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

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DOD) guidelines are based on the best information available at the time of publication. The guidelines 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 such, nor should the guidelines 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 providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in each unique clinical situation using a patient-centered approach.

These guidelines are not intended to represent VA or DOD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both, within these guidelines does not guarantee coverage of civilian sector care.

Version 5.0 – 2025

Prepared by:

The Primary Care Management of Chronic Kidney Disease Clinical Practice Guideline Work Group

With support from:

Office of Quality and Patient Safety, Veterans Health Administration and Clinical Quality Improvement Program, Defense Health Agency

Version 5.0 – 2025

Based on evidence reviewed through June 2024

Table of Contents

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 Council (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) The development and updating of VA/DOD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and well-being.

In 2019, the VA and DOD published a CPG for the Primary Care Management of Chronic Kidney Disease (2019 VA/DOD CKD CPG), which was based on evidence reviewed through November 2018. Since the release of that CPG, the evidence base on CKD has expanded. Consequently, a recommendation to update the 2019 guideline using published data from September 2018 to June 2024 was initiated in 2023. This updated CPG's use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach reflects a more rigorous application of the methodology than previous iterations.(2) Therefore, the strength of some recommendations might have been modified because of changes in the quality of the supporting evidence (see Evidence Quality and Recommendation Strength).

This CPG provides an evidence-based framework for evaluating and managing adult patients, 18 years or older, who have or are at risk for CKD, in the primary care setting to improve clinical outcomes. Successful implementation of this CPG will:

- Assess the patient's condition;
- Determine the most appropriate treatment plan in collaboration with the patient;
- Optimize each patient's functional independence, health outcomes, and quality of life;
- Minimize preventable complications and morbidity; and
- Emphasize the use of patient-centered care.

II. Background

A. Description of Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function characterized by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73m^2 or a normal GFR with other markers of kidney disease such as proteinuria, hematuria, or abnormal imaging of the kidneys, present for greater than three months, with implications for health.(3) In 2002, the National Kidney Foundation (NKF) published treatment guidelines that classified five stages of CKD based on declining estimated GFR (eGFR) measurements.(4) Subsequently, Kidney Disease: Improving Global Outcomes (KDIGO) released a CKD guideline in 2012, updated in 2024, which classified CKD based on cause, GFR, and severity of albuminuria.(3,4) The risk of kidney failure requiring dialysis, cardiovascular disease (CVD) events, and mortality increases with each higher stage of CKD.(5-7) Additionally, for any given stage of CKD, the presence of albuminuria is associated with increasing risk of CKD progression, CVD events, and mortality. The

stages of CKD and the relative risk of these complications are presented in Sidebar 9. The majority of patients with CKD are asymptomatic until CKD stage G5 when uremic symptoms develop, at which time kidney replacement therapy (KRT) may be recommended depending on patients' co-occurring conditions and values. Interventions described in this CPG can slow the progression of CKD, improve cardiovascular outcomes, and reduce mortality. Testing within populations at high risk for CKD is suggested to identify patients that may benefit from additional preventive measures and/or therapies.

B. Epidemiology and Impact in the General Population

The prevalence of CKD (stages G1-G5) in the adult United States (U.S.) population was 14% between 2017 and 2020.(8,9) Only 9% of patients with CKD are aware of their kidney disease despite efforts to raise community awareness.(10) Furthermore, 40% of adults with advanced kidney disease (stages G4-G5) do not know they have the condition.(11) CKD is more commonly present in aging populations, with the highest prevalence being in patients 65 years or older and in racial minorities.(8,11) CKD is often associated with conditions prevalent among adults with advanced age, such as type 2 diabetes mellitus, hypertension, and CVD.

CKD is associated with higher morbidity, mortality, and healthcare costs. In 2021, the adjusted all-cause mortality rate for Medicare beneficiaries ≥66 years old with CKD was more than double that of beneficiaries without CKD (101.8 deaths with CKD compared to 46.3 deaths without CKD per 1,000 person-years).(12) In adults aged 18-64 years with CKD insured by Medicaid, adjusted all-cause mortality rates increased from 2019-2021 before beginning to level-off or slightly decrease by 2022. Despite this trend, overall CKD mortality in younger adults was still higher than the pre-pandemic level. This is also significantly higher than the age-adjusted mortality rate for the U.S. population during the same period.(12) In 2021, while only 13.5% of Medicare fee-for-service beneficiaries aged ≥66 years had CKD, Medicare expenses for individuals with CKD were $76.8 billion, accounting for nearly one-quarter of the total Medicare spending for this age group.(12)

C. Chronic Kidney Disease in the Department of Veterans Affairs and the Department of Defense

CKD prevalence is likely underestimated within the VA and DOD health systems. First, the presence of CKD could be an exclusion criterion for continued active service, thereby disincentivizing screening and non-disclosure, if known. Second, testing for CKD remains low, even among individuals with known risk factors such as diabetes mellitus. The National Health and Nutrition Examination Survey (NHANES) from 1999 to 2016 showed that the prevalence of CKD stages G1-G4 based on the presence of albuminuria or an eGFR less than 60 mL/min/1.73 m^2 within the U.S. population ranges from 13-16%. Published data on the prevalence of CKD in the DOD remain limited; however, estimates of CKD prevalence based on diagnostic codes range from 1.9% to 5.4%.(13-15) Based on data from the VA Renal Information System (VA-REINS), the prevalence of CKD based on diagnostic codes among nearly 7 million individuals who used the VA for care in 2014 was 3.2%; however, between 1.1 and 2.5 million may meet criteria depending on operational definition.(16) The same analysis estimated that the cost of CKD care for Veterans not requiring dialysis or transplantation increased from $12.2 billion in Fiscal Year 2006 to $17.9 billion in Fiscal Year 2014 with an

average annual cost per Veteran increasing from approximately $13,400 for a Veteran with stage G3a CKD to $58,700 for a Veteran with stage G5 CKD.

The accurate diagnosis of CKD has significant implications for the health of Veterans, service members, and their families. These health effects “include the psychological impact and stigma of the diagnosis, potential disqualification from continued active service or deployment to austere locations, restrictions on duty stations and career-broadening assignments, implications for service-connected conditions, and challenges in obtaining affordable life insurance due to “pre-existing conditions”. Additionally, a diagnosis of CKD in a family member may necessitate enrollment in the exceptional family member program (EFMP), which can restrict duty assignments to ensure essential services are available for their family. However, underdiagnosis could delay or impede treatment or place service members or family members in a location without proper medical support.

D. Social Determinants of Health

a. Social Determinants of Health and Chronic Kidney Disease

It is the collective influence of medical, environmental, and social factors that increases the risk of developing CKD and hastens its progression.(17) Social determinants of health (SDOH) are non-clinical factors such as economic stability, housing safety, food security, community engagement, and access to quality education and healthcare, that help explain the demographic and socioeconomic differences witnessed in both the U.S. and across the globe.(18) In essence, SDOH create imbalances in the health of certain communities.(19)

Factors such as poverty, unemployment, and other sociodemographic factors contribute to poor health and increased mortality.(20-23) Living in a high poverty neighborhood may increase risk of incident CKD and CKD progression.(24) Black and Hispanic communities experience higher incidence of end-stage kidney disease (ESKD), as well as metabolic diseases such as obesity and type 2 diabetes mellitus. Studies have tied food and housing insecurity to higher rates of hypertension and other chronic diseases, such as CVD, and subsequently CKD.(25,26) Increased prevalence of kidney disease has also been noted in Americans with fewer than 12 years of education. Investment in efforts to reduce these socioeconomic differences are critical for reducing the incidence and severity of CKD.(27)

b. Social Determinants of Health in the VA/DOD

Racial/ethnic differences appear to be moderated within the VA and DOD’s equal-access systems compared to the general U.S. population,(28) but they can still be demonstrated. A cohort study of DOD beneficiaries aged 18-64 years receiving care between 2015 and 2018 found that CKD prevalence was higher in Black versus White beneficiaries and higher among those with lower socioeconomic status (as measured by sponsor’s rank and median household income by sponsor’s zip code) in confounder-adjusted models.(29) While studies of mortality among VA patients with CKD do not report consistent findings, data in a 2018 evidence review suggest that mortality rates remain higher among Black versus White Veterans with stage G4 CKD (but not stage G5 CKD).(30) A cohort study of VA patients with CKD between 1998-2008 also found that multi-morbidity was more common in Black compared to White patients and more common in Hispanics in urban areas compared to rural areas with the highest rate of multi-morbidity in Hispanics in insular islands.(31) A 2024 cohort study of 547,188 U.S. Veterans with new-onset

CKD within the VA between 2005-2016, followed for up to 10 years, found that Black Veterans were on average 7.8 years younger than White Veterans at CKD onset and had persistently >2-fold higher likelihood of requiring KRT, consistent with trends observed in the general U.S. population. A cohort study of VA patients with incident stage G3 and G4 CKD found that both Black and Hispanic patients experienced faster progression to stage G5 CKD compared with non-Hispanic White patients, despite higher rates of nephrology referral and visits among Black and Hispanic Veterans.(32)

Dispensing patterns of medications that can slow CKD progression among patients with diabetes differ by race/ethnicity within the VA and DOD.(33-35) Within the VA, there is considerable facility-level variation in overall prescribing of sodium-glucose cotransporter-2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1 RA).(34,36) In 2019-2020, after accounting for patient- and system-level factors, American Indian or Alaska Native; Asian, Native Hawaiian, or other Pacific Islander; Black; and multiracial patients received fewer SGLT2i and GLP-1 RA prescriptions compared to White patients, with Black patients having the lowest odds of being prescribed these medications.(35) In a cohort of VA patients with comorbid CKD, diabetes, and atherosclerotic cardiovascular disease (ASCVD) in 2020, SGLT2i use was low (11.5%); in a multivariable model, Black Veterans were less likely to be prescribed an SGLT2i compared with White Veterans, and women were almost half as likely to be prescribed an SGLT2i compared with men. In the same cohort, GLP-1 RA use was also low (9.4%); in a multivariate model, Black and Hispanic patients were less likely to receive GLP-1 RA than White and non-Hispanic patients, respectively, while female sex was associated with higher odds of GLP-1 RA prescription.(36) Additionally, there was an increased likelihood of treatment discontinuation among Blacks and Hispanics for both GLP-1 RA and SGLT2i, which was associated with increased risk of complications, such as heart failure hospitalization and death.(37) Among DOD beneficiaries with diabetes in 2019, use of a SGLT2i or GLP-1 RA was low (13.1% and 12.5% respectively); in a multivariable model, the adjusted odds ratio (OR) for using either SGLT2i or GLP-1 RA was significantly lower in all groups except Native American/Alaska Native when compared to White adults.(38)

c. Interventions to Address Social Determinants of Health in CKD

To effectively address differences in health outcomes, system-level solutions are crucial. The nephrology community has taken an initial step in mitigating observed differences in kidney health by recommending use of a race-free GFR estimation, which has been adopted by most labs. Equations for calculating eGFR have historically included a race coefficient for Black individuals based on epidemiologic data. As a result, these equations risk overestimating kidney function in some Black individuals and can delay the recognition of CKD, implementation of treatment, and referral for kidney transplantation. In 2021, a new CKD-EPI eGFR equation that did not include race was released by the NKF and American Society of Nephrology (ASN). The VA National Kidney Medicine Program and VA National Pathology and Laboratory Medicine Programs developed a collaborative, national strategic plan to implement the race-neutral equation.(39) Use of the 2021 race-free GFR equation balances the equation performance across the ethnic groups, which may generally result in lower eGFR in Black individuals and higher eGFR in non-Black individuals, and may thereby reclassify individual patients into different a CKD stage.(15) However, the impact of this change on clinical outcomes, such as rate of transplantation or mortality, is still to be determined. In general, using accurate risk prediction tools to customize

medical care – such as making informed referrals to specialists – enhances patient-centered care. This approach ensures that each patient receives appropriate treatment tailored to their specific needs and risks.

