130/80 mmHg] versus higher [$<140/90$ mmHg] with a median follow-up of 1.6 to 3.8 years). Based on this earlier meta-analysis, a low BP target of $<125/75$ mmHg to 130/80 mmHg was not significantly associated with reduction in kidney function decline, risk of CV mortality, or all-cause mortality compared to a BP target of $<140/90$ mmHg. Additionally, lower targets were associated with increased risk of adverse outcomes such as hypotension, increased risk of falling (particularly in the elderly), pre-renal azotemia, electrolyte disturbances, drug-drug interaction, as well as increased pill burden and difficulty with adherence.[\[99\]](#) Based on that set of studies, the 2014 CKD CPG Work Group suggested against lowering BP to a target of less than 130/80 mmHg in patients with CKD stages 1 to 4, even in the presence of proteinuria. Although there was a signal for benefit in two of the trials based on post hoc subgroup analyses, the Work Group cited concerns about increased risk of adverse outcomes and resource burdens for the patient due to the need for more frequent visits and monitoring.[\[99\]](#)

For the 2019 CKD CPG evidence review, several studies evaluated risk of CKD progression to ESRD and markers of CKD progression, a critical outcome for this guideline. Similar to the evidence reviewed in the 2014 CKD CPG to determine the optimal BP goal in patients with CKD, treatment to more intensive BP goals did not demonstrate a benefit in reducing kidney function decline. In an SR and meta-analysis of nine trials in patients with non-diabetic CKD (n=5,316), there was no statistically significant difference in the annual rate of change in GFR, doubling of SCr level or 50% reduction in GFR, incidence of ESRD, or composite renal outcomes between patients treated to more intensive targets compared to standard BP targets.[\[97\]](#) In a subgroup analysis of patients with CKD in SPRINT, Cheung et al. (2017) found no statistically significant difference in the composite of $\geq 50\%$ decrease in eGFR from baseline or ESRD. However, it was noted that patients in the intensive treatment group were at an increased risk of a $\geq 30\%$ decline in eGFR compared to the standard treatment group. This decline was thought to be due to an acute hemodynamic effect of treatment, as the rate of change in eGFR did not differ between treatment groups after six months follow-up.[\[95\]](#) The long-term extension studies for AASK [\[98\]](#) and MDRD [\[96\]](#) found no statistically significant between-group differences in risk of CKD progression to ESRD. Additional research is needed to determine whether patients with CKD and significant proteinuria may benefit from treatment to a more intensive BP goal to prevent decline in kidney function.

Evidence regarding the effect of BP control on mortality was variable. Results from a subgroup analysis of 2,646 SPRINT participants with CKD (66% with baseline eGFR ≥ 45 mL/minute/1.73 m²) demonstrated a 28% lower rate of all-cause mortality in patients randomized to more intensive systolic BP target of <120 mmHg (n=1,330) compared to those in the standard BP target of <140 mmHg (n=1,316) treatment group.[\[95\]](#) Achieved systolic BP/diastolic BP was approximately 123/66 mmHg with more intensive treatment compared to 135/72 mmHg in the standard treatment group; not surprisingly, the intensive group was prescribed more antihypertensive agents (mean 2.9 versus 2.0). It is important to note that patients with DM, proteinuria >1 g/d and orthostatic hypotension were excluded from the study, and the mean age of the subgroup was approximately 72 years of age (44% ≥ 75 years).[\[95\]](#) An SR by Malhotra et al. (2017), with evidence rated as high for the critical outcome of mortality, included 18 RCTs comparing

intensive BP control to standard BP control (variable targets, five studies did not have defined BP targets) in 15,924 patients, including 1,094 patients from SPRINT, aged 18 to 80 years with stage 3 to 5 CKD with mean follow-up of 3.6 years.[94] The mean baseline systolic BP was 148 mmHg, with a decrease to 132 mmHg in the intensive treatment group and to 140 mmHg in the less intensive treatment group. Treatment to more intensive BP targets significantly reduced mortality regardless of CKD severity; however, there was no significant difference when only those studies with defined BP targets were included (evidence rated as moderate).[94] The SR and meta-analysis by Tsai et al. (2017) included 8,127 patients with non-diabetic CKD (median age 55 years) from nine RCTs and found no statistically significant difference in mortality between more intensive and standard BP targets (with or without defined BP targets). The evidence from this SR was rated as low for the critical outcome of mortality.[97] The long-term observational extension of the MDRD trial found that intensive BP lowering (mean arterial pressure [MAP] <92 mmHg; equivalent to approximately <125/75 mmHg) significantly reduced mortality compared to a standard target (MAP <107 mmHg; approximately <140/90 mmHg).[96] In addition, the long-term follow-up of the AASK trial reported a significant difference in the risk of mortality (adjusted analysis) between strict (MAP ≤92 mmHg) compared to usual (MAP 102–107 mmHg; approximately 135/85 to 140/90 mmHg) BP targets.[98]

The Work Group sought data on the risk of side effects associated with antihypertensive use, with electrolyte imbalances as a critical outcome. In the SPRINT subgroup analysis by Cheung et al. (2017), the incidence of hypotension was higher in the intensive treatment group (1.2%) compared to standard treatment (0.9%), a difference that was not statistically significant ($p=0.17$).[95] There was also no significant differences in bradycardia or injurious falls. There was a statistically significant increased risk of hypokalemia, hyperkalemia, and acute kidney injury (AKI) in the intensive treatment group compared to the standard target group. However, the strength of evidence was low due to serious limitations and imprecision in the data.[95] Although reports of AKI were higher in the intensive treatment group, a review of serious adverse events (not included as part of the evidence review for this CPG) reported as AKI resulting in or occurring during hospitalization or emergency department visits in patients in SPRINT noted that most cases of AKI were mild and resulted in complete recovery of kidney function.[100]

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the relevant evidence.[94-99] Though there does not appear to be a benefit with regard to progression of CKD, treatment to more intensive BP targets may reduce mortality in patients with CKD. However, confidence in the overall quality of the evidence was low. The Work Group also noted potential subgroup considerations when considering the evidence for a benefit on mortality. For example, patients with DM, 1 g/day or more proteinuria, and medical conditions that may limit life expectancy to less than three years were excluded from SPRINT;[95] however, the meta-analysis of 18 trials by Malhotra et al. (2017), that also included data from SPRINT, reported that the benefit of more intensive treatment on mortality was consistent across several subgroups, including whether or not the patient had DM.[94] Therefore, given the studies evaluating different patient populations as well as different BP targets, it is not possible to make a recommendation for a specific BP target for all patients with CKD. Providers may refer to the VA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care (VA/DoD Hypertension CPG)^b for further discussion of BP targets. The Work Group suggests that a lower BP target (e.g., 120 to

^b 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>

130/<80 mmHg) as opposed to the previous BP goal of less than 140/90 mmHg could be considered for reducing mortality in patients with CKD, taking into consideration risk versus benefit on an individual basis, and after discussion of the treatment plan with the patient. The decision to treat to a lower BP goal should respect patient preferences and capabilities, including the need for additional medications, which may affect adherence to the medication regimen, as well as the risk of adverse effects, which may require additional monitoring. Thus, the Work Group decided upon a “Weak for” recommendation.

Recommendation

21. In patients with non-diabetic chronic kidney disease, hypertension, and albuminuria, we recommend the use of an angiotensin-converting enzyme inhibitor to prevent progression of chronic kidney disease. Angiotensin II receptor blockers may be substituted for patients with an angiotensin-converting enzyme inhibitor-induced cough.
(Strong for | Not reviewed, Not changed)

22. In patients with chronic kidney disease, diabetes, hypertension, and albuminuria, we recommend the use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers to slow the progression of chronic kidney disease, unless there is documentation of intolerance.
(Strong for | Not reviewed, Amended)

23. We recommend against the use of combination renin-angiotensin-aldosterone system blockade (an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker, or an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker with a direct renin inhibitor) in patients with chronic kidney disease.
(Strong against | Not reviewed, Not changed)

Discussion

These recommendations are carried forward from the 2014 CKD CPG without an updated review of the evidence. The supporting evidence to recommend an ACEI (or ARB if unable to tolerate an ACEI) in patients with non-diabetic CKD, hypertension, and albuminuria, [101-113] and an ACEI or ARB in patients with CKD, DM, hypertension, and albuminuria are dated before 2008.[114-120] The evidence to recommend against the use of combination of an ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor are dated prior to 2014.[121-125] The data for the use of ARBs in patients with non-diabetic CKD are primarily based on evidence from surrogate outcomes as reviewed in the 2008 CKD CPG.

The recommendation for use of an ACEI or ARB as the initial regimen is based primarily on their beneficial effects on kidney outcomes and significant benefit to slow CKD progression. Results from Nakamura et al. (2010), which were part of the evidence review for the 2014 CKD CPG, showed that ACEIs or ARBs are equally effective in controlling BP in CKD,[126] but the data are limited regarding CV benefits of ACEIs or ARBs compared to other antihypertensive agents in patients with CKD. An SR included in the 2008 CKD CPG showed that treatment with an ACEI reduces the risk for ESRD by 31%, with a 30% reduction in the composite outcome of doubling SCr and ESRD compared to treatment without an ACEI.[105] The REIN-2 and the AASK trials demonstrate that ACEI therapy slows the progression of non-diabetic CKD in patients with proteinuria. Both trials were also reviewed as part of the evidence for BP target recommendations in the 2014 CKD CPG.[103,104,107-110] The evidence that ARBs or ACEIs slow the progression of CKD in

patients with CKD and DM with albuminuria is primarily based on the Irbesartan Diabetic Nephropathy Trial (IDNT),^[118] the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial,^[115] and the Collaborative Study Group.^[117] Both IDNT and RENAAL demonstrated a reduction in the primary endpoint of composite all-cause mortality, doubling of SCr, and ESRD with an ARB compared to placebo, and in IDNT also compared to a dihydropyridine calcium channel blocker (CCB), in patients with type 2 DM and nephropathy.^[115,118] In addition, an ACEI has been reported to be beneficial in patients with type 1 DM with albuminuria to reduce the combined risk of death, dialysis, or transplantation.^[117]

Regarding the selection of second- or third-line agents for antihypertensive therapy in patients with CKD, there are limited data available to guide the clinician. Two small RCTs that were part of the evidence review for the 2014 CKD CPG showed that a dihydropyridine CCB was as efficacious as an ACEI in controlling BP,^[127] as was a loop diuretic compared to an antihypertensive control group. The decision for the use of these or other antihypertensive classes should be considered based on the potential for CV benefit and the patient's comorbidities and preference. Refer to the VA/DoD Hypertension CPG^c for more complete information on the safety of all antihypertensive agents, and stepwise, sequential, and combination therapy. Further research on comparative benefits of the different antihypertensive agents for long-term CV and kidney outcomes in patients with CKD are needed.

Use of ACEIs or ARBs will commonly increase SCr (up to 30% within the first two weeks after initiation) and potassium, so patients with CKD on renin-angiotensin-aldosterone system (RAAS) inhibitors require monitoring of potassium and SCr for safety reasons.^[128] It is unclear whether treatment with an ARB would be an appropriate alternative in patients who develop hyperkalemia on an ACEI. One study that was not part of the evidence review reported that the change in serum potassium was not significantly different in patients with mild kidney impairment on an ACEI compared to an ARB; in patients with moderate kidney dysfunction, there was an increase in potassium of 0.28 mEq/L above baseline (4.6 mEq/L) with the ACEI compared to an increase in potassium of 0.12 mEq/L seen with the ARB, but the difference was not statistically significant.^[129] If potassium becomes elevated, measures to reduce hyperkalemia that may be considered include 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 or consideration of a potassium binder, if appropriate. If efforts to control hyperkalemia are not effective, the option of discontinuing treatment with the ACEI or ARB may be considered after discussing the risk versus benefits and preferences with the patient.

While it is common for patients with ACEI-induced cough to 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. In an SR of patients with prior angioedema associated with an ACEI, the risk of angioedema on subsequent treatment with an ARB was 9.4% for cases described as possible per the reports, and 3.5% for confirmed cases.^[130] Another review estimated that the risk of cross-reactivity of angioedema with an ARB ranged from less than 7% to 17% in patients who previously experienced angioedema with an ACEI.^[131]

^c 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>

Therefore, an ARB should be used with caution in patients who have previously experienced angioedema with an ACEI.[\[130\]](#)

The Work Group acknowledges that the evidence for these recommendations is based primarily on data reviewed for the 2008 CKD CPG, and therefore, used a different evidence grading system. Given the positive renal benefit with an ACEI in non-diabetic CKD and albuminuria and with an ACEI or ARB in diabetic patients with CKD and albuminuria, the Work Group maintained these as “Strong for” recommendations for clinical practice. Additional data are needed to determine the CV outcome benefit with an ACEI or ARB in these patients with CKD.

Combination RAAS blockade

The recommendation against use of combination RAAS blockade (an ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor) in patients with CKD is based on the 2014 CKD CPG evidence review. Although studies evaluating combination therapy with two agents that block the RAAS have reported a greater benefit in reduction of albuminuria in patients with CKD (trials also included patients with DM) compared to those receiving monotherapy,[\[132-136\]](#) clinical trials did not demonstrate long-term benefit of reducing kidney disease progression with combination RAAS blockade in patients with CKD.[\[121-123\]](#) There was no significant difference between treatment with combination ACEI and ARB versus ACEI or ARB monotherapy on progression to ESRD,[\[121,122,125\]](#) death,[\[121,122,124,125\]](#) or measures of kidney function impairment including first occurrence of eGFR decline,[\[122\]](#) >50% increase in SCr,[\[121\]](#) or doubling SCr.[\[124,125\]](#) In addition, in one clinical trial there was no significant difference between a combination of ACEI or ARB with a direct renin inhibitor versus monotherapy with either ACEI or ARB for the primary composite outcome that included CV and renal endpoints.[\[123\]](#) Treatment with combination therapy increased the risk for hyperkalemia,[\[122-125\]](#) AKI,[\[122,125\]](#) and hypotension [\[123-125\]](#) compared to monotherapy. Thus, the Work Group agrees that the harms outweigh the benefit and support the 2014 CKD CPG “Strong against” recommendation for the use of combination RAAS blockade with an ACEI and ARB, or ACEI or ARB in combination with a direct renin inhibitor in patients with CKD.

Based on the evidence review for the 2014 CKD CPG, data were 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 other RAAS blockade compared to monotherapy in patients with CKD. Results from one SR [\[137\]](#) and two controlled trials (one randomized, open-label) [\[138,139\]](#) showed that additional RAAS blockade with a mineralocorticoid receptor antagonist further reduced proteinuria versus the comparator group. However, one trial [\[140\]](#) and one SR [\[125,141\]](#) reported no significant difference in all-cause mortality or doubling SCr in patients receiving an ACEI who were randomized to an ARB, a mineralocorticoid receptor antagonist, or placebo. The lack of benefit from the addition of a mineralocorticoid receptor antagonist to an ACEI or ARB or both, other than reduction in proteinuria, was also demonstrated in a more recent SR that was not a part of the 2014 CKD CPG evidence review.[\[141\]](#) 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.

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. When multiple RAAS blockers are used, the risk for hyperkalemia is further increased.[\[122,124,125,137,141\]](#) Most trials

evaluating combination RAAS blockade in patients with CKD excluded patients with a serum potassium >5 mEq/L [123,138,139] or >5.5 mEq/L.[121,122,125,142] 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 and AKI, which can also place additional burden and risk on the patient. Frequency of monitoring should take into account baseline serum potassium and renal function, adherence to low potassium diet, use of concomitant medications that may increase the risk for hyperkalemia, or conditions that may contribute to volume depletion. Providers may wish to consider nephrology consultation or collaboration in assessment of risk/benefit and development of monitoring plan.

As these three recommendations are all *Not reviewed*, and either *Amended* or *Not changed*, the Work Group did not systematically review the relevant evidence in this CPG update. Evidence supporting the use of an ACEI (or ARB if unable to tolerate an ACEI) in patients with non-diabetic CKD, hypertension, and albuminuria,[101-113] and an ACEI or ARB in patients with CKD, DM, hypertension, and albuminuria,[114-120] stem from the 2008 CPG evidence review, while the evidence to recommend against the use of a combination of an ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor, were reviewed during the 2014 CPG update.[121-125] While the body of evidence has some limitations, the Work Group's confidence in the quality of evidence and patient values and preferences support the Work Group's decision to carry forward these "Strong for" and "Strong against" recommendations.

See [Appendix K](#) for additional information on the use of ACEI and ARB in patients with CKD.

c. Anemia Medications

Recommendation

24. We suggest initiation of oral iron therapy to support iron requirements in patients with chronic kidney disease.

(Weak for | Not reviewed, Amended)

Discussion

Iron deficiency is common in patients with CKD for a variety of reasons. Bleeding (e.g., menstrual, GI, operative) and medications that may decrease intestinal iron absorption, such as phosphate binders or gastric acid inhibitors, may contribute to iron depletion. In addition, patients with CKD are at increased risk of inflammation, resulting in elevated hepcidin levels, which may also contribute to poor GI absorption of iron and decreased iron release from macrophages.

Diagnosing iron deficiency may be challenging in patients with CKD, and iron deficiency is a major cause of hyporesponsiveness to erythropoiesis-stimulating agent (ESA) therapy. Transferrin is the plasma iron transport protein, and low transferrin saturation reflects iron deficiency. Ferritin is the cellular storage protein for iron but may not accurately reflect iron stores because it is also a non-specific acute-phase reactant and may be elevated when there is infection and/or inflammation. Anemia may improve with iron supplementation in patients with CKD with normal ferritin levels, reflecting "functional iron deficiency," so targeting higher ferritin targets may be necessary.[143] There is limited evidence to support specific ferritin and transferrin saturation levels to initiate iron therapy or to be used as targets.

However, the 2006 KDOQI guidelines, not included in this evidence base, suggested ferritin levels be maintained above 100 ng/mL and transferrin saturation more than 20% in patients with CKD not on dialysis,[\[2\]](#) while the 2012 KDIGO guidelines recommended a trial of iron therapy if ferritin is ≤ 500 ng/mL and transferrin saturation is $\leq 30\%$.[\[144\]](#)

Correction of absolute or relative iron deficiency is an important part of anemia management in patients with CKD, and several factors should be considered when determining the best route of administration for iron repletion for an individual patient. No studies have shown significant differences between most oral iron preparations with regard to efficacy and tolerability. Ferrous sulfate, which is the most commonly used oral iron preparation, is inexpensive and easily accessible; however, side effects (primarily GI related), drug interactions, and pill burden may hinder adherence and limit use of oral iron therapy.[\[145-147\]](#) Small studies using radiolabeled iron preparations in iron-deficient women without CKD showed that every-other-day dosing of iron may be more effective at raising iron levels than conventional daily dosing due to the increase in hepcidin levels that occurs in some patients. Additionally, less frequent dosing may also help improve tolerability.[\[148,149\]](#) A comprehensive SR by Albaramki et al. showed that IV iron therapy was associated with a small but significant increase in hemoglobin, ferritin, and transferrin saturation levels compared to oral iron.[\[150\]](#) A subsequent meta-analysis by Shepshelovich et al. showed that patients treated with IV iron were more likely to achieve an increase in hemoglobin with similar rates of all-cause mortality, ESA dose increases, blood transfusions, and adverse effects compared to oral iron therapy.[\[151\]](#) Concerns associated with the use of parenteral iron preparations include risk of anaphylaxis and hypotension, higher cost, as well as need for infusion capabilities. Newer IV iron preparations (e.g., iron sucrose, sodium ferric gluconate, ferric carboxymaltose, ferumoxytol) are associated with lower risk of severe adverse reactions, including anaphylaxis, compared to iron dextran. Depending on the product, IV iron may be given as an infusion or IV push over several visits without the added pill burden, making parenteral iron a more convenient option for selected patients. However, the availability of infusion capabilities and increase in resource utilization for preparation and administration of IV iron and observation for potential adverse reactions, as well as the need for IV access (which may be limited in patients who need to preserve blood vessels for future dialysis access) may make IV iron less practical.

Blood transfusion can quickly correct anemia and furnish some iron. Risks associated with blood transfusion include allergic reactions, transfusion of blood-borne infection, acute or delayed hemolytic reactions, transfusion-related lung injury, and iron overload. Additionally, pre-transplant blood transfusions may cause allosensitization which may be associated with longer wait times to transplantation and increased rejection and graft loss post-transplant. Thus, blood transfusion is avoided in non-emergent situations whenever possible, particularly in potential transplant candidates.[\[152\]](#)

Iron-based phosphate binders, such as ferric citrate, may be an option for patients with CKD, iron deficiency anemia and hyperphosphatemia. Ferric citrate decreases serum phosphate, increases ferritin and transferrin saturation and increases hemoglobin in patients with CKD not on dialysis.[\[146\]](#) The most common side effects associated with ferric citrate use include diarrhea, constipation, discolored feces and nausea. However, use of ferric citrate is associated with significant cost and pill burden (up to 12 tablets per day) as well as risk of iron overload.

As this is a *Not reviewed, Amended* recommendation, the Work Group did not systematically review evidence related to this recommendation and instead carried forward evidence included in the 2014

CPG.[143,150] In addition to the evidence reviewed in 2014, more recent evidence also supports this recommendation.[2,144-149,151,152] The Work Group’s confidence in the quality of the evidence is low. While the body of evidence had some limitations, including use of a surrogate outcome, it supports the use of oral iron over IV iron; however, parenteral iron may be used based on patient preferences regarding side effects, prior response to treatment, and accessibility/feasibility to IV iron therapy. As a result, the Work Group decided upon a “Weak for” recommendation.

Recommendation

25. We recommend against initiating erythropoiesis-stimulating agents in patients with chronic kidney disease for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension.

(Strong against | Not reviewed, Amended)

26. We recommend against initiating erythropoiesis-stimulating agents at a hemoglobin level greater than 10 g/dL.

(Strong against | Not reviewed, Not changed)

Discussion

Anemia, typically normocytic and normochromic, is a common complication in patients with CKD, usually most prevalent when eGFR is consistently below 30 mL/min. Anemia has been associated with fatigue, dyspnea, adverse effects on cardiac function as well as mental and cognitive decline. Common factors for anemia in CKD include lack of effective erythropoietin (EPO) production by diseased kidneys, shortened life of red blood cells in the uremic state, and chronic inflammatory state attributed to uremia resulting in altered iron absorption and decreased EPO responsiveness.

Early diagnosis and treatment of anemia in patients with CKD are the cornerstones of clinical management, so regular surveillance for anemia in patients with CKD is recommended. The 2006 KDOQI guidelines recommended the use of hemoglobin to define anemia and evaluation when hemoglobin falls below 13.5g/dL in males and below 12g/dL in females.[2] Anemia of CKD is a diagnosis of exclusion;[2] thus, evaluation for other causes of anemia similar to patients with normal renal function, including nutritional deficiencies, blood loss, systemic illness, and defective erythropoiesis should be undertaken. While EPO deficiency contributes to anemia in patients with CKD, checking EPO levels is not recommended since serum EPO levels are usually inappropriately low in patients with CKD and generally not helpful in establishing the differential diagnosis of anemia. If other causes of anemia have been excluded and anemia does not respond to iron supplementation, referral of patients with CKD to a nephrologist to assess the need for therapy with ESAs should be considered.

Though rare, risks and complications associated with blood transfusions can occur and include volume overload, allergic reaction, transmission of blood-borne infection, hemolytic reactions, transfusion-related acute lung injury, and iron overload. Aside from avoiding adverse events associated with red blood cell transfusions, limiting transfusions also averts the potential risk of alloimmunization in potential transplant candidates. Thus, minimizing blood transfusions in stable patients with CKD is recommended.

ESA treatment is effective in raising the mean hemoglobin and reduces the need for blood transfusions in patients with stage 3 to 5 CKD,[\[153-156\]](#) but treatment with ESAs has also been associated with potential harms and significant burdens. Controlled trials on ESA treatment in patients with CKD and anemia from previous versions of the CKD CPG used to support these recommendations, including the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE), and Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trials, showed greater risks for death, serious adverse CV reactions, and stroke with higher hemoglobin targets compared to lower hemoglobin targets.[\[156-158\]](#) Additionally, in patients with a history of malignancy, ESA use was associated with increased adverse events, including increased mortality from cancer, tumor progression, and thrombotic events.[\[159\]](#) Other burdens associated with ESA use for patients with CKD not on dialysis include drug cost, frequent clinic visits for ESA injections, and need for laboratory monitoring. Additional burdens to the provider managing ESA therapy include increase in resource utilization for laboratory monitoring, pharmacy and clinic nursing staff to dispense and administer medication, and ongoing surveillance of patient condition for prompt identification of critical findings requiring cessation of ESA treatment. ESA should be initiated after weighing the risks related to blood transfusion and ESA therapy with the benefits of alleviation of symptoms and avoiding blood transfusions. Primary care providers should, therefore, consider referral to nephrology or specialized clinic for ESA management.

As these recommendations are *Not reviewed* and either *Amended* or *Not changed*, the Work Group did not systematically review evidence related to them and instead carried forward evidence included in the 2014 CKD CPG.[\[153-158\]](#) In addition to the evidence reviewed in 2014, more recent evidence also supports these recommendations.[\[2,83,148,159-165\]](#) There is insufficient evidence to recommend specific thresholds for starting ESAs or for maintaining hemoglobin within a specific target range; however, TREAT allowed for use of ESAs as rescue therapy when hemoglobin decreased below 9mg/dL, and ESAs were started in CREATE trial when hemoglobin was below 10.5g/dL in the lower hemoglobin group. Therefore, the Work Group agreed that hemoglobin level less than 9-10mg/dL would be reasonable for initiation of ESAs with use of a higher threshold if the patient was symptomatic. ESA dose should be adjusted based on response to iron therapy and the rate of hemoglobin changes while on ESA therapy. Guidance from the FDA, released in 2011, advised initiation of ESA treatment when hemoglobin falls below 10 g/dL, lowering or stopping ESA when hemoglobin level rises above 10g/dL and individualizing ESA dosing to use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.[\[163\]](#) Patients with certain comorbidities, such as heart failure or pulmonary disease, may need higher hemoglobin levels to alleviate symptoms. Based on available trial data, the Work Group recommends against initiating ESAs at a hemoglobin level greater than 10g/dL and against offering ESAs to patients with CKD for the purpose of achieving a hemoglobin target above 11.5g/dL due to increased risk of stroke and hypertension.

Hypoxia-inducible factor prolyl-hydroxylase domain (HIF-PHD) inhibitors, such as vadadustat and roxadustat, may represent a novel alternative to ESA for the management of anemia in patients with CKD. HIF-PHD inhibitors appear to induce endogenous EPO synthesis and enhance iron mobilization. They have been shown to increase hemoglobin levels in anemic patients with CKD but are not currently FDA approved.[\[161,164,165\]](#) The role of HIF-PHD inhibitors in the management of anemia in patients with CKD needs to be further elucidated.

d. Bone Health Medications

Recommendation

27. We suggest against offering calcitriol or active vitamin D analogs to patients with stage 3 and 4 chronic kidney disease and elevated parathyroid hormone levels.

(Weak against | Not reviewed, Amended)

Discussion

Active vitamin D compounds effectively decrease parathyroid hormone (PTH) levels in all studies, but the effects of active vitamin D compounds on serum calcium and phosphate levels and other effects on bone histomorphometric changes were inconsistent. Some studies showed significant increases in serum calcium and phosphate levels [166,167] while others noted no differences in serum calcium or phosphate values.[168-171] Palmer et al. (2009) reviewed studies describing bone histomorphometric changes, bone density, and fractures in patients with CKD treated with active vitamin D compounds.[172] Studies reporting changes in bone histomorphometry, which included small numbers of patients, suggested that oral calcitriol may slightly improve osteitis fibrosa, but may increase the risk of osteomalacia. In one study of 25 patients, no significant differences were found in bone mineral density at femoral neck or lumbar spine after 12 months of oral calcitriol therapy. In another study of 38 patients reported in the same SR, calcitriol did not improve fracture rates. Interestingly, while Thadhani et al. (2012) found significantly higher S_{Cr} levels in the paricalcitol group when compared to placebo,[167] differences in eGFR were not observed with cystatin C-based eGFR measurements. Researchers attributed the discrepancy in eGFR outcomes to a reported increase in creatinine production by active vitamin D drugs.

As this is a *Not reviewed, Amended* recommendation, the Work Group did not systematically review evidence related to this recommendation but reviewed the evidence from the 2014 CPG.[166-172] Confidence in the quality of the evidence is low because data demonstrated inconsistent outcomes with use of active vitamin D compounds on different markers of mineral bone disease. In the absence of consistent evidence pointing toward kidney, bone or CV benefit (other than reduction in PTH levels) and the potential for hypercalcemia and cost burden, we suggest not offering calcitriol or active vitamin D analogs to patients with stage 3 and 4 CKD. Active vitamin D analogs or calcitriol may be useful in the management of secondary hyperparathyroidism in patients with CKD stage 5 or patients on dialysis, but use should be managed by a nephrologist. Given these considerations, the Work Group carried forward the “Weak against” recommendation.

Recommendation

28. We suggest against offering calcimimetics to patients with stage 3 and 4 chronic kidney disease and elevated parathyroid hormone levels.

(Weak against | Not reviewed, Amended)

Discussion

Calcimimetic agents (oral cinacalcet or IV etelcalcetide) are FDA approved for the control of secondary hyperparathyroidism in patients with ESRD. Cinacalcet is also approved for treatment of hypercalcemia related to parathyroid carcinoma and in patients with primary hyperparathyroidism who are not surgical

candidates for parathyroidectomy. Calcimimetics are not approved for use in patients with CKD who are not on dialysis.

Chonchol et al. (2009) showed that cinacalcet effectively lowered PTH levels compared to placebo in a 32-week study of patients with CKD stages 3 and 4; however, approximately two-thirds of patients treated with cinacalcet developed hypocalcemia, and cinacalcet therapy led to a 20% increase in serum phosphorus levels.[\[173\]](#) Since the 2014 CKD CPG evidence review, a retrospective study by Perez-Ricart et al. (2016) of 32 patients with stage 3 to 5 CKD not on dialysis, treated with cinacalcet for at least one year, demonstrated a significant drop in PTH, but with an increase in serum phosphorus and a decrease in serum calcium levels.[\[174\]](#) The clinical significance of these biochemical changes is uncertain, but no studies have documented any bone/mineral or CV benefit of calcimimetic treatment in the CKD population. Due to lack of evidence of benefit and the substantial risk of developing hypocalcemia and a moderate possibility of developing hyperphosphatemia with cinacalcet therapy, the Work Group suggests against the use of calcimimetics for the management of hyperparathyroidism in patients with stage 3 and 4 CKD.

As this is a *Not reviewed, Amended* recommendation, the Work Group did not systematically review evidence related to this recommendation, but reviewed the evidence from the 2014 CPG and amended the language of the recommendation.[\[173\]](#) In addition to the evidence reviewed in 2014, more recent evidence also supports this recommendation.[\[174\]](#) The Work Group's confidence in the quality of existing evidence is low because of the small patient population and few patients with CKD stage 3 and 4 who were not on dialysis and who received calcimimetics. Lowering PTH levels in patients with CKD who are not on dialysis has not shown a significant benefit compared to using calcitriol or active vitamin D analogues (see [Recommendation 27](#)). Potential harms include electrolyte abnormalities and cost. The Work Group therefore decided on a "Weak against" recommendation.

Recommendation

29. There is insufficient evidence to recommend for or against the use of phosphate binders to reduce mortality, progression of chronic kidney disease, or major cardiovascular outcomes in patients with stage 2 to 5 chronic kidney disease.

(Neither for nor against | Reviewed, New-replaced)

Discussion

The evidence review for this update of the CKD CPG on the use of phosphate binders in patients with CKD included one SR and meta-analysis conducted by Ruospo et al. (2018).[\[175\]](#) This meta-analysis included three studies comparing sevelamer to placebo or usual care, and three studies comparing lanthanum to placebo or usual care, concluding that treatment with these phosphate binders did not reduce mortality, MI, decline in renal function or progression to ESRD. There was also no reduction in stroke with sevelamer versus placebo or usual care. In addition, there was no significant difference in mortality or change in eGFR with iron-based phosphate binders (based on data from two studies) or calcium (based on data from one study) compared to placebo or usual care. When sevelamer was compared to calcium (based on data from two studies), there was no statistically significant difference in mortality. Although there is epidemiologic evidence not included in the evidence review that hyperphosphatemia is associated with increased

mortality in patients on dialysis,[\[176-179\]](#) there is no evidence that the use of a phosphate binder will provide long-term outcome benefit.

Phosphate binders effectively reduce serum phosphorus, but there is some variability in provider and patient preferences regarding their use. Adverse events associated with phosphate binders include constipation, diarrhea, nausea, and hypercalcemia, though the risk depends on the phosphate binder selected. Increased pill burden, cost of the medication, and need for lab monitoring should also be considered. Patients may elect to rely on dietary phosphate restriction, though nutrition evaluation should be considered to ensure that patients meet adequate protein needs.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the relevant evidence.[\[175\]](#) The Work Group's confidence in the quality of the evidence is very low due to the limited number of high quality trials and lack of long-term data. There is therefore insufficient evidence to recommend for or against the use of phosphate binders in patients with CKD with normal serum phosphorus. Though phosphate binders are effective at reducing phosphate levels and hyperphosphatemia has been associated with increased mortality in dialysis patients, use of phosphate binders has not been associated with improvement in mortality or CV outcomes. Additional research focusing on the long-term effects of phosphate binders in the CKD population is needed. Thus, the Work Group opted for a "Neither for nor against" recommendation.

e. Other Medications to Slow CKD Progression

Recommendation

30. We suggest the use of sodium bicarbonate supplementation in patients with chronic kidney disease and metabolic acidosis to slow the progression of chronic kidney disease.

(Weak for | Not reviewed, Amended)

Discussion

An SR by Susantitaphong et al. (2012) of six studies with a total of 312 patients assessing the use of sodium bicarbonate as alkali therapy demonstrated that, for studies with a duration longer than two months, sodium bicarbonate therapy was associated with improvement in eGFR and a lower incidence of dialysis initiation.[\[180\]](#) In five of the six trials, the mean serum bicarbonate level at enrollment was less than 22 mEq/L. Treatment with sodium bicarbonate did not increase BP or worsen edema. The largest study in that SR was an RCT by de Brito-Ashurst et al. (2009) of 134 patients with CKD stage 4 who were observed for 24 months.[\[181\]](#) They found that treatment of metabolic acidosis (plasma bicarbonate levels >16 mEq/L and <20 mEq/L) with oral sodium bicarbonate was associated with slower decline in creatinine clearance (9% versus 45%; risk ratio [RR] 0.15; $p < 0.0001$) and decreased progression to ESRD (6.5% versus 33%; RR 0.13; $p < 0.001$).

An alternative form of alkali therapy is a diet rich in fruits and vegetables. While not included in the 2014 CKD CPG evidence review, Goraya et al. (2014) treated 108 patients with CKD stage 3 for three years with usual care, oral sodium bicarbonate, or fruits and vegetables as the alkali therapy ($n=36$ for each arm).[\[182\]](#) Both the sodium bicarbonate and fruits and vegetables groups had less of a decline in eGFR compared to usual care. There was no increase in BP or hyperkalemia in either treatment arm, however, patients enrolled in the study were selected to be at low risk for hyperkalemia. While this additional study

confirms the benefit of preserving kidney function with alkali therapy, the small number of patients and the pre-selection for not developing hyperkalemia prevents recommending fruits and vegetables as an alternative alkali therapy over sodium bicarbonate.

As this is a *Not reviewed, Amended* recommendation, the Work Group did not systematically review evidence related to this recommendation but reviewed the evidence from the 2014 CPG.[\[180\]](#) The only newly published data since the last evidence review was the trial by Goraya et al. (2014) described above.[\[182\]](#) The data supporting sodium bicarbonate therapy to improve the plasma bicarbonate therapy in patients with metabolic acidosis is consistent across the trials, but the total number of patients included in the SR is small. Therefore, confidence in the quality of evidence remains very low. Patients may have trouble tolerating the gas from oral sodium bicarbonate, and the large size and number of pills required may affect medication adherence. Future research should include trials with larger number of patients to validate the long-term effect of alkali therapy on CKD progression as well as use of alternative types of alkali therapy, such as sodium citrate, potassium citrate, or potassium bicarbonate, which may be better tolerated than oral sodium bicarbonate or diets low in animal protein. The efficacy and safety of fruits and vegetables as a source of alkali should be studied in larger trials that include patients with advanced CKD.

Recommendation

31. In patients with chronic kidney disease and asymptomatic hyperuricemia, there is insufficient evidence to recommend for or against the use of urate-lowering therapy for the purpose of slowing progression of chronic kidney disease.

(Neither for nor against | Reviewed, New-added)

Discussion

The evidence review conducted for the 2019 CPG regarding the use of urate-lowering therapy in delaying CKD progression included one SR and meta-analysis,[\[183\]](#) two RCTs,[\[184,185\]](#) and one post hoc subgroup analysis[\[186\]](#) of an RCT. An SR and meta-analysis by Pisano et al. (2017) showed that use of allopurinol was associated with lower incidence of progression to ESRD in patients with stage 2-4 CKD compared to the control.[\[183\]](#) There was no difference in change in eGFR from baseline in a combined analysis of either allopurinol or febuxostat versus usual care or placebo. The evidence concerning eGFR is low quality due to the high inconsistency and indirectness in the studies used for the meta-analysis. Several of the studies included in the meta-analysis had high risk of bias, and the authors did not include in the meta-analysis all studies that had sufficient data for analysis. An RCT by Kimura et al. (2018) compared febuxostat to placebo in CKD and found no difference in rates of change in renal function, stroke, or combined CV events.[\[185\]](#) Another RCT by Mukri et al. (2018) compared febuxostat to usual care and found no difference in change in eGFR from baseline or difference in CV events.[\[184\]](#) In a post hoc subgroup analysis of one RCT comparing febuxostat to allopurinol, there was no statistically significant difference in change in eGFR, but the trial was only six months in duration.[\[185,186\]](#) Studies addressed patients with stage 2 or greater CKD with hyperuricemia and found that treatment longer than three months was associated with positive outcomes.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the relevant evidence.[\[183-186\]](#) Confidence in the quality of the evidence is very low due to serious limitations in study quality, inconsistent outcomes, and variable follow-up range. There is insufficient evidence that

urate-lowering therapy slows CKD progression. However, patients with CKD are at increased risk for gout, and use of urate-lowering therapy should be considered to mitigate the risk of gout flares, which may be very painful. Diminishing the risk of gout flares would also obviate the need for non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and steroids, which are used in the management of acute gout and may be problematic in the CKD population. Pill burden, medication side effects, and treatment costs should be considered before prescribing urate-lowering therapy. Initiation of urate lowering therapy may precipitate gouty attacks in some patients. Patients should be educated on this possibility, and overlapping prophylactic therapy may be considered for a few weeks to address this concern. In addition, an FDA boxed warning was recently added to the product information for febuxostat.[\[187\]](#) Before prescribing allopurinol, providers should consider testing for the human leukocyte antigen (HLA)-B*5801 allele due to the elevated risk for developing severe cutaneous adverse reactions (SCAR) in patients who carry this allele. The HLA-B*5801 allele is most common in those of Asian descent, and patients of Korean descent with CKD stage 3 or greater and all patients of Han Chinese or Thai descent are at high risk for severe allopurinol hypersensitivity reaction. The consensus from the Work Group is that benefits may slightly outweigh harms/burden for this treatment. Thus, the Work Group decided upon a “Neither for nor against” recommendation.

Recommendation

32. In patients at risk for rapidly progressing autosomal dominant polycystic kidney disease, we suggest offering tolvaptan in consultation with a nephrologist to slow decline in estimated glomerular filtration rate.

(Weak for | Reviewed, New-added)

Discussion

Tolvaptan has been found to slow the intermediate endpoint of decline in eGFR by about 1 mL/minute/1.73 m²/year in patients with rapidly progressing autosomal dominant polycystic kidney disease (ADPKD), although use of tolvaptan has been associated with an increased incidence of adverse effects. The long-term safety and efficacy for the reduction of hard renal outcomes, such as need for dialysis or transplant, have yet to be established.[\[188-190\]](#)

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial in patients with ADPKD suggested that treatment with tolvaptan was associated with a slower decline in eGFR compared to placebo (mean change in eGFR of -2.72 mL/minute/1.73 m²/year with tolvaptan versus -3.7 mL/minute/1.73 m²/year with placebo over 36 months).[\[188\]](#) However, more patients on tolvaptan discontinued study treatment due to adverse events, including increases in hepatotoxicity and aquaretic side effects such as thirst, polyuria, nocturia, urinary frequency; 23% of tolvaptan patients withdrew from the study compared with 14% in the placebo group. The Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial also showed slower decline in eGFR of 2.34 mL/min/1.73 m² with tolvaptan compared to 3.61 mL/min/1.73 m² with placebo over a one year period.[\[189\]](#) A lower overall incidence of adverse events was noted in REPRISE; however, only patients who tolerated tolvaptan during an 8-week screening phase were randomized to the active portion of this trial. Patients in this selected group receiving tolvaptan again reported a 7% absolute increase of adverse effects including aquaretic side effects, diarrhea, and fatigue (9.5% in the tolvaptan group versus 2.5% in the placebo group).

Besides the more common side effects noted above, significant concerns for the safety of tolvaptan have been identified with respect to hepatotoxicity. An increased risk of hepatic adverse events (10.9% in the tolvaptan group versus 5.3% in the placebo group; HR: 4.91) was observed in REPRISÉ.[\[189\]](#) Most cases of elevated hepatic enzymes improved with interruption or discontinuation of tolvaptan, and the risk for liver toxicity may be mitigated with monthly monitoring of liver function tests facilitating early identification of hepatotoxicity. However, a 2018 FDA post-marketing review of tolvaptan reported a single case of liver failure requiring transplantation, despite monthly monitoring.[\[191\]](#) Considering the concern for hepatotoxicity, an FDA Risk Evaluation and Mitigation Strategy (REMS) has created a certification process for prescribers and a patient registry to limit prescriptive access for tolvaptan to those registered in the REMS program.[\[192\]](#) While these programs may reduce the risk for safety and adverse events, they cannot eliminate it entirely and the importance of a committed prescriber and a compliant patient are paramount to the safe use of this medication.

Patients with ADPKD who are expected to benefit the most from tolvaptan include those with eGFR over 30 mL/minute/1.73 m² with rapidly progressing disease. As ADPKD presents with a wide range of penetrance and rates of decline in renal function and significant toxicity may result from the agent, the Work Group strongly advises consultation with a nephrologist to identify patients likely to benefit from tolvaptan prior to initiation of therapy. Appropriate patient selection with regard to the patient's ability to tolerate side effects, maintain adequate hydration, and comply with frequent lab monitoring, as well as retain uninterrupted access to the medication and a committed nephrologist experienced in managing tolvaptan, must be carefully considered prior to offering therapy and be weighed against the potential benefit of a 1 mL/minute/1.73 m²/year slowing of the decrease in eGFR.

Significant variability in provider and patient preferences, as well as variability in acceptance and tolerance of this treatment, is anticipated. The risk of adverse effects, the importance of maintaining adequate hydration, and closely monitoring liver function tests, medication costs, and access to nephrology care should be discussed with the patient prior to initiating therapy.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed the available, relevant evidence.[\[188-190\]](#) While overall confidence in the quality of the safety data evidence is moderate, it is lower for the efficacy data due to reliance on surrogate outcomes. Limitations of the current body of evidence include reliance on the use of surrogate outcomes and modeling systems for data analysis as well as an absence of long-term data demonstrating a reduction in ADPKD progression to ESRD. Despite tolerability and safety concerns, there is no other primary therapy available for patients with rapidly progressive ADPKD at this time. Thus, the Work Group has decided upon a "Weak for" recommendation for the use of tolvaptan in rapidly progressing ADPKD, to be prescribed in conjunction with a nephrologist. Further studies to assess the efficacy in reducing hard renal outcomes, such as need for dialysis and renal transplant, and safety of tolvaptan with long-term data are needed.

E. Contrast-Associated Kidney Injury Management

The risk of AKI following exposure to iodinated contrast media has been questioned. Although widely perceived as a common risk for AKI, recent epidemiologic studies, particularly among patients receiving IV contrast for computed tomography, have questioned the risks associated with contrast administration. McDonald et al. (2014) found similar rates of AKI among more than 20,000 propensity-matched patients

undergoing computed tomography with or without contrast enhancement (OR: 0.94; 95% CI: 0.83-1.07; $p=0.38$).^[193] In another analysis, the same investigators found no difference in the risk of AKI associated with contrast exposure after stratifying by level of eGFR.^[194] In contradistinction, however, in a separate cohort of more than 20,000 propensity-matched patients undergoing computed tomography with or without contrast enhancement, Davenport et al. (2013) found an increased risk of AKI among patients with a baseline SCr >1.5 mg/dL following IV contrast exposure (OR: 1.45; 95% CI: 1.11-1.89; $p=0.007$) with increasing risk with higher baseline SCr.^[195] In a separate analysis, the same investigators found that IV iodinated contrast was associated with an odds of AKI of 1.40 (95% CI: 1.00-1.97) for patients with an eGFR of 30-44 mL/minute/1.73 m² and of 2.96 (95% CI: 1.22-7.17) for patients with an eGFR of <30 mL/minute/1.73 m².^[195] Based on these data, the Work Group concluded that patients with underlying kidney disease with reduced eGFR are at increased risk of CA-AKI following IV contrast administration. The risk of AKI following intra-arterial contrast exposure, as occurs during coronary and non-coronary angiography, is likely higher than the risk following IV contrast exposure.^[196-198] The risk of AKI following contrast exposure should be considered in deciding whether to perform contrast-enhanced diagnostic and therapeutic procedures; alternative imaging procedures should be considered, and the risks and benefits of using contrast should be explicitly discussed with patients for informed SDM. The risk of AKI associated with contrast exposure should not, however, prevent the performance of contrast-enhanced tomography and diagnostic or therapeutic angiography when indicated.

Among some patients with CKD (e.g., patients with DM and an eGFR <60 mL/minute/1.73 m² or non-diabetic patients with an eGFR <45 mL/minute/1.73 m²), strategies to minimize the risk of CA-AKI should be implemented. These include use of the least nephrotoxic contrast media (low-osmolar or iso-osmolar contrast media), minimization of the volume of administered contrast media and avoidance of concomitant nephrotoxins, including, particularly, NSAIDs. Specific recommendations are provided below.

Recommendation

33. For patients at increased risk for iodinated contrast-associated acute kidney injury, we recommend volume expansion with intravenous isotonic saline prior to and following iodinated contrast administration (see [Algorithm Module D](#) for additional information).

(Strong for | Reviewed, Amended)

Discussion

The 2014 CKD CPG suggested that patients at increased risk for CA-AKI receive volume expansion with IV isotonic crystalloid solutions (saline or sodium bicarbonate) prior to and following contrast administration and suggested offering oral hydration to patients in which IV hydration is not feasible. Although there are only a limited number of studies directly comparing IV isotonic crystalloid to oral fluid administration in patients at high-risk for the development of CA-AKI, the Work Group concluded that the strength of evidence supporting the use of isotonic crystalloid to mitigate the risk for development of CA-AKI in high-risk patients is strong based on studies demonstrating greater risk reduction associated with isotonic as compared to hypotonic fluid administration and associated with higher volumes of administered isotonic fluids. Based on the results of RCTs published since the 2014 CKD CPG evidence review, the Work Group concluded that there is no evidence to support an added benefit to sodium bicarbonate administration compared to isotonic saline. Additionally, in the absence of commercially available isotonic sodium bicarbonate for IV infusion, bicarbonate solutions must be compounded by adding concentrated sodium

bicarbonate to sterile water or 5% dextrose in water. The Work Group concluded that there is a potential risk of harm associated with sodium bicarbonate administration based on the risk of compounding errors and an increased cost without evidence of benefit.

The 2014 CKD CPG evidence review identified a single meta-analysis of 513 patients of six trials comparing IV saline (five trials utilizing isotonic [0.9%] saline and one trial utilizing 0.45% saline) compared to various regimens of “oral fluid” administration.[\[199\]](#) Detailed analysis of the included trials reveals marked heterogeneity in the oral fluid administration arms. Three of the six studies included the administration of IV saline post-procedure and two involved the administration of water plus either oral sodium bicarbonate or oral sodium chloride. Only one study compared IV isotonic saline to unrestricted oral fluids.[\[200\]](#) In this study, only one patient (3.7%) in the saline group developed CA-AKI, defined based on an increase in SCr by 0.5 mg/dL within 48 hours of contrast exposure, as compared to nine patients (34.6%) in the oral hydration group ($p=0.005$). The study was terminated early after only 53 patients were enrolled due to the high rate of CA-AKI in the oral hydration group. Based on this data, oral hydration should not be considered adequate for prophylaxis for CA-AKI.

Since the 2014 CKD CPG evidence review, Nijssen et al. (2017) compared IV isotonic saline (3-4 mL/kg/hr for four hours pre- and post-contrast exposure or 1 mL/kg/hr for 12 hours pre- and post-contrast exposure) to no IV fluids among 660 patients with an eGFR of 30-59 mL/minute/1.73 m² undergoing either contrast-enhanced computed tomography (52%) or angiography (48%) with a mean administered contrast volume of 90 mL.[\[201\]](#) CA-AKI developed in 2.6% of patients who did not receive IV saline versus 2.7% of those receiving IV saline ($p=0.47$). Kooiman et al. (2014) compared pre-procedural administration of 250 mL of 1.4% bicarbonate to no IV fluids in 138 patients with CKD undergoing computed tomography pulmonary angiography and found an incidence of CA-AKI in 9.2% of patients receiving no IV fluids as compared to 7.1% of patients randomized to IV 1.4% bicarbonate (RR: 1.29; 95% CI: 0.41-4.03).[\[202\]](#) Given the relatively small volume of IV fluids administered and the overall small sample size, strong conclusions cannot be drawn from this study.

Two studies, not included in the evidence base, compared the administration of post-procedural isotonic saline to no fluid administration among patients undergoing primary percutaneous coronary angiography (PCI) in the setting of acute ST-segment elevation myocardial infarction (STEMI).[\[203,204\]](#) In this setting, it is logistically difficult to provide pre-procedural fluids due to the urgency of angiography. Among 216 patients presenting with acute STEMI, Luo et al. observed a reduction in the incidence of CA-AKI from 35% to 20% (RR: 0.81; 95% CI: 0.69-0.96; $p=0.015$) across all patients. There was minimal benefit observed among low-risk patients; however, among patients with moderate to very high risk, the reduction in the incidence of CA-AKI ranged between 29% and 56%.[\[203\]](#) In the second study, the incidence of CA-AKI was 10.8% among the 204 patients randomized to intra- and post-procedural infusion of isotonic saline as compared to 21.1% among patients randomized to no fluids ($p=0.016$).[\[204\]](#) In an as-treated analysis, accounting for 74 patients who were randomized to no saline and required saline infusion due to severe hypotension, primarily in the setting of right ventricular infarction, and for 42 patients randomized to saline infusion in whom it needed to be discontinued due to the development of significant heart failure, the incidence of CA-AKI associated with saline infusion was 6.6% compared to 21% among patients who did not receive saline. After multivariable adjustment, the OR for development of CA-AKI associated with saline administration was 0.29 (95% CI: 0.14-0.66; $p=0.003$).

Brar et al. (2014) compared the use of higher volumes of IV saline (3 mL/kg over one hour followed by 1.5-5 mL/kg/hr over four hours guided by left ventricular end-diastolic pressure [LVEDP]) compared to a standard regimen of 3 mL/kg over one hour followed by 1.5 mL/kg/hour over four hours in 396 patients with an eGFR <60 mL/minute/1.73 m² and decreased left ventricular function undergoing coronary angiography.[205] CA-AKI developed in 6.7% of patients randomized to LVEDP-guided fluid administration (total saline volume 1,727±583 mL) compared to 16.3% of patients in the control arm (total saline volume 812±142 mL; RR: 0.41; 95% CI: 0.22-0.79; p=0.005).

Several trials have compared isotonic saline to isotonic sodium bicarbonate for prevention of CA-AKI with variable results. An Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review identified 30 articles comparing IV sodium bicarbonate to IV isotonic saline.[206] Nineteen of these were included in the pooled meta-analysis; six studies concluded that sodium bicarbonate reduced the incidence of CA-AKI compared to IV saline and 13 found no difference. The pooled meta-analysis found no statistically significant difference between sodium bicarbonate and saline (pooled RR: 0.93; 95% CI: 0.68-1.27). Two additional studies have been published since the AHRQ review.[207,208] Solomon et al. (2015) found no difference in either CA-AKI (14.5% with sodium bicarbonate versus 12.1% with isotonic saline; p=0.20) or a composite endpoint of mortality, need for dialysis, or a sustained 20% reduction in eGFR at six months (14.9% with sodium bicarbonate versus 16.3% with saline; p=0.78) among 391 patients with an eGFR <45 mL/minute/1.73 m² undergoing coronary or non-coronary angiography.[208]

The Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial evaluated 4,993 patients with DM with an eGFR <60 mL/minute/1.73 m² or without DM and an eGFR <45 mL/minute/1.73 m² undergoing coronary or non-coronary angiography in a 2x2 factorial design comparing IV isotonic sodium bicarbonate to IV isotonic saline and N-acetylcysteine to placebo.[207] In the comparison of isotonic sodium bicarbonate to isotonic saline, CA-AKI occurred in 9.5% of patients assigned to sodium bicarbonate as compared to 8.3% of patients assigned to isotonic saline (OR: 1.16; 95% CI: 0.96-1.41; p=0.13). The primary study endpoint of death, need for dialysis, or a persistent 50% increase in SCr at day 90 occurred in 4.4% of patients in the sodium bicarbonate arm and 4.7% of patients in the saline arm (OR: 0.91; 95% CI: 0.72-1.22; p=0.62). Thus, the Work Group concluded that there was no benefit to sodium bicarbonate compared to saline.

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed the evidence identified in the evidence review conducted for this CPG update [201,202,205-207] and considered the assessment of the evidence put forth in the 2014 CPG.[199] Findings from other studies outside of the SR also supported the recommendation.[203,204,208] The Work Group determined that the strength of evidence favoring the administration of isotonic IV crystalloid was low with conflicting data from poor quality studies, but evidence suggests that larger volumes of IV fluids were associated with greater benefit and those with more advanced CKD were more likely to benefit. Thus, the Work Group decided upon a “Strong for” recommendation. The Work Group suggests that IV isotonic crystalloid be administered to reduce the risk of CA-AKI in high-risk patients (i.e., patients with DM and an eGFR <60 mL/minute/1.73 m² or non-diabetic patients with an eGFR <45 mL/minute/1.73 m² undergoing angiography with intra-arterial contrast administration or patients with an eGFR <30-45 mL/minute/1.73 m² undergoing contrast-enhanced computed tomography), if there is no medical contraindication. The optimal rate and volume of infusion is uncertain; the Work Group suggests, from a practical standpoint,

that patients with CKD undergoing outpatient angiographic or contrast-enhanced computed tomographic procedures be given at least 3 mL/kg of isotonic saline over one hour pre-procedure continued at a rate of 1-1.5 mL/kg/hour during the procedure, and at least an additional 6 mL/kg of isotonic saline over 2-6 hours (rate of 1-3 mL/kg/hour) post-procedure. For inpatients, the Work Group suggests the administration of isotonic saline at 1 mL/kg/hour for at least 6-12 hours pre-procedure, intra-procedure and for at least 6-12 hours post-procedure. These suggestions assume that an assessment of volume status has been done by the treating providers and that patients are reasonably considered to be able to tolerate this amount of fluid.

Recommendation

34. We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury.

(Strong against | Reviewed, New-replaced)

Discussion

Studies evaluating the benefit of N-acetylcysteine for the prevention of CA-AKI have been inconsistent. An AHRQ Comparative Effectiveness Review identified 67 RCTs and 11 observational studies, 54 of which, encompassing 4,749 patients, were included in a pooled meta-analysis.[\[206\]](#) The pooled RR for CA-AKI was 0.78 (95% CI: 0.59-1.03) for high-dose (>1200 mg/day) N-acetylcysteine and 0.75 (95% CI: 0.63-0.89) for low-dose (\leq 1200 mg/day) N-acetylcysteine.

The PRESERVE trial evaluated 4,993 patients with DM with an eGFR <60 mL/minute/1.73 m² or without DM and an eGFR <45 mL/minute/1.73 m² undergoing coronary or non-coronary angiography in a 2x2 factorial design comparing IV isotonic sodium bicarbonate to IV isotonic saline and N-acetylcysteine to placebo.[\[207\]](#) N-acetylcysteine was given as 1,200 mg by mouth one hour pre-angiography and one hour post-angiography and then continued at 1,200 mg by mouth twice daily for a total of 10 doses. CA-AKI occurred in 9.1% of patients assigned to N-acetylcysteine compared to 8.7% of patients assigned to placebo (OR: 1.06; 95% CI: 0.87-1.28; p=0.13). The primary study endpoint of death, need for dialysis, or a persistent 50% increase in SCr at day 90 occurred in 4.6% of patients in the N-acetylcysteine arm and 4.5% of patients in the placebo arm (OR: 1.02; 95% CI: 0.78-1.33; p=0.88). While no direct patient harm was associated with oral N-acetylcysteine, IV N-acetylcysteine is associated with a risk of anaphylaxis.

While these studies were limited to patients who were medically stable, there is insufficient data to recommend use of this agent in patients who are medically unstable, such as patients undergoing imaging procedures in the setting of sepsis or acute decompensated heart failure. Furthermore, in these settings, it is difficult to differentiate between AKI associated with contrast exposure and AKI due to other factors. In a recent meta-analysis N-acetylcysteine was not effective in preventing AKI following cardiac surgery.[\[209\]](#)

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the studies identified in the evidence review conducted for this CPG update.[\[206,207\]](#) The quality of the evidence was low. However, the two large RCTs (Acetylcysteine for Contrast-induced Nephropathy Trial [ACT] and PRESERVE),[\[206,207\]](#) which randomized a total of more than 7,300 patients to N-acetylcysteine or placebo, provide strong evidence that N-acetylcysteine is ineffective in the prevention of CA-AKI.

Additionally use of N-acetylcysteine is associated with potential side effects and increased costs. Thus, the Work Group decided upon a “Strong against” recommendation.