Healthcare systems and primary care providers (PCPs) play a crucial role in facilitating early CKD diagnosis, managing CKD risk factors, and educating patients. Incorporating CKD detection into the workflow for preventive visits, automating lab monitoring, implementing care management protocols for patients with diabetes and hypertension, and using checklists/reminders help to ensure that all patients receive appropriate and timely evaluations. The Indian Health Service (IHS) successfully reduced the incidence of diabetes-related ESKD by 54% by implementing routine lab reporting of GFR in the electronic medical record, annual monitoring of urine albumin-to-creatinine ratio (UACR), use of renin-angiotensin-aldosterone system inhibitors (RAASi), and clinical diabetes education programs with culturally relevant patient education materials.(40)

Further, leveraging technology and the electronic health record to identify and track at-risk patients in CKD registries streamlines the monitoring process and has the potential to improve compliance with testing, use of reno-protective medications, immunizations, clinic follow-up, and referrals.(41,42) The VA Chronic Kidney Disease Patient Report provides laboratory values, comprehensive information about use of medications to reduce MACE (Major Adverse Cardiovascular Event) and prevent progression of CKD, as well as data on nutrition and nephrology consultation for VA primary care patients, stratified by CKD stage.(43) The VA Primary Care Equity Dashboard provides patient data regarding “kidney health evaluation for patients with diabetes” to include annual measurement of eGFR and UACR among patients with diabetes and hypertension control, among other measures, stratified by race/ethnicity, sex, rurality, and neighborhood poverty level.(43) Both reports can assist primary care teams with CKD population management.

Collaborative teams, including patient aligned care teams (PACTs), nephrology providers, dietitians, and social workers, can ensure comprehensive care by understanding and mitigating obstacles like financial constraints, transportation issues, and language barriers. For patients with CKD, who often remain asymptomatic until the disease advances, education about their diagnosis and interventions that may slow the progression of CKD is important. Developing patient education materials that account for a patient’s perspective and are available in their preferred language and in various formats (e.g., written, video) enhances patient engagement, which can improve adherence to clinical recommendations.(41) Engaging community leaders in educational outreach campaigns targeting at-risk groups or involving them in patient advocacy committees to identify and leverage community resources can help address barriers and improve outcomes.

III. Scope of This Guideline

This CPG is based on published clinical evidence and related information available through June 30, 2024. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). Although the CPG is intended to improve quality of care and clinical outcomes (see Introduction), it is not intended to define a standard of care (i.e., mandated or strictly required care).

A. Guideline Audience

This CPG is intended for use by VA and DOD primary care providers and others on the health care team involved in assessing and managing patients who have or are at risk for CKD.

B. Guideline Population

This CPG is intended for adults (18 years or older) who have or are at risk for CKD, are eligible for care in the VA and DOD healthcare delivery systems, and who are being treated in an ambulatory or clinical setting. This includes Veterans and Service Members as well as their eligible adult dependents. This CPG does not provide recommendations for management of CKD in children or adolescents.

IV. Highlighted Features of This Guideline

A. Highlights in This Guideline Update

The current document is an update to the 2019 VA/DOD CKD CPG. The major strength of this CPG is in the coordination and collaboration of the multidisciplinary team, ensuring a broad representation of providers engaged in CKD care. The following significant updates highlight the importance of clinicians reviewing this version of the CPG:

- Updated Algorithms;
- Updated Sidebars; and
- Added 6 new recommendations, reviewed and replaced 4 recommendations, reviewed and amended 7 recommendations, carried over 2 recommendations not changed, and carried over 4 recommendations amended from the 2019 VA/DOD CKD CPG.

The methodology used in developing this CPG reflects a more rigorous application of the GRADE methodology than previous versions. The result is a refined CPG that includes methodologically rigorous, evidence-based recommendations for the management of individuals with or at risk for CKD.

This CPG also provides expanded recommendations on research needed to strengthen future guidelines.

B. Components of This Guideline

This CPG provides clinical practice recommendations for the primary care management of patients with or at risk for CKD (see Recommendations). In addition, the Algorithms integrate the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research. To

accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, a patient summary, and a quick reference guide, which can be found at https://www.healthquality.va.gov/index.asp.

C. Demographic Terminology in This Guideline

The demographic terms used in this guideline are derived from the published literature sources included in the systematic review (SR) and evidence base. The Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and improve clarity and consistency. In order to accurately present the research evidence on which this CPG is based, the Work Group made every effort to use the same terminology as reported in the published literature base of SRs, clinical trials, and other studies. Consequently, usage of demographic terms in this CPG may vary and appear inconsistent.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Linda Fried, MD, MPH, and Amy R. Schwartz, MD, from VA; and Mai T. Nguyen, MD, and Jonathan Sosnov, MD, from DOD. The Work Group was comprised of individuals with the following areas of expertise: nephrology, internal medicine, renal social work, clinical pharmacy, primary care, family medicine, kidney dietetics, and ambulatory care. Table 1 lists the Work Group and Guideline Development Team members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG;
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review;
- Identifying discussion topics for the patient focus group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

Sigma Health Consulting and Duty First Consulting were contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veteran Affairs	**Linda Fried, MD, MPH (Champion)**
	Amy R. Schwartz, MD (Champion)
	Cynthia Delgado, MD, FASN, FNKF
	Holly Kramer, MD, MPH
	Manjula Kurella Tamura, MD, MPH
	Sankar Dass Navaneethan, MD, MS, MPH
	Ian Pace, PharmD
	Paul M. Palevsky, MD, FACP, FASN, FISN, FNKF (Advisor)
	Diane Rybacki, MSN, ACNP-BC
	Carol Toms, MSW, LICSW
	Sunil P. Verma, MD, MPH
Department of Defense	**Mai T. Nguyen, MD, FACP, FASN (Champion)**
	Jonathan Sosnov, MD (Champion)
	Jonathan Casey Brown, DO, MPH
	Wendy Caesar-Gibbs, RD
	Kaitlin Lichty, MS, RD
	John W. Morrison, Jr., DO, MPH, MBA, FACP
	Michael Petitt, PharmD
	Maura Watson, DO, MPH, FACP, FASN
	Jesse Wickham, DO, FACP
VA Evidence Based Practice, Office of Quality and Patient Safety Veterans Health Administration	James Sall, PhD, FNP-BC
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	Jennifer Ballard-Hernandez, DNP, RN, FNP-BC
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Clinical Quality Improvement Program Defense Health Agency	Margaret Rincon, PharmD
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	Isabella M. Alvarez, MA, BSN, RN
	Gwendolyn Holland, MSN, RN
	Lynn M. Young, BSN, RN, CIC

Organization	Names*
Sigma Health Consulting, LLC	Frances M. Murphy, MD, MPH
	James G. Smirniotopoulos, MD
	James Reston, PhD, MPH
	Joann Fontanarosa, PhD
	William Wester, MLIS
	Erin Gardner, MPH, PMP
	Kristen D'Anci, PhD
	Annie Tran, MPH
	Zyna Egbe, BS
	Dhara Patel, MPH
	Rachel McCausland, MPH
	Susan Connor, PhD
	Sophie Roberts, BS
	Dan Sztubinski, BS
	Emilio Berdiel, MPH
	Aggee Loblack, MPH
	Jen de Richemond, MLIS, AHIP
Duty First Consulting	Kate Johnson, BS
	Jake Fausnacht, BS

*Additional contributor information is available in Appendix D

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the Guideline for Guidelines, an internal document of the VA/DOD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DOD CPGs.(44) The Guideline for Guidelines is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(45) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction)(46):

- 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*). 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 incorporates the four domains.(47) A Strong recommendation generally indicates High or Moderate confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility). A recommendation's strength (i.e., Strong versus Weak) does not reference its clinical importance (e.g., a Weak recommendation is evidence-based and still important to clinical care).

In some instances, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for a particular therapy or intervention. The way this finding is expressed in the CPG might vary. The Work Group might include a statement among its recommendations acknowledging insufficient evidence for or against a commonly practiced intervention, particularly if it lacks supporting clinical evidence and poses potential risks (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might choose to remain silent in cases evidence is lacking for a rarely used intervention or when an intervention, despite the absence of recent evidence, is considered the standard of care and has a favorable balance of benefits and harms.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in Table 2. The strength of each recommendation is shown in Recommendations.

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations; the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision-making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies (e.g., randomized controlled trials [RCTs]) might be inherently more difficult, are typically considered lower quality evidence and, in turn, are usually Weak recommendations. Recommendations on topics for which rigorous studies can be designed

and conducted (e.g., RCTs) may more often be Strong recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, then the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2,48) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(49) For example, the U.S. Preventative Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(50)

Recommendation categories are used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, United Kingdom).(51,52) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2025 VA/DOD CKD CPG recommendation categories can be found in Recommendations. Appendix C outlines the 2019 VA/DOD CKD CPG's recommendation categories.

Table 3. 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 and 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, where the evidence has not been reviewed and the recommendation has not changed
	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

Evidence Reviewed	Recommendation Category	Definition
	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)(51) and Garcia, et al. (2014)(52)

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the Guideline for Guidelines.(44) Further, the Guideline for Guidelines refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),(53) as well as disclosure statements (i.e., standard disclosure form completed at least twice by CPG Work Group members and the guideline development team).(44) The disclosure form inquires about relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires about any other relationships or activities that could be perceived to have influenced, or give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments, ProPublica).

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often differ from those of providers.(48) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DOD Leadership arranged a virtual patient focus group on April 25, 2024. The focus group aimed to gain insights into the perspectives of individuals who received care in the VA and DOD healthcare systems for CKD and incorporated these insights into the CPG, as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and impacts of their care on their lives and their family members' lives.

The patient focus group was comprised of a convenience sample of eight participants, which included four women and four men. Participants were mixed in terms of receiving care from VA or DOD, with one participant also receiving care from civilian providers. The time of CKD diagnosis ranged from childhood to midlife, with half of the participants having received at least one kidney transplant. The Work Group acknowledged that this convenience sample was not representative of all individuals who have undergone treatment for CKD within the VA and DOD healthcare systems, and thus, findings were not generalizable and did not comprise evidence. For more information on the patient focus group methods and findings, see Appendix E. Patient focus group participants were provided with the opportunity to review the final draft of this CPG and share additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified individuals from VA and DOD healthcare systems and external organizations generally viewed as experts in their respective fields. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review may be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual health care providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithms serve as a tool to prompt providers to consider key decision points in the care of patients who have or are at risk for CKD. The Work Group will submit suggested performance metrics for VA and DOD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DOD internal implementation plans and policies. Additionally, implementation will entail wide dissemination through publication in the medical literature, online access to the final CPG, educational programs, and ideally, electronic medical record programming in the form of clinical decision support tools at the point-of-care.

VII. Approach to Care in the Department of Veterans Affairs and the Department of Defense

A. Patient-Centered Care

VA and DOD encourage providers to be sensitive to demographic, cultural, and other differences that affect patients' values, needs, and preferences. aimed at treating the condition while also optimizing the individual's overall health and well-being. Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.(54,55) A holistic health approach (https:/www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and well-being goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. Guideline recommendations should be applied in a holistic approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities.

B. Shared Decision-Making

This CPG encourages providers to practice shared decision-making (SDM), a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(56) Shared decision-making is emphasized in "Crossing the Quality Chasm", an Institute of Medicine, now NAM, report in 2001 (57) and is a core component of a patient-centered, whole health approach. Moreover, the unique role of SDM in nephrology

care has been previously recognized in CPGs published by the Renal Physicians Association.(58) Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, possible outcomes, and levels and/or settings of care, especially where patient heterogeneity in weighing risks and benefits might exist. The VA and DOD have embraced SDM. Providers are encouraged to use SDM to individualize treatment goals and plans based on patient capabilities, needs, values, and preferences (see Recommendations 8-10).

C. Patients with Co-Occurring Conditions

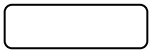
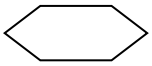
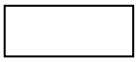
Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to managing CKD. Many Veterans, Active-Duty Service members, and their families have one or more co-occurring conditions. Because CKD is often accompanied by co-occurring conditions, managing CKD collaboratively with other care providers is often best. Some co-occurring conditions may require early specialist consultation to determine necessary changes in treatment or establish a common understanding of how care should be coordinated.

VIII. Algorithm

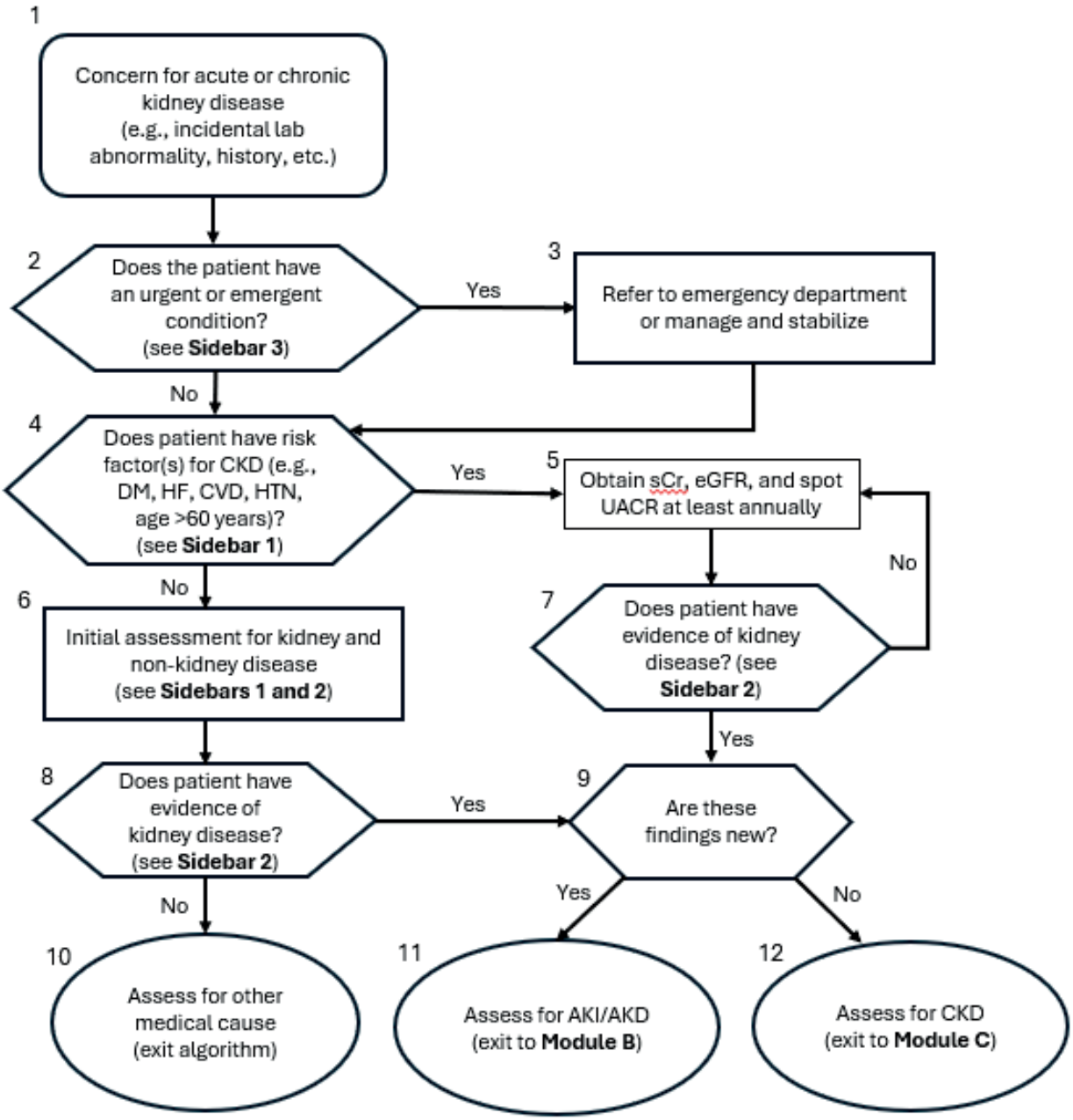
This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision-making process used in the treatment and primary care management of patients with CKD. The algorithm format represents a simplified flow of the management of patients with CKD and helps foster efficient decision-making by providers. It includes:

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

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(59) Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

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 algorithm

Module A. Initial Assessment of Kidney Disease



Abbreviations: AKD: acute kidney disease; AKI: acute kidney injury; BP: blood pressure; CKD: chronic kidney disease; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HF: heart failure; HTN: hypertension; sCr: serum creatinine; UACR: urine albumin-to-creatinine ratio

Sidebar 1: At-Risk Populations

- Diabetes mellitus, hypertension, cardiovascular disease, heart failure
- Patients aged 60 years and over
- Systemic illness (e.g., systemic lupus erythematosus, multiple myeloma, malignancy)
- Systemic infections (e.g., HIV, Hepatitis B or C)
- Structural kidney or urinary tract abnormalities
- History of AKI/AKD, recurrent pyelonephritis, or nephrolithiasis
- Family history of kidney disease (e.g., ADPKD, ApoL1-associated kidney disease)
- Obesity, Metabolic Syndrome, or Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
- History of gout
- History of pregnancy complications (e.g., preeclampsia, pre-term delivery, gestational diabetes, small for gestational age, stillbirth)
- Nephrotoxins

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AKD: acute kidney disease; AKI: acute kidney injury; ApoL1: Apolipoprotein L1; HIV: human immunodeficiency virus

Sidebar 2A: eGFR Calculation

- eGFR should be calculated using one of the CKD-EPI formulas without race
- For most individuals, the 2021 CKD-EPI creatinine formula is adequate for diagnosis and follow-up
- The 2021 CKD-EPI combined creatinine-cystatin C formula is more accurate and can be considered to confirm CKD, for dosing of medications with a narrow therapeutic window, or to better estimate risk of adverse outcomes (see Appendix J)
- Cystatin C formula alone should be used in patients with either:
  - Very low creatinine generation (e.g., neuromuscular disease, spinal cord injury, large lower extremity amputation, or severe muscle loss from malnutrition or disease)
  - Very high creatinine generation (e.g., body builders, anabolic steroid use, high muscle mass, or intake of creatine supplements)

Abbreviations: CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate

Sidebar 2B: Initial Assessment of Kidney Disease

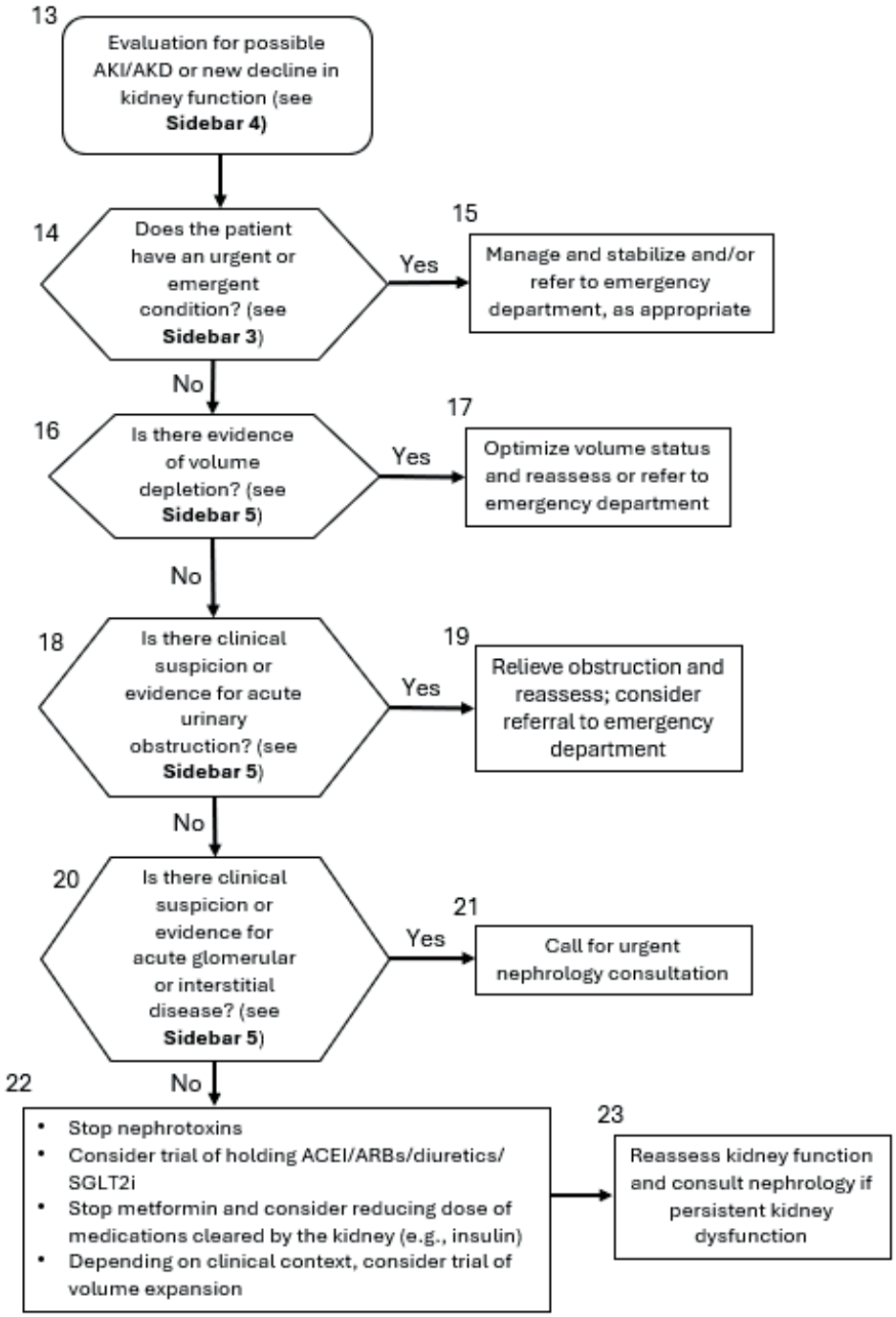
- History:
  - Symptoms of volume depletion (e.g., lightheadedness, dizziness) or overload (e.g., pedal edema, dyspnea)
  - Cause of volume depletion (e.g., diarrhea, vomiting, decreased oral intake, heat exposure)
  - Medications and supplements (e.g., NSAIDs, diuretics, SGLT2i therapy, BP medication changes)
  - Recent illnesses/infections (e.g., upper respiratory infection, osteomyelitis)
  - Urinary symptoms (e.g., hematuria, obstructive symptoms)
  - Constitutional or rheumatologic symptoms
- Physical: vital signs, assessment of volume status
- Labs: electrolytes, creatinine, urinalysis, urine albumin-to-creatinine ratio/urine protein-to-creatinine ratio - assess lab trends then repeat labs as clinically appropriate
  - Rule out AKI/AKD (see Module B)
  - Consider checking cystatin C (see Sidebar 2A and Appendix J)

Abbreviations: AKD: acute kidney disease; AKI: acute kidney injury; BP: blood pressure; NSAID: non-steroidal anti-inflammatory drug; SGLT2i: sodium-glucose cotransporter-2 inhibitor

Sidebar 3: Urgent/Emergent Conditions

- Clinical signs:
  - Unstable vital signs
  - Signs or symptoms of decompensated heart failure/symptomatic volume overload (e.g., shortness of breath, rales, jugular venous distention)
  - Signs or symptoms of uremia (e.g., nausea, vomiting, altered level of consciousness, pericarditis)
  - Anuria or oliguria
- Abnormal labs:
  - Significantly abnormal potassium
  - Acute unexplained decline in kidney function
  - Severe acid-base disturbance

Module B. Evaluation and Intervention for AKI/AKD or New Decline in Kidney Function



Abbreviations: ACEI: angiotensin converting enzyme Inhibitor; AKD: acute kidney disorder; AKI: acute kidney injury; ARB: Angiotensin II receptor blocker; SGLT2i: sodium-glucose cotransporter-2 inhibitor

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 m^2 for <3 months
  - Decrease in GFR by >35% or increase in sCr by >50% for <3 months
  - Kidney damage (structural) for <3 months

Definitions taken from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int., Suppl. 2012; 2: 1-138. Chapters 2.1 and 2.5.