Recommendation

35. We recommend against the use of renal replacement therapy for iodinated contrast-associated acute kidney injury prophylaxis.

(Strong against | Reviewed, Amended)

Discussion

There are limited data on the benefit of RRT for the prevention of CA-AKI. The proposed mechanism of benefit for this intervention, rapid removal of the administered dye load, lacks biological plausibility as it would take 8-12 hours of intermittent hemodialysis and a longer duration of continuous RRT to remove more than 90% of the administered dye load. In addition, some of the clinical trials of RRT have used change in SCr, a surrogate marker of CA-AKI that is removed by RRT, as a primary outcome. In a meta-analysis of six trials of hemodialysis not included in the evidence base, Cruz et al. (2012) found a pooled RR of 1.61 (95% CI: 1.13-2.28) for the development of AKI with hemodialysis compared to standard management.[\[210\]](#) In three trials of hemofiltration and hemodiafiltration, Cruz et al. reported a pooled RR of 0.46 (95% CI: 0.12-1.70); however, two of the three trials demonstrating benefit used change in SCr as the primary outcome. In the AHRQ Comparative Effectiveness Review, Subramaniam et al. (2016) found similar results and, based on the limitations of the studies and the risks of the procedures, concluded that the evidence was insufficient to support a clinically important benefit of RRT.[\[206\]](#) Given the potential for harm and the burden of therapy, including the need for insertion of large-bore central venous catheters to provide dialysis, the need to transfer patients to intensive care units to provide continuous hemofiltration and the expense of treatment, the Work Group recommends against the use of RRT for prevention of CA-AKI.

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed the evidence identified in the evidence review conducted for this CPG update [\[206\]](#) and considered the assessment of the evidence put forth in the 2014 CPG.[\[211\]](#) Although the confidence in the quality of the evidence is very low, given the absence of benefit with a trend towards harm associated with prophylactic hemodialysis and the potential harms associated with implementing RRT, the Work Group decided upon a “Strong against” recommendation.

Other Interventions for the Prevention of CA-AKI

Data suggest that statin therapy may provide a benefit for prevention of CA-AKI through cholesterol metabolism-independent mechanisms. An AHRQ Comparative Effectiveness Review identified 19 studies encompassing 10,574 individuals with varying combinations of co-interventions (IV saline, IV bicarbonate, and N-acetylcysteine) and comparators.[\[206\]](#) In a pooled analysis of studies comparing statin plus IV saline to IV saline alone, statin use was associated with a non-statistically significant reduction in the risk of CA-AKI (RR: 0.68; 95% CI: 0.39-1.20). In the pooled analysis of statins plus N-acetylcysteine plus IV fluids compared to N-acetylcysteine plus IV fluids, the risk reduction attained statistical significance (RR: 0.52; (95% CI: 0.29-0.93). Liang et al. (2017) subsequently performed a meta-analysis of 15 RCTs (n=2,673) to assess the effectiveness of moderate to high-dose rosuvastatin in preventing CA-AKI.[\[212\]](#) In the pooled meta-analysis, patients treated with high-dose rosuvastatin had a 55% lower risk of CA-AKI (RR: 0.45; 95%

CI: 0.35-0.58; $p < 0.0001$) in comparison to both low-dose rosuvastatin and placebo. The benefit was modestly attenuated in patients with CKD (RR: 0.53; 95% CI: 0.30-0.93; $p = 0.03$). However, there is the potential that the observed benefit is due to artifact associated with changes in creatinine kinetics associated with initiation of statin therapy. The Work Group therefore chose to make no recommendation regarding the use of statin therapy for prevention of CA-AKI in patients undergoing non-emergent angiography, noting that the majority of patients with CKD who undergo angiographic procedures have additional indications for statin therapy.

Other interventions that have been evaluated for the prevention of CA-AKI include diuretics, dopamine, fenoldopam, adenosine antagonists and ascorbic acid. These agents have either been associated with insufficient evidence of benefit or harm with regard to the prevention of CA-AKI.[\[206\]](#) Although acute diuretic administration has been associated with increased risk of CA-AKI, there is no evidence to support discontinuation of chronic diuretic therapy in the periprocedural period to alter risk of CA-AKI.

The use of remote ischemic preconditioning, which is outside the scope of this evidence review, has been associated with benefit in early clinical trials, but should be considered to be an experimental intervention.[\[213\]](#)

VII. Future Research

Research focusing on patients with CKD is lacking because CKD is a common exclusion criterion in many trials. As a result, much of the CKD research is based on retrospective observational studies with the associated biases or secondary cohort analyses of RCTs that did not target patients with CKD as the primary population. Future research should include more trials that specifically target patients with CKD and CKD specific outcomes.

Additional studies are needed to determine:

- Adherence to guideline recommendations and improvements in patient outcomes
- Effects on non-nephrology-related outcomes, such as vascular disease, nutritional status, functional status, and mental health, in studies specific to patients with CKD
- Critical elements of comprehensive intervention that lead to desired outcomes, including interdisciplinary care, education, behavior change approaches, and spiritual and emotional support
- Benefits and risks of screening patients for CKD; the VA's large population of patients with CKD would make this an ideal trial for the VA
- Value/utility of prediction tools, such as KFRE, with regard to mortality and optimal timing of referral to nephrology and for dialysis access
- Likelihood of obtaining a functional arteriovenous access following PICC lines versus alternative approaches for vascular access
- Timing (e.g., stage of CKD) at which nephrology referral improves outcomes
- Benefits of interdisciplinary care interventions for patients with CKD, including identifying characteristics of patients with CKD that would benefit from interdisciplinary teams; supported self-efficacy and PCC
- Feasibility and impact of non-face-to-face care in collaboration with nephrology (e.g., telehealth, electronic consults, and programs such as Specialty Care Access Network-Extension for Community Healthcare Outcomes [SCAN-ECHO])
- Benefits of patient education, including early education interventions, technology based learning (mobile apps), peer-to-peer education, motivational interviewing, and education with family
- Effect of SDM on CKD outcomes; these studies should also seek to identify how to best achieve positive outcomes with SDM, the knowledge and tools needed to implement SDM regarding initiation and type of dialysis, and comparing SDM conducted by a primary care provider versus a nephrologist
- Outcomes of comparing supportive care compared to dialysis between similar populations with equivalent comorbidities
- Optimal timing of palliative care initiation in advanced CKD
- Benefits of concurrent palliative care and dialysis, and feasibility and utility of palliative dialysis

- Long-term impact of hyperphosphatemia and whether interventions to lower phosphate levels affect sequelae of hyperphosphatemia
- Long-term effect of glitazones, sodium glucose transporter inhibitors and dipeptidyl peptidase 4 inhibitors on renal outcomes in patients with CKD
- Long-term effect of BP lowering on renal outcomes to determine the optimal blood pressure lowering goal for patients with CKD
- Optimal pain management for patients with CKD

Appendix A: Evidence Review Methodology

A. Developing the Key Questions

The CPG Champions, along with the Work Group, were tasked with identifying KQs to guide the SR of the literature on CKD. These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by AHRQ. [Table A-1](#) provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [214]

PICOTS Element	Description
Patients, Population, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
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.
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.
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.
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).
Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions, Work Group, 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. Due to resource constraints, all developed KQs could not be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority, and those were included in the review. [Table A-2](#) contains the final set of KQs used to guide the SR for this CPG.

Once the KQs were finalized, the Work Group prioritized the outcomes they had defined for each KQ based on how important the Work Group judged each outcome to be. Ranking outcomes by their relative importance can help focus attention on those outcomes that are considered most important for clinical decision making when making judgements regarding the overall quality of the evidence to support a recommendation.

Using GRADE methodology, the Work Group rated each outcome on a 1-9 scale (7-9, critical for decision making; 4-6, important, but not critical, for decision making; and 1-3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see [Outcomes](#)); however, only outcomes judged to be critical were used to determine the overall quality of evidence (see [Grading Recommendations](#)).

a. Population(s)

- Key Question 1
 - ◆ Adults without a CKD diagnosis
- Key Question 2, 4-7, 9-11
 - ◆ Adults with CKD
- Key Question 3
 - ◆ Adults with advanced CKD (stages 4/5) or overt proteinuria
- Key Question 8
 - ◆ Adults with advanced CKD (stages 4/5) advanced age, or other life threatening conditions
- Key Question 12
 - ◆ Adults with CKD exposed to iodinated contrast

b. Interventions

- Key Question 1
 - ◆ Tests
 - ◆ Testing/screening for CKD
 - ◆ Labeling with a CKD diagnosis
- Key Question 2
 - ◆ Tests
 - ◆ Creatinine
 - ◆ eGFR (various methods of calculation)
 - ◆ Proteinuria
 - ◆ Albumin
 - ◆ Cystatin C
 - ◆ Risk calculator
- Key Question 3
 - ◆ Tool
 - ◆ Use of a specific equation
- Key Question 4
 - ◆ Vascular access devices, such as:
 - ◆ PICC lines
 - ◆ Midlines

- ◆ Subclavian lines
- ◆ IV pacemakers
- Key Question 5
 - ◆ Nephrology referral
 - ◆ Multidisciplinary/interdisciplinary care:
 - ◆ Physician extenders
 - ◆ Physician assistants
 - ◆ Nurse practitioners
 - ◆ Pharmacists
 - ◆ Social workers
 - ◆ Vascular access teams
 - ◆ CKD education teams
 - ◆ Dietician/nutritionist
 - ◆ Early referral/multidisciplinary/ interdisciplinary care
- Key Question 6
 - ◆ Education
 - ◆ Including medical nutritional therapy
 - ◆ One education approach
- Key Question 7
 - ◆ Shared decision making
 - ◆ One shared decision making approach
- Key Question 8
 - ◆ Conservative management (e.g., supportive care, palliative care)
- Key Question 9
 - ◆ Calcium versus non-calcium phosphate binders in patients with hyperphosphatemia
 - ◆ Treatment of hyperuricemia
 - ◆ DPP-4 inhibitors (“gliptins”)
 - ◆ SGLT2 inhibitors
 - ◆ GLP-1 agonists
 - ◆ TZD
 - ◆ Metformin
 - ◆ Tolvaptan

- Key Question 10
 - ◆ Aggressive BP treatment for low BP goals / lower BP versus treatment to standard BP goals
- Key Question 11
 - ◆ Pain control intervention, such as:
 - ◆ Opioids
 - ◆ Non-opioid analgesics: NSAIDs (oral, topical, parenteral) and cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, salicylates
 - ◆ Antiepileptic drugs: gabapentin, pregabalin
 - ◆ Antidepressants: Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitor (SNRIs)
 - ◆ Non-pharmacological treatments
- Key Question 12
 - ◆ Iso-osmolar contrast agent (iodixanol) versus low-osmolar contrast agents (and are there differences among the low-osmolar agents)
 - ◆ Intravenous crystalloid versus oral hydration
 - ◆ Regimen for intravenous fluid administration (this would include LVEDP guided therapy and high-flow therapies using devices that match urine output and fluid administration)
 - ◆ Isotonic (1.3%) sodium bicarbonate versus isotonic (0.9%) saline
 - ◆ N-acetylcysteine versus no N-acetylcysteine
 - ◆ Statin versus no statin
 - ◆ Other agents (e.g., fenoldopam, dopamine, theophylline, furosemide, mannitol)
 - ◆ RRT versus no RRT

c. Comparators

- Key Question 1
 - ◆ No testing/screening for CKD
 - ◆ No labeling with CKD diagnosis
- Key Question 2
 - ◆ Other tests
 - ◆ No tests
 - ◆ Routine care
 - ◆ Creatinine alone

- Key Question 3
 - ◆ Use of a different equation
 - ◆ Use of CKD stages
- Key Question 4
 - ◆ No vascular access devices
 - ◆ Alternative vascular access devices
 - ◆ Peripheral IV
 - ◆ Epicardial pacemakers
- Key Question 5
 - ◆ Patients managed by PCPs alone
 - ◆ Late referral/multidisciplinary/interdisciplinary care
- Key Question 6
 - ◆ No education
 - ◆ Alternative education approach
- Key Question 7
 - ◆ No SDM
 - ◆ Alternative SDM approach
- Key Question 8
 - ◆ Dialysis
- Key Question 9
 - ◆ Placebo
 - ◆ Other drug
- Key Question 10
 - ◆ Less aggressive BP goals/higher or standard BP goals
- Key Question 11
 - ◆ No intervention
 - ◆ Alternate intervention
- Key Question 12
 - ◆ No intervention
 - ◆ Alternate intervention
 - ◆ Alternate contrasting agent

d. Outcomes

- Key Question 1
 - ◆ Critical outcomes
 - Risk of CKD progression to ESRD
 - Mortality
 - CV morbidity/stroke/amputation
 - ◆ Important outcomes
 - Markers of CKD progression
 - Hospitalization/emergency department (ED) use/nursing home placement
 - QoL
 - Cost-related outcomes
- Key Question 2
 - ◆ Critical outcomes
 - Risk of CKD progression to ESRD
 - Mortality
 - CV morbidity/stroke/amputation
 - ◆ Important outcomes
 - Morbidity- Anemia
 - Morbidity- Bone health
 - Hospitalization/ED use/nursing home placement
 - Functional status
- Key Question 3
 - ◆ Critical outcomes
 - Risk of CKD progression to ESRD
 - ◆ Important outcomes
 - Mortality
 - Hospitalization/ED use/nursing home placement
 - Patient satisfaction
 - Success of fistula and graft formation
 - Referral to nephrologist and/or evaluation for preemptive kidney transplant
- Key Question 4
 - ◆ Critical outcomes
 - Success of fistula and graft formation

- ◆ Important outcomes
 - Placement/location of a permcath
- Key Question 5
 - ◆ Critical outcomes
 - Risk of CKD progression to ESRD
 - Mortality
 - ◆ Important outcomes
 - Markers of CKD progression
 - CV morbidity/stroke/amputation
 - Functional status
 - QoL
 - Cost-related outcomes
- Key Question 6
 - ◆ Critical outcomes
 - Risk of CKD progression to ESRD
 - ◆ Important outcomes
 - Markers of CKD progression
 - Mortality
 - Hospitalization/ED use/nursing home placement
 - Functional status
 - QoL
 - Patient satisfaction
- Key Question 7
 - ◆ Critical outcomes
 - QoL
 - Patient satisfaction
 - ◆ Important outcomes
 - Risk of CKD progression to ESRD
 - Mortality
 - Hospitalization/ED use/nursing home placement
 - Functional status
 - Caregiver burden/impact on family

- Key Question 8
 - ◆ Critical outcomes
 - Mortality
 - ◆ Important outcomes
 - Hospitalization/ED use/nursing home placement
 - Functional status
 - QoL
 - Patient satisfaction
 - Caregiver burden/impact on family
 - Cost-related outcomes
- Key Question 9
 - ◆ Critical outcomes
 - Risk of CKD progression to ESRD
 - Markers of CKD progression
 - Mortality
 - CV morbidity/stroke/amputation
 - ◆ Important outcomes
 - Risk/adverse events/toxicity
- Key Question 10
 - ◆ Critical outcomes
 - Risk of CKD progression to ESRD
 - Markers of CKD progression
 - Mortality
 - CV morbidity/stroke/amputation
 - Hospitalization/ED use/AKI (include electrolyte imbalances)
 - ◆ Important outcomes
 - Morbidity- Falls
 - QoL
- Key Question 11
 - ◆ Critical outcomes
 - Pain control
 - Risk of CKD progression to ESRD

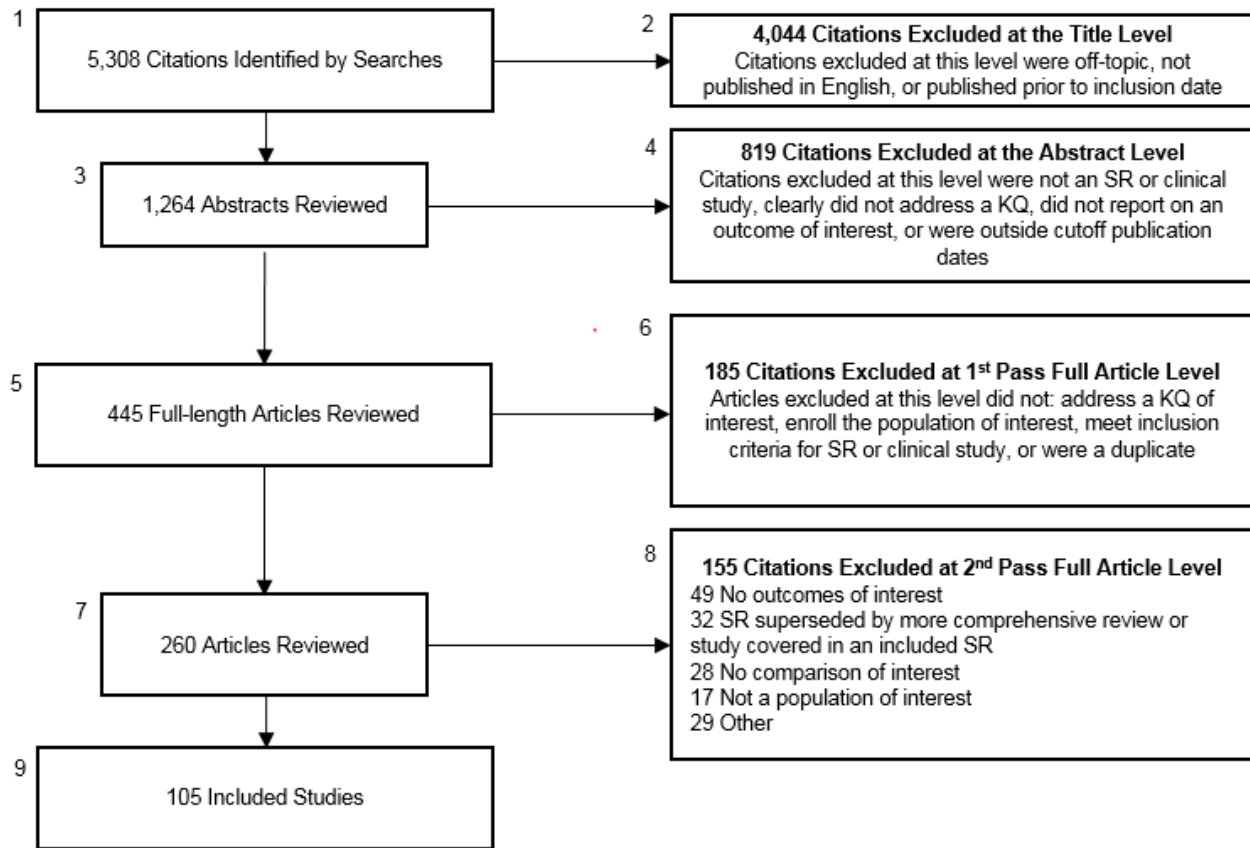
- Opioid Use
 - Risks/adverse events/toxicity (including low BP, acute renal failure, and falls)
- ◆ Important outcomes
 - Functional status
- Key Question 12
 - ◆ Critical outcomes
 - AKI within 2-5 days
 - Persistent decline in kidney function
 - Mortality
 - ◆ Important outcomes
 - Failure to deliver indicated care due to fear of AKI (renalism)
 - Cost-related outcomes

B. Conducting the Systematic Review

Based on the decisions made by the Champions and Work Group members regarding the scope, the KQs, and the PICOTS statements, the Lewin Team produced an SR protocol prior to conducting the review. The protocol was reviewed and approved by the Champions and Work Group members. It described in detail the final set of KQs, the methodology to be used during the SR process, and the inclusion/exclusion criteria to be applied to each potential study, including, but not limited to, study type, sample size, and PICOTS criteria.

Extensive literature searches identified 5,308 citations potentially addressing the KQs of interest to this evidence review. Of those, 4,044 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, 1,264 abstracts were reviewed with 819 of those being excluded for the following reasons: not an SR or clinical study (see the [General Criteria for Inclusion in Systematic Review](#) and [Key Question Specific Criteria](#)), did not address a KQ of interest to this review, did not enroll population of interest, or published prior to December 2013. A total of 445 full-length articles were reviewed. Of those, 185 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or SR, or being a duplicate. A total of 260 full length articles were thought to address one or more KQs and were further reviewed. Of these, 155 were ultimately excluded. Reasons for their exclusion are presented in [Figure A-1](#). Overall, 105 studies addressed one or more of the KQs 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. Study Flow Diagram



Abbreviations: KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

[Figure A-1. Study Flow Diagram](#) is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 5,308 citations identified by searches
 - a. Right to Box 2: 4,044 citations excluded at the title level
 - i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
 - b. Down to Box 3: 1,264 abstracts reviewed
2. Box 3: 1,264 abstracts reviewed
 - a. Right to Box 4: 819 citations excluded at the abstract level
 - i. Citations excluded at this level were not an SR or clinical study, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates

- b. Down to Box 5: 445 full-length articles reviewed
3. Box 5: 445 full-length articles reviewed
 - a. Right to Box 6: 185 citations excluded at 1st pass full article level
 - i. Articles excluded at this level did not: address a KQ of interest, enroll the population of interest, meet inclusion criteria for SR or clinical study, or were a duplicate
 - b. Down to Box 7: 260 articles reviewed
4. Box 7: 260 articles reviewed
 - a. Right to Box 8: 155 citations excluded at 2nd pass full article level
 - i. 49 No outcomes of interest
 - ii. 32 SR superseded by more comprehensive review or study covered in an included SR
 - iii. 28 No comparison of interest
 - iv. 17 Not a population of interest
 - v. 29 Other
 - b. Down to Box 9: 105 included studies
5. Box 9: 105 included studies

Table A-2. Evidence Base for KQs

Question Number	Question	Number of Studies & Type of Studies
1	What are the benefits and harms of screening/testing for and/or labeling a patient with a CKD diagnosis? Do outcomes vary by sub-population (including those with acute kidney injury)?	1 cohort study
2	What laboratory tests should be used to optimize the diagnosis and staging of CKD for the purpose of stratifying risks for CKD complications?	9 SRs, 16 cohort studies
3	Among patients with advanced CKD eGFR <45 mL/minute/1.73 m ² or eGFR <30 mL/minute/1.73 m ² might be the studied populations) or overt proteinuria, what prediction tools will best distinguish risks for ESRD progression, and what thresholds of risk should influence decisions for nephrology referral and vascular access implementation?	5 cohort studies
4	How do prior vascular access devices impact the success of fistula and graft formation?	1 cohort study, 1 case-control study
5	In patients with CKD, at what stage does nephrology referral and multidisciplinary/interdisciplinary care improve outcomes?	3 SRs, 2 RCTs, 1 quasi-experimental controlled study, 2 retrospective cohort studies, 1 nested case-control study
6	What is the benefit of education on CKD outcomes? What methods of delivering education are the most effective?	1 SR, 3 RCTs, 1 non-randomized controlled clinical trial
7	What is the benefit of shared decision making on CKD outcomes? How should shared decision making be achieved most effectively?	2 cross-sectional studies
8	In what populations would conservative management (e.g., supportive care, palliative care) vs. dialysis have similar outcomes?	1 SR, 3 cohort studies
9	What is the effectiveness of pharmacological interventions for improving CKD outcomes?	5 SRs, 10 RCTs, 5 post hoc subgroup analyses of RCTs, 1 open-label extension of an RCT, 1 cohort study
10	What are optimal blood pressure goals for patients with CKD?	2 SRs, 1 subgroup analysis of an RCT, 2 observational extensions of RCTs
11	In patients with CKD, what is the optimal approach to pain management?	No relevant studies identified
12	In patients with CKD, what is the comparative effectiveness of interventions used to prevent contrast-associated kidney injury?	11 SRs, 14 RCTs
Total Evidence Base		105 studies

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; m: meter; mL: milliliter; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Review

- Clinical studies or SRs published on or after December 1, 2013 to September 14, 2018. If multiple SRs address a KQ, we selected the most recent and/or comprehensive review. SRs were supplemented with clinical studies published subsequent to the SR.
- Studies must have been published in English.
- Publication must have been a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- SRs must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the one used by the AHRQ Evidence-based Practice Center). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review.
- Intervention studies must have assessed screening/diagnostic tests, risk prediction tools, pharmacological or non-pharmacological treatment approaches and be a prospective RCT with an independent control group. Randomized crossover trials were included only if data from the first period (prior to treatment crossover) was reported separately. For certain KQs non-randomized study designs were acceptable (see Key Question Specific Criteria below).
- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see Key Question Specific Criteria below).
- Study must have enrolled at least 85% of patients who meet the study population criteria: adults who have (or may have) CKD.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria

- For KQ 1, 3–5, and 7, SRs of acceptable study designs, RCTs and comparative observational studies, such as large prospective (>100 patients/arm) or retrospective (>200 patients/arm) cohort or case-controlled studies were required.
- For KQ 2, SRs of acceptable study designs, RCTs, and prospective or retrospective cohort studies that compare a diagnostic test to clinical assessment, a different diagnostic test, or no diagnostic test with regard to ability to stratify risk of CKD complications were required.
- For KQs 6 and 8–12, SRs of acceptable study designs and RCTs were required. If there was insufficient evidence from these study designs for any KQ, we considered evidence from large prospective (>100 patients/arm) or retrospective (>200 patients/arm) cohort or case-controlled studies.

Information regarding the bibliographic databases, date limits, and platform/provider can be found in [Table A-3](#), below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in [Appendix E](#).

Table A-3. Bibliographic Database Information

	Name	Date Limits	Platform/Provider
Bibliographic Database Information	Cochrane Database of Systematic Reviews (Cochrane Reviews)	December 1, 2013 to September 16, 2018	Wiley
	EMBASE (Excerpta Medica)	December 1, 2013 to September 15, 2018	Elsevier
	Health Technology Assessment Database (HTA)	December 1, 2013 to September 16, 2018	Wiley
	MEDLINE/PreMEDLINE	December 1, 2013 to September 15, 2018	Elsevier
	PubMed (In-process and Publisher records)	December 1, 2013 to September 14, 2018	National Library of Medicine
Grey Literature	AHRQ Website	December 1, 2013 to September 27, 2018	AHRQ

C. Convening the Face-to-face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and one half day face-to-face meeting of the CPG Champions and Work Group members on November 13 – 16, 2018. These experts were gathered to develop and draft the clinical recommendations for an update to the 2014 CKD CPG. Lewin presented findings from the evidence review 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 were asked to categorize and carry forward recommendations from the 2014 CKD CPG, modifying the recommendations as necessary. The members also developed new clinical practice recommendations not presented in the 2014 CKD CPG based on the 2018 evidence review. The subject matter experts were divided into three smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and 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.

In addition to developing recommendations during the face-to-face meeting, the Work Group members also revised the 2014 CKD CPG algorithms to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2013, as necessary, to update the algorithms.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[215]

- 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, 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, conducted by ECRI, assessed the confidence in the quality of the evidence base using GRADE methodology and assigned a rating of “High,” “Moderate,” “Low,” or “Very Low.” The outcomes judged to be critical were used to determine the overall quality of evidence. Per GRADE, if the quality of evidence differs across the critical outcomes, the lowest quality of evidence for any of the relevant critical

outcomes determines the overall quality of the evidence for a recommendation; the overall confidence cannot be higher than the lowest confidence in effect estimates for any outcome that is determined to be critical for clinical decision making.[\[18,216\]](#)

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 resource 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 co-occurring conditions 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 practicality of the recommendation.

The framework below ([Table A-4](#)) was used by the Work Group to guide discussions on each domain.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Balance of desirable and undesirable outcomes	<ul style="list-style-type: none"> 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? 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Is there high or moderate quality evidence that answers this question? What is the overall certainty of this evidence? 	<ul style="list-style-type: none"> High Moderate Low Very low
Values and preferences	<ul style="list-style-type: none"> 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? 	<ul style="list-style-type: none"> Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	<ul style="list-style-type: none"> 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? 	<ul style="list-style-type: none"> 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.^[217] 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.^[215] 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.

Occasionally, instances may occur when the Work Group feels there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

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 ...”)
- No recommendation for or against (or “There is insufficient evidence...”)
- 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.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

A set of recommendation categories was adapted from those used by NICE.^[14,15] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2014 CKD CPG. The categories and definitions can be found in [Table A-5](#).

Table A-5. Recommendation Categories and Definitions*

Evidence Reviewed	Recommendation Category	Definition
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) [14] and Garcia et al. (2014) [15]

Abbreviation: CPG: clinical practice guideline

b. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as “New-added,” “New-replaced,” “Not changed,” “Amended,” or “Deleted.”

“Reviewed, New-added” recommendations were original, new recommendations that were not in the 2014 CKD CPG. “Reviewed, New-replaced” recommendations were in the previous version of the guideline, but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as “Reviewed, Not changed” were carried forward from the previous version of the CPG unchanged.

For recommendations carried forward to the updated CPG with review of the evidence and slightly modified wording, the “Reviewed, Amended” recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive (i.e., not clinically meaningful) language changes deemed necessary. The evidence used to support these recommendations was carried forward from the previous version of the CPG and/or was identified in the evidence review for the update.

Recommendations could have also been designated “Reviewed, Deleted.” These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the

extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

c. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without an updated SR of the evidence. Due to time and budget constraints, the update of the CKD CPG could not review all available evidence on management of CKD, but instead focused its KQs on areas of new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated SR of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as “Not reviewed.” If evidence had not been reviewed, recommendations could have been categorized as “Not changed,” “Amended,” or “Deleted.”