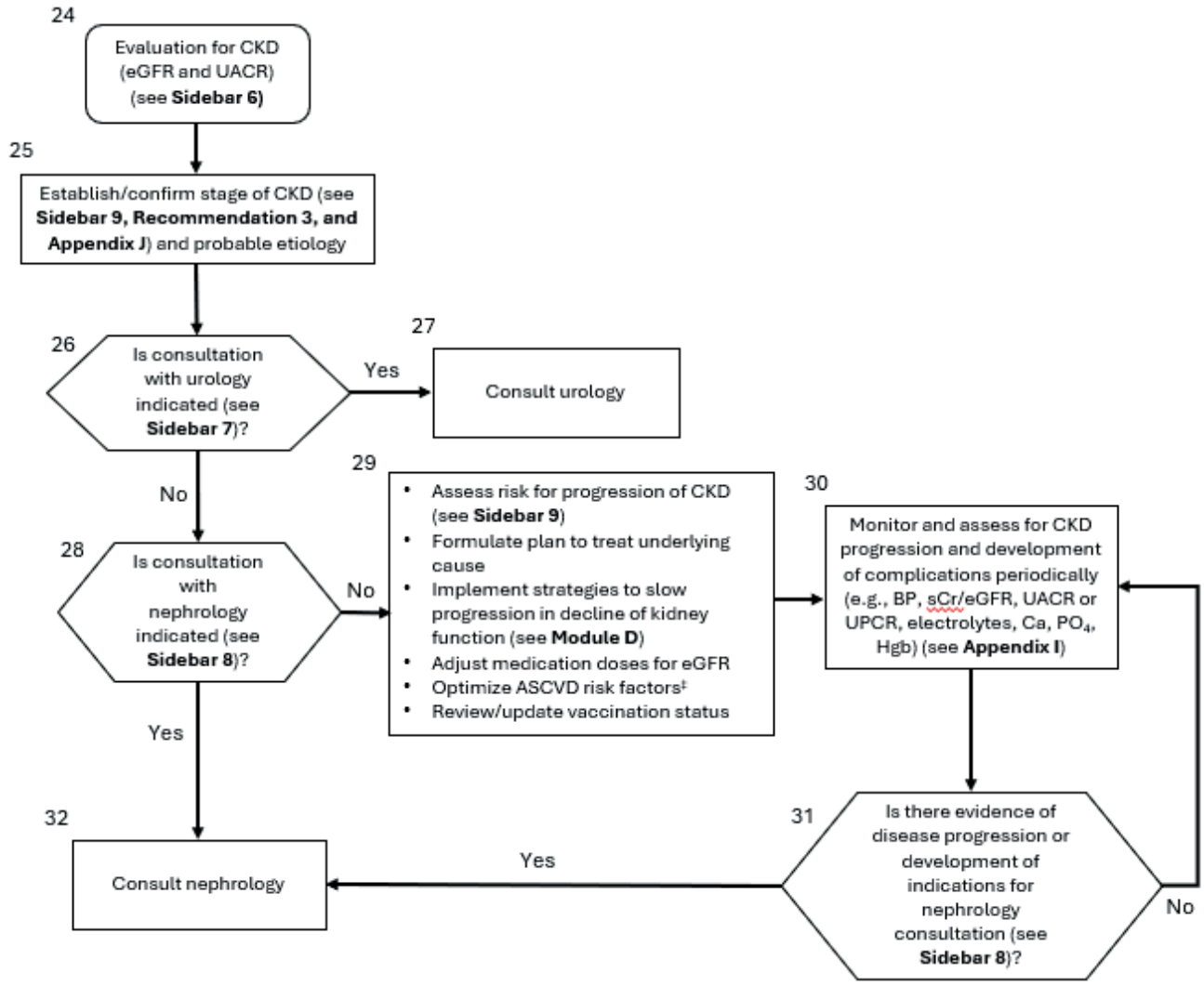
Abbreviations: AKD: acute kidney disorder; AKI: acute kidney injury; dL: deciliter; GFR: glomerular filtration rate; hr: hour; kg: kilogram; m: meter; mg: milligram; min: minute; mL: milliliter; sCr: serum creatinine

Sidebar 5: Assessment for AKD

- For volume depletion (e.g., lightheadedness or dizziness, hypotension, orthostasis)
- For 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 glomerular or interstitial disease (e.g., hematuria, dysmorphic RBCs or RBC casts, new onset or acute increase in albuminuria) with:
  - Recent illness (e.g., infection)
  - Constitutional or rheumatologic symptoms
  - Rash
  - Edema
  - Hemoptysis

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

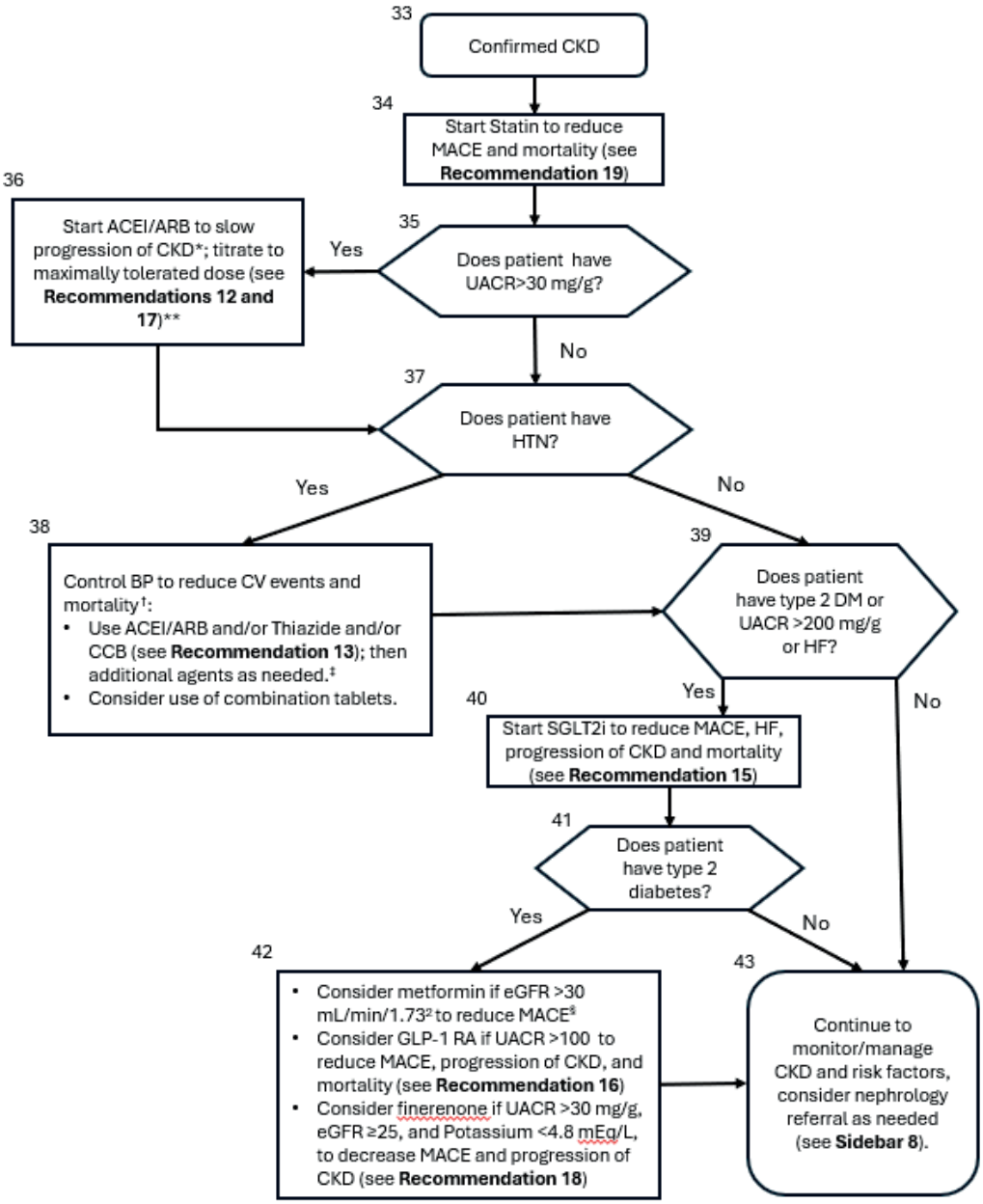
Module C. Evaluation and Management of CKD



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

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; Ca: calcium; PO_4: orthophosphate; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hgb: hemoglobin; hr: hour; kg: kilogram; mL: milliliter; PO_4: orthophosphate; sCr: serum creatinine; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein-to-creatinine ratio

Module D. Pharmacologic Management of CKD in Patients Not on Dialysis



The WG recommends stepwise addition of pharmacotherapies to slow progression of CKD and reduce MACE, noting that trials of SGLT2i, GLP-1 RA, and finerenone were each conducted on a background of ACEI/ARB therapy; however, the benefits of various combinations are unknown.

* Strongest evidence for kidney protection with ACEI/ARB is in UACR>300 mg/g.
** In patients with HF, sacubitril/valsartan may be used as an alternative to ACEI/ARB.
† See VA/DOD Hypertension CPG
‡ Depending on co-occurring conditions
§ See VA/DOD Diabetes CPG

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure; CCB: calcium channel blocker; CKD: chronic kidney disease; CV: cardiovascular; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; g: gram; GLP-1 RA: glucagon-like peptide-1 receptor agonists; HF: heart failure; HTN: hypertension; L: liter; MACE: major adverse cardiovascular events; mEq: milliequivalent; mg: milligram; SGLT2i: sodium-glucose co-transporter-2 inhibitor; UACR: urine albumin-to-creatinine ratio

Sidebar 6: Criteria for CKD

- Markers of kidney damage (1 or more):
  - Albuminuria (UACR ≥30 mg/g) on at least two measurements separated by ≥3 months
  - Urine sediment abnormalities
  - Persistent hematuria
  - Evidence of kidney tubular disorders (e.g., renal tubular acidosis)
  - Abnormalities detected by histology or imaging
  - History of kidney transplantation

AND/OR

- Decreased GFR <60 mL/min/1.73 m^2 (GFR categories G3a-G5) for ≥3 months

Source: CKD Evaluation and Management – KDIGO

Abbreviations: CKD: chronic kidney disease; GFR: glomerular filtration rate; UACR: urine albumin-to-creatinine ratio

Sidebar 7: Indications for Urology Consultation

- Gross hematuria
- Microhematuria in the absence of albuminuria
- Kidney masses or complex kidney cysts
- Symptomatic or obstructing nephrolithiasis
- Hydronephrosis or bladder abnormalities
- Persistent urinary symptoms despite treatment (e.g., nocturia, hesitancy, urgency, incontinence)
- Urinary retention

Sidebar 8: Potential Indications for Nephrology Consultation

- eGFR <30 mL/min/1.73 m^2
- Rapid decline of eGFR (>5 mL/min/1.73 m^2 per year)
- 5-year risk of kidney failure >3-5% (see Risk Equations Table)
- Non-diabetics with confirmed heavy albuminuria (UACR >300 mg/g, 24-hr urine protein >500 mg, UPCR >0.5 g/g)
- Diabetes with persistent (>1000 mg/g) albuminuria despite RAASi/SGLT2i, or inability to use RAASi/SGLT2i
- Hematuria with albuminuria, glomerular hematuria (e.g., dysmorphic RBC, RBC casts), or hematuria after negative urologic work-up
- Polycystic kidney disease (PKD)
- Kidney transplant recipient
- CKD in a patient <45 years
- Suspected genetic cause of CKD
- Unclear origin of kidney dysfunction or albuminuria
- Metabolic management (prevention) of kidney stone disease
- Electrolyte abnormalities (e.g., hyperkalemia, hyponatremia)