“Not reviewed, Not changed” recommendations refer to recommendations from the previous version of the CKD CPG that were carried forward unchanged to the updated version. The category of “Not reviewed, Amended” was used to designate recommendations which were modified from the 2014 CKD CPG.

Recommendations could also have been categorized as “Not reviewed, Deleted” if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2019 version of the guideline are noted in the [Recommendations](#). The categories for the recommendations from the 2014 CKD CPG are noted in [Appendix D](#).

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2014 CKD CPG to support the amended “carried forward” recommendations. The Work Group also considered tables, appendices, and other sections from the 2014 CKD CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14-20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in the section titled [Peer Review Process](#). After revisions were made based on the feedback received during the

peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket card, and patient summary. The final 2019 CKD CPG was submitted to the EBPWG in September 2019.

Appendix B: Patient Focus Group Methods and Findings

A. Methods

In April 2018, the VA and the DoD commenced the effort to update the VA/DoD CKD CPG. As part of the effort to update this CPG, the VA and DoD Leadership, along with the CKD Champions and The Lewin Team, held a patient focus group on June 11, 2018, at the Audie L. Murphy Memorial VA Hospital - South Texas Veterans Health Care System. The aim of the focus group was to further understand and incorporate the perspective of patients with CKD who are covered and/or receive their care through the VA and/or DoD healthcare systems, as patients are most affected by the recommendations put forth in the CPG. The focus group explored patients' perspectives on a set of topics related to management of CKD in the VA and DoD healthcare systems, including patients' knowledge of treatments for CKD, views on the delivery of care, patients' priorities and treatment challenges, as well as the impact of comorbidities on the patients and their treatments for CKD.

Participants for the focus group were recruited by several of the CPG Champions and members of the Work Group. Patient focus group participants were not intended to be a representative sample of VA and DoD patients who have CKD. However, recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the guideline development process. Patients were not incentivized for their participation or reimbursed for travel expenses.

The CKD CPG Champions and Work Group, with support from Lewin, developed a set of questions to help guide the focus group discussion. The focus group facilitator led the discussion using the previously prepared questions as a general guide to elicit the most important information from the patients regarding their experiences and views about their treatment and overall care. By design, the flow of the discussion was subject to the information, knowledge, and interests of the focus group participants, so not all of the listed questions were addressed.

Nine participants participated in the focus group, eight men and one woman. Five participants were receiving care from the VA and four were receiving care from the DoD.

B. Findings

a. Recognize the importance of communication and collaboration between care providers, particularly between nephrologists and primary care.

- Providers should coordinate patient care across specialties. While patients often excel at self-advocacy, primary care providers should communicate treatment plans to other providers and create a cohesive strategy for managing all of patients' medical conditions.
- Educate providers on contrast-induced nephropathy (CIN). If contrast agents are needed during imaging procedures, patient should be informed of the potential risks to kidney functioning.

b. Understand patient-specific goals, priorities, values, and preferences and use shared decision making to develop a patient-centered plan for treatment. Patients greatly value quality of life and the ability to maintain their lifestyle.

- Use two-way communication and shared decision making to develop an individualized treatment plan; discuss treatment options in conjunction with each patient's goals, priorities, values, and preferences.
- Understand that patients vary in their treatment goals. For some, preservation of current quality of life is often preferable to aggressive treatment.

c. Educate patients about their kidney disease. Diagnosis often comes as a shock to patients, and understanding why they have kidney disease is of great importance to patients. Patients often fear that exposure to chemicals during their military deployment may have led to their CKD.

- Educate patients on the specific cause(s) of their kidney disease. Patients were very surprised when they found out that they had CKD. In looking for a reason for their diagnosis, many focused on their military deployment and the chemicals they were exposed to.
- Patients were generally unaware that managing their hypertension contributes to managing their kidney disease. Educating patients on how blood pressure relates to kidney function may improve their understanding of CKD and allow them to better manage their treatment.

d. Provide nutrition and dietary guidance keeping in mind patient's individual lifestyle and cultural differences. The patients who had seen a dietitian stated that it helped them adhere to their nutrition plan while those who did not reported difficulty maintaining a healthy diet.

- Encourage patients to see a dietitian in order to improve adherence to their nutritional treatment plan. Patients and their family members who were referred to a dietitian said that they benefitted from their advice and found it much easier to maintain a healthy diet.

e. Patients' biggest fear regarding their kidney disease is having to go on dialysis; they observe others on dialysis and infer what it would be like for them. Educating patients about the experience of dialysis may alleviate their fears and give them a better understanding of their treatment options.

- Patients' biggest fear related to their kidney disease is that they will be forced to go on dialysis. Based on conversations with friends and family who have undergone dialysis, patients fear that their quality of life will drastically deteriorate. Some elderly patients expressed that they may choose to forgo dialysis to preserve their quality of life.

f. Create a support group for kidney disease patients. Patients have a number of fears regarding their kidney disease, particularly having to go on dialysis, and may benefit from discussing these issues with other patients at various stages of CKD.

- Participants expressed a desire to join a support group for people with kidney disease and their families.

g. Offer telemedicine and other technology options to augment care, but recognize these options may not align with the preferences of all patients.

- Patients did not have any strong preferences regarding the use of telemedicine and electronic health technology. Older participants tended to prefer face-to-face interactions with providers, while younger participants appreciated having the option of virtual meetings and were open to using medical mobile apps and other technology-based tools to aid in their care

Appendix C: Evidence Table

Table C-1. Evidence Table^{a,b,c,d}

Recommendation	2014 Strength of Recommendation	Evidence	2019 Strength of Recommendation	Recommendation Category
1. In the general population, there is insufficient evidence to recommend for or against periodic evaluation for chronic kidney disease.	Weak for	[29,30] Additional References: [31,32]	Neither for nor against	Reviewed, New-replaced
2. When screening or stratifying risk for chronic kidney disease, we recommend including urine albumin-to-creatinine ratio testing in addition to estimated glomerular filtration rate to optimize the diagnosis and staging of chronic kidney disease.	–	[33] Additional References: [3]	Strong for	Reviewed, New-added
3. In patients with an estimated glomerular filtration rate <60 mL/minute/1.73 m ² , we suggest one-time cystatin C-based estimated glomerular filtration to confirm diagnosis and/or refine staging of chronic kidney disease.	–	[36] Additional References: [34,35,37,38]	Weak for	Reviewed, New-added
4. We suggest the use of a validated risk prediction model as a clinical decision support aid in the management of patients with chronic kidney disease.	–	[39,41,44-48] Additional References: [3,34,40-43,49]	Weak for	Reviewed, New-added

^a 2014 Strength of Recommendation column: Refer to the [Grading Recommendations](#) section for more information on how the strength of the recommendation was determined using GRADE methodology.

^b Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through the 2018 evidence review or included in the evidence base for the 2014 or 2008 VA/DoD CKD CPG. The second set of references in the evidence column (called “Additional References”) includes references that provide additional information related to the recommendation, but which were not systematically identified through a literature review. These references were not included in the evidence base for the recommendation and therefore did not influence the strength and direction of the recommendation.

^c 2019 Strength of Recommendation column: Refer to the [Grading Recommendations](#) section for more information on how the strength of the recommendation was determined using GRADE methodology.

^d Recommendation Categorization column: Refer to the [Recommendation Categorization](#) section for more information on the description of the categorization process and the definition of each category.

Recommendation	2014 Strength of Recommendation	Evidence	2019 Strength of Recommendation	Recommendation Category
5. When assessing the risk of progression to end-stage renal disease, there is insufficient evidence to recommend a specific risk prediction calculator.	–	[39,41,44-48] Additional References: [3,34,40-43,49]	Neither for nor against	Reviewed, New-added
6. There is currently insufficient evidence to recommend a <i>specific threshold</i> of risk, renal function, or proteinuria to refer patients for a nephrology evaluation and management of chronic kidney disease (see Algorithm: Module C, Sidebar 8 for indications for nephrology consultation).	Weak for	[50-55]	Neither for nor against	Reviewed, New-replaced
7. We suggest interdisciplinary care (including dietitians, pharmacists, and social workers in addition to physicians and nurses) for patients with later-stage chronic kidney disease.	Weak for	[56-59]	Weak for	Reviewed, New-replaced
8. When providing patient education, there is insufficient evidence to recommend for or against a particular health education program or modality to prevent chronic kidney disease progression (see discussion).	Weak for	[60-63]	Neither for nor against	Reviewed, New-replaced
9. For patients who are at high risk for requiring hemodialysis/renal-replacement and need long-term venous access, we suggest against peripherally inserted central catheter (PICC) lines to optimize future dialysis vascular access options, while considering patient values and preferences.	–	[65,66] Additional References: [64]	Weak against	Reviewed, New-added
10. We suggest utilizing shared decision making regarding renal replacement therapy (versus conservative management) in part to improve patient satisfaction.	–	[67,68] Additional References: [23]	Weak for	Reviewed, New-added
11. In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life is the priority, we suggest evaluation for renal replacement therapy with sufficient time for comprehensive preparation.	–	[50,53,67-74] Additional References: [23,75]	Weak for	Reviewed, New-added
12. In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom avoiding hospitalization, death in hospitals, or intensive procedures is the priority, we suggest offering conservative management over dialysis.	–	[50,53,67-74] Additional References: [23,75]	Weak for	Reviewed, New-added

Recommendation	2014 Strength of Recommendation	Evidence	2019 Strength of Recommendation	Recommendation Category
13. In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life may not be the priority, there is insufficient evidence to recommend for or against dialysis to improve quality of life.	–	[50,53,67-74] Additional References: [23,75]	Neither for nor against	Reviewed, New-added
14. We suggest the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with chronic kidney disease.	Weak for	[76-78] Additional References: [2]	Weak for	Not reviewed, Not changed
15. In selected patients with stage 3 and 4 chronic kidney disease, we suggest offering a dietary protein intake of 0.6 to 0.8 g/kg/day as it may slow the decline in estimated glomerular filtration rate and progression to end-stage renal disease.	Weak for	[79,80]	Weak for	Not reviewed, Amended
16. We suggest offering metformin as a first-line therapy for the treatment of type 2 diabetes in patients with stage 1 to 3 chronic kidney disease to reduce all-cause mortality.	–	[82] Additional References: [83]	Weak for	Reviewed, New-added
17. We recommend offering sodium-glucose co-transporter 2 inhibitors as an option for add-on therapy for the treatment of type 2 diabetes in patients with stage 1 to 3 chronic kidney disease to reduce chronic kidney disease progression and the risk of cardiovascular events.	–	[84,85]	Strong for	Reviewed, New-added
18. We recommend offering liraglutide or dulaglutide (glucagon-like peptide-1 receptor agonists) as an option for add-on therapy for the treatment of type 2 diabetes in patients with chronic kidney disease to reduce chronic kidney disease progression.	–	[87,88]	Strong for	Reviewed, New-added
19. In patients with chronic kidney disease and type 2 diabetes, there is insufficient evidence to recommend for or against the use of thiazolidinediones or dipeptidyl peptidase-4 inhibitors to decrease progression of chronic kidney disease or mortality.	–	[91-93]	Neither for nor against	Reviewed, New-added
20. We suggest intensive blood pressure management beyond the standard target (e.g., less than 140/90 mmHg) to reduce mortality in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 m ² .	–	[94-99] Additional References: [100]	Weak for	Reviewed, New-added

Recommendation	2014 Strength of Recommendation	Evidence	2019 Strength of Recommendation	Recommendation Category
21. In patients with non-diabetic chronic kidney disease, hypertension, and albuminuria, we recommend the use of an angiotensin-converting enzyme inhibitor to prevent progression of chronic kidney disease. Angiotensin II receptor blockers may be substituted for patients with an angiotensin-converting enzyme inhibitor-induced cough.	Strong for	[101-128,130,131] Additional References: [129]	Strong for	Not reviewed, Not changed
22. In patients with chronic kidney disease, diabetes, hypertension, and albuminuria, we recommend the use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers to slow the progression of chronic kidney disease, unless there is documentation of intolerance.	Strong for	[101-128,130,131] Additional References: [129]	Strong for	Not reviewed, Amended
23. We recommend against the use of combination renin-angiotensin-aldosterone system blockade (an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker, or an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker with a direct renin inhibitor) in patients with chronic kidney disease.	Strong against	[101-128,130,131] Additional References: [129]	Strong against	Not reviewed, Not changed
24. We suggest initiation of oral iron therapy to support iron requirements in patients with chronic kidney disease.	Weak for	[143,150] Additional References: [2,144-149,151,152]	Weak for	Not reviewed, Amended
25. We recommend against initiating erythropoiesis-stimulating agents in patients with chronic kidney disease for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension.	Strong against	[153-158] Additional References: [2,83,148,159-165]	Strong against	Not reviewed, Amended
26. We recommend against initiating erythropoiesis-stimulating agents at a hemoglobin level greater than 10 g/dL.	Strong against	[153-158] Additional References: [2,83,148,159-165]	Strong against	Not reviewed, Not changed
27. We suggest against offering calcitriol or active vitamin D analogs to patients with stage 3 and 4 chronic kidney disease and elevated parathyroid hormone levels.	Weak against	[166-172]	Weak against	Not reviewed, Amended

Recommendation	2014 Strength of Recommendation	Evidence	2019 Strength of Recommendation	Recommendation Category
28. We suggest against offering calcimimetics to patients with stage 3 and 4 chronic kidney disease and elevated parathyroid hormone levels.	Weak against	[173] Additional References: [174]	Weak against	Not reviewed, Amended
29. There is insufficient evidence to recommend for or against the use of phosphate binders to reduce mortality, progression of chronic kidney disease, or major cardiovascular outcomes in patients with stage 2 to 5 chronic kidney disease.	Weak against	[175] Additional References: [176-179]	Neither for nor against	Reviewed, New-replaced
30. We suggest the use of sodium bicarbonate supplementation in patients with chronic kidney disease and metabolic acidosis to slow the progression of chronic kidney disease.	Weak for	[180,181] Additional References: [182]	Weak for	Not reviewed, Amended
31. In patients with chronic kidney disease and asymptomatic hyperuricemia, there is insufficient evidence to recommend for or against the use of urate-lowering therapy for the purpose of slowing progression of chronic kidney disease.	–	[183-186]	Neither for nor against	Reviewed, New-added
32. In patients at risk for rapidly progressing autosomal dominant polycystic kidney disease, we suggest offering tolvaptan in consultation with a nephrologist to slow decline in estimated glomerular filtration rate.	–	[188-190] Additional References: [191,192]	Weak for	Reviewed, New-added
33. For patients at increased risk for iodinated contrast-associated acute kidney injury, we recommend volume expansion with intravenous isotonic saline prior to and following iodinated contrast administration (see Algorithm Module D for additional information).	Weak for	[199,201,202,205-208] Additional References: [200,203,204]	Strong for	Reviewed, New-replaced
34. We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury.	Neither for nor against	[206,207] Additional References: [209]	Strong against	Reviewed, New-replaced
35. We recommend against the use of renal replacement therapy for iodinated contrast-associated acute kidney injury prophylaxis.	Strong against	[206,211] Additional References: [210]	Strong against	Reviewed, Amended

Appendix D: 2014 Recommendation Categorization Table

Table D-1. 2014 Recommendation Categorization Table^{a,b,c,d,e}

2014 Location		2014 Recommendation Text	2014 Grade	Recommendation Category	2019 Recommendation
Rec Number	Page				
1	17	<p>Topic – Military Occupational Risk of CKD</p> <p>Recommendation – 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.</p>	Weak for	Not reviewed, Deleted	--
2	18	<p>Topic – Periodic Evaluation</p> <p>Recommendation – We suggest that periodic evaluation for CKD be considered in patients with the following:</p> <ul style="list-style-type: none"> 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) <p><i>(Carryover modified from the 2008 CPG)</i></p>	Weak for	Reviewed, New-replaced	Recommendation 1
3	21	<p>Topic – Intravenous Isotonic Crystalloid Solutions</p> <p>Recommendation – 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.</p>	Weak for	Reviewed, New-replaced	Recommendation 33

^a 2014 Location columns: The first two columns indicate the location of each recommendation within the 2014 VA/DoD CKD CPG.

^b 2014 Recommendation Text column: The 2014 Recommendation Text column contains the wording of each recommendation from the 2014 VA/DoD CKD CPG.

^c 2014 Grade column: Refer to the [Grading Recommendations](#) section for more information on how the strength of the recommendation was determined using GRADE methodology.

^d Recommendation Category column: This column indicates the way in which each 2014 VA/DoD CKD CPG recommendation was updated.

^e 2019 Recommendation column: For recommendations that were carried forward to the 2019 VA/DoD CKD CPG, this column indicates the new recommendation(s) to which they correspond.

2014 Location		2014 Recommendation Text	2014 Grade	Recommendation Category	2019 Recommendation
Rec Number	Page				
4	22	Topic – Oral versus IV Volume Expansion Recommendation – We suggest offering oral hydration to patients in which IV hydration is not feasible for CIN prophylaxis.	Weak for	Reviewed, Deleted	--
5	3	Topic –N-acetylcysteine (NAC) Recommendation – Given inconsistent evidence, we do not recommend for or against the routine administration of N-acetylcysteine (NAC) for CIN prophylaxis.	Neither for nor against	Reviewed, New-replaced	Recommendation 34
6	24	Topic –Renal Replacement Therapy Recommendation – We recommend against the use of renal replacement therapy (RRT) for CIN prophylaxis.	Strong against	Reviewed, Amended	Recommendation 35
7	24	Topic –Short-Term Statin Therapy Recommendation – We suggest not initiating statin therapy for the purpose of CIN prophylaxis in patients undergoing elective angiography.	Weak against	Reviewed, New-replaced	--
8	25	Topic – Theophylline Therapy Recommendation – We suggest not offering theophylline therapy for CIN prophylaxis for patients undergoing elective coronary angiography.	Weak against	Not reviewed, Deleted	--
9	27	Topic – Dietary Sodium Restriction Recommendation – 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	Not reviewed, Not changed	Recommendation 14
10	28	Topic – Dietary Protein Restriction Recommendation – 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). <i>(Carryover modified from the 2008 CPG)</i>	Weak for	Not reviewed, Amended	Recommendation 15
11	29	Topic – Weight Loss Recommendation – 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	Not reviewed, Deleted	--

2014 Location		2014 Recommendation Text	2014 Grade	Recommendation Category	2019 Recommendation
Rec Number	Page				
12	30	<p>Topic – Exercise</p> <p>Recommendation – 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.</p>	Weak for	Not reviewed, Deleted	--
13	31	<p>Topic – Health Education</p> <p>Recommendation – 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.</p>	Weak for	Reviewed, New-replaced	Recommendation 8
14	32	<p>Topic – Smoking Cessation</p> <p>Recommendation – 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.</p>	Weak for	Not reviewed, Deleted	--
15	34	<p>Topic – Model of Care</p> <p>Recommendation – 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.</p>	Weak for	Reviewed, New-replaced	Recommendation 7
16	34	<p>Topic – Model of Care</p> <p>Recommendation – 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:</p> <ol style="list-style-type: none"> eGFR <30 mL/minute/1.73 m² to facilitate education and planning for renal replacement therapy (dialysis or kidney transplant) Kidney function that is rapidly worsening without obvious cause Metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism) CKD of unclear etiology after initial work-up, or has a known or suspected kidney condition requiring specialized care Nephrotic range proteinuria Nephrolithiasis 	Weak for	Reviewed, New-replaced	Recommendation 6

2014 Location		2014 Recommendation Text	2014 Grade	Recommendation Category	2019 Recommendation
Rec Number	Page				
17	36	<p>Topic – Immunization</p> <p>Recommendation – We recommend that treatment with the following vaccinations be considered for patients with CKD as a measure to prevent infections:</p> <ul style="list-style-type: none"> 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* <p>(*Note: Live vaccines, including nasal influenza (LAIV), may be contraindicated in patients with CKD and severe immunodeficiency including treatment with immunosuppressive agents)</p> <p><i>(Carryover modified from the 2008 CPG)</i></p>	Strong for	Not reviewed, Deleted	--
18	37	<p>Topic – Nephrotoxins and Adverse Drug Events Avoidance</p> <p>Recommendation – We recommend that clinicians avoid or limit the use of nephrotoxic medications for patients with CKD.</p> <p><i>(Carryover modified from the 2008 CPG)</i></p>	Strong for	Reviewed, Deleted	--
19	37	<p>Topic – Nephrotoxins and Adverse Drug Events Avoidance</p> <p>Recommendation – 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.</p> <p><i>(Carryover modified from the 2008 CPG)</i></p>	Weak for	Reviewed, Deleted	--
20	41	<p>Topic – Correction of Acidosis</p> <p>Recommendation – We suggest the use of bicarbonate supplementation in CKD patients with metabolic acidosis to slow the progression of CKD.</p>	Weak for	Not reviewed, Amended	Recommendation 30
21	41	<p>Topic – Blood Pressure Targets</p> <p>Recommendation – In adult patients with stages 1-4 CKD, we recommend that blood pressure targets should be less than 140/90 mmHg.</p> <p><i>(Carryover modified from the 2008 CPG)</i></p>	Strong for	Not reviewed, Deleted	--

2014 Location		2014 Recommendation Text	2014 Grade	Recommendation Category	2019 Recommendation
Rec Number	Page				
22	43	<p>Topic – Renin-Angiotensin Aldosterone System (RAAS) Blockade</p> <p>Recommendation – 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.</p> <p><i>(Carryover modified from the 2008 CPG)</i></p>	Strong for	Not reviewed, Not changed	Recommendation 21
23	43	<p>Topic – Renin-Angiotensin Aldosterone System (RAAS) Blockade</p> <p>Recommendation – 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.</p> <p><i>(Carryover modified from the 2008 CPG)</i></p>	Strong for	Not reviewed, Amended	Recommendation 22
24	43	<p>Topic – Renin-Angiotensin Aldosterone System (RAAS) Blockade</p> <p>Recommendation – 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.</p>	Strong against	Not reviewed, Not changed	Recommendation 23
25	50	<p>Topic – Statins for Cardiovascular Risk Reduction</p> <p>Recommendation – 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.</p>	Strong for	Not reviewed, Deleted	--
26	50	<p>Topic – Statins for Cardiovascular Risk Reduction</p> <p>Recommendation – We suggest against the use of statins prescribed with the intent of slowing eGFR decline or preserving kidney function.</p>	Weak against	Not reviewed, Deleted	--
27	54	<p>Topic – Glycemic Control</p> <p>Recommendation – 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.</p> <p><i>(Carryover modified from the 2008 CPG)</i></p>	Strong against	Not reviewed, Deleted	--

2014 Location		2014 Recommendation Text	2014 Grade	Recommendation Category	2019 Recommendation
Rec Number	Page				
28	56	<p>Topic – Iron Therapy</p> <p>Recommendation – We suggest initiation of oral iron therapy (in preference to parenteral) to support iron requirements in patients with CKD stages 3 and 4.</p>	Weak for	Not reviewed, Amended	Recommendation 24
29	57	<p>Topic – Safety and Efficacy of Erythropoiesis-Stimulating Agents</p> <p>Recommendation – 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.</p>	Strong against	Not reviewed, Amended	Recommendation 25
30	57	<p>Topic – Safety and Efficacy of Erythropoiesis-Stimulating Agents</p> <p>Recommendation – We recommend against initiating ESAs at a hemoglobin level greater than 10 g/dL.</p>	Strong against	Not reviewed, Not changed	Recommendation 26
31	59	<p>Topic – Correction of Vitamin D Deficiency</p> <p>Recommendation – We suggest offering supplemental vitamin D to correct vitamin D deficiency in patients with CKD stages 3 or 4.</p>	Weak for	Not reviewed, Deleted	--
32	60	<p>Topic – Active Vitamin D Use</p> <p>Recommendation – 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.)</p>	Weak against	Not reviewed, Amended	Recommendation 27
33	62	<p>Topic – Phosphate Binders</p> <p>Recommendation – We suggest not offering phosphate binders to patients with stage 3 and 4 CKD with normal serum phosphorous. <i>(Carryover modified from the 2008 CPG)</i></p>	Weak against	Reviewed, New-replaced	Recommendation 29
34	63	<p>Topic – Calcimimetics</p> <p>Recommendation – 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.</p>	Weak against	Not reviewed, Amended	Recommendation 28

Appendix E: Participant List

Jennifer Bell, MD

Primary Care Physician
Defense Health Agency National Capital Region
Arlington, VA

Christopher Barrett Bowling, MD, MSPH

Geriatrician
Durham VA Health Care System
Durham, NC

Susan T. Crowley, MD, MBA, FASN

Nephrologist
VA New England Healthcare System
West Haven, CT

Christopher Dyer, MD, FACP

Chief, Renal Section
South Texas Veterans Health Care System
San Antonio, TX

Elaine Furmaga, PharmD

National Clinical Pharmacy Program Manager
VA Pharmacy Benefits Management Services
Hines, IL

Janet Hank, RN, BSN, CNN

Nurse Manager, Hemodialysis
VA Eastern Colorado Health Care System
Denver, CO

Maj Sara Koepke, RDN, CSR, CNSC

Dietitian
Langley Air Force Base
Hampton, VA

Mai Nguyen, MD, FACP, FASN

Chief, Nephrology
Brooke Army Medical Center
Assistant Professor
Uniformed Services University of the Health
Sciences
San Antonio, TX

Paul M. Palevsky, MD, FACP, FASN, FNKF

Nephrologist
Chief, Renal Section
VA Pittsburgh Healthcare System
Professor of Medicine and Clinical &
Translational Science
University of Pittsburgh
Pittsburgh, PA

David Patterson, PharmD

Supervising Pharmacist (Clinical Coordinator)
Blanchfield Army Community Hospital
Fort Campbell, KY

Jeffrey Penfield, MD

Nephrologist
VA North Texas Health Care System
Dallas, TX

Michael G. Shlipak, MD, MPH

Associate Chief of Medicine for Research
Development
San Francisco VA Medical Center
San Francisco, CA

Evan Steil, MD, MBA, MHA, FAAFP, FACHE

Deputy Commander for Quality and Safety;
Family Physician
Womack Army Medical Center
Fort Bragg, NC

Lt Col Jonathan Sosnov, MD, MSc

Clinical Medicine Flight Commander
375 MDOS
Scott AFB, IL

Laura Stubna, MS, RD, LDN, CNSC

Dietitian
VA Pittsburgh Healthcare System
Pittsburgh, PA

Carol Toms, MSW, LICSW

Social Worker
Seattle VA Medical Center
Seattle, WA

Lt Col. Jesse Wickham DO, FACP

Program Director Nephrology Fellowship
Brooke Army Medical Center
San Antonio, TX

Appendix F: Literature Review Search Terms and Strategy

A. Embase.com syntax

Question	Set #	Concept	Strategy
Question 1 – What are the benefits and harms of screening/testing for and/or labeling a patient with a CKD diagnosis? a) Do outcomes vary by sub-population (including those with acute kidney injury)?	#1	Patients with the potential to be diagnosed with chronic kidney disease (CKD)	'chronic kidney failure'/exp OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD):ti,ab
	#2	Testing/screening for CKD	'diagnostic procedure'/exp/mj OR (detect* OR diagnos* OR evaluat* OR identif* OR screen* OR test*):ti
	#3	Labeling with a CKD diagnosis	'disease classification'/de OR diagnosis/mj OR 'early diagnosis'/de OR 'patient coding'/de OR ((earlier OR early) NEXT/1 (detect* OR diagnos* OR identif*)):ti,ab OR label*:ti
	#4	Benefits/harms	behavior/exp/mj OR 'diagnostic error'/exp OR 'disease burden'/exp OR 'health care planning'/exp OR 'patient attitude'/de OR 'patient care'/de OR 'risk benefit analysis'/de OR survival/de OR (attitude* OR effect OR effects OR impact* OR perceiv* OR perception* OR react* OR advantage* OR benefi* OR empower* OR planning OR positive* OR pro OR pros OR survival OR useful* OR value OR burden* OR concern* OR con OR cons OR distress* OR harm* OR negativ* OR overdiagnos* OR underdiagnos*):ti
	#5	Combine sets	#1 AND (#2 OR #3) AND #4
	#6	Apply general hedges	See General Hedges at the end of this table
	#7	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 2 – What laboratory tests should be used to optimize the diagnosis and staging of CKD for the purpose of stratifying risks for CKD complications?	#1	Patients with the potential to be diagnosed with chronic kidney disease (CKD) (Especially Veterans with spinal cord injury or amputations, or patients with advanced liver disease)	'chronic kidney failure'/exp OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD):ti,ab
	#2	Primary care setting (i.e., non-hospital setting)	'hospital patient'/exp OR 'intensive care'/de OR 'intensive care unit'/de OR (hospital* OR inpatient* OR ICU OR 'intensive care'):ti
	#3	Combine population and setting sets	#1 NOT #2
	#4	Creatinine, eGFR, (various methods of calculation), proteinuria, albumin, cystatin c, risk calculator	'albumin level'/exp/mj OR 'creatinine blood level'/mj OR 'creatinine clearance'/mj OR 'creatinine urine level'/mj OR 'glomerulus filtration rate'/exp/mj OR 'kidney function test'/mj OR 'protein urine level'/mj OR 'protein blood level'/mj OR (EGFR OR (glomer* NEXT/1 filtration NEXT/1 rate*)):ti
	#5		(albumin/mj OR creatinine/mj OR 'cystatin c'/mj OR proteinuria/mj OR (albumin* OR creatinine OR 'cystatin c' OR proteinuria):ti) AND ('analytical parameters'/exp OR diagnosis/exp OR 'diagnostic procedure'/exp OR staging/de OR (determin* OR diagnos* OR level* OR screen* OR staging OR test* OR algorithm* OR calculat* OR equation* OR formula* OR index OR ratio* OR scor* OR tool*):ti,ab)
	#6		(risk* NEAR/2 (algorithm* OR calculat* OR equation* OR formula* OR index* OR indices OR scor* OR tool*)):ti,ab
	#7	Combine intervention sets	#4 OR #5 OR #6
	#8	Combine all sets	#3 AND #7
	#9	Apply general hedges	See General Hedges at the end of this table
	#10	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table
	#11	Focus on CKD results	#11 AND ('chronic kidney failure'/exp/mj OR (CKD OR kidney* OR renal):ti)