- Complications of CKD (e.g., anemia, metabolic acidosis, hyperphosphatemia, hyperparathyroidism)
- Patient's level of disease exceeds the comfort level of the primary care provider

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; g: gram; hr: hour; m: meter; mg: milligram; min: minute; mL: milliliter; RAASi: renin-angiotensin-aldosterone system inhibitor; RBC: red blood cell; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein-to-creatinine ratio

Sidebar 9: CKD Staging* and Prognosis

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

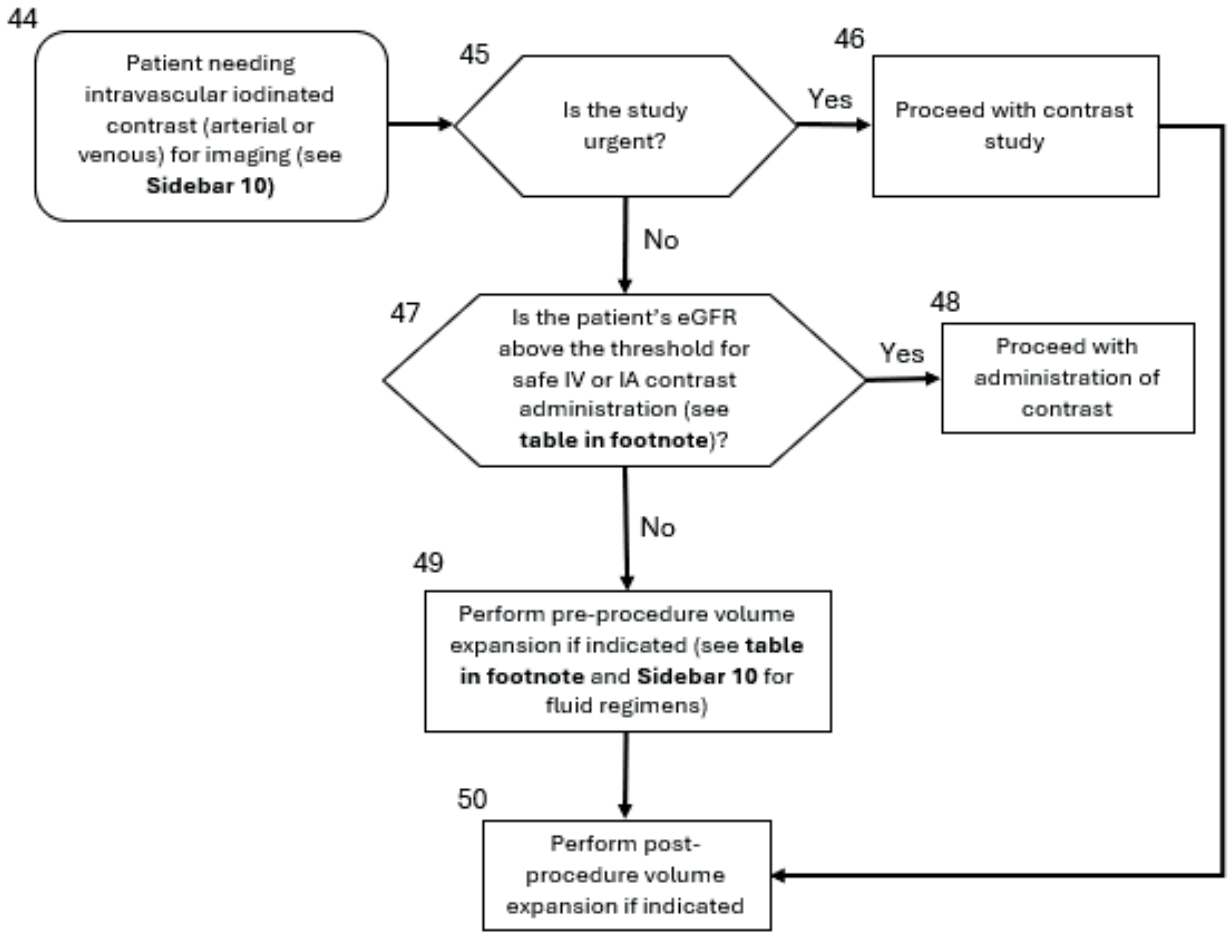
Reproduced from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4S): S117–S314.

*ICD-10 codes for CKD stages: G1 (N18.1); G2 (N18.2); G3a (N18.31); G3b (N18.32); G4 (N18.4); G5 (N18.5); G5D (N18.6, dialysis dependent kidney failure)

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk

Abbreviations: CKD: chronic kidney disease; g: gram; GFR: glomerular filtration rate; mg: milligram; mmol: millimole

Module E. Management of Patients with CKD Requiring Iodinated Contrast



eGFR Threshold (mL/min/1.73 m^2)		Peri-Procedural Fluid Administration
CT (IV)	Angiography (IA)	
<30	<45	All patients
30-44	45-59	At discretion of ordering clinician in individuals with multiple risk factors (e.g., heavy albuminuria, high frequency NSAID administration)
>45	>60	Not indicated

Abbreviations: CT: computed tomography; eGFR: estimated glomerular filtration rate; IA: intra-arterial; IV: intravenous; NSAID: non-steroidal anti-inflammatory drug

Sidebar 10: Considerations for When Studies Requiring Iodinated Contrast Are Indicated

- Consider a non-iodinated contrast study as an alternative (e.g., CO_2, group 2 and 3 GBCM) (see Appendix Q)
- Use minimum amount of contrast necessary for appropriate testing
- Assess for risk factors for CA-AKI:
  - Decreased kidney function
  - Diabetes mellitus
  - Albuminuria
  - Heart failure
  - Volume depletion
  - Concomitant nephrotoxin exposure (especially NSAIDs)
- Fluid administration regimens (see Recommendation 22 and Appendix Q for additional information)
  - For outpatients or inpatients: isotonic electrolyte solution (e.g., 0.9% saline) infused at 3 mL/kg over one hour pre-procedure and 6 mL/kg over 2-4 hours post-procedure
  - For inpatients: 1 mL/kg per hour for 6-12 hours pre- and post-procedure

Abbreviations: CA-AKI: contrast associated acute kidney injury; CO_2: carbon dioxide; GBCM: gadolinium-based contrast media; kg: kilogram; mL: milliliter; NSAIDs: non-steroidal anti-inflammatory drugs

IX. Recommendations

The evidence-based clinical practice recommendations listed in the table below were developed using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Table 4. Evidence-Based Clinical Practice Recommendations with Strength and Category

While some of these recommendations may clearly be an element in a particular phase of care, others may require consideration throughout the continuum of care.

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Diagnosis, Assessment and Lab Monitoring		1.	We suggest testing for chronic kidney disease (i.e., urine albumin/creatinine ratio and estimated glomerular filtration rate [eGFR]) in patients with one or more of the following associated risk factors: • Age over 60 years • Diabetes • Hypertension • Cardiovascular disease, including heart failure	Weak for	Reviewed, Amended
		2.	We recommend using urine albumin-to-creatinine ratio and estimated glomerular filtration rate for predicting chronic kidney disease progression.	Strong for	Reviewed, Amended
		3.	In patients with an estimated glomerular filtration rate <60 mL/minute/1.73 m², we suggest estimating glomerular filtration rate with a combined creatinine and cystatin C formula for risk prediction.	Weak for	Reviewed, Amended
		4.	We suggest the use of a validated end-stage kidney disease risk prediction model (e.g., kidney failure risk equation [KFRE]) for the management of stage G3-G5 chronic kidney disease.	Weak for	Reviewed, Amended
General Management Strategies	*Team Management and Education*	5.	When providing patient education about chronic kidney disease, there is insufficient evidence to recommend for or against any specific health education program or mode of delivery.	Neither for nor against	Reviewed Amended
		6.	We suggest interdisciplinary care (e.g., including dietitians, pharmacists, social workers, providers, nurses, and palliative care) for patients with chronic kidney disease.	Weak for	Not reviewed, Amended
		7.	For patients who need long-term venous access and are at high risk for requiring kidney replacement therapy, we suggest against peripherally inserted central catheter (PICC) lines to optimize success of future dialysis vascular access, while considering patient values and preferences.	Weak against	Not reviewed, Amended

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
General Management Strategies (continued)	*Indication for Referral to Nephrology for Kidney Replacement Therapy Including Dialysis and Kidney Transplant*	8.	We suggest utilizing shared decision-making regarding kidney replacement therapy versus conservative management.	Weak for	Not reviewed, Not changed
		9.	In patients with high co-occurring conditions/low functional status, we suggest nephrology referral with sufficient time for comprehensive preparation for conservative management or dialysis for treatment of kidney failure, depending on patient values and preferences.	Weak for	Not reviewed, Amended
		10.	In patients with high co-occurring conditions/low functional status approaching the need for dialysis, there is insufficient evidence to recommend for or against dialysis to improve quality of life.	Neither for nor against	Not reviewed, Amended
Pharmacologic Management of CKD and Associated Conditions	*Hypertension Medications*	11.	We suggest intensive blood pressure management to reduce mortality and major adverse cardiovascular events in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 m².	Weak for	Reviewed, Amended
		12.	In patients with hypertension and albuminuria (i.e., urine albumin-to-creatinine ratio [UACR] >30 mg/g), we recommend the use of either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker to slow the progression of chronic kidney disease.	Strong for	Reviewed, Amended
		13.	We suggest the addition of a thiazide diuretic or calcium channel blocker to reduce blood pressure in patients with chronic kidney disease and hypertension not controlled on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.	Weak for	Reviewed, New-added
	Other Medications to Decrease Cardiovascular Disease and Kidney Outcomes	14.	In patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) currently on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, we suggest continuing therapy, unless there is drug intolerance or other adverse event.	Weak for	Reviewed, New-added
		15.	We recommend the addition of sodium-glucose co-transporter 2 inhibitors to maximally tolerated angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, in patients with chronic kidney disease who have one or more of the following: • Type 2 diabetes • Albuminuria (UACR >200 mg/g) • Heart failure to reduce the risk of major adverse cardiovascular events, heart failure, progression of kidney disease, and mortality,	Strong for	Reviewed, New-replaced

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
			and continuing sodium-glucose co-transporter 2 inhibitors until start of dialysis.		
Pharmacologic Management of CKD and Associated Conditions (continued)	*Other Medications to Decrease Cardiovascular Disease and Kidney Outcomes (continued)*	16.	We recommend adding a glucagon-like peptide-1 receptor agonist to an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in patients with type 2 diabetes and albuminuric chronic kidney disease to reduce the progression of chronic kidney disease, major adverse cardiovascular events, and all-cause mortality.	Strong for	Reviewed, New-replaced
		17.	In patients with chronic kidney disease and heart failure, we suggest sacubitril/valsartan as an alternative to monotherapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.	Weak for	Reviewed, New-added
		18.	We suggest the addition of a non-steroidal mineralocorticoid receptor antagonist (e.g., finerenone) in individuals on maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker who meet **all** the following criteria: • Type 2 diabetes • Albuminuria >30 mg/g • eGFR ≥25 mL/min/1.73 m^2 • Potassium <4.8 mEq/L for the purpose of decreasing major adverse cardiovascular events and slowing progression of chronic kidney disease.	Weak for	Reviewed, New-added
		19.	In patients with chronic kidney disease not on dialysis, we recommend the initiation of statins to reduce major adverse cardiovascular events and mortality.	Strong for	Reviewed, New-added
		20.	In patients with autosomal dominant polycystic kidney disease, we recommend referral to a nephrology provider for evaluation and assessment of appropriateness of treatment with tolvaptan.	Strong for	Reviewed, New-replaced
	Other Kidney Disease Related Complications	21.	In patients with chronic kidney disease, we suggest using potassium binders in the management of persistent, non-life-threatening hyperkalemia.	Weak for	Reviewed, New-added
Contrast-Associated Kidney Injury		22.	For patients with chronic kidney disease undergoing imaging utilizing iodinated contrast media who are at increased risk for iodinated contrast-associated acute kidney injury, we recommend intravenous volume expansion with isotonic crystalloid (see Algorithm Module E and Appendix Q for additional information).	Strong for	Reviewed, New-replaced

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
		23.	We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury.	Strong against	Reviewed, Not changed

[a] For additional information, please refer to Determining Recommendation Strength and Direction
[b] For additional information, please refer to Recommendation Categorization

Recommendation

1. We suggest testing for chronic kidney disease (i.e., urine albumin/creatinine ratio and estimated glomerular filtration rate [eGFR]) in patients with one or more of the following associated risk factors:
    - Age over 60 years
    - Diabetes
    - Hypertension
    - Cardiovascular disease, including heart failure

    (Weak for | Reviewed, Amended)

Discussion

This recommendation for testing for CKD is based on very low-quality evidence from the current evidence review (60-63) and evidence carried forward from the 2019 VA/DOD CKD CPG.(64) The evidence suggests that patients with age greater than 60 years, diabetes mellitus, hypertension, and CVD, including heart failure, are at higher risk for CKD progression and that these factors identify a large proportion of individuals with CKD. The evidence also indicates that testing for CKD using UACR in addition to eGFR is needed (60-64) since albuminuria is an important prognostic marker for assessing the risk of future progression to kidney failure. Missing opportunities for early diagnosis, prognostic assessment, and management leaves patients at greater risk of further disease progression and complications.