Question	Set #	Concept	Strategy
Question 3 – Among patients with advanced CKD (eGFR<45 or eGFR<30 might be the studied populations) or overt proteinuria, what prediction tools will best distinguish risks for ESRD progression, and what thresholds of risk should influence decisions for nephrology referral and vascular access implementation?	#1	Patients with advanced CKD or overt proteinuria	((‘chronic kidney failure’/exp OR (‘chronic kidney disease’ OR ‘chronic kidney failure’ OR ‘chronic kidney insufficiency’ OR ‘chronic renal disease’ OR ‘chronic renal failure’ OR ‘chronic renal insufficiency’ OR CKD):ti,ab) AND (advanced OR EGFR OR ‘glomerulus filtration rate’ OR GFR OR ‘stage 3’ OR ‘stage 3a’ OR ‘stage 3b’ OR serious OR severe):ti,ab) OR proteinuria/exp OR proteinuria:ti,ab
	#2	Use of a specific equation for risk	(CKDEPI OR ‘CKD-EPI’ OR KFRE):ti,ab OR ((‘disease exacerbation’/de OR ‘disease severity assessment’/de OR risk/exp OR (predict* OR progression OR risk*):ti,ab) AND (algorithm* OR calculat* OR equation* OR formula* OR index* OR indices OR ratio* OR scor* OR tool*):ti,ab)
	#3	End-stage renal disease	‘end stage renal disease’/de OR (‘end stage’ OR endstage OR ESKD OR ESRD OR ESKF OR ESRF OR ‘stage 5’ OR ‘stage v’):ti,ab
	#4	Combine sets	#1 AND #2 AND #3
	#5	Apply general hedges	See General Hedges at the end of this table
	#6	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table
Question 4 – How do prior vascular access devices impact the success of fistula and graft formation?	#1	Patients with CKD	‘chronic kidney failure’/exp OR (‘chronic kidney disease’ OR ‘chronic kidney failure’ OR ‘chronic kidney insufficiency’ OR ‘chronic renal disease’ OR ‘chronic renal failure’ OR ‘chronic renal insufficiency’ OR CKD):ti,ab
	#2	Patient preparing for or undergoing dialysis	dialysis/exp OR (dialysis OR hemodialysis OR haemodialysis OR predialysis):ti,ab
	#3	Arteriovenous fistula, arteriovenous graft, vascular access for hemodialysis	‘arteriovenous fistula’/exp OR ‘arteriovenous graft’/de OR ((AV OR ‘arteriovenous’ OR arteriovenous) NEXT/1 (fistula* OR graft OR grafts)) OR ((‘vascular access’/de OR ‘vascular access device’/de OR ‘vascular access’:ti,ab) AND (hemodialysis/exp OR (haemodialysis OR hemodialysis OR dialysis):ti,ab))
	#4	Success, failure, pre-existing central lines and catheters	(failure OR maturation OR placement OR patency OR (pre NEXT/1 exist*) OR preexist* OR preserv* OR previous* OR prior OR (protect* NEAR/1 vein*) OR problem* OR success*):ti,ab
	#5	Combine sets	(#1 OR #2) AND #3 AND #4
	#6	Apply general hedges	See General Hedges at the end of this table
	#7	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 5 – In patients with CKD, at what stage does nephrology referral and multidisciplinary/interdisciplinary care improve outcomes?	#1	Patients with CKD	'chronic kidney failure'/exp OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD):ti,ab
	#2	Nephrology referral	'patient referral'/de OR ((nephrologist* OR specialist* OR specialty) NEAR/2 (consult* OR refer*)):ti,ab OR (consult* OR nephrologist* OR refer OR refer* OR specialist* OR specialty):ti
	#3	Multidisciplinary/interdisciplinary care (including: physician extenders, physician assistants, nurse practitioners, pharmacists, social workers, vascular access teams, CKD education teams, and dietician/nutritionists)	'advanced practice provider'/exp OR dietitian/de OR 'interdisciplinary communication'/de OR 'medical specialist'/de OR nephrologist/de OR 'nurse practitioner'/exp OR pharmacist/de OR 'social worker'/de OR teamwork/de OR (((collaborative OR integrat*) NEXT/1 (approach* OR care OR model* OR treatment*)) OR 'inter-disciplinary' OR interdisciplinary OR 'multi-disciplinary' OR multidisciplinary OR dietician* OR (nurse NEXT/1 practitioner*) OR nutritionist* OR (physician NEXT/1 (assistant* OR extender*)) OR (social NEXT/1 worker*) OR team*):ti,ab
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply general hedges	See General Hedges at the end of this table
	#6	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table
Question 6 – What is the benefit of education on CKD outcomes? What methods of delivering education are the most effective?	#1	Patients with CKD	'chronic kidney failure'/exp OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD):ti,ab
	#2	Education	education/de OR 'educational program'/de OR 'health education'/de OR 'health literacy'/de OR 'patient education'/de OR learning/de OR 'nutrition education'/de OR 'self care'/de OR (patient* NEAR/5 educat*):ti,ab OR (class OR classes OR educat* OR instruction* OR knowledge OR literacy OR program* OR 'self care' OR 'self management' OR teach*):ti
	#3	Medical nutrition therapy	'nutritional counseling'/de OR (((diet* OR nutrition*) NEAR/2 (counsel* OR therap*)) OR 'medical nutrition therapy' OR MNT):ti,ab
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply general hedges	See General Hedges at the end of this table
	#6	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table
Question 7 – What is the benefit of shared decision making on CKD outcomes? How should shared decision making be achieved most effectively?	#1	Patients with CKD	'chronic kidney failure'/exp OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD):ti,ab
	#2	Shared decision-making	'shared decision making'/de OR 'doctor patient relation'/de OR 'patient participation'/de OR 'patient preference'/de OR ('collaborative decision-making' OR 'collaborative decisionmaking' OR ((individual* OR 'patient-centered' OR 'patient centred') NEXT/1 (care OR decision* OR treatment*)) OR "patient centeredness" OR "patient centredness" OR (shared NEXT/2 decision*) OR (patient NEAR (clinician OR doctor OR physician)) OR (patient NEAR/2 (choice* OR choos* OR engag* OR involv* OR participat* OR prefer*)) OR (treatment NEXT/1 (choice* OR decision*)):ti,ab
	#3	Combine sets	#1 AND #2
	#4	Apply general hedges	See General Hedges at the end of this table
	#5	Apply SR, RCT, and observational study hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 8 – In what populations would conservative management (e.g., supportive care, palliative care) vs. dialysis have similar outcomes?	#1	Patients with advanced CKD (stages 4/5), advanced age, or other life-threatening conditions	'end stage renal disease'/exp OR (((('end stage' OR endstage) NEAR/1 (renal OR kidney)) OR ESRD):ti,ab
	#2		((('kidney disease' OR 'kidney failure' OR 'kidney insufficiency' OR 'renal disease' OR 'renal failure' OR 'renal insufficiency') NEAR/2 (advanced OR severe OR 'stage 4' OR 'stage 4-5' OR 'stage 4/5' OR 'stage 5' OR terminal)):ti,ab
	#3	Conservative management (e.g., supportive care, palliative care)	'advance care planning'/de OR 'conservative treatment'/de OR 'palliative therapy'/exp OR ('comfort care' OR ((conservative OR nondialy* OR 'non-dialysis' OR 'non-dialytic' OR palliative) NEXT/2 (care OR manag* OR therap* OR treatment*))) OR 'supportive care':ti,ab
	#4	Combine sets	(#1 OR #2) AND #3
	#5	Apply general hedges	See General Hedges at the end of this table
	#6	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 9 – What is the effectiveness of pharmacological interventions for improving CKD outcomes?	#1	Patients with CKD	'chronic kidney failure'/exp OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD):ti,ab
	#2	Calcium/non-calcium phosphate binders (treatment of hyperphosphatemia)	'phosphate binding agent'/exp OR 'hyperphosphatemia'/dm_dt OR (((phosphate* OR phosphorus) AND bind*) OR 'aluminum hydroxide' OR 'cal-glu' OR 'calcium acetate' OR 'calcium carbonate' OR 'calcium chloride' OR 'calcium gluconate' OR calphron OR 'caltrate 600' OR 'ferric citrate' OR fosrenol OR eliphos OR lanthanum OR 'magnesium hydroxide' OR (milk NEXT/1 magnesium) OR 'os-cal' OR 'oysco 500' OR phoslo OR renagel OR renvela OR sevelamer OR 'sucroferric oxyhydroxide' OR tums OR velphoro):ti,ab
	#3	Uricosuric agents (treatment of hyperuricemia)	'uricosuric agent'/exp OR hyperuricemia/dm_dt OR (antihyperuricemi* OR (anti NEXT/1 hyperuricemi*) OR ('uric acid reabsorption' NEXT/1 inhibitor*) OR acetazolamide OR acifugan OR allopurinol OR alopurin OR apazone OR arhalofenate OR benecid OR benemid OR benuryl OR benzbromarone OR besuric OR desuric OR benziodarone OR doqualast OR elitek OR epaminurad OR febuxostat OR halofenate OR indacrinone OR irtemazole OR lesinurad OR lopurin OR narcaricin OR pegloticase OR prednisone OR 'pro-cid' OR probecid OR probenecid OR rasburicase OR ticrynafen OR 'tienilic acid' OR traxanox OR ulfinpyrazone OR uloric OR verinurad OR zoxazolamine OR zurampic OR zylprim):ti,ab
	#4	Dipeptidyl-peptidase 4 inhibitors (gliptins)	'dipeptidyl peptidase IV inhibitor'/exp OR (((('dipeptidyl-peptidase' OR dipeptidylpeptidase OR 'DPP-4' OR 'DPP-iv' OR DPP4 OR DPPIV) NEAR/2 inhibitor*) OR gliptin* OR alogliptin OR anagliptin OR bisegliptin OR carmegliptin OR denagliptin OR dutogliptin OR evogliptin OR galvus OR gemigliptin OR gosogliptin OR 'isoleucine thiazolidide' OR januvia OR linagliptin OR melogliptin OR omarigliptin OR onglyza OR saxagliptin OR sitagliptin OR teneligliptin OR tradjenta OR trelagliptin OR 'valine pyrrolidide' OR vildagliptin):ti,ab
	#5	Sodium-glucose cotransporter-2 inhibitor (gliflozins)	'sodium glucose cotransporter 2 inhibitor'/exp OR (((SGLT2 OR SGLT-2 OR 'sodium glucose' OR 'sodium dependent glucose') NEAR/3 inhibitor*) OR gliflozin* OR atigliflozin OR bexagliflozin OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR forxiga OR invokana OR ipragliflozin OR licogliflozin OR jardiance OR luseogliflozin OR mizagliflozin OR 'remogliflozin etabonate' OR 'sergliflozin etabonate' OR sotagliflozin):ti,ab
	#6	GLP-1 agonists	'glucagon like peptide 1 receptor agonist'/exp OR (('GLP-1' OR 'glucagon like peptide 1') AND agonist*) OR albiglutide OR dulaglutide OR exenatide OR liraglutide OR lixisenatide OR semaglutide
	#7	Thiazolidinedione	'2,4 thiazolidinedione derivative'/de OR (thiazolidine OR thiazolidinedione* OR TZD*):ti,ab
	#8	Tolvaptan	tolvaptan/de OR (samsca OR tolvaptan):ti,ab
	#9	Metformin	metformin/de OR (dimethylbiguanidine OR dimethylguanylguanidine OR fortamet OR glucophage OR glumetza OR riomet):ti,ab
	#10	Combine sets	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
	#11	Apply general hedges	See General Hedges at the end of this table
	#12	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 10 – What are optimal blood pressure goals for CKD patients?	#1	Patients with CKD	'chronic kidney failure'/exp OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD):ti,ab
	#2	Aggressive blood pressure treatment for low blood pressure goals / lower blood pressure	'antihypertensive agent'/exp/mj OR 'antihypertensive therapy'/mj OR 'blood pressure regulation'/mj OR ('anti-hypertensive' OR 'anti-hypertensives' OR antihypertensive*):ti
	#3		'blood pressure measurement'/mj OR 'blood pressure monitor'/mj OR 'blood pressure monitoring'/mj
	#4		('elevated blood pressure'/exp/mj OR 'hypertension'/mj OR 'systolic blood pressure'/mj OR ('blood pressure' OR hypertension OR hypertensive):ti) AND ('patient monitoring'/mj OR 'disease management'/exp/mj OR (standard OR sprint):ti,ab OR (aggressive* OR aim OR aiming OR aims OR control* OR intensive* OR lower OR goal OR goals OR manag* OR measur* OR monitor* OR nonaggressive* OR optimal* OR reduc* OR strict* OR stringent OR target* OR therap* OR treat*):ti)
	#5	Combine sets	#1 AND (#2 OR #3 OR #4)
	#6	Apply general hedges	See General Hedges at the end of this table
	#7	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table
Question 11 – In patients with CKD, what is the optimal approach to pain management?	#1	Patients with CKD	'chronic kidney failure'/exp OR 'kidney polycystic disease'/de OR ('chronic kidney disease' OR 'chronic kidney failure' OR 'chronic kidney insufficiency' OR 'chronic renal disease' OR 'chronic renal failure' OR 'chronic renal insufficiency' OR CKD OR 'polycystic kidney'):ti,ab
	#2	Pain	calcinosis/de OR pain/exp OR neuropathy/exp OR (ADPKD OR calcinosis OR calciphylaxis OR colic OR headache* OR migraine* OR neuropath* OR pain*):ti,ab
	#3	Opioids	'opiate agonist'/exp OR 'narcotic analgesic agent'/exp OR (opiate* OR opioid* OR buprenorphine OR fentanyl OR hydromorphone OR levorphanol OR methadone OR morphine* OR oxycodone OR oxycontin OR tramadol):ti,ab
	#4	Non-opioid analgesics: NSAIDs (oral, parenteral, topical)	'nonsteroid antiinflammatory agent'/exp OR (('non-steroid' OR 'non-steroidal' OR nonsteroid*) NEXT/1 ('anti-inflammatory' OR antiinflammatory) NEXT/1 (agent* OR drug* OR medication* OR medicine*)):ti,ab OR (advil OR ibuprofen OR ketorolac OR naproxen OR NSAID* OR motrin OR sulindac OR salsalate OR toradol OR diclofenac OR etodolac OR fenoprofen OR flurbiprofen OR indomethacin OR ketoprofen OR meclofenamate OR mefenamic acid OR meloxicam OR nabumetone OR oxaprozin OR piroxicam OR tolmetin):ti,ab
	#5	Non-opioid analgesics: COX-2 inhibitors	'cyclooxygenase 2 inhibitor'/exp OR (((('cox-2' OR cyclooxygenase) AND inhibitor*) OR celebrex OR celecoxib OR coxib*)):ti,ab
	#6	Non-opioid analgesics: acetaminophen, salicylates	paracetamol/de OR 'salicylic acid derivative'/exp OR (acetaminophen OR 'acetylsalicylic acid' OR aspirin OR paracetamol OR tylenol):ti,ab
	#7	Antiepileptic drugs: pregabalin OR gabapentin	gabapentin/de OR 'gabapentin enacarbil'/de OR pregabalin/de OR (gabapentin OR horizant OR lyrica OR neurontin OR pregabalin):ti,ab
	#8	Antidepressants: TCAs, SSRIs, SNRIs	'antidepressant agent'/de OR 'serotonin uptake inhibitor'/exp OR 'tricyclic antidepressant agent'/exp OR (antidepressant* OR antidepressive* OR (anti NEXT/1 depress*) OR (serotonin NEXT/2 (reuptake OR uptake) NEXT/1 inhibitor*) OR SSRI* OR SNRI* OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR duloxetine OR desvenlafaxine OR levomilnacipran OR venlafaxine):ti,ab

Question	Set #	Concept	Strategy
Question 11 – In patients with CKD, what is the optimal approach to pain management? (continued)	#9	Nonpharmacologic treatments	acupuncture/exp OR biofeedback/exp OR ‘cognitive behavioral therapy’/exp OR meditation/de OR ‘transcutaneous electrical nerve stimulation’/de OR (((‘non-pharmacologic’ OR ‘non-pharmacological’ OR nonpharmacologic*) NEXT/2 (manag* OR therap* OR treat*)) OR biofeedback OR (cognitive NEXT/1 behav* NEXT/1 (therap* OR treatment*)) OR acupuncture OR massage OR meditation OR nonopiate* OR nonopioid* OR (transcutaneous NEXT/1 electric* NEXT/2 (neurostimulat* OR stimulat*)):ti,ab
	#10	General CKD pain studies	(colic* OR neuropath* OR pain*):ti AND (CKD OR dialysis OR haemodialysis OR hemodialysis OR kidney* OR nephro* OR renal):ti AND (alleviat* OR control* OR manag* OR relief OR reliev* OR therap* OR treat*):ti
	#11	Combine sets	(#1 AND #2 AND (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)) OR #10
	#12	Apply general hedges	See General Hedges at the end of this table
	#13	Apply SR, RCT, and comparative observational study hedges	See Study Type Hedges at the end of this table
Question 12 – In patients with CKD, what is the comparative effectiveness of interventions used to prevent contrast-associated kidney injury?	#1	Patients with CKD	‘chronic kidney failure’/exp OR (‘chronic kidney disease’ OR ‘chronic kidney failure’ OR ‘chronic kidney insufficiency’ OR ‘chronic renal disease’ OR ‘chronic renal failure’ OR ‘chronic renal insufficiency’ OR CKD):ti,ab
	#2	Exposure to iodinated contrast with potential for contrast-associated kidney injury	‘contrast induced nephropathy’/de OR ((contrast OR radiocontrast) NEXT/2 induced NEXT/2 (nephropathy OR nephrotoxicity)) OR (‘contrast nephropathy’ OR ‘contrast nephrotoxicity’):ti,ab
	#3		(‘kidney disease’/exp OR ((kidney OR renal) AND (disease* OR failure OR injur* OR insufficiency OR nephropath* OR nephrotox*)):ti,ab) AND (‘contrast medium’/exp OR (contrast* OR radiocontrast*)):ti,ab)
	#4	Combine population sets	#1 AND (#2 OR #3)
	#5	General prevention	prevention:lnk OR prevention/de OR ‘prevention and control’/de OR ‘primary prevention’/de OR prophylaxis/de OR protection/de OR ‘renal protection’/de OR (decreas* OR lower OR prevent* OR prophyla* OR protect*):ti,ab
	#6	Iso-osmolar contrast agent (iodixanol) vs. low-osmolar contrast agents	osmolarity/exp OR (‘iso-osmolar’ OR isoosmolar OR ‘low osmolar’ OR hexabrix OR imeron OR iobitridol OR iodixanol OR iohexol OR iomeprol OR iopamidol OR iopromide OR ioversol OR ioxaglate OR ioxilan OR isovue OR omnipaque OR optiray OR oxilan OR ultravist OR visipaque OR xenetix):ti,ab
	#7	Intravenous crystalloid vs. oral hydration	crystalloid/de OR crystalloid*ti,ab OR ‘oral rehydration solution’/de OR (oral* NEAR/2 (hydrat* OR rehydrat*)):ti,ab
	#8	Regimen for intravenous fluid administration (this would include left ventricular end-diastolic pressure (LVEDP)-guided therapy and high-flow therapies using devices that match urine output and fluid administration)	(‘fluid therapy’/exp OR ((fluid* NEAR/2 (administ* OR deliver* OR therap* OR treat*)) OR hydrat* OR rehydrat*):ti,ab) AND (‘heart left ventricle enddiastolic pressure’/de OR diuresis/exp OR (balanced OR diuresis OR guided OR ‘high flow’ OR ‘left ventricular end-diastolic pressure’ OR LVEDP OR match* OR regimen* OR ‘renal guard’ OR renalguard OR strateg* OR system OR systems):ti,ab)
	#9	Isotonic (1.3%) sodium bicarbonate vs. isotonic (0.9%) saline	(bicarbonate/de OR ‘sodium chloride’/de OR (‘sodium bicarbonate’ OR saline OR ‘sodium chloride’):ti,ab) AND (‘isotonic solution’/de OR isotonic:ti,ab)
	#10	N-acetylcysteine vs. no N-acetylcysteine	acetylcysteine/de OR ((acetyl* NOT acetylsalicylic) OR NAC OR acetadote OR ‘acys-5’ OR cetylev OR mucomyst OR mucosil):ti,ab

Question	Set #	Concept	Strategy
Question 12 – In patients with CKD, what is the comparative effectiveness of interventions used to prevent contrast-associated kidney injury? (continued)	#1	Statin vs. no statin	'hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp OR ('HMG-CoA' OR hydroxymethylglutaryl OR statin* OR altoprev OR atorvastatin OR bervastatin OR cerivastatin OR compactin OR crestor OR crivastatin OR dalvastatin OR fluindostatin OR glenvastatin OR lescol OR lipitor OR livalo OR lovastatin OR mevinolin OR monacolin* OR pitavastatin OR pravachol OR pravastatin OR rosuvastatin OR simvastatin OR tenivastatin OR zocor):ti,ab
	#12	Other agents (e.g., fenoldopam, dopamine, theophylline, furosemide, mannitol)	dopamine/de OR fenoldopam/exp OR furosemide/de OR mannitol/de OR theophylline/de OR (dopamine OR fenoldopam OR furosemide OR mannitol OR theophylline):ti,ab
	#13	Renal replacement therapy vs. no renal replacement therapy	'renal replacement therapy'/exp OR ('renal replacement' OR 'renal support'):ti,ab
	#14	Combine intervention sets	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
	#15	Combine population and intervention sets	#4 AND #14
	#16	Apply general hedges	See General Hedges at the end of this table
	#17	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table
General Hedges Applied to Each Search		Limit to humans and newly added publications	AND ([humans]/lim OR [article in press]/lim OR [in process]/lim)
		Exclude lingering animal studies	NOT (mouse OR mice OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine):ti
		Exclude studies focusing on children	NOT ((adolescen* OR child* OR infant* OR neonat* OR newborn* OR paediatric* OR pediatric*):ti NOT adult:ti)
		Limit to English language publications and to results with abstracts	AND [English]/lim AND [abstracts]/lim
		Remove undesired publication types (e.g., conferences, editorials)	NOT ('conference paper'/exp OR ('case report' OR book OR editorial OR erratum OR letter OR note OR 'short survey')/de OR (book OR conference OR editorial OR erratum OR letter OR note OR 'short survey'):it OR ('a case' OR 'a patient' OR 'year old'):ti,ab OR (book OR 'conference proceeding'):pt OR ('case report' OR comment):ti)
		Limit to results added to the database since the prior literature search (December 2013)	AND [1-12-2013]/sd NOT [11-9-2018]/sd

Question	Set #	Concept	Strategy
Study Type Hedges Applied as Needed (per Key Question Specific Criteria provided earlier in this report)		Limit to meta-analyses and systematic reviews	AND ('meta analysis'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de OR ('meta analysis' OR 'meta analytic' OR metaanaly* OR 'research synthesis' OR 'systematic review' OR pooled OR pooling OR search*):ti,ab OR ('critical review' OR 'evidence based' OR systematic*):ti OR cochrane:jt)
		Limit to randomized controlled trials	AND ('random sample'/de OR 'randomized controlled trial'/de OR randomization/de OR ('cross-over' OR crossover OR random*):ti,ab OR ((single OR double OR triple) NEXT/1 blind*):ti,ab)
		Limit to comparative observational and/or diagnostic cohort studies	AND ('case control study'/exp OR 'cohort analysis'/de OR 'controlled study'/exp OR 'cross-sectional study'/de OR 'diagnostic test accuracy study'/de OR epidemiology/exp/mj OR 'follow up'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de OR ('case control' OR 'case series' OR cohort OR compar* OR 'controlled study' OR 'controlled trial' OR 'cross sectional' OR 'follow-up' OR followup OR longitudinal OR 'matched controls' OR placebo OR prospective OR retrospective):ti,ab OR (epidemiolog* OR versus OR vs):ti)

Appendix G: Alternative Text Descriptions of Algorithms

The following outlines narratively describe [Module A](#), [Module B](#), [Module C](#), and [Module D](#). An explanation of the purpose of the algorithms and description of the various shapes used within the algorithms can be found in the [Algorithm](#) section. The sidebars referenced within these outlines can also be found in the [Algorithm](#) section.