The evidence base for targeted testing for CKD in a general population consisted of one prospective population-based cohort study in the Netherlands.(64) The study compared three testing approaches using eGFR and UACR to identify patients with CKD who have a higher rate of incident CVD events and kidney function decline. Testing those with diabetes, hypertension, and CVD history resulted in 16% of the population being tested and identified 36% of those with CKD. By adding those aged >60 years, 29% of the population were tested and 59% of those with CKD were identified. Targeted testing of those with low socioeconomic status did not improve CKD diagnosis. However, the study did not include a no-screening comparison and did not evaluate the potential benefits of identifying high-risk patients (e.g., whether identification led to better treatment and outcomes for these patients).

One large cohort study (61) evaluated all patients who met eGFR criteria for stage G3 CKD in the U.S. The TriNetX database revealed that 81% had hypertension, 38% had type 2 diabetes, 18.7% had established CVD, and 16.4% had heart failure. The study showed that 64.3% of patients with stage G3 CKD were undiagnosed, defined as absence of the appropriate diagnostic code. The prevalence of undiagnosed CKD increased with age, and the factors associated with undiagnosed

CKD were female sex, stage G3a CKD, and no medical history of diabetes or hypertension. One limitation of this study was the very low overall frequency of UACR testing (1.8%).

One large cross-sectional study (62) of 199.81 million U.S. adults reported that 1.04 million adults who did not meet eGFR or albuminuria criteria for diagnosis of CKD had a high risk (≥5%) of CKD progression (probability of ≥40% decline in eGFR or kidney failure) within 3 years. Among these adults, 98% had hypertension, 44% had diabetes, and 72% had heart failure. Among the 102,320 persons who did not meet criteria for CKD but had a 3-year risk ≥10%, 97% had hypertension, 38% had diabetes, and 98% had heart failure. Among those with albuminuria (UACR ≥30 mg/g) and preserved eGFR, 24% (3.73 million adults) had a 3-year risk of CKD progression ≥5%, and 59% of this high-risk group had diabetes. The remaining 41% (1.51 million adults) with high risk would generally not be tested for albuminuria using standard quality metrics.

Evidence from one multinational cohort study (60) found an increased risk of kidney failure following prevalent or incident cardiovascular events (coronary heart disease, stroke, and/or heart failure). Mean age at baseline was 53 years (standard deviation: 17), and mean follow-up was 4.2 years. At baseline, 15% had diabetes, 9.5% had prevalent coronary heart disease, 3.2% prior stroke, 3.3% heart failure, and 4.4% prior atrial fibrillation. Patients with prevalent cardiovascular events were at higher risk of kidney failure requiring chronic dialysis or kidney transplant, with hazard ratios (HRs) ranging from 1.1 to 1.4. Additionally, though mean baseline eGFR was 89 mL/min/1.73m^2, HRs for kidney failure requiring chronic dialysis or kidney transplant after an incident cardiovascular event ranged from 1.99 for stroke to 4.5 for heart failure. Among survivors, the highest risk was seen in the first 3 months after the cardiovascular event, persisting for 2 years and returning to baseline 3 years after the cardiovascular event.

Evidence from 1 SR with 4 studies (63) suggests that hypertension is associated with an increased risk of incident CKD. The risk appears to be slightly higher in males compared to females. The same finding was observed when incident CKD and incident kidney failure were combined in the analysis.

Other risk factors for the development of CKD include but are not limited to obesity/metabolic syndrome/metabolic dysfunction-associated steatotic liver disease (MASLD), Hepatitis B and C, family history of CKD, history of gout, nephrotoxic medications, history of pregnancy complications (preeclampsia, pre-term delivery, gestational diabetes, small for gestational age, stillbirth), and those born prematurely or who were small for their gestational age.(65-75)

Research that analyzed the impact of acute kidney injury (AKI) or acute kidney disease (AKD) on CKD progression was generally of lower quality evidence, and the Work Group reviewed four observational studies. Muiru et al. (76) concluded that there was no significant change in kidney function from baseline following an AKI sustained during hospitalization. Ikizler et al. (77) found that patients who experienced an AKI during hospitalization were significantly more likely than those without AKI to experience CKD progression and all-cause mortality, but no association was noted with AKI and risk of MACE or heart failure. Weisbord et al. (78) noted that patients with AKI were more likely to develop the composite endpoint of death, need for dialysis, or permanent kidney impairment within 90 days of sustaining AKI. However, the incidence of clinically significant contrast-associated AKI was low, and there was no difference between patients with and without AKI requiring hospitalization between 4- and 90-days post angiography. Lastly, Sykes et al. (79)

concluded that progression to KRT was higher for patients that had more severe and frequent AKI, but no association was noted with AKI and mortality.

While the results of these four studies are mixed, the Work Group agreed that there is evidence to suggest that severe and repeated AKI in the setting of CKD could result in the progression of CKD, even if the long-term clinical significance of that impact is still in question. Though these studies were not definitive, studies of AKI in patients without CKD have repeatedly shown an association with increased risk of CKD and ESKD.(70,75,80) Such findings certainly bolster the concept of an association between AKI and CKD progression. These studies suggested that the impact of AKI on the risk of mortality and CVD is negligible, even though CKD is a risk factor for CVD and all-cause mortality. Providers are often reticent to proceed with contrast-enhanced studies in patients with advanced CKD; however, since the risk of long-term harm associated with contrast-associated AKI is small, it is reasonable to proceed with the appropriate imaging studies to reduce the delay in diagnosis or treatment.

Optimally, to make a recommendation on testing, there would be evidence such as an RCT with clinical endpoints that randomly assign patients, providers, or practices to either testing or usual care strategies, but no such trial has been conducted. However, there is a rational expectation that testing for CKD may be helpful, given the availability of treatments to slow CKD. Identification of patients with CKD provides an opportunity to slow CKD progression. In addition, since patients with CKD have elevated CVD risk, implementing or intensifying measures to prevent CVD could also improve patient outcomes. Potential harms of testing include risk of over-diagnosis and "labelling" patients with a diagnosis, which could result in negative impacts on patient finances, employment status, their family members, psychosocial and mental health, and insurance coverage. While the proposed testing (eGFR and UACR) is not resource-intensive and testing is readily available in VA/DOD, there is unnecessary cost and resource use for those misdiagnosed with CKD. Providers have a responsibility to their patients to ensure that CKD case finding among patients with conditions associated with heightened CKD risk are accompanied by strong evidence and that there is the opportunity to counsel patients about treatment plans (see Algorithm Module A).

There is some variability in provider and patient preferences regarding CKD testing. Some patients may not want to be tested, as the results may cause increased anxiety about being diagnosed. However, the benefits outweigh the harms due to new treatment options that decrease the progression of CKD in both individuals with and without diabetes. The patient focus group expressed preference for earlier diagnosis and concerns about late identification of CKD, as well as emphasized the importance of follow-up. The decision to test for CKD should be individualized, based on SDM with the patient.

The Work Group systematically reviewed evidence related to this recommendation.(60-64) Therefore, it is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was Very low. The benefits of targeted testing for CKD with UACR and eGFR in those with age over 60 years, diabetes mellitus, hypertension, and CVD, including heart failure, outweigh the potential harms, which include anxiety, cost, and resource utilization. Patient values and preferences vary somewhat because some patients may not want to be tested. Thus, the Work Group decided upon a *Weak for* recommendation. The Work Group recommends that future

research be prioritized to identify the most promising population(s) for potential CKD testing and its optimal frequency.

Recommendation

2. We recommend using urine albumin-to-creatinine ratio and estimated glomerular filtration rate for predicting chronic kidney disease progression.
   (Strong for | Reviewed, Amended)

Discussion

CKD is defined as persistent abnormalities of kidney structure or function. Criteria for CKD require either markers of kidney damage (e.g., hematuria, albuminuria) or decreased GFR to be present for a minimum of 3 months. While many individuals have eGFR assessed with a routine chemistry panel, albuminuria is not routinely assessed (81) in those without diabetes or known CKD. Tio et al. used NHANES data to model risk of progression of CKD. At baseline, they found that 60% of individuals with CKD had elevated albuminuria but an eGFR >60 mL/min/1.73m^2. The majority of these individuals did not have diabetes, so many individuals with CKD who are at high risk for progression may go undiagnosed without including albuminuria testing.(62) Additionally, the studies of SGLT2i and CKD, which included individuals with albuminuria and eGFR >60 mL/min/1.73 m^2,(82,83) showed benefit regarding delaying CKD progression across all levels of eGFR and albuminuria. Therefore, only using eGFR to detect CKD represents missed opportunities to identify individuals who would benefit from treatment.

Both albuminuria and decreased eGFR are important prognostic findings. Though not included in the current evidence review, a study of 1,024,977 individuals from the general population, high-risk cardiovascular cohorts, and CKD cohorts found that both eGFR and albuminuria independently predicted the risk of mortality. Additionally, in the CKD cohorts, both factors independently predicted the risk of ESKD.(84) In the current evidence report, Grams et al. analyzed the association of eGFR and albuminuria with kidney outcomes in a 114 cohort, patient-level meta-analysis of 27,503,140 individuals. They found that both eGFR and albuminuria were associated with adverse kidney outcomes.(85) The evidence base revealed that the use of prediction formulas can further improve prediction of risk of progression (see Recommendation 4), and prediction formulas, such as the Kidney Failure Risk Equation (KFRE), require both eGFR and albuminuria.(86)

The Work Group systematically reviewed the evidence from the 2019 VA/DOD CKD CPG Evidence Synthesis Report, as well as the evidence for Key Questions 1, 2, and 8 from the current evidence base. Though the quality of studies on albuminuria and eGFR was Low to Moderate and the overall confidence in the quality of evidence was Low, the Work Group felt that a strong recommendation was justified since ESKD is a catastrophic disease with available treatments to delay the risk of progression. Testing both eGFR and albuminuria will identify more individuals at risk of progression who would benefit from treatment, than eGFR alone. This recommendation is consistent with patient preferences for earlier recognition and treatment. Thus, the benefit outweighs the risk and supports a *Strong for* recommendation.

Recommendation

3. In patients with an estimated glomerular filtration rate <60 mL/minute/1.73 m², we suggest estimating glomerular filtration rate with a combined creatinine and cystatin C formula for risk prediction.
   (Weak for | Reviewed, Amended)

Discussion

Though eGFR is most commonly calculated using creatinine-based formulas, combining creatinine and cystatin C generally improves estimation of eGFR. Serum creatinine (sCr) levels are affected by creatinine generation (related to muscle mass), tubular excretion, and kidney function. Cystatin C is an alternative that is less biased by muscle mass than creatinine for estimating kidney function. However, there are also non-kidney function factors that affect cystatin C levels, such as fat mass and inflammation (see Appendix J).(87) While not part of the current evidence base, studies have found that there is often a discrepancy between creatinine eGFR and cystatin C eGFR.(88) The most accurate eGFR formulas in most patients appears to be the combined creatinine-cystatin C equation, where the non-kidney determinants appear to counteract each other.(89)

The combined eGFR also appears to be a better predictor of adverse outcomes compared with creatinine eGFR alone, though the data were somewhat mixed. Earlier studies not included in the evidence base have found that cystatin C eGFR has a linear and stronger association with mortality compared to creatinine eGFR, which shows a U-shaped association with mortality.(90,91) A significantly lower eGFR by cystatin C is associated with an increased risk of adverse outcomes.(88,92) In the Osteoporotic Fractures in Men Sleep Study, which was part of the 2019 VA/DOD CKD CPG evidence synthesis, Canales et al. found that the combined cystatin C-creatinine eGFR was better at classifying individual mortality risk.(93) In contrast, Shardlow et al. found that the combined formula versus the creatinine or cystatin C alone formulas were similar for risk prediction in the Renal Risk in Derby Study.(94) In the current evidence report, Grams et al. performed a patient level meta-analysis and found that the combined cystatin-creatinine eGFR was a better predictor of progression of kidney disease, cardiovascular outcomes, and healthcare utilization than the eGFR based on creatinine alone.(85)

The Work Group systematically reviewed the evidence from the 2019 VA/DOD CKD CPG, as well as relevant studies in the 2025 VA/DOD CKD CPG evidence base, though cystatin C was not a focus of the current SR. The quality of studies was Low. The Work Group agreed that the combined cystatin C-creatinine formula is more accurate for predicting the risk of CKD progression, and determining this risk could be informative for patients and providers in guiding treatment. Cystatin C is becoming more widely available, but it is not as widely available as serum creatinine. The importance of having cystatin C available for military members, given the impact of muscle mass on creatinine and the possibility that a CKD diagnosis could drive operational decisions, was felt to be an important consideration for this recommendation. A muscular individual could be incorrectly characterized as having CKD, which could limit their deployability and potentially degrade operational strength. Likewise, an incorrect diagnosis could restrict their options for duty stations or assignments. While the cost has declined, the cystatin C assay is more expensive than serum creatinine. The Work Group felt that a *Weak for* recommendation was indicated.

Recommendation

4. We suggest the use of a validated, end-stage kidney disease risk prediction model (e.g., kidney failure risk equation [KFRE]) for the management of stage G3-G5 chronic kidney disease.
   (Weak for | Reviewed, Amended)

Discussion

Various risk prediction equations have been developed over the past decade to aid providers in caring for those with CKD. The KFRE (https://www.kidneyfailurerisk.com), developed in 2011 from the Canadian Chronic Kidney Disease cohort, uses variables that are easy to ascertain (age, sex, eGFR, UACR, bicarbonate, albumin, phosphorus, calcium).(95) Both versions of the KFRE (4-variable and 8-variable) have high discriminatory ability to differentiate between those who develop kidney failure from those who do not. The KFRE was validated in a meta-analysis that included >725,000 participants from over 31 different cohorts representing 30 countries.(96) Since then, other investigative teams have attempted to develop similar risk prediction tools such as the Klinrisk model (based on machine learning) and VA CKD risk prediction model.(95,97,98) Further, the CKD Prognosis Consortium has also developed models to predict the risk of >40% decline in eGFR, development of advanced CKD, and progression to kidney failure (https://www.ckdpc.org/risk-models.html). Use of a validated risk prediction equation may help providers counsel patients, guide care, and optimize resource utilization targeting those at higher risk for progression, specifically patients with stage G3 or higher CKD. Kidney failure risk prediction may also assist with identifying individuals who need more intensive management or who may benefit from multidisciplinary care.

While the current evidence identified several studies, they were of Low quality, and most studies were conducted primarily outside the U.S. Major et al. reported the utility of KFRE in the United Kingdom and noted that the adoption of KFRE in primary care increased the overall referrals to nephrology for CKD care while reducing unnecessary referrals.(99) While not part of the evidence base, Duggal and colleagues similarly noted using VA data that current laboratory-based guidelines for nephrology referral identified patients who were, on average, at low risk for progression, most of whom were not referred.(100) CKD burden is high among U.S. Veterans, and appropriate referrals would not only help better utilize the limited resource that is available, but also avoid unnecessary anxiety and burden associated with referral to specialty care. Despite prior evidence about the utility of risk prediction equations to optimize CKD care, studies comparing different risk prediction equations on their impact on referral patterns, clinical quality metrics (e.g., use of recommended therapies, blood pressure [BP] control, glycemic control) and clinical outcomes (e.g., rates of CKD progression) are limited. Further, most new models were compared to the KFRE without examining their impact on clinical practice, such as whether they can augment UACR testing, adopt evidence-based therapy, etc. To establish the superiority of one equation or model over another, additional studies are warranted.

Findings from the patient focus group emphasized the importance of informing the patient about the risk of kidney disease progression. Even though some information technology resources would be needed, such risk prediction tools can be easily implemented (feasibility) within electronic medical records and help facilitate appropriate use of resources.

The Work Group systematically reviewed the evidence related to this recommendation from both the 2025 and 2019 VA/DOD CKD CPG evidence bases. The Work Group specified the risk prediction models that have been validated, delineated their clinical utility, and clarified the population for whom each was studied (see Risk Equations Table below). Therefore, this recommendation is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of evidence was Low. The body of evidence had some limitations as the studies did not compare the utility of the risk prediction equations to standard practice, and studies did not assess the impact of implementing these equations in a broader population in the U.S. The benefit of including a risk prediction equation slightly outweighed the potential harms such as anxiety or uncertainty about kidney disease progression. Patient values and preferences were similar as the patient focus group expressed their interest in knowing the risk of CKD progression. Thus, the Work Group decided upon a *Weak for* recommendation.

Useful equations in CKD diagnosis, staging and risk assessment

Clinical Utility	Useful for	Equation (calculator website)	Required patient data	Comments
Predicts 2- and 5-yr risk of kidney failure in patients with CKD stage G3-G5	Patients with eGFR <60	Kidney Failure Risk Equation (KFRE)(95) (https://www.kidneyfailurerisk.com/)	Four-variable equation: age, sex, eGFR, UACR Eight-variable equation: age, sex, eGFR, UACR, serum calcium, phosphate, bicarbonate, albumin	• Validated in >2 million in >30 countries • Validated in pediatric, transplant and ethnically diverse populations • Incorporated in national/international guidelines including KDIGO CPG • Included in Clinical Decision Support Console in CPRS (VAMC)
Estimates 2- and 4-yr risk of ESKD, CVD and death	Patients with eGFR <30	CKD G4+ (CKD-PC) risk calculator (101) (https://ckdpcrisk.org/lowgfrevents/)	Age, sex, race, eGFR, SBP, history of CVD, DM, UACR, smoking status	• Calculates competing risks of ESKD, CVD and death • May be useful in SDM since risk of CVD and mortality is higher than risk of ESKD in most older/frail patients
Predicts risk of 40% decline in kidney function or kidney failure	Patients with eGFR >60	40% decline in kidney function in 3-years (102) (https://ckdpcrisk.org/gfrdecline40/)	Age, sex, eGFR, UACR, SBP, antihypertensive medication use, diabetes, history of heart failure, history of coronary heart disease, history of atrial fibrillation, smoking status, BMI In diabetics: hemoglobin A1c, insulin use, use of oral diabetes medication	• 40% decline in kidney function more applicable in those with early CKD • Used as surrogate marker for FDA/clinical trials • Overall lower C-statistic in Grams model (compared to Ferguson model) but Grams model developed/validated in larger population and Ferguson model developed/validated in Canadian patients; no

				online calculator available for Ferguson model
Estimates 5-year probability of eGFR <60	Patients with CKD	Risk of Developing Reduced Kidney Function (103) (http://ckdpcrisk.org/ckdrisk)	Diabetes status, age, sex, race, eGFR, CVD, BMI, smoking history, DM treatment, HgbA1C, UACR, HTN	
Estimates probability of having eGFR <60 mL/min/ 1.73m^2	Patients without known CKD	Screening for Occult Renal Disease (SCORED) score (104) (https://nccd.cdc.gov/ckd/Calculators.aspx)	Age, sex, anemia, HTN, DM, history of CVD, history of CHF, PVD	
Conversion of UPCR or dipstick to UACR	Patients with or at-risk for CKD	Conversion of UPCR and dipstick to UACR (105) (http://ckdpcrisk.org/pcr2acr)	Crude equation: UPCR (mg/g) or urine dipstick protein Adjusted equation: sex, hypertension, and diabetes	• Many risk calculators include UACR but UACR data not always available so conversion enables clinicians to estimate UACR from other readily available measures of albuminuria • Urine dipstick is low-cost and rapidly available, even in resource-restricted locations • Albuminuria is subject to intra-individual biological variability (first morning void thought to be most accurate) • Caution in non-albumin proteinuria (e.g., multiple myeloma, amyloidosis). • Similar estimates for KFRE calculated when using predicted vs. observed ACR (105)
Estimates 10-year and 30-year risk of CVD (composite CVD risk and individual risk of ASCVD and HF)	Patients without known CVD or HF, aged 30-79 years	AHA Predicting Risk of Cardiovascular Disease Events (PREVENT) equations (106) (https://professional.heart.org/en/guidelines-and-statements/prevent-calculator)	Age, sex, total cholesterol, HDL, SBP, BMI, eGFR, DM status, smoking status, use of antihypertensive medication, use of lipid-lowering medication Optional factors: UACR, A1C, zip code (for estimating SDI)	• Performed better than PCE (106,107) • 1% increase in PREVENT risk estimate associated with increased CVD mortality (HR: 1.09)(107)

Abbreviations: A1C: glycated hemoglobin; ACR: albumin-to-creatinine ratio; ASCVD: atherosclerotic CVD; BMI: body mass index; CHF: congestive heart failure; CKD: chronic kidney disease; CKD-PC: Chronic Kidney Disease Prognosis

Consortium; CPG: clinical practice guideline; CPRS: computerized patient record system; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HgbA1c: hemoglobin A1c; HDL: high density lipoprotein; HF: heart failure; HR: hazard ratio; HTN: hypertension; KDIGO: Kidney Disease: Improving Global Outcomes; MCVD: monogenic CVD; PCE: pooled cohort equation; PVD: peripheral vascular disease; SBP: systolic blood pressure; SDI: Social Determinants of Health Index; UACR: urine ACR; UPCR: urine protein-to-creatinine ratio; VAMC: Veterans Affairs Medical Center

Recommendation

5. When providing patient education about chronic kidney disease, there is insufficient evidence to recommend for or against any specific health education program or mode of delivery.
   (Neither for nor against | Reviewed, Amended)

Discussion

The evidence review identified two RCTs, Easom et al. (108) and Molnar et al.,(109) and one SR by Stevenson et al.(110) The Easom RCT (108) enrolled 240 participants with eGFR less than 30 mL/min/1.73 m^2 who were not yet on dialysis to determine the effect of education on KRT selection. The participants received either face-to-face (FTF) education or education via telemedicine. The major aim was for patients to be able to select a dialysis modality after their third class. Standardized curriculum was presented at grade 5-7 literacy level to both FTF and telemedicine classes, and questionnaires were distributed after each class. At baseline, 47.1% of the FTF group and 52.2% of the telemedicine group did not feel they had enough information to select a dialysis modality. Approximately two-thirds of participants attended all three classes. Following the third class, only 7.4% of the FTF group and 13.2% of the telemedicine group still felt they did not have enough information to select a dialysis modality. Additionally, the results showed that, when educated, the number of patients who would choose a home modality more than doubled, increasing from 12.9% in the FTF group and from 22.2% to 50% in the telemedicine group. Analysis of patients who were enrolled but never attended a class and subsequently initiated KRT showed that 8% started on a home modality, similar to the home modality rate of 10% in the 2015 U.S. Renal Data System (USRDS). Comparatively, 43% of the study participants who attended at least one class subsequently initiated KRT on a home modality.