Module A: Screening for CKD and Initial Assessment

1. Module A has two entry points, at Box 1 and Box 10. Beginning at Box 1, in the shape of a rounded rectangle: “Incidental finding of abnormal electrolytes, creatinine, proteinuria, hematuria, new highly elevated BP, or peripheral edema”
2. Box 1 connects Box 2, in the shape of a rectangle: “Initial assessment for kidney (see Sidebars 1 and 2) and non-kidney disease”
3. Box 2 connects to Box 3, in the shape of a hexagon, asks the question: “Does the patient have an urgent or emergent condition? (see Sidebar 3)”
 - a. If the answer is “Yes” to Box 3, then Box 4, in the shape of a rectangle: “Refer to emergency department or manage and stabilize”
 - b. If the answer is “No” to Box 3, then Box 5, in the shape of a hexagon, asks the question: “Does patient have evidence of kidney disease? (see Sidebar 2)”
 - i. If the answer is “Yes” to Box 5, then Box 6, in the shape of a hexagon, asks the question: “Are these findings new?”
 - 1) If the answer is “Yes” to Box 6, then Box 7, in the shape of an oval: “Assess for AKI/AKD (exit to Module B)”
 - 2) If the answer is “No” to Box 6, then Box 8, in the shape of an oval: “Assess for CKD (exit to Module C)”
 - ii. If the answer is “No” to Box 5, then Box 9, in the shape of a rectangle: “Assess for other medical cause (exit algorithm)”
4. Beginning at Box 10, in the shape of a rounded rectangle: “Patients at risk for CKD (Sidebar 1)”
5. Box 10 connects Box 11, in the shape of a rectangle: “Periodically obtain SCr, eGFR, urinalysis, and spot uACR”
6. Box 11 connects to Box 12, in the shape of a hexagon, asks the question: “Does the patient have an urgent or emergent condition? (see Sidebar 3)”
 - a. If the answer is “Yes” to Box 12, then Box 4, in the shape of a rectangle: “Refer to emergency department or manage and stabilize”

- b. If the answer is “No” to Box 12, then Box 13, in the shape of a hexagon, asks the question: “Does patient have evidence of kidney disease? (see Sidebar 2)”
 - i. If the answer is “Yes” to Box 13, then Box 6, in the shape of a hexagon, asks the question: “Are these findings new?”
 - 1) If the answer is “Yes” to Box 6, then Box 7, in the shape of an oval: “Assess for AKI/AKD (exit to Module B)”
 - 2) If the answer is “No” to Box 6, then Box 8, in the shape of an oval: “Assess for CKD (exit to Module C)”
 - ii. If the answer is “No” to Box 13, then to Box 11, in the shape of a rectangle: “Periodically obtain SCr, eGFR, urinalysis, and spot uACR”

Module B: Evaluation for AKI or New Decline in Renal Function

1. Module B begins at Box 14, in the shape of a rounded rectangle: “Evaluation for possible AKI/AKD or new decline in renal function (see Sidebar 4)”
2. Box 14 connects to Box 15, in the shape of a hexagon, asks the question: “Does the patient have an urgent or emergent condition? (see Sidebar 3)”
 - a. If the answer is “Yes” to Box 15, then Box 16, in the shape of a rectangle: “Refer to emergency department or manage and stabilize”
 - b. If the answer is “No” to Box 15, then Box 17, in the shape of a hexagon, asks the question: “Is there evidence of volume depletion, or volume overload? (see Sidebar 5)”
 - i. If the answer is “Yes” to Box 17, then Box 18, in the shape of a rectangle: “Optimize volume status and reassess or refer to emergency department”
 - ii. If the answer is “No” to Box 17, then Box 19, in the shape of a hexagon, asks the question: “Is there clinical suspicion or evidence for urinary obstruction? (see Sidebar 5)”
 - 1) If the answer is “Yes” to Box 19, then Box 20, in the shape of a rectangle: “Refer to emergency department”
 - 2) If the answer is “No” to Box 19, then Box 21, in the shape of a hexagon, asks the question: “Is there clinical suspicion or evidence for acute nephritis or nephrosis? (see Sidebar 5)”
 - a) If the answer is “Yes” to Box 21, then Box 22, in the shape of a rectangle: “Call for urgent nephrology consultation”
 - b) If the answer is “No” to Box 21, then Box 23, in the shape of a rectangle: “Stop nephrotoxins/metformin, consider holding ACEI/ARBs/diuretics, and consider reducing dose of insulin or other renally cleared medications; depending on clinical context, consider trial of hydration”
3. Box 23 connects to Box 24, in the shape of a rectangle: “Reassess renal function and consult nephrology if persistent renal dysfunction (see Sidebar 8)”

Module C: Evaluation for CKD

1. Module C begins at Box 25, in the shape of a rounded rectangle: “Evaluation for CKD (see Sidebar 6)”
2. Box 25 connects Box 26, in the shape of a hexagon, asks the question: “Is consultation with urology indicated? (see Sidebar 7; referral should be made following shared decision making with patient that ensures the referral focus is consistent with the patient values and preferences)”
 - a. If the answer is “Yes” to Box 26, then Box 27, in the shape of a rectangle: “Consult urology”
 - b. If the answer is “No” to Box 26, then Box 28, in the shape of a hexagon, asks the question: “Is consultation with nephrology indicated? (see Sidebar 8; referral should be made following shared decision making with patient that ensures the referral focus is consistent with the patient values and preferences)”
 - i. If the answer is “Yes” to Box 28, then Box 29, in the shape of a rectangle: “Consult nephrology”
 - ii. If the answer is “No” to Box 28, then Box 30, in the shape of a rectangle: “Establish stage of CKD (see Sidebars 9a and 9b) and probable etiology”
3. Box 30 connects to Box 31, in the shape of a rectangle: “Assess risk for progression of CKD (See Table 2: Risk Prediction Equations Developed for Patients with CKD); formulate treatment plan to treat underlying cause; implement strategies to slow progression in decline of kidney function (see Sidebar 10); adjust medication doses for eGFR; optimize ASCVD risk factors (As appropriate, refer to the following VA/DoD Clinical Practice Guidelines: Chronic Heart Failure, Diabetes, Hypertension, Dyslipidemia, Overweight and Obesity, and Tobacco Cessation); review/update vaccination status”
4. Box 31 connects to Box 32, in the shape of a rectangle: “Monitor and assess for CKD progression and development of complications periodically with BP, SCr/eGFR, uACR or uPCR, electrolytes, CaPO₄, Hgb”
5. Box 32 connects to Box 33, in the shape of a hexagon, asks the question: “Is there evidence of disease progression or development of indications for nephrology consultation (see Sidebar 8)?”
 - a. If the answer is “Yes” to Box 33, then to Box 29, in the shape of a rectangle: “Consult nephrology”
 - b. If the answer is “No” to Box 33, then to Box 32, in the shape of a rectangle: “Monitor and assess for CKD progression and development of complications periodically with BP, SCr/eGFR, uACR or uPCR, electrolytes, CaPO₄, Hgb”

Module D: Management of Patients with CKD Requiring Iodinated Contrast

1. Module D begins at Box 34, in the shape of a rounded rectangle: “Patient needing a study requiring iodinated contrast (see Sidebar 11)”
2. Box 34 connects Box 35, in the shape of a hexagon, asks the question: “Is the study urgent (e.g., STEMI)?”
 - a. If the answer is “Yes” to Box 35, then Box 36, in the shape of a hexagon, asks the question: “Is the patient’s eGFR above the threshold for safe contrast administration (see Sidebar 12)”
 - i. If the answer is “Yes” to Box 36, then Box 38, in the shape of a rectangle: “Proceed with administration of contrast”
 - ii. If the answer is “No” to Box 36, then Box 39, in the shape of a rectangle: “If it does not delay procedure, administer pre-procedure fluids at 3 mL/kg for 1 hour; proceed with study and then administer IV normal saline at 1 mL/kg/hr for 6-12 hours post-procedure.”
 - 1) Box 39 connects to Box 45, in the shape of a rectangle: “Check labs 2-3 days after contrast administration and manage AKI as appropriate if present”
 - b. If the answer is “No” to Box 35, then Box 37, in the shape of a hexagon, ask the question: “Is the patient’s eGFR above the threshold for safe contrast administration (see Sidebar 12)”
 - i. If the answer is “Yes” to Box 37, then Box 38, in the shape of a rectangle: “Proceed with administration of contrast”
 - ii. If the answer is “No” to Box 37, then Box 40, in the shape of a hexagon, ask the question: “Is the patient in decompensated heart failure?”
 - 1) If the answer is “Yes” to Box 40, then Box 41, in the shape of a rectangle: “Heart failure should be treated and contrast exam deferred if clinically appropriate”
 - 2) If the answer is “No” to Box 40, then Box 42, in the shape of a hexagon, ask the question: “Is the patient hospitalized?”
 - a) If the answer is “Yes” to Box 42, then Box 43, in the shape of a rectangle: “Administer IV normal saline at 1 mL/kg/hr for 6-12 hours pre-procedure and 6-12 hours post-procedure”
 - i) Box 43 connects to Box 45, in the shape of a rectangle: “Check labs 2-3 days after contrast administration and manage AKI as appropriate if present”

- b) If the answer is “No” to Box 42, then Box 44, in the shape of a rectangle: “Administer IV normal saline at 3 mL/kg for 1 hour pre-procedure and 6 mL/kg over 2-4 hours post-procedure”
 - i) Box 44 connects to Box 45, in the shape of a rectangle: “Check labs 2-3 days after contrast administration and manage AKI as appropriate if present”

Appendix H: Management of CKD Table

Concerns:	Interventions:
Medications	<ul style="list-style-type: none"> • Adjust medication dose based on eGFR or CrCl as indicated • Eliminate/avoid nephrotoxic agents • Assess medication adherence • Assess for medication side effects since drug clearance may be reduced in patients with renal dysfunction and side effects may contribute to non-adherence
Education/behavior change support	<ul style="list-style-type: none"> • Nutrition assessment and referral • Education on CKD self-management • Education on RRT options • Screen for depression or health-related mental illness
Diabetes	<ul style="list-style-type: none"> • Optimize glycemic control • Consider use of metformin, GLP-1 agonist, SGLT2 inhibitor, as indicated (See Recommendations 15-18 and VA/DoD DM CPG^a)
Proteinuria	<ul style="list-style-type: none"> • In patients with albuminuria >300 mg/g of creatinine, consider the use of RAAS blockade as tolerated based on BP
Hypertension	<ul style="list-style-type: none"> • Optimize blood pressure control (See Recommendations 19-22 and VA/DoD Hypertension CPG^b) • Consider use of ACEI or ARB, particularly in patients with DM and patients with proteinuria • Optimize volume status • Dietary sodium restriction
Vaccination (Hepatitis B, pneumococcal vaccine, influenza)	<ul style="list-style-type: none"> • Assess Hepatitis B status and vaccinate, if non-immune • Update pneumococcal vaccines • Update influenza vaccination annually • Provide age-appropriate vaccination (e.g., MMR, VZV, Tdap/Td)
Anemia	<ul style="list-style-type: none"> • Assessment of underlying cause of anemia • Assessment for nutritional deficiency and replacement of iron, B₁₂, and folate stores as appropriate • Referral to nephrology if patient has CKD stage 3b or higher and persistent hemoglobin <10 for consideration of ESA • Referral for IV iron, if patient has persistent iron deficiency despite trial of oral iron therapy (after age-appropriate evaluation for etiology or if patient unable to tolerate oral iron deficiency)
CV health	<ul style="list-style-type: none"> • Encourage physical activity, considering the guidance of 150 min/week of aerobic activity as appropriate • Achieve and maintain ideal body weight/BMI • Assess and treat dyslipidemia (see VA/DoD Dyslipidemia CPG^c) • Assess risks/benefits of aspirin therapy • Recommend tobacco cessation
Medical nutrition therapy	<ul style="list-style-type: none"> • Review of dietary habits with respect to sodium, protein, phosphorus, and potassium as indicated
Pain	<ul style="list-style-type: none"> • Avoid NSAID use, including OTC and prescription (oral/topical) • See VA/DoD Opioid Therapy for Chronic Pain CPG^d

Concerns:	Interventions:
Iodinated contrast agents	<ul style="list-style-type: none"> • See Recommendations 31-34 and Algorithm
Gadolinium	<ul style="list-style-type: none"> • Avoid use of gadolinium if eGFR <30 mL/min/1.73 m² or current AKI (Appendix N)
Nuclear medicine contrast	<ul style="list-style-type: none"> • No concerns for renal toxicity so may use as clinically indicated
Resistant hypertension	<ul style="list-style-type: none"> • Defined as BP >140/90 mmHg and optimal dose of 3 anti-hypertensive drugs that include a diuretic • Consider referral for nephrology evaluation
Recurrent kidney stones	<ul style="list-style-type: none"> • Referral to urology for symptomatic or obstructive nephrolithiasis • Referral to nephrology for metabolic evaluation of recurrent nephrolithiasis

^a See the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/cd/diabetes/index.asp>

^b See the VA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/cd/htn/index.asp>

^c See the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/cd/lipids/index.asp>

^d See the VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Available at: <https://www.healthquality.va.gov/guidelines/pain/cot/index.asp>

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin II receptor blockers; BMI: body mass index; BP: blood pressure; CPG: clinical practice guideline; CrCl: creatinine clearance; CV: cardiovascular; DM: diabetes mellitus; DoD: Department of Defense; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; GLP-1: glucagon-like peptide-1; IV: intravenous; MMR: measles, mumps, and rubella; NSAID: non-steroidal anti-inflammatory drug; OTC: over-the-counter; RRT: renal replacement therapy; SGLT2: sodium-glucose cotransporter-2; Td: tetanus and diphtheria; Tdap: tetanus, diphtheria, and pertussis; VA: Department of Veteran Affairs; VZV: varicella zoster virus

Appendix I: Monitoring of CKD Table

Assessment:	Monitoring:
Hypertension	<ul style="list-style-type: none"> • Check BP at each visit. For additional guidance on the proper measurement of hypertension refer to the VA/DoD Clinical Practice Guideline for Management of Hypertension in Primary Care^a • Consider home blood pressure monitoring • Consider ABPM • Clinical exam for volume status
Proteinuria	<ul style="list-style-type: none"> • Quantify with 24 hour urine collection, uACR, or uPCR – frequency depends on severity of proteinuria • Screening for development of diabetic nephropathy and hypertensive nephrosclerosis
Renal function	<ul style="list-style-type: none"> • Check SCr – frequency depending on severity of renal dysfunction and stability/rate of decline of renal function • Consider one-time cystatin C measurement to confirm CKD diagnosis and stage
Electrolytes, Acidosis	<ul style="list-style-type: none"> • Check electrolytes and bicarbonate level - frequency varies based on severity of renal dysfunction and medication use (e.g., diuretics, ACEI or ARB)
Anemia	<ul style="list-style-type: none"> • Check hemoglobin – frequency depends on severity of renal dysfunction and comorbidities • Evaluate for and supplement nutritional deficiency, as indicated

^a 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>

Abbreviations: ABPM: ambulatory blood pressure monitoring; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; BP: blood pressure; CKD: chronic kidney disease; DoD: Department of Defense; SCr: serum creatinine; uACR: urine albumin-to-creatinine ratio; uPCR: urine protein-to-creatinine ratio; VA: Department of Veteran Affairs

Appendix J: Special Considerations When Caring for Older Veterans with CKD

CKD disproportionately affects older adults. The prevalence of CKD increases as Veterans age, from <5% among those 18-44 years to nearly 50% among Veterans >85 years old.[30] The majority of the 13,000 Veterans who transition to ESRD annually are >65 years old (median age 70.3).[218] A geriatric approach to care that addresses the higher prevalence of geriatric conditions, such as dementia, functional limitations, and multi-complexity may be appropriate for older Veterans with CKD.

Table J-1. Relevance and Application of Geriatric Approach to Older Veterans with CKD Using the 5 M’s[219]

	Relevance to CKD	Approach
Mind	Cognitive impairment increases at lower eGFR. Cognitive impairment is common among older adults with ESRD. Depressive symptoms are associated with prevalent CKD, worsening kidney function and ESRD. In ESRD, depression is associated with worse outcomes.	<ul style="list-style-type: none"> • Simplify CKD self-management tasks including medication regimens when possible • Include family or caregivers in decision making • Address depression to improve QoL
Mobility	Mobility impairment and function decline are common. Functional limitations are associated with death and adverse health outcomes in CKD. At dialysis initiation 50% of older adults are dependent in ADLs, 25% need nursing home level care. Falls are common among older adults with CKD and ESRD.	<ul style="list-style-type: none"> • Use an SDM approach that considers prognosis • Anticipate increased need for functional assistance after dialysis initiation • Consider PT/OT/physical activity to maintain or improve function and reduce fall risk
Medications	Polypharmacy is common in CKD and the risk for adverse drug events and poor health outcomes is high.	<ul style="list-style-type: none"> • Reduce number of medications and streamline medication regimens as appropriate • Avoid use of nephrotoxic medications • Adjust medication doses for eGFR, particularly when eGFR falls below 30 mL/minute/1.73 m², to reduce risk for adverse effects and drug reactions • Surveil for drug-drug interactions
Multi-complexity	CKD occurs in patients with multiple chronic conditions. Patients are asked to self-manage multiple conditions and often receive conflicting treatment recommendations (e.g., NSAIDs for arthritis)	<ul style="list-style-type: none"> • Address, review and simplify complex self-management regimens • Address and resolve conflicting treatment recommendations
Matters most to me	CKD patients face complex decisions and often need to make trade-offs. Some therapeutic options, such as initiation of dialysis have tremendous impact on lifestyle and QoL.	<ul style="list-style-type: none"> • Assist patients in formulating and verbalizing goals of care when needed • Include patient preferences and priorities for SDM that supports the patient’s goals of care. Complete life sustaining treatment directive.

Abbreviations: ADL: activities of daily living; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; NSAID: non-steroidal anti-inflammatory drug; OT: occupational therapy; PT: physical therapy; QoL: quality of life; SDM: shared decision making

A. Other Considerations

Heterogeneity in life expectancy: Older adults can expect to live fewer years than younger patients, however there is variability in life expectancy at all ages. For example, the top quartile of 80 year olds with eGFR 30-44 mL/minute/1.73 m² may live an additional seven years or more compared to the lowest quartile who may live less than two years.[\[220\]](#)

Competing risk of mortality: Many older adults are likely to die before they experience kidney failure or require dialysis.[\[221\]](#)

Challenges estimated and interpreting eGFR: Older adults were not included in large numbers in the studies used to develop eGFR equations, so these equations may not be accurate in older adults.

Exclusion of older adults from clinical trials: Older adults or those with multiple chronic conditions are often excluded from clinical trials, limiting the generalizability of those studies to older populations.

Appendix K: Nephrotoxic Agents and Medication Dose Adjustments in CKD

A. Background

This appendix provides information on avoiding or limiting the use of nephrotoxic medications in patients with CKD and is intended to provide general guidance for the primary care provider on the more common or critical nephrotoxic medications and on medications where particular caution or dose adjustment is advised in patients with CKD. The majority of the available literature on nephrotoxicity of medications is from case reports, pharmacokinetic or pharmacodynamic data, or surveillance [222] or database studies.[223] In addition to the information provided, the product information should be consulted for contraindications or precautions in patients with CKD, or specific recommendations on dosing modifications, where appropriate, according to the patient's kidney function. Nephrotoxicity remains an important consideration in the care of patients with CKD and an area where additional research is needed.[224]

B. Nephrotoxic Medications

According to an analysis of the FDA Adverse Event Reporting System (FAERS) database from 2004 (quarter 1) to 2015 (quarter 3), 2.1% of more than 7.2 million adverse events reported overall were reports of AKI. Of these, the medications most commonly associated with a report of AKI included aprotinin, sodium phosphate, furosemide, vancomycin, and metformin. In addition, of the reports of AKI, the majority (64.8%) were identified as new potential nephrotoxins, with only 16.5% due to known nephrotoxins and 18.6% possible nephrotoxins. Many commonly used medications may be nephrotoxic to patients with CKD. Examples of these categories of medications include:

- Analgesics (NSAIDs, aspirin at high doses)
- Antimicrobials (acyclovir, adefovir, aminoglycosides, amphotericin B, cephalosporins, penicillins, beta-lactamase inhibitors, cidofovir, foscarnet, ganciclovir, pentamidine, quinolones, rifampin, sulfonamides, vancomycin)
- Antiretrovirals (atazanavir, indinavir, tenofovir)
- Bisphosphonates (pamidronate, zoledronic acid)
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Chemotherapeutic agents (alkylating agents, cisplatin, methotrexate, mitomycin, interferon-alpha, proteasome inhibitors, vascular endothelial growth factor (VEGF) inhibitors, checkpoint inhibitors)
- Contrast dye (See [Recommendations 33-35 on CA-AKI management](#) and [Algorithm Module D](#))
- Diuretics (loop diuretic, thiazides, triamterene)
- Proton pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)
- Others (allopurinol, gold sodium thiomalate, lithium, quinine, sodium phosphate)
- Herbal products (aristolochic acid, cats claw, licorice root)

Nephrotoxicity may result from various mechanisms and result in different manifestations. Drugs may alter intraglomerular hemodynamics, induce inflammation (glomerulonephritis or interstitial nephritis), or form crystals, which would manifest as renal dysfunction, hematuria or proteinuria. In addition, drugs may cause rhabdomyolysis and thrombotic microangiopathy, which may also cause renal injury. Direct tubular injury more commonly presents with electrolyte abnormalities, including Fanconi-like syndrome. Finally, some medications may induce or exacerbate hypertension. General recommendations include avoiding use of nephrotoxic medications or use of non-nephrotoxic alternatives whenever possible, adjusting medication dose based on kidney function, ensuring adequate hydration, and close monitoring of the patient for evidence of nephrotoxicity when high-risk medications are used.

C. Medication dose adjustments in CKD

Many common medications are renally eliminated, and reduced kidney function may lead to drug accumulation with toxic effects specific to the drug. Dose adjustments are most often based on the patient’s SCr, CrCl, or eGFR. The extent of dose reduction typically depends on the level of kidney function, and some medications may be contraindicated in those with severe renal dysfunction. Most often, as the data to evaluate the need for dose adjustment in patients with CKD is part of the FDA approval process, recommendations frequently rely primarily on the manufacturer’s product labeling, though recommendations for dose adjustment may change based on post-marketing studies (e.g., as for metformin). Several references are also available with compiled drug information on recommended dosing based on kidney function; however, the information may vary among sources. [Table K-1](#) includes a select list of commonly used medications that may require dose adjustment based on kidney function or that warrant caution in patients with CKD.

Table K-1. Selected Medications with Recommended Dose Adjustments or to be Used with Caution in Patients with CKD*

Category	Medications
Antibiotics and antiviral agents	<ul style="list-style-type: none"> All antibiotics and antiviral agents with the exception of: macrolides, clindamycin, ceftriaxone, and metronidazole
CV agents	<ul style="list-style-type: none"> Atenolol, sotalol, digoxin, dofetilide, potassium-sparing diuretics <u>Thiazide diuretics</u>: chlorthalidone, hydrochlorothiazide, and indapamide <u>RAAS inhibitors</u>: ACEIs, ARBs, aliskiren, eplerenone, and spironolactone
Direct oral anticoagulants	<ul style="list-style-type: none"> Apixaban, dabigatran, edoxaban, rivaroxaban, low molecular weight heparins
Antilipemics	<ul style="list-style-type: none"> <u>Statins</u>: fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin <u>Fibric acid derivatives</u>: fenofibrate and gemfibrozil
Analgesics (see Appendix L)	<ul style="list-style-type: none"> Codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, NSAIDs, COX-2 inhibitors

Category	Medications
Hypoglycemic agents	<ul style="list-style-type: none"> • Insulin, metformin, exenatide • <u>Sulfonylureas</u>: glyburide, chlorpropamide • <u>Alpha-glucosidase inhibitors</u>: acarbose, miglitol • <u>Meglitinides</u>: nateglinide, repaglinide • <u>DPP-4 inhibitors</u>: alogliptin, saxagliptin, sitagliptin • <u>SGLT2 inhibitors</u>: canagliflozin, dapagliflozin, empagliflozin
Gastrointestinal agents	<ul style="list-style-type: none"> • <u>H2 antagonists</u>: cimetidine, famotidine, ranitidine • <u>Proton pump inhibitors</u>: dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Antidepressants	<ul style="list-style-type: none"> • Bupropion, citalopram, escitalopram, duloxetine, mirtazapine, paroxetine, venlafaxine
Agents for gout	<ul style="list-style-type: none"> • Allopurinol, colchicine
Bisphosphonates	<ul style="list-style-type: none"> • Alendronate, etidronate, ibandronate, pamidronate, risedronate, zoledronic acid
Antipsychotic or antimanic agents	<ul style="list-style-type: none"> • Lithium, paliperidone, risperidone
Anticonvulsants	<ul style="list-style-type: none"> • Gabapentin, pregabalin, levetiracetam, topiramate
Anti-cancer therapies	<ul style="list-style-type: none"> • Cytotoxic drugs, targeted agents, biologics
PDE5 inhibitors	<ul style="list-style-type: none"> • Sildenafil, tadalafil
Dementia medications	<ul style="list-style-type: none"> • Memantine, halantamine

*This is not a comprehensive list; consult individual product information or alternate drug information resources for dosing information and/or precautions in patients with kidney function impairment. Also refer to previous discussion and list of potentially nephrotoxic medications.

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; COX-2: cyclooxygenase-2; CV: cardiovascular; DPP-4: dipeptidyl peptidase-4; NSAIDs: non-steroidal anti-inflammatory drug; PDE5: phosphodiesterase type 5; RAAS: renin-angiotensin-aldosterone system; SGLT2: sodium-glucose cotransporter-2

Renal dysfunction may also exacerbate the adverse effects of some medications. For example, though an increase in potassium is a well-described side effect of ACEIs, ARBs, potassium-sparing diuretics, trimethoprim, digoxin, and heparin, patients with CKD are more likely to experience clinically significant hyperkalemia, particularly if these medications are used in concomitantly. Similarly, patients with CKD may have an underlying acidosis and are more likely to develop metformin-associated lactic acidosis. The manufacturer's product information should be consulted to determine appropriate dosing based on the patient's kidney function, and monitoring for these adverse effects should be performed.

Use of an ACEI or an ARB is frequently recommended in patients with CKD ([see Recommendation 22, RAAS Blockade](#)). ACEI and ARB are useful in the management of hypertension. Additionally, ACEI and ARBs have been associated with both an antiproteinuric and renoprotective effect. General considerations and precautions on the use of these agents in patients with CKD are as follows:

- Start with lower doses in patients with CKD (except fosinopril, due to partial compensation by hepatobiliary elimination)
- Start with lower doses in patients concurrently being treated with a diuretic
- Use with caution in patients with renal artery stenosis (bilateral or solitary kidney)

- Monitor potassium and kidney function closely (e.g., one-to-two weeks after initiation or dose adjustment)
- Concomitant therapy with potassium-sparing diuretics, potassium supplements, and/or additional RAAS blockers may result in hyperkalemia
- FDA boxed warning: due to the potential risk for fetal morbidity and mortality in patients taking an ACEI or ARB during pregnancy, it is recommended that therapy be discontinued prior to conception (if possible) or as soon as a woman becomes pregnant and alternate therapy should be considered
- ACEIs are contraindicated in patients with a history of angioedema on an ACEI; ARB should be use with caution in patients with a history of angioedema on an ACEI due to risk of cross-reactivity
- ARBs may be considered in patients unable to tolerate an ACEI due to cough

Metformin use warrants caution in patients with CKD (see [Recommendation 16](#)) due to the risk of lactic acidosis. Metformin is primarily renally eliminated, and according to the product information, the risk of metformin accumulation and lactic acidosis increases with the degree of kidney dysfunction. Although the risk is very low (reported as less than 10 cases/100,000 patient-years), the mortality rate associated with metformin-associated lactic acidosis is reported to be approximately 50%.^[225] Pooled data from an SR reported no cases of lactic acidosis during 70,490 patient-years of metformin use.^[226] Despite prior FDA guidance, nearly half of the trials allowed inclusion of patients with a SCr >1.5 mg/dL. One trial in the review, which included patients with renal insufficiency (mean plasma creatinine 1.5-2.5 mg/dL) and at least one contraindication to metformin, reported no cases of lactic acidosis.^[227] According to updated FDA guidance, metformin is contraindicated in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m²), while initiation is not recommended in patients with eGFR between 30-45 mL/minute/1.73 m², and risk/benefit of continuing metformin should be assessed if eGFR falls below 45 mL/minute/1.73 m²).^[83] Temporary discontinuation of metformin at the time of, or prior to, intravascular iodinated radiocontrast should be considered due to the risk of lactic acidosis.^[83] In addition to [Recommendations 16-19](#) of this CPG, Appendix B: Pharmacotherapy in the VA/DoD DM CPG^a may also be consulted for further guidance on diabetes management (e.g., pertaining to alpha-glucosidase inhibitors, metformin, DPP-4 inhibitors, GLP-1 agonists, insulin, meglitinides, SGLT2 inhibitors, sulfonylureas).

Certain patients with CKD and other comorbid diseases may be at a higher risk than others for drug toxicity.^[228] For example, patients with DM, advanced age and volume depletion (or states of effective volume depletion) may be at increased risk for nephrotoxicity. Concomitant use of multiple nephrotoxic drugs or medications with the potential for drug interactions are also of concern. Repeated and frequent use of higher doses of nephrotoxic drugs may increase risk of kidney damage; however, specific data are lacking.

Review of the medication list in patients with CKD and medication dose adjustment is essential to the optimal care of these patients. Clinical decisions regarding the use of a particular medication and dose

^a See the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/cd/diabetes/index.asp>

adjustments should consider not only the patient's renal function, but also the severity of and alternative therapies for the underlying condition for which the drug was prescribed. Agents with wide therapeutic indices or less potential for adverse effects are preferred. When prescribing medications to patients with CKD, start at a lower dose and then gradually titrate the medication upward. When available, monitoring of drug levels or other clinical parameters (blood sugar and heart rate) should also be conducted.

Currently, there are limited data that address measures to improve safety and reduce the risk of adverse drug events due to nephrotoxic or renally-cleared medications, including prescription drugs, over-the-counter medications, and nutritional or herbal supplements for patients with CKD. [\[229\]](#) The utility of a pharmacovigilance system to reduce adverse drug events in CKD should be the subject of future research.

Appendix L: Pain Management in CKD

Research on optimal pain management in patients with CKD is lacking, so guidelines established for the general population, like the World Health Organization three-step analgesic ladder, may be adapted for patients with CKD.[\[230\]](#) Specifically, caution with the use of certain medications in patients with CKD should be exercised.[\[231\]](#) Knowledge of potential risk of nephrotoxicity ([Appendix K](#)) as well as drug pharmacokinetics is paramount in determining the optimal pain management strategy in patients with CKD.

For mild pain, non-pharmacologic measures and non-opioid medications are recommended, with acetaminophen considered the first-line pharmacotherapy. Oral and parenteral NSAIDs are generally not recommended in patients with CKD. NSAIDs, including COX-2 inhibitors, have been associated with drug-induced kidney injury in patients with normal kidney function as well as in patients with CKD.[\[222,232,233\]](#) NSAIDs may cause kidney damage due to reversible reductions in renal blood flow as well as idiosyncratic reactions, such as interstitial nephritis, papillary necrosis and glomerulopathy.[\[228,234\]](#) Studies have also described recurrence of NSAID-induced nephrotic syndrome with topical analgesics. Systemic absorption of these agents has also been described with topical NSAIDs, and thus their use cannot be routinely recommended in patients with CKD. Despite the risk of nephrotoxicity, NSAID use is common in patients with CKD. In one survey of more than 12,000 adults in the U.S., current use (defined as nearly every day for ≥ 30 days) was reported in 2.5% and 5% of the patients with mild and moderate-to-severe CKD, respectively. Surprisingly, whether or not patients with CKD were aware that their disease was not associated with reduced use of NSAIDs, 66% of patients with moderate-to-severe CKD reported using NSAIDs for one year or longer, despite the fact that NSAID avoidance is recommended by most nephrologists.[\[235\]](#) Because some NSAIDs may be obtained without a prescription, it is important that providers obtain a thorough medication history, including an accurate assessment of NSAID use, provide education on the risk versus benefit of use, and recommend alternate therapies, as indicated. If NSAID use is required, strategies to mitigate risk of NSAID nephrotoxicity include correcting volume depletion before initiating therapy, maintaining euvolemia during therapy, minimizing NSAID dose and duration, consideration of topical rather than oral or parenteral NSAIDs, and routinely monitoring renal function (if chronic use is unavoidable).[\[228,234\]](#)

For moderate or severe pain, opioids may be indicated. However, as many opioids and/or their metabolites are renally excreted, the risk of overdose or toxicity is increased in patients with renal dysfunction. Accumulation of normeperidine (an active metabolite of meperidine) may cause central nervous system toxicity, including inducing psychosis and decreasing the seizure threshold, so meperidine is contraindicated in CKD.[\[230\]](#) Codeine and morphine are metabolized to toxic compounds, and severe respiratory depression and narcolepsy have been reported in patients with renal failure, so caution must be used in patients with renal dysfunction.[\[231\]](#) Similarly, impaired renal function results in decreased tramadol excretion, but tramadol is not metabolized to nephrotoxic metabolites so may be preferred. Opiates primarily metabolized in the liver such as oxycodone, fentanyl, and methadone, may be useful, but adjustment of the dose or dosing frequency is still recommended.[\[236\]](#) Finally, the risk of opioid dependence should be carefully assessed to mitigate the risk of opioid-related adverse events, including overdose. Providing naloxone rescue and/or referral to long-term discontinuation program should be

considered in those on chronic opioid therapy. Providers should refer to the VA/DoD Management of Opioid Therapy for Chronic Pain CPG for further information.^a

Adjunctive medications may be beneficial, particularly for neuropathic pain. Gabapentinoids, anticonvulsants and TCAs (e.g., amitriptyline, nortriptyline) work via different mechanisms and are efficacious for management of chronic pain syndromes. Anticonvulsants (e.g., carbamazepine, valproate) may be associated with hematologic abnormalities and hepatic toxicity, while TCAs are associated with anticholinergic side effects (e.g., dry mouth, urinary retention) and cardiotoxicity. Gabapentinoids are relatively well-tolerated, so may be preferred; however, both gabapentin and pregabalin are renally excreted, so dose adjustment is needed in patients with renal dysfunction.^[237] Use of adjunctive medications in conjunction with non-opioids and opioids may not only improve overall control of pain but may also reduce opioid requirement.

Use of non-pharmacologic measures may be efficacious for certain types of pain and avoids the potential for nephrotoxicity or other adverse effects related to impaired drug clearance in patients with renal dysfunction. Non-pharmacologic therapies include transcutaneous electrical stimulation, topical thermal therapy, ultrasound stimulation, acupuncture, chiropractic manipulation, massage or rehabilitation programs, biofeedback, and psychotherapy.^[237]

As with all patients, assessment of etiology of pain, utility of non-pharmacologic measures and managing patient expectations are key. Determining cause of pain may help to establish the most effective type of therapy, urgency for pain control and expected duration of therapy. Additionally, goals of pain management should be discussed and established with the patient. The lowest effective dose of opioids should be used in combination with non-opioids and non-pharmacologic therapies to achieve therapeutic goals. Importantly, the efficacy of pain control and presence of side effects should be routinely assessed and adjustments made to any pain regimen as needed.

^a See the VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Available at: <https://www.healthquality.va.gov/guidelines/Pain/cot/>

Appendix M: Military occupational exposures and CKD

Military personnel have unique environmental and occupational exposures, some of which have been associated with kidney disease. Contact with tactical herbicides (e.g., Agent Orange) was identified as an occupational exposure concern in the Vietnam War era. Authoritative reviews have endorsed the association of dioxin-containing herbicides with the development of malignancy, including Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukemia, and other B-cell lymphomas. In addition, exposure has been linked to non-cancer effects such as DM and hypertension.[238] Kidney disease may be a secondary outcome of exposures because of malignancy or DM.

More recently, garrison exposures (i.e., exposure of personnel to environmental toxins occurring on U.S. military installations during normal training) has been raised as a military occupational health concern. The finding of garrison ground water contaminated by potentially hazardous chemicals (e.g., perchloroethylene [PCE], trichloroethylene [TCE], vinyl chloride [VC], and benzene) resulted in legislation in 2012 extending cost-free healthcare (or reimbursements for out of pocket expenses) to qualified Veterans and their dependents affected by 15 specific health conditions, including kidney toxicity and kidney cancer.[239] A Final Rule in 2017 went further to established presumptive service-connection for Veterans with any of eight conditions, including kidney and/or bladder cancer.[239]

Military occupational exposure to airborne hazards is another area of active investigation.[240] Airborne hazards include particulate matter (PM) and gaseous air pollutants arising from a variety of sources (e.g., burn pits, fuel combustion, explosions, dust/sand, aircraft engine exhaust, aqueous fire-fighting foams). Nearly 50 compounds have been deemed “chemicals of interest” with the potential for long-term health effects. Twelve identified pollutants target the kidney, resulting in kidney cancer, renal tubular degeneration, and nephropathy in animal studies.[238] While previous studies offer limited evidence for military airborne hazard exposure and the development of kidney disease, the health effects of repeated exposure, and exposure to combinations of airborne toxins, remain undefined.[238] More recent non-military population-based evidence reinforces the association of exposure to air pollutants with CKD.[241] Therefore, a history of airborne exposures should be sought.

We suggest that providers take a detailed military occupational history from each patient newly diagnosed with CKD, perform an environmental exposure assessment, and document the history and findings. The VA War Related Illness and Injury Study Center (WRIISC) is a good resource for additional details of the evidence for health risks following garrison exposures, airborne hazards, herbicides, and biological and radiation exposures (www.warrelatedillness.va.gov) as well as information on evaluating Veterans with environmental exposure concerns (<https://www.warrelatedillness.va.gov/education/factsheets/evaluating-veterans-with-environmental-exposure-concerns.pdf>). For a patient with environmental hazard exposure and unexplained CKD despite local evaluation, an inter-facility consultation with the WRIISC may be warranted.

Appendix N: Nephrolithiasis

Nephrolithiasis is a common occurrence affecting up to 10.6% of people in the United States.^[242] Any history of a kidney stone results in a diagnosis of CKD because recurrent obstruction can lead to progressive kidney disease. Passing a kidney stone can be quite painful, and urgent treatment by a radiologist or urologist may be advised, particularly for patients with urosepsis, AKI, evidence of obstruction, or intractable pain. Urologists treat active stones with a variety of procedures such as cystoscopy with stone extraction, lithotripsy, laparoscopic stone retrieval, and stent placement. However, most patients with acute renal colic may be managed medically with analgesics, hydration and alpha-blockers until the stone passes. The likelihood that a stone will spontaneously pass or not is dependent on stone size and location.

Nephrologists do little for active stones, but can provide therapy to prevent future stones from forming. Medical therapy for stone prevention should be directed at the type of stones the patient forms and any metabolic etiology identified. If possible, stones should be sent for analysis. In recurrent stone formers there may be a benefit in obtaining a 24-hour urine stone risk profile with referral to a kidney stone specialist to determine treatment. All patients with history of nephrolithiasis should be educated on non-pharmacologic measures to prevent future stone formation. Drinking enough water to form at least two liters of urine per day is recommended. Though the two most common stones are calcium oxalate and calcium phosphate, restriction of dietary calcium is not recommended. Instead, a low-sodium diet, in addition to a high water intake, will reduce urinary calcium excretion and may be useful in preventing a recurrence for the majority of kidney stone formers. Further treatment depends on the results of stone analysis or 24-hour urine stone risk profile and may include use of a thiazide diuretic for hypercalciuria, potassium citrate for hypocitraturia, allopurinol or potassium citrate for hyperuricosuria, potassium citrate for uric acid stones, and tiopronin or captopril with urinary alkalization for cystine stones.

Appendix O: Gadolinium

Gadolinium is an element that is used to enhance MRI. Because it is a heavy metal, gadolinium requires a binding agent to make it both soluble as well as non-toxic. Gadolinium with a binding agent is called a gadolinium binding contrast agent (GBCA). Before 2006, GBCAs were thought to be safe. Excessive doses of GBCAs were used for MRI studies and GBCAs were also used in place of iodinated contrast agents for radiocontrast enhancement in order to prevent radiocontrast-induced nephropathy in patients with CKD.

In 2006, Grobner reported the association of GBCAs with nephrogenic systemic fibrosis (NSF), an irreversible systemic fibrotic disease, in dialysis patients.^[243] NSF is a systemic fibrotic disease seen only in patients with kidney dysfunction who received GBCAs. There is a paucity of recent studies to understand NSF or the mechanism of injury because there are no new cases and animal models are limited. All older data exist in the form of retrospective observational studies.

Risk factors for NSF include severe renal dysfunction, dialysis dependence, AKI, liver transplant, hepatorenal syndrome, and the type and dose of GBCA. The risk of NSF increases with cumulative doses of GBCAs. There are several different GBCAs. The GBCAs with the highest risk for NSF are linear non-ionic binders. Cyclic and ionic GBCAs have a lower risk of causing NSF. There are few or no non-confounded cases of NSF with some of the lower risk GBCAs, but this may have been related to market share so there is still a concern for NSF with these GBCAs.^[244]

Once the link between GBCA, kidney disease, and NSF was made, measures to mitigate NSF were instituted. GBCA doses were reduced, GBCAs were no longer used as a radiocontrast agent in patients with CKD, high-risk GBCAs were replaced with lower-risk GBCAs, and patients on dialysis or with severe kidney dysfunction were restricted from receiving GBCAs. With these changes, no further cases of NSF have been reported.

Physicians should consider using alternative imaging for patients with CKD stage 4-5, transplant recipients, dialysis patients, and patients with AKI. It is not clear if iodinated contrast poses a higher risk for patients with CKD stage 4 or 5 than a GBCA. If a GBCA is determined to be necessary, the lowest dose should be used, and repeated doses should be avoided. High risk GBCAs (linear non-ionic) should not be used. Further research should be done to see if there are specific types of GBCA agents that could be used safely in patients with reduced kidney function.

Appendix P: Abbreviation List

Abbreviation	Definition
AASK	African American Study of Kidney Disease
ACEI	angiotensin-converting enzyme inhibitor
ACT	Acetylcysteine for Contrast-induced Nephropathy Trial
ADPKD	autosomal dominant polycystic kidney disease
ADPKD-OM	Autosomal dominant polycystic kidney disease outcomes model
AHRQ	Agency for Healthcare Research and Quality
AKD	acute kidney disorder
AKI	acute kidney injury
APOL1	apolipoprotein L1
ARB	angiotensin receptor blocker
AVF	arteriovenous fistulas
AWARD-7	Dulaglutide Versus Insulin Glargine in Patients with Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease
BP	blood pressure
BMI	body mass index
CA-AKI	contrast-associated acute kidney injury
CCB	calcium channel blocker
CDC	Centers for Disease Control and Prevention
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CEAPIR	European Kidney Patients' Federation
CI	confidence interval
CKD	chronic kidney disease
CORETH	Choice of Renal Replacement Therapy
COI	conflict of interest
COR	contracting officer's representative
COX-2	cyclooxygenase-2
CPGs	clinical practice guidelines
CPR	cardiopulmonary resuscitation
CrCl	calculated creatinine clearance
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta
CRISP	Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease
CV	cardiovascular
CVD	cardiovascular disease
DM	diabetes mellitus
DoD	Department of Defense
DPP-4	dipeptidyl peptidase-4
EASE	Encourage Autonomous Self-Enrichment
EBPWG	Evidence-Based Practice Work Group
eGFR	estimated glomerular filtration rate

Abbreviation	Definition
ERBP	European Renal Best Practice
ESRD	end-stage renal disease
FDA	U.S. Food and Drug Administration
FAERS	U.S. Food and Drug Administration Adverse Event Reporting System
GBCA	gadolinium binding contrast agents
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HbA1c	glycated hemoglobin
HIF-PHD	hypoxia-inducible factor prolyl-hydroxylase domain
HLA	human leukocyte antigen
IDNT	Irbesartan Diabetic Nephropathy Trial
IDT	interdisciplinary team
ITT	intention-to-treat
IV	intravenous
IOM	Institute of Medicine
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KFRE	Kidney Failure Risk Equation
KQs	key questions
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
LVEDP	left ventricular end-diastolic pressure
MACE	major adverse cardiovascular event
MAP	mean arterial pressure
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MRI	magnetic resonance imaging
MV	mechanical ventilation
NAM	National Academy of Medicine
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NKF	National Kidney Foundation
NSAID	non-steroidal anti-inflammatory drug
NSF	nephrogenic systemic fibrosis
PCI	percutaneous coronary angiography
PICC	peripherally inserted central catheter
PICOTS	the population, intervention, comparison, outcome, timing and setting
PIONEER-6	Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
PIV	peripheral intravenous

Abbreviation	Definition
PCC	patient-centered care
PCE	perchloroethylene
PCP	primary care physician
PDE5	phosphodiesterase type 5
PTH	parathyroid hormone
QoL	quality of life
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cell
RCTs	randomized controlled trials
RD	registered dietitian
REIN-2	Ramipril Efficacy In Nephropathy
REMS	Risk Evaluation and Mitigation Strategy
RENAAL	angiotensin II antagonist losartan
REPRISE	Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD
RR	risk ratio
RRT	renal replacement therapy
SCAN-ECHO	Specialty Care Access Network-Extension for Community Healthcare Outcomes
SCAR	severe cutaneous adverse reactions
SCr	serum creatinine
SDM	shared decision making
SF-36	36-Item Short Form Survey
SGLT2	Sodium-glucose Cotransporter-2
SNRI	serotonin and norepinephrine reuptake inhibitor
SPRINT	Systolic Blood Pressure Intervention Trial
SR	systematic review
SSRI	selective serotonin reuptake inhibitors
STEMI	ST-segment elevation myocardial infarction
SUSTAIN-6	Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
TCA	tricyclic antidepressant
TCE	trichloroethylene
TEMPO	Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes
TKV	total kidney volume
TPV	total parenteral nutrition
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TZD	thiazolidinediones
uACR	urine albumin-to-creatinine ratio
uPCR	urine protein-to-creatinine ratio
U.S.	United States
USPSTF	U.S. Preventive Services Task Force

Abbreviation	Definition
USRDS	United States Renal Data System
VA	Department of Veterans Affairs
VAHCS	VA Health Care System
VC	vinyl chloride
VEGF	vascular endothelial growth factor
WVIISC	Department of Veterans Affairs War Related Illness and Injury Study Center

References

1. U.S. Department of Veterans Affairs/Department of Defense Health Executive Committee (HEC). *Evidence based practice work group charter*. <https://www.healthquality.va.gov/documents/EvidenceBasedPracticeWGCharter123020161.pdf>. Updated January 9, 2017.
2. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis*. May 2006;47(5 Suppl 3):S11-145. PMID: 16678659.
3. Kidney Disease Improving Global Outcomes. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl* (2011). Jan 2013;3(1):19-62. PMID: 25018975.
4. 2018 United States renal data system annual data report. Ann Arbor, MI: USRDS Coordinating Center;2018. <https://www.usrds.org/adr.aspx>.
5. Whaley-Connell A, Shlipak MG, Inker LA, et al. Awareness of kidney disease and relationship to end-stage renal disease and mortality. *Am J Med*. Jul 2012;125(7):661-669. PMID: 22626510.
6. *Chronic kidney disease initiative*. 2018; <http://www.cdc.gov/ckd>. Updated December 27, 2018, 2018.
7. Saran R, Tilea A, Shahinian V, et al. Identification of chronic kidney disease in the Veterans Affairs healthcare system. *J Am Soc Nephrol*. 2016;27(527A).
8. Smith TJ, Marriott BP, Dotson L, et al. Overweight and obesity in military personnel: Sociodemographic predictors. *Obesity (Silver Spring)*. Jul 2012;20(7):1534-1538. PMID: 22314620.
9. U.S. Department of Veteran Affairs. *No 'legacy effect' - long-term follow-up of large va diabetes study finds no significant drop in heart attacks or strokes despite tight glucose control*. 2018; <https://www.research.va.gov/currents/1018-Long-term-follow-up-of-large-VA-diabetes-study.cfm>. Updated October 24, 2018. Accessed June 24, 2019.
10. Smoley BA, Smith NL, Runkle GP. Hypertension in a population of active duty service members. *J Am Board Fam Med*. Nov-Dec 2008;21(6):504-511. PMID: 18988717.
11. U.S. Department of Veteran Affairs, Department of Defense. Guideline for guidelines. Veterans Health Administration, Office of Quality & Performance, Evidence Review Subgroup; Revised January 29, 2019.
12. Newberry SJ, Ahmadzai N, Motala A, et al. AHRQ methods for effective health care. *Surveillance and identification of signals for updating systematic reviews: Implementation and early experience*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
13. Guirguis-Blake J, Calonge N, Miller T, Siu A, Teutsch S, Whitlock E. Current processes of the U.S. Preventive Services Task Force: Refining evidence-based recommendation development. *Ann Intern Med*. Jul 17 2007;147(2):117-122. PMID: 17576998.
14. National Institute for Health and Care Excellence. *The guidelines manual*. 2012; <http://www.nice.org.uk/article/pmg6/resources/non-guidance-the-guidelines-manual-pdf>. Accessed September 16, 2019.
15. Martinez Garcia L, McFarlane E, Barnes S, Sanabria AJ, Alonso-Coello P, Alderson P. Updated recommendations: An assessment of NICE clinical guidelines. *Implement Sci*. 2014;9:72. PMID: 24919856.
16. White CM, Ip S, McPheeters M, et al. AHRQ methods for effective health care using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews. *Methods guide for effectiveness and comparative effectiveness reviews*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
17. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, R Graham, M Mancher, D Miller Wolman, et al., editors. *Clinical practice guidelines we can trust*. Washington, DC: National Academies Press;2011.
18. Schunemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 10. Integrating values and consumer involvement. *Health Res Policy Syst*. 2006;4:22. PMID: 17147811.
19. Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: Definitions and applications to improve outcomes. *J Am Acad Nurse Pract*. Dec 2008;20(12):600-607. PMID: 19120591.
20. Stewart M, Brown JB, Donner A, et al. The impact of patient-centered care on outcomes. *J Fam Pract*. Sep 2000;49(9):796-804. PMID: 11032203.

21. Fiscella K, Meldrum S, Franks P, et al. Patient trust: Is it related to patient-centered behavior of primary care physicians? *Med Care*. Nov 2004;42(11):1049-1055. PMID: 15586831.
22. Institute of Medicine. *Crossing the quality chasm: A new health system for the 21st century*. Washington DC: National Academies Press; 2001.
23. Renal Physicians Association. Shared decision-making in the appropriate initiation of and withdrawal from dialysis. October 2010:12.
24. Bowling CB, Plantinga L, Phillips LS, et al. Association of multimorbidity with mortality and healthcare utilization in chronic kidney disease. *J Am Geriatr Soc*. Apr 2017;65(4):704-711. PMID: 27880003.
25. Bowling CB, Booth JN, 3rd, Gutierrez OM, et al. Nondisease-specific problems and all-cause mortality among older adults with CKD: The REGARDS study. *Clin J Am Soc Nephrol*. Oct 7 2014;9(10):1737-1745. PMID: 25278551.
26. Hall RK, Haines C, Gorbak SM, et al. Incorporating geriatric assessment into a nephrology clinic: Preliminary data from two models of care. *J Am Geriatr Soc*. Oct 2016;64(10):2154-2158. PMID: 27377350.
27. Bowling CB, Vandenberg AE, Phillips LS, McClellan WM, Johnson TM, 2nd, Echt KV. Older patients' perspectives on managing complexity in CKD self-management. *Clin J Am Soc Nephrol*. Apr 3 2017;12(4):635-643. PMID: 28389529.
28. Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. Proposal for clinical algorithm standards. *Med Decis Making*. Apr-Jun 1992;12(2):149-154. PMID: 1573982.
29. Vart P, Reijneveld SA, Bultmann U, Gansevoort RT. Added value of screening for CKD among the elderly or persons with low socioeconomic status. *Clin J Am Soc Nephrol*. Apr 7 2015;10(4):562-570. PMID: 25779994.
30. O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality risk stratification in chronic kidney disease: One size for all ages? *J Am Soc Nephrol*. Mar 2006;17(3):846-853. PMID: 16452492.
31. ASN emphasizes need for early detection of kidney disease, a silent killer [press release]. 2013.
32. Qaseem A, Hopkins RH, Jr., Sweet DE, Starkey M, Shekelle P. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: A clinical practice guideline from the American college of physicians. *Ann Intern Med*. Dec 17 2013;159(12):835-847. PMID: 24145991.
33. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet*. Jun 12 2010;375(9731):2073-2081. PMID: 20483451.
34. Ix JH, de Boer IH, Wassel CL, Criqui MH, Shlipak MG, Whooley MA. Urinary creatinine excretion rate and mortality in persons with coronary artery disease: The heart and soul study. *Circulation*. Mar 23 2010;121(11):1295-1303. PMID: 20212276.
35. Murtaugh MA, Jacobs DR, Jr., Yu X, Gross MD, Steffes M. Correlates of urinary albumin excretion in young adult blacks and whites: The coronary artery risk development in young adults study. *Am J Epidemiol*. Oct 1 2003;158(7):676-686. PMID: 14507604.
36. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. Sep 5 2013;369(10):932-943. PMID: 24004120.
37. Colantonio LD, Tanner RM, Warnock DG, et al. The role of cystatin-c in the confirmation of reduced glomerular filtration rate among the oldest old. *Arch Med Sci*. Feb 1 2016;12(1):55-67. PMID: 26925119.
38. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. Jul 5 2012;367(1):20-29. PMID: 22762315.
39. Echouffo-Tcheugui JB, Kengne AP. Risk models to predict chronic kidney disease and its progression: A systematic review. *PLoS Med*. 2012;9(11):e1001344. PMID: 23185136.
40. Tangri N, Kitsios GD, Inker LA, et al. Risk prediction models for patients with chronic kidney disease: A systematic review. *Ann Intern Med*. Apr 16 2013;158(8):596-603. PMID: 23588748.
41. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: A meta-analysis. *JAMA*. Jan 12 2016;315(2):164-174. PMID: 26757465.
42. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. Apr 20 2011;305(15):1553-1559. PMID: 21482743.
43. Farrington K, Covic A, Aucella F, et al. Clinical practice guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR <45 ml/min/1.73 m²). *Nephrol Dial Transplant*. Nov 2016;31(suppl 2):ii1-ii66. PMID: 27807144.

44. Grams ME, Li L, Greene TH, et al. Estimating time to ESRD using kidney failure risk equations: Results from the african American study of kidney disease and hypertension (AASK). *Am J Kidney Dis.* Mar 2015;65(3):394-402. PMID: 25441435.
45. Yamanouchi M, Hoshino J, Ubara Y, et al. Value of adding the renal pathological score to the kidney failure risk equation in advanced diabetic nephropathy. *PLoS One.* 2018;13(1):e0190930. PMID: 29338014.
46. Drawz PE, Goswami P, Azem R, Babineau DC, Rahman M. A simple tool to predict end-stage renal disease within 1 year in elderly adults with advanced chronic kidney disease. *J Am Geriatr Soc.* May 2013;61(5):762-768. PMID: 23617782.
47. Chen PM, Wada T, Chiang CK. Prognostic value of proteinuria and glomerular filtration rate on taiwanese patients with diabetes mellitus and advanced chronic kidney disease: A single center experience. *Clin Exp Nephrol.* Apr 2017;21(2):307-315. PMID: 27339442.
48. Chen SC, Lin MY, Huang TH, et al. Variability in estimated glomerular filtration rate by area under the curve predicts renal outcomes in chronic kidney disease. *ScientificWorldJournal.* 2014;2014:802037. PMID: 25401155.
49. Schroeder EB, Yang X, Thorp ML, et al. Predicting 5-year risk of RRT in stage 3 or 4 CKD: Development and external validation. *Clin J Am Soc Nephrol.* Jan 6 2017;12(1):87-94. PMID: 28028051.
50. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. *Cochrane Database Syst Rev.* Jun 18 2014(6):CD007333. PMID: 24938824.
51. Tseng CL, Kern EF, Miller DR, et al. Survival benefit of nephrologic care in patients with diabetes mellitus and chronic kidney disease. *Arch Intern Med.* Jan 14 2008;168(1):55-62. PMID: 18195196.
52. Minutolo R, De Nicola L, Zamboli P, et al. Management of hypertension in patients with CKD: Differences between primary and tertiary care settings. *Am J Kidney Dis.* Jul 2005;46(1):18-25. PMID: 15983953.
53. Lonnemann G, Duttlinger J, Hohmann D, Hickstein L, Reichel H. Timely referral to outpatient nephrology care slows progression and reduces treatment costs of chronic kidney diseases. *Kidney Int Rep.* Mar 2017;2(2):142-151. PMID: 29318212.
54. Orlando LA, Owen WF, Matchar DB. Relationship between nephrologist care and progression of chronic kidney disease. *N C Med J.* Jan-Feb 2007;68(1):9-16. PMID: 17500426.
55. Chen SC, Chang JM, Chou MC, et al. Slowing renal function decline in chronic kidney disease patients after nephrology referral. *Nephrology (Carlton).* Dec 2008;13(8):730-736. PMID: 19019170.
56. Fogelfeld L, Hart P, Miernik J, et al. Combined diabetes-renal multifactorial intervention in patients with advanced diabetic nephropathy: Proof-of-concept. *J Diabetes Complications.* Mar 2017;31(3):624-630. PMID: 28041817.
57. Shi Y, Xiong J, Chen Y, et al. The effectiveness of multidisciplinary care models for patients with chronic kidney disease: A systematic review and meta-analysis. *Int Urol Nephrol.* Feb 2018;50(2):301-312. PMID: 28856498.
58. Valentijn PP, Pereira FA, Ruospo M, et al. Person-centered integrated care for chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials. *Clin J Am Soc Nephrol.* Mar 7 2018;13(3):375-386. PMID: 29438975.
59. Low S, Lim SC, Wang J, et al. Long-term outcomes of patients with type 2 diabetes attending a multidisciplinary diabetes kidney disease clinic. *J Diabetes.* Jul 2018;10(7):572-580. PMID: 29154443.
60. Zimbudzi E, Lo C, Misso ML, et al. Effectiveness of self-management support interventions for people with comorbid diabetes and chronic kidney disease: A systematic review and meta-analysis. *Syst Rev.* Jun 13 2018;7(1):84. PMID: 29898785.
61. Joboshi H, Oka M. Effectiveness of an educational intervention (the Encourage Autonomous Self-Enrichment Program) in patients with chronic kidney disease: A randomized controlled trial. *Int J Nurs Stud.* Feb 2017;67:51-58. PMID: 27918931.
62. Barahimi H, Zolfaghari M, Abolhassani F, Rahimi Foroushani A, Mohammadi A, Rajaei F. E-learning model in chronic kidney disease management: A controlled clinical trial. *Iran J Kidney Dis.* Jul 2017;11(4):280-285. PMID: 28794290.
63. Yamagata K, Makino H, Iseki K, et al. Effect of behavior modification on outcome in early- to moderate-stage chronic kidney disease: A cluster-randomized trial. *PLoS One.* 2016;11(3):e0151422. PMID: 26999730.

64. Pisoni RL, Arrington CJ, Albert JM, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: An instrumental variable analysis. *Am J Kidney Dis.* Mar 2009;53(3):475-491. PMID: 19150158.
65. El Ters M, Schears GJ, Taler SJ, et al. Association between prior peripherally inserted central catheters and lack of functioning arteriovenous fistulas: A case-control study in hemodialysis patients. *Am J Kidney Dis.* Oct 2012;60(4):601-608. PMID: 22704142.
66. McGill RL, Ruthazer R, Meyer KB, Miskulin DC, Weiner DE. Peripherally inserted central catheters and hemodialysis outcomes. *Clin J Am Soc Nephrol.* Aug 8 2016;11(8):1434-1440. PMID: 27340280.
67. Robinski M, Mau W, Wienke A, Girndt M. Shared decision-making in chronic kidney disease: A retrospection of recently initiated dialysis patients in Germany. *Patient Educ Couns.* Apr 2016;99(4):562-570. PMID: 26527307.
68. Van Biesen W, van der Veer SN, Murphey M, Loblova O, Davies S. Patients' perceptions of information and education for renal replacement therapy: An independent survey by the European Kidney Patients' Federation on information and support on renal replacement therapy. *PLoS One.* 2014;9(7):e103914. PMID: 25079071.
69. Foote C, Kotwal S, Gallagher M, Cass A, Brown M, Jardine M. Survival outcomes of supportive care versus dialysis therapies for elderly patients with end-stage kidney disease: A systematic review and meta-analysis. *Nephrology (Carlton).* Mar 2016;21(3):241-253. PMID: 26265214.
70. Wong SPY, Yu MK, Green PK, Liu CF, Hebert PL, O'Hare AM. End-of-life care for patients with advanced kidney disease in the US Veterans Affairs health care system, 2000-2011. *Am J Kidney Dis.* Jul 2018;72(1):42-49. PMID: 29331475.
71. Tam-Tham H, Quinn RR, Weaver RG, et al. Survival among older adults with kidney failure is better in the first three years with chronic dialysis treatment than not. *Kidney Int.* Sep 2018;94(3):582-588. PMID: 29803405.
72. Brown MA, Collett GK, Josland EA, Foote C, Li Q, Brennan FP. CKD in elderly patients managed without dialysis: Survival, symptoms, and quality of life. *Clin J Am Soc Nephrol.* Feb 6 2015;10(2):260-268. PMID: 25614492.
73. Murtagh FE, Addington-Hall JM, Edmonds PM, et al. Symptoms in advanced renal disease: A cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *J Palliat Med.* Dec 2007;10(6):1266-1276. PMID: 18095805.
74. Tamura A, Goto Y, Miyamoto K, et al. Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-induced nephropathy in patients with mild renal insufficiency undergoing an elective coronary procedure. *Am J Cardiol.* Oct 1 2009;104(7):921-925. PMID: 19766757.
75. Grubbs V, Moss AH, Cohen LM, et al. A palliative approach to dialysis care: A patient-centered transition to the end of life. *Clin J Am Soc Nephrol.* Dec 5 2014;9(12):2203-2209. PMID: 25104274.
76. de Brito-Ashurst I, Perry L, Sanders TA, et al. The role of salt intake and salt sensitivity in the management of hypertension in South Asian people with chronic kidney disease: A randomised controlled trial. *Heart.* Sep 2013;99(17):1256-1260. PMID: 23766446.
77. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol.* Dec 2013;24(12):2096-2103. PMID: 24204003.
78. Slagman MC, Waanders F, Hemmelder MH, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: Randomised controlled trial. *BMJ.* Jul 26 2011;343:d4366. PMID: 21791491.
79. Nezu U, Kamiyama H, Kondo Y, Sakuma M, Morimoto T, Ueda S. Effect of low-protein diet on kidney function in diabetic nephropathy: Meta-analysis of randomised controlled trials. *BMJ Open.* May 28 2013;3(5). PMID: 23793703.
80. Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev.* Jul 8 2009(3):CD001892. PMID: 19588328.
81. U.S. Food and Drug Administration. *FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function.* 2017; <https://www.fda.gov/Drugs/DrugSafety/ucm493244.htm>. Accessed September 15, 2019.
82. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: A systematic review. *Ann Intern Med.* Feb 7 2017;166(3):191-200. PMID: 28055049.

83. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. 2016. <https://www.fda.gov/Drugs/DrugSafety/ucm493244.htm>. Accessed 12/10/2018.
84. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. Jan 5 2019;393(10166):31-39. PMID: 30424892.
85. Lo C, Toyama T, Wang Y, et al. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst Rev*. Sep 24 2018;9:CD011798. PMID: 30246878.
86. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. Jun 13 2019;380(24):2295-2306. PMID: 30990260.
87. Mann JFE, Fonseca V, Mosenzon O, et al. Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes and chronic kidney disease: Results from the LEADER trial. *Circulation*. 2018;0(0).
88. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): A multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. Aug 2018;6(8):605-617. PMID: 29910024.
89. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. Nov 10 2016;375(19):1834-1844. PMID: 27633186.
90. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. Aug 29 2019;381(9):841-851. PMID: 31185157.
91. McGill JB, Yki-Jarvinen H, Crowe S, Woerle HJ, von Eynatten M. Combination of the dipeptidyl peptidase-4 inhibitor linagliptin with insulin-based regimens in type 2 diabetes and chronic kidney disease. *Diab Vasc Dis Res*. Jul 2015;12(4):249-257. PMID: 25941160.
92. Perl S, Cook W, Wei C, Iqbal N, Hirshberg B. Saxagliptin efficacy and safety in patients with type 2 diabetes and moderate renal impairment. *Diabetes Ther*. Sep 2016;7(3):527-535. PMID: 27402391.
93. Chen YH, Chiang MH, Liu JS, et al. Thiazolidinediones and risk of long-term dialysis in diabetic patients with advanced chronic kidney disease: A nationwide cohort study. *PLoS One*. 2015;10(6):e0129922. PMID: 26083376.
94. Malhotra R, Nguyen HA, Benavente O, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: A systematic review and meta-analysis. *JAMA Intern Med*. Oct 1 2017;177(10):1498-1505. PMID: 28873137.
95. Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol*. Sep 2017;28(9):2812-2823. PMID: 28642330.
96. Ku E, Glidden DV, Johansen KL, et al. Association between strict blood pressure control during chronic kidney disease and lower mortality after onset of end-stage renal disease. *Kidney Int*. May 2015;87(5):1055-1060. PMID: 25493952.
97. Tsai WC, Wu HY, Peng YS, et al. Association of intensive blood pressure control and kidney disease progression in nondiabetic patients with chronic kidney disease: A systematic review and meta-analysis. *JAMA Intern Med*. Jun 1 2017;177(6):792-799. PMID: 28288249.
98. Ku E, Gassman J, Appel LJ, et al. BP control and long-term risk of ESRD and mortality. *J Am Soc Nephrol*. Feb 2017;28(2):671-677. PMID: 27516235.
99. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: Blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med*. Apr 19 2011;154(8):541-548. PMID: 21403055.
100. Rocco MV, Sink KM, Lovato LC, et al. Effects of intensive blood pressure treatment on acute kidney injury events in the systolic blood pressure intervention trial (SPRINT). *Am J Kidney Dis*. Mar 2018;71(3):352-361. PMID: 29162340.
101. The GISEN Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (gruppo italiano di studi epidemiologici in nefrologia). *Lancet*. Jun 28 1997;349(9069):1857-1863. PMID: 9217756.
102. Del Vecchio L, Pozzi M, Salvetti A, et al. Efficacy and tolerability of manidipine in the treatment of hypertension in patients with non-diabetic chronic kidney disease without glomerular disease. Prospective,

- randomized, double-blind study of parallel groups in comparison with enalapril. *J Nephrol.* Mar-Apr 2004;17(2):261-269. PMID: 15293527.
103. Iino Y, Hayashi M, Kawamura T, et al. Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension--a report of the Japanese losartan therapy intended for the global renal protection in hypertensive patients (JLIGHT) study. *Hypertens Res.* Jan 2004;27(1):21-30. PMID: 15055252.
 104. Ishimitsu T, Kobayashi T, Honda T, et al. Protective effects of an angiotensin II receptor blocker and a long-acting calcium channel blocker against cardiovascular organ injuries in hypertensive patients. *Hypertens Res.* Apr 2005;28(4):351-359. PMID: 16138566.
 105. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med.* Jul 17 2001;135(2):73-87. PMID: 11453706.
 106. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med.* Aug 19 2003;139(4):244-252. PMID: 12965979.
 107. Luno J, Barrio V, Goicoechea MA, et al. Effects of dual blockade of the renin-angiotensin system in primary proteinuric nephropathies. *Kidney Int Suppl.* Dec 2002(82):S47-52. PMID: 12410855.
 108. Matsuda H, Hayashi K, Saruta T. Distinct time courses of renal protective action of angiotensin receptor antagonists and ACE inhibitors in chronic renal disease. *J Hum Hypertens.* Apr 2003;17(4):271-276. PMID: 12692572.
 109. Nielsen S, Dollerup J, Nielsen B, Jensen HA, Mogensen CE. Losartan reduces albuminuria in patients with essential hypertension. An enalapril controlled 3 months study. *Nephrol Dial Transplant.* 1997;12 Suppl 2:19-23. PMID: 9269694.
 110. Plum J, Bunten B, Nemeth R, Grabensee B. Effects of the angiotensin II antagonist valsartan on blood pressure, proteinuria, and renal hemodynamics in patients with chronic renal failure and hypertension. *J Am Soc Nephrol.* Dec 1998;9(12):2223-2234. PMID: 9848776.
 111. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo italiano di studi epidemiologici in nefrologia (gisen). Ramipril efficacy in nephropathy. *Lancet.* Oct 17 1998;352(9136):1252-1256. PMID: 9788454.
 112. Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA.* Nov 20 2002;288(19):2421-2431. PMID: 12435255.
 113. Remuzzi A, Perico N, Sangalli F, et al. ACE inhibition and ANG II receptor blockade improve glomerular size-selectivity in iga nephropathy. *Am J Physiol.* Mar 1999;276(3):F457-466. PMID: 10070170.
 114. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med.* Mar 6 2001;134(5):370-379. PMID: 11242497.
 115. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* Sep 20 2001;345(12):861-869. PMID: 11565518.
 116. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American microalbuminuria study group. *Am J Med.* Nov 1995;99(5):497-504. PMID: 7485207.
 117. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *New England Journal of Medicine.* 1993;329(20):1456-1462.
 118. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* Sep 20 2001;345(12):851-860. PMID: 11565517.
 119. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* Sep 20 2001;345(12):870-878. PMID: 11565519.

120. Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *JAMA*. Jan 26 1994;271(4):275-279. PMID: 8295285.
121. Fernandez Juarez G, Luno J, Barrio V, et al. Effect of dual blockade of the renin-angiotensin system on the progression of type 2 diabetic nephropathy: A randomized trial. *Am J Kidney Dis*. Feb 2013;61(2):211-218. PMID: 22939518.
122. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. Nov 14 2013;369(20):1892-1903. PMID: 24206457.
123. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. Dec 6 2012;367(23):2204-2213. PMID: 23121378.
124. Susantitaphong P, Sewaralthahab K, Balk EM, Eiam-ong S, Madias NE, Jaber BL. Efficacy and safety of combined versus single renin-angiotensin-aldosterone system blockade in chronic kidney disease: A meta-analysis. *Am J Hypertens*. Mar 2013;26(3):424-441. PMID: 23382494.
125. Fink HA, Ishani A, Taylor BC, et al. *Chronic kidney disease stages 1-3: Screening, monitoring, and treatment*. Rockville MD: Agency for Healthcare Research and Quality (US); 2012.
126. Nakamura T, Fujiwara N, Kawagoe Y, Sugaya T, Ueda Y, Koide H. Effects of telmisartan and enalapril on renoprotection in patients with mild to moderate chronic kidney disease. *Eur J Clin Invest*. Sep 2010;40(9):790-796. PMID: 20584070.
127. Esnault VL, Brown EA, Apetrei E, et al. The effects of amlodipine and enalapril on renal function in adults with hypertension and nondiabetic nephropathies: A 3-year, randomized, multicenter, double-blind, placebo-controlled study. *Clin Ther*. Mar 2008;30(3):482-498. PMID: 18405787.
128. Palmer BF. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: What to do if the serum creatinine and/or serum potassium concentration rises. *Nephrol Dial Transplant*. Oct 2003;18(10):1973-1975. PMID: 13679467.
129. Bakris GL, Siomos M, Richardson D, et al. ACE inhibition or angiotensin receptor blockade: Impact on potassium in renal failure. VAL-K study group. *Kidney Int*. Nov 2000;58(5):2084-2092. PMID: 11044229.
130. Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: A meta-analysis. *Ann Allergy Asthma Immunol*. Nov 2008;101(5):495-499. PMID: 19055203.
131. Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. *Ann Pharmacother*. Apr 2011;45(4):520-524. PMID: 21427294.
132. Jacobsen P, Andersen S, Jensen BR, Parving HH. Additive effect of ACE inhibition and angiotensin II receptor blockade in type I diabetic patients with diabetic nephropathy. *J Am Soc Nephrol*. Apr 2003;14(4):992-999. PMID: 12660333.
133. Jacobsen P, Andersen S, Rossing K, Hansen BV, Parving HH. Dual blockade of the renin-angiotensin system in type 1 patients with diabetic nephropathy. *Nephrol Dial Transplant*. Jun 2002;17(6):1019-1024. PMID: 12032191.
134. Jacobsen P, Andersen S, Rossing K, Jensen BR, Parving HH. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. *Kidney Int*. May 2003;63(5):1874-1880. PMID: 12675866.
135. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The candesartan and lisinopril microalbuminuria (CALM) study. *BMJ*. Dec 9 2000;321(7274):1440-1444. PMID: 11110735.
136. Rossing K, Christensen PK, Jensen BR, Parving HH. Dual blockade of the renin-angiotensin system in diabetic nephropathy: A randomized double-blind crossover study. *Diabetes Care*. Jan 2002;25(1):95-100. PMID: 11772908.
137. Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. Jul 8 2009(3):CD007004. PMID: 19588415.

138. Wang W, Li L, Zhou Z, Gao J, Sun Y. Effect of spironolactone combined with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers on chronic glomerular disease. *Exp Ther Med*. Dec 2013;6(6):1527-1531. PMID: 24255685.
139. Furumatsu Y, Nagasawa Y, Tomida K, et al. Effect of renin-angiotensin-aldosterone system triple blockade on non-diabetic renal disease: Addition of an aldosterone blocker, spironolactone, to combination treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. *Hypertens Res*. Jan 2008;31(1):59-67. PMID: 18360019.
140. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol*. Dec 2009;20(12):2641-2650. PMID: 19926893.
141. Bolognani D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. Apr 29 2014(4):CD007004. PMID: 24782282.
142. Edwards NC, Steeds RP, Chue CD, Stewart PM, Ferro CJ, Townend JN. The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. *Br J Clin Pharmacol*. Mar 2012;73(3):447-454. PMID: 21950312.
143. Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: A randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant*. Nov 2014;29(11):2075-2084. PMID: 24891437.
144. Locatelli F, Bárány P, Covic A, et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: A European renal best practice position statement. *Nephrology Dialysis Transplantation*. 2013;28(6).
145. Chertow GM, Block GA, Neylan JF, Pergola PE, Uhlig K, Fishbane S. Safety and efficacy of ferric citrate in patients with nondialysis-dependent chronic kidney disease. *PLoS One*. 2017;12(11):e0188712. PMID: 29186198.
146. Fishbane S, Block GA, Loram L, et al. Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol*. Jun 2017;28(6):1851-1858. PMID: 28082519.
147. Negri AL, Urena Torres PA. Iron-based phosphate binders: Do they offer advantages over currently available phosphate binders? *Clin Kidney J*. Apr 2015;8(2):161-167. PMID: 25815172.
148. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: Two open-label, randomised controlled trials. *Lancet Haematol*. Nov 2017;4(11):e524-e533. PMID: 29032957.
149. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood*. Oct 22 2015;126(17):1981-1989. PMID: 26289639.
150. Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev*. Jan 18 2012;1:CD007857. PMID: 22258974.
151. Shephelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: An updated systematic review and meta-analysis. *Am J Kidney Dis*. Nov 2016;68(5):677-690. PMID: 27321965.
152. Scornik JC, Bromberg JS, Norman DJ, Bhandari M, Gitlin M, Petersen J. An update on the impact of pre-transplant transfusions and allosensitization on time to renal transplant and on allograft survival. *BMC Nephrol*. Oct 10 2013;14:217. PMID: 24107093.
153. Akizawa T, Gejyo F, Nishi S, et al. Positive outcomes of high hemoglobin target in patients with chronic kidney disease not on dialysis: A randomized controlled study. *Ther Apher Dial*. Oct 2011;15(5):431-440. PMID: 21974695.
154. Patel M, Thimons DG, Winston JL, Langholff W, McGowan T. An open-label, randomized, multicenter, controlled study of epoetin alfa for the treatment of anemia of chronic kidney disease in the long term care setting. *J Am Med Dir Assoc*. Mar 2012;13(3):244-248. PMID: 21450214.
155. Villar E, Lievre M, Kessler M, et al. Anemia normalization in patients with type 2 diabetes and chronic kidney disease: Results of the NEPHRODIAB2 randomized trial. *J Diabetes Complications*. Jul-Aug 2011;25(4):237-243. PMID: 21601481.

156. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. Nov 19 2009;361(21):2019-2032. PMID: 19880844.
157. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. Nov 16 2006;355(20):2085-2098. PMID: 17108343.
158. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. Nov 16 2006;355(20):2071-2084. PMID: 17108342.
159. U.S. Food and Drug Administration. *Information on erythropoiesis-stimulating agents (ESA) epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp)*. 2017; <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109375.htm>. Updated March 31, 2017. Accessed September 26, 2019.
160. Block GA, Fishbane S, Rodriguez M, et al. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD stages 3-5. *American Journal of Kidney Diseases*. 2015;65(5):728-736.
161. Martin ER, Smith MT, Maroni BJ, Zuraw QC, deGoma EM. Clinical trial of vadadustat in patients with anemia secondary to stage 3 or 4 chronic kidney disease. *Am J Nephrol*. 2017;45(5):380-388. PMID: 28343225.
162. Umanath K, Jalal DI, Greco BA, et al. Ferric citrate reduces intravenous iron and erythropoiesis-stimulating agent use in ESRD. *J Am Soc Nephrol*. Oct 2015;26(10):2578-2587. PMID: 25736045.
163. *FDA drug safety communication: Modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease*. 2011; <http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm>. Accessed September 16, 2019.
164. Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney Int*. Nov 2016;90(5):1115-1122. PMID: 27650732.
165. Provenzano R, Besarab A, Sun CH, et al. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. *Clin J Am Soc Nephrol*. Jun 6 2016;11(6):982-991. PMID: 27094610.
166. de Boer IH, Sachs M, Hoofnagle AN, et al. Paricalcitol does not improve glucose metabolism in patients with stage 3-4 chronic kidney disease. *Kidney Int*. Feb 2013;83(2):323-330. PMID: 22913981.
167. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: The PRIMO randomized controlled trial. *JAMA*. Feb 15 2012;307(7):674-684. PMID: 22337679.
168. Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM. A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3-4 CKD. *Clin J Am Soc Nephrol*. Sep 5 2014;9(9):1620-1626. PMID: 24970869.
169. Patel A, Robertson J, Darwin C, et al. Double-blind study comparing doxercalciferol and placebo in vitamin D-replete CKD patients. *Dialysis & Transplantation*. 2011;40(6):252-257.
170. Kovesdy CP, Lu JL, Malakauskas SM, Andress DL, Kalantar-Zadeh K, Ahmadzadeh S. Paricalcitol versus ergocalciferol for secondary hyperparathyroidism in CKD stages 3 and 4: A randomized controlled trial. *Am J Kidney Dis*. Jan 2012;59(1):58-66. PMID: 21885174.
171. Fishbane S, Chittineni H, Packman M, Dutka P, Ali N, Durie N. Oral paricalcitol in the treatment of patients with CKD and proteinuria: A randomized trial. *Am J Kidney Dis*. Oct 2009;54(4):647-652. PMID: 19596163.
172. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. Oct 7 2009(4):CD008175. PMID: 19821446.
173. Chonchol M, Locatelli F, Abboud HE, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet HCl in participants with CKD not receiving dialysis. *Am J Kidney Dis*. Feb 2009;53(2):197-207. PMID: 19110359.
174. Perez-Ricart A, Galicia-Basart M, Alcalde-Rodrigo M, Segarra-Medrano A, Sune-Negre JM, Montoro-Ronsano JB. Effectiveness of cinacalcet in patients with chronic kidney disease and secondary hyperparathyroidism not receiving dialysis. *PLoS One*. 2016;11(9):e0161527. PMID: 27588942.
175. Ruospo M, Palmer SC, Natale P, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). *Cochrane Database Syst Rev*. Aug 22 2018;8:CD006023. PMID: 30132304.

176. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am J Kidney Dis.* Apr 1998;31(4):607-617. PMID: 9531176.
177. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* Aug 2004;15(8):2208-2218. PMID: 15284307.
178. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol.* Oct 2001;12(10):2131-2138. PMID: 11562412.
179. Kalantar-Zadeh K, Kuwae N, Regidor DL, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int.* Aug 2006;70(4):771-780. PMID: 16820797.
180. Susantitaphong P, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: A systematic review. *Am J Nephrol.* 2012;35(6):540-547. PMID: 22653322.
181. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol.* Sep 2009;20(9):2075-2084. PMID: 19608703.
182. Goraya N, Simoni J, Jo CH, Wesson DE. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int.* Nov 2014;86(5):1031-1038. PMID: 24694986.
183. Pisano A, Cernaro V, Gembillo G, D'Arrigo G, Buemi M, Bolignano D. Xanthine oxidase inhibitors for improving renal function in chronic kidney disease patients: An updated systematic review and meta-analysis. *Int J Mol Sci.* Oct 31 2017;18(11). PMID: 29088122.
184. Mukri MNA, Kong WY, Mustafar R, et al. Role of febuxostat in retarding progression of diabetic kidney disease with asymptomatic hyperuricemia: A 6-months open-label, randomized controlled trial. *EXCLI J.* 2018;17:563-575. PMID: 30108461.
185. Kimura K, Hosoya T, Uchida S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: A randomized trial. *Am J Kidney Dis.* Dec 2018;72(6):798-810. PMID: 30177485.
186. Sezai A, Soma M, Nakata K, et al. Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD). *J Cardiol.* Oct 2015;66(4):298-303. PMID: 25649025.
187. FDA adds boxed warning for increased risk of death with gout medicine uloric (febuxostat) [press release]. Drug Safety Communications: U.S. Food and Drug Administration, 02/21/2019 2019.
188. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med.* Dec 20 2012;367(25):2407-2418. PMID: 23121377.
189. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med.* Nov 16 2017;377(20):1930-1942. PMID: 29105594.
190. Torres VE, Higashihara E, Devuyst O, et al. Effect of tolvaptan in autosomal dominant polycystic kidney disease by CKD stage: Results from the TEMPO 3:4 trial. *Clin J Am Soc Nephrol.* May 6 2016;11(5):803-811. PMID: 26912543.
191. Application number: 204441orig1s000 summary review. FDA;2018. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000SumR.pdf.
192. Risk evaluation and mitigation strategies | rems. 2019; <https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems>. Updated August 8, 2019. Accessed December 12, 2019.
193. McDonald RJ, McDonald JS, Carter RE, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. *Radiology.* Dec 2014;273(3):714-725. PMID: 25203000.
194. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of intravenous contrast material-mediated acute kidney injury: A propensity score-matched study stratified by baseline-estimated glomerular filtration rate. *Radiology.* Apr 2014;271(1):65-73. PMID: 24475854.
195. Davenport MS, Khalatbari S, Dillman JR, Cohan RH, Caoili EM, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. *Radiology.* Apr 2013;267(1):94-105. PMID: 23360737.
196. Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. *N Engl J Med.* May 30 2019;380(22):2146-2155. PMID: 31141635.

197. James MT, Samuel SM, Manning MA, et al. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: A systematic review and meta-analysis. *Circ Cardiovasc Interv.* Feb 2013;6(1):37-43. PMID: 23322741.
198. Kooiman J, Seth M, Nallamothu BK, Heung M, Humes D, Gurm HS. Association between acute kidney injury and in-hospital mortality in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv.* Jun 2015;8(6):e002212. PMID: 26047992.
199. Hiremath S, Akbari A, Shabana W, Fergusson DA, Knoll GA. Prevention of contrast-induced acute kidney injury: Is simple oral hydration similar to intravenous? A systematic review of the evidence. *PLoS One.* 2013;8(3):e60009. PMID: 23555863.
200. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract.* Jan 2003;93(1):C29-34. PMID: 12411756.
201. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): A prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet.* Apr 1 2017;389(10076):1312-1322. PMID: 28233565.
202. Kooiman J, Sijpkens YW, van Buren M, et al. Randomised trial of no hydration vs. sodium bicarbonate hydration in patients with chronic kidney disease undergoing acute computed tomography-pulmonary angiography. *J Thromb Haemost.* Oct 2014;12(10):1658-1666. PMID: 25142085.
203. Luo Y, Wang X, Ye Z, et al. Remedial hydration reduces the incidence of contrast-induced nephropathy and short-term adverse events in patients with st-segment elevation myocardial infarction: A single-center, randomized trial. *Intern Med.* 2014;53(20):2265-2272. PMID: 25318787.
204. Jurado-Roman A, Hernandez-Hernandez F, Garcia-Tejada J, et al. Role of hydration in contrast-induced nephropathy in patients who underwent primary percutaneous coronary intervention. *Am J Cardiol.* May 1 2015;115(9):1174-1178. PMID: 25759106.
205. Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: The POSEIDON randomised controlled trial. *Lancet.* May 24 2014;383(9931):1814-1823. PMID: 24856027.
206. Subramaniam RM, Wilson RF, Turban S, et al. Contrast-induced nephropathy: Comparative effectiveness of preventive measures. *AHRQ Comparative Effectiveness Reviews.* January 2016;15(16). PMID: 26866209.
207. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med.* Feb 15 2018;378(7):603-614. PMID: 29130810.
208. Solomon R, Gordon P, Manoukian SV, et al. Randomized trial of bicarbonate or saline study for the prevention of contrast-induced nephropathy in patients with CKD. *Clin J Am Soc Nephrol.* Sep 4 2015;10(9):1519-1524. PMID: 26185263.
209. Mei M, Zhao HW, Pan QG, Pu YM, Tang MZ, Shen BB. Efficacy of n-acetylcysteine in preventing acute kidney injury after cardiac surgery: A meta-analysis study. *J Invest Surg.* Feb 2018;31(1):14-23. PMID: 28060555.
210. Cruz DN, Goh CY, Marenzi G, Corradi V, Ronco C, Perazella MA. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: A systematic review. *Am J Med.* Jan 2012;125(1):66-78 e63. PMID: 22195531.
211. Song K, Jiang S, Shi Y, Shen H, Shi X, Jing D. Renal replacement therapy for prevention of contrast-induced acute kidney injury: A meta-analysis of randomized controlled trials. *Am J Nephrol.* 2010;32(5):497-504. PMID: 20975263.
212. Liang M, Yang S, Fu N. Efficacy of short-term moderate or high-dose rosuvastatin in preventing contrast-induced nephropathy: A meta-analysis of 15 randomized controlled trials. *Medicine (Baltimore).* Jul 2017;96(27):e7384. PMID: 28682890.
213. Hu J, Liu S, Jia P, et al. Protection of remote ischemic preconditioning against acute kidney injury: A systematic review and meta-analysis. *Crit Care.* Apr 20 2016;20(1):111. PMID: 27095379.
214. Agency for Health Research and Quality. The effective health care program stakeholder guide appendix d: Research questions & PICO(TS) 2011. <https://www.ahrq.gov/research/findings/evidence-based-reports/stakeholderguide/appendixc.html>.
215. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol.* Jul 2013;66(7):726-735. PMID: 23570745.

216. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. Apr 2011;64(4):395-400. PMID: 21194891.
217. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. *J Clin Epidemiol*. Jul 2013;66(7):719-725. PMID: 23312392.
218. Kalantar-Zadeh K, Crowley ST, Beddhu S, et al. Renal replacement therapy and incremental hemodialysis for Veterans with advanced chronic kidney disease. *Semin Dial*. May 2017;30(3):251-261. PMID: 28421638.
219. Tinetti M, Huang A, Molnar F. The geriatrics 5m's: A new way of communicating what we do. *J Am Geriatr Soc*. Sep 2017;65(9):2115. PMID: 28586122.
220. Bowling CB, Batten A, O'Hare AM. Distribution of survival times in a real-world cohort of older adults with chronic kidney disease: The median may not be the message. *J Am Geriatr Soc*. May 2015;63(5):1033-1035. PMID: 25989569.
221. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. Oct 2007;18(10):2758-2765. PMID: 17855638.
222. Douros A, Bronder E, Klimpel A, Erley C, Garbe E, Kreutz R. Drug-induced kidney injury: A large case series from the Berlin case-control surveillance study. *Clin Nephrol*. Jan 2018;89 (2018)(1):18-26. PMID: 29035197.
223. Ingrassiotta Y, Sultana J, Giorgianni F, et al. The burden of nephrotoxic drug prescriptions in patients with chronic kidney disease: A retrospective population-based study in southern Italy. *PLoS One*. 2014;9(2):e89072. PMID: 24558471.
224. Matzke GR, Aronoff GR, Atkinson AJ, Jr., et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. Dec 2011;80(11):1122-1137. PMID: 21918498.
225. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf*. Apr 1999;20(4):377-384. PMID: 10230584.
226. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. Apr 14 2010(4):CD002967. PMID: 20393934.
227. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: Reconsideration of traditional contraindications. *Eur J Intern Med*. Oct 2002;13(7):428. PMID: 12384131.
228. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician*. Sep 15 2008;78(6):743-750. PMID: 18819242.
229. Boussadi A, Caruba T, Karras A, et al. Validity of a clinical decision rule-based alert system for drug dose adjustment in patients with renal failure intended to improve pharmacists' analysis of medication orders in hospitals. *Int J Med Inform*. Oct 2013;82(10):964-972. PMID: 23831104.
230. Koncicki HM, Unruh M, Schell JO. Pain management in CKD: A guide for nephrology providers. *Am J Kidney Dis*. Mar 2017;69(3):451-460. PMID: 27881247.
231. Brown S, Lascarides P, Stickevers S. Treating pain in patients with chronic kidney disease: A review of the literature. *Practical Pain Management*. 2014;14(9).
232. Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. *Am J Epidemiol*. Nov 1 2006;164(9):881-889. PMID: 17005625.
233. Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: Systematic review and meta-analysis. *BMC Nephrol*. Aug 1 2017;18(1):256. PMID: 28764659.
234. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. *Am Fam Physician*. May 15 2007;75(10):1487-1496. PMID: 17555141.
235. Plantinga L, Grubbs V, Sarkar U, et al. Nonsteroidal anti-inflammatory drug use among persons with chronic kidney disease in the United States. *Ann Fam Med*. Sep-Oct 2011;9(5):423-430. PMID: 21911761.
236. Kurella M, Bennett WM, Chertow GM. Analgesia in patients with ESRD: A review of available evidence. *Am J Kidney Dis*. Aug 2003;42(2):217-228. PMID: 12900801.
237. The Joint Commission on Accreditation of Healthcare Organizations, The National Pharmaceutical Council. *Pain: Current understanding of assessment, management, and treatments; section III: Types of treatments.*

2001. <https://www.npcnow.org/system/files/research/download/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf>.
238. The National Academies Press. *Veterans and agent orange: Update 11*. Washington, D.C.: The National Academies Press; 2018.
239. *Camp Lejeune*. 2017; <https://www.warrelatedillness.va.gov/education/exposures/camp-lejeune.asp>. Updated November 20, 2017.
240. *Long-term health consequences of exposure to burn pits in Iraq and Afghanistan*. Washington, D.C.2011.
241. Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. *J Am Soc Nephrol*. Jan 2018;29(1):218-230. PMID: 28935655.
242. Scales CD, Jr., Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. *Eur Urol*. Jul 2012;62(1):160-165. PMID: 22498635.
243. Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. Apr 2006;21(4):1104-1108. PMID: 16431890.
244. American College of Radiology Committee on Drugs and Contrast Media. *ACR manual on contrast media*. American College of Radiology;2018. <https://www.acr.org/Clinical-Resources/Contrast-Manual>.