Molnar et al. (109) randomized 140 patients from 3 multidisciplinary kidney clinics across Ontario, Canada, to either usual care or use of a web-based Interactive Health Communication Application (IHCA) in addition to usual care. Those receiving usual care received education about dialysis modalities by clinic nurses. The web-based IHCA was designed specifically to promote home KRT and included social support components (e.g., moderated forum of patients). Patients randomized to IHCA were oriented to the website and asked to log in monthly. The study's objective was to assess whether IHCA would increase selection of a home dialysis modality. Of note, 64% intended to use a home dialysis modality at enrollment, which was much higher than anticipated and might reflect self-selection bias or strict inclusion criteria. The study did not show a difference in home dialysis modality selection in the intervention group. However, uptake of the intervention was low, with 43.2% of participants in the IHCA group accessing the website in the previous month at the 6-month mark and 29.6% at 1-year follow-up. Additionally, the researchers identified several challenges, including poor recruitment and difficulty maintaining patient interest in a web-based intervention, which may be attributed to the older patient population affected by CKD.

Stevenson et al. (2019) (110) reviewed 43 studies in patients with CKD to evaluate the efficacy of eHealth interventions to change health behaviors (e.g., diet, medication) and improve outcomes (e.g., BP control, hospitalizations, quality of life, patient satisfaction with care). Of those 43 studies, only 2 RCTs (BRIGHT and MESMI) met inclusion criteria for the current evidence review. These studies, which assessed the use of an educational website/DVD versus usual care, revealed no difference between groups in medication adherence or BP control. However, studies showed a higher quality of life (QoL) at 6 months for those in the intervention group. The authors cited significant concern for bias and methodological limitations in the included studies, highlighting the need for high-quality research to determine the impact of eHealth interventions.

The patient focus group found that patients valued receiving education from their provider on how to prevent the progression of CKD. They also wanted their providers, especially those in outlying/remote areas, to receive more education about how to manage patients with CKD and when a nephrology referral would benefit their patients' kidney care. These patients preferred a multidisciplinary team approach to care and intentional communication from their providers regarding treatment of their CKD. Moreover, they were comfortable using a variety of delivery options for their care, including telehealth, in-person visits, or a mix of both.

The Work Group systematically reviewed evidence from the 2019 VA/DOD CKD CPG Evidence Synthesis Report as well as the studies cited in the current evidence base,(108-110) so the recommendation is *Reviewed, Amended*. The overall quality of the evidence was Very low, and no specific educational program appeared to be superior. However, the potential benefits of education include increasing compliance with therapies to slow the progression of CKD, enabling patients to make an informed choice regarding KRT that includes transplant and conservative care, and ensuring patients are actively involved in their medical care. Potential harms were small, but feasibility, resource use, and availability may vary significantly. Patients in the focus group strongly stated that they desired education earlier in the course of their CKD and wanted providers to receive more education on available treatment options to provide patients with all available options. However, patient preferences are likely significantly varied, not only in how much information a patient desires, but also in how they prefer to receive education. Thus, the Work Group decided on a *Neither for nor Against* recommendation.

Recommendation

6. We suggest interdisciplinary care (e.g., including dietitians, pharmacists, social workers, providers, nurses, and palliative care) for patients with chronic kidney disease.
   (Weak for | Not reviewed, Amended)

Discussion

The outcomes utilizing an interdisciplinary team (IDT) to provide care to patients with CKD are not well established, and the studies identified in the 2019 VA/DOD CKD CPG evidence review had serious limitations and inconsistency with mixed results.(111-114) An SR and meta-analysis of 21 studies with a mix of cohort and RCT designs by Shi et al. indicated that IDTs may reduce all-cause mortality, hospitalization rates, need for dialysis initiation with a catheter, and eGFR decline, with the greatest benefit in patients with late stage G4 or stage G5 CKD.(113) However, a second SR by Valentijn et al. did not reveal differences in all-cause mortality, eGFR decline, or rate of KRT with IDT care, although they demonstrated that IDTs were associated with decreased rates of hospitalizations and improved BP control.(114) An RCT by Foglefeld et al. showed that

IDT appointments with coordinated care focused on tight control of BP, blood sugars, lipids, and albuminuria in patients with diabetes and CKD stage G3-G4 may slow progression to ESKD compared with usual care. However, the study was not blinded, only enrolled 120 subjects, and had a high attrition rate.(111)

Other research, not included in the evidence base, showed that patients with late-stage CKD (eGFR <30 mL/min per 1.73m^2) using interdisciplinary care were more successful in their ESKD transition. In a single-center retrospective cohort study, those in the interdisciplinary care program were more likely to start home dialysis compared to average rates seen in the USRDS (23% vs. 11% USRDS). Additionally, 12% underwent pre-emptive kidney transplant and 51% started in-center hemodialysis (ICHD) with an arteriovenous fistula (AVF) or graft (AVG). Overall, more program participants achieved optimal transition to ESKD (58% vs. 30% USRDS) independent of patient race, ethnicity, and payor.(115)

Participants in the 2019 and 2025 VA/DOD CKD CPG patient focus groups highlighted the benefits of an IDT in their care. They felt an IDT enhanced the development of individualized treatment plans, tailored education about the benefit of interventions, and augmented support in making lifestyle changes, thereby increasing patients' ability to adhere to their individual plans. Additionally, one participant in the 2025 patient focus group asserted that IDT care provided patients with consistent messaging with respect to interventions and lifestyle modifications.

As this is a *Not reviewed, Amended* recommendation, the Work Group systematically reviewed the relevant evidence from the 2019 VA/DOD CKD CPG.(111-114) The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had very serious limitations and serious inconsistency with mixed results, but IDT may have some beneficial effects on outcomes (e.g., reduced hospitalization, slowing CKD progression, improved BP control). While the patient focus groups felt that IDT care was beneficial, large variation exists in patients' values and preferences due to the time commitment associated with IDT care. Resource use, access to services, and feasibility of IDT care must also be considered. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

7. For patients who need long-term venous access and are at high risk for requiring kidney replacement therapy, we suggest against peripherally inserted central catheter (PICC) lines to optimize success of future dialysis vascular access, while considering patient values and preferences.
   (Weak against | Not reviewed, Amended)

Discussion

Peripherally inserted central catheters (PICC) are attractive options for long-term intravenous (IV) access, though they also pose risk, particularly for patients with CKD. These lines are easy to place, inexpensive, and convenient for patients and nurses. Additionally, use of these vascular devices may eliminate the need for repeated venipuncture for labs and peripheral intravenous (PIV) lines and may result in shorter hospitalizations and cost savings when used for outpatient IV antibiotics and infusion therapy. However, PICC lines may be complicated by phlebitis, catheter-related infection, and venous thrombosis, which may increase resource use and healthcare costs. One prospective study revealed an overall thrombosis rate of 71.9%

resulting in partial or complete obliteration of vessel lumen, though <5% of patients were symptomatic.(116)

Clinicians should also be aware that PICC lines and other vascular access devices may negatively impact future hemodialysis access by damaging central and peripheral vessels. Mature AVFs are associated with superior patency and lower complication rates compared with AVGs or dialysis catheters and are considered the gold standard for hemodialysis vascular access.(117) Since PICC lines are often placed in the basilic, brachial, and cephalic veins and terminate in the thorax, use of PICC lines may result in stenosis of the venous structures needed for future hemodialysis access. In the 2019 VA/DOD CKD CPG evidence review, two observational studies were identified, and both demonstrated that prior PICC line use was associated with increased risk of failure to achieve a functional AVF or AVG.(118,119) Using a case-control design with 120 patients who had no functioning AVF and 162 controls with functioning AVF, El Ters et al. found that prior PICC use was associated with higher odds of an inability to achieve a functioning AVF.(118) A retrospective review of 33,918 incident hemodialysis patients in the USRDS registry who initiated hemodialysis with a central venous catheter as their sole access revealed that PICC use was common, with 12.6% of these patients having had at least one PICC and 30% having had more than one PICC. Further, 53% had PICC lines placed within 2 years of hemodialysis initiation and the remaining 47% had PICC lines placed after starting dialysis.(119) They also showed that prior PICC placement was associated with a lower likelihood of successful AVF.(119) Thus, the potential risk of failing to achieve adequate vascular access for hemodialysis must be balanced against the benefits of IV access with PICC lines.

When making decisions regarding vascular access, patient condition and preferences as well as other patient care alternatives should also be considered. Long-term dialysis access might be less of a concern for patients who do not wish to pursue KRT or have significant co-occurring conditions such that mortality or other risks outweigh the likelihood of progression to ESKD. KDOQI recommends vessel preservation for patients with CKD G3-G5,(120) and estimates of ESKD risk may be made through proper CKD staging or by using a validated risk equation (see Recommendation 4) to better inform the SDM process. Some patients are not bothered by venipuncture, while others may experience significant pain and anxiety with lab draws and PIV placements. Using ultrasound to guide PIV placement in veins of the hand, limiting venipuncture to one limb, and avoiding venipuncture and vascular device placement in the cephalic, median antebrachial, antecubital, basilic, or subclavian veins may be helpful in patients with small veins and limited vascular access options, preserving larger proximal veins as much as possible for future dialysis access. Small-bore tunneled jugular catheters or midlines, which are much shorter than PICC lines, may be acceptable options to avoid the risks a PICC line could pose on the success of future dialysis access. However, data on the impact of these vascular access devices on dialysis access success is lacking. Since most PICC lines are placed for prolonged IV antibiotic therapy, the use of oral medications or newer antibiotics that require less frequent IV dosing (e.g., dalbavancin) may preclude the need for long-term IV access. However, 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. Collaboration with nurses, infectious disease specialists, and nephrology providers is important to optimize vascular access options, particularly for patients who may progress to ESKD.

As this is a *Not reviewed, Amended* recommendation, no new evidence was obtained. Two observational studies were identified in the 2019 VA/DOD CKD CPG SR, which both demonstrated that PICC lines were associated with an increased risk of failure to achieve a working AVF or AVG.(118,119) The Work Group rated these studies as Moderate quality evidence with limitations being their observational study designs and the potential for bias and confounding. The harms of failure to achieve adequate hemodialysis access were determined to outweigh the benefits of vascular access with PICC lines, especially with the availability of alternative vascular access options (e.g., small-bore tunneled internal jugular catheters, ultrasound-guided PIV placement), and the development of newer medications with longer duration of action. Patient values were somewhat varied, as referenced above. Thus, the Work Group decided on a *Weak against* recommendation.

Recommendation

8. We suggest utilizing shared decision-making regarding kidney replacement therapy versus conservative management.
   (Weak for | Not reviewed, Not changed)

9. In patients with high co-occurring conditions/low functional status, we suggest nephrology referral with sufficient time for comprehensive preparation for conservative management or dialysis for treatment of kidney failure, depending on patient values and preferences.
   (Weak for | Not reviewed, Amended)

10. In patients with high comorbidities/low functional status approaching the need for dialysis, there is insufficient evidence to recommend for or against dialysis to improve quality of life.
    (Neither for nor against | Not reviewed, Amended)

Discussion

The clinical management and care of patients with advanced CKD is complex. In particular, the decision to pursue KRT in the very elderly, frail, or medically complex CKD population is challenging for patients, their families, and providers alike. While the initiation of dialysis may prolong life, the choice to pursue dialysis should not be a foregone conclusion, and both clinical parameters and socioeconomic factors must be considered when making these decisions. Conservative management without dialysis, focusing on symptom management, is a reasonable treatment option that may better align with patients' values and preferences. It is important for providers to use SDM to determine patients' goals of care and educate patients about their options in an unbiased manner to assist patients in making an informed decision.(121)

Only two studies regarding the impact of SDM in the management of patients with advanced CKD were identified in the evidence base for the 2019 VA/DOD CKD CPG. Both provided Very low quality evidence that patient satisfaction increased when patients were actively involved with modality selection.(122,123) The German Choice of Renal Replacement therapy (CORETH) project evaluated the difference in patient satisfaction between peritoneal dialysis (PD) and ICHD, showing a statistically significant increase in patient satisfaction for those who participated in the process of modality choice.(122) The European Kidney Patients' Federation (CEAPIR) surveyed approximately 4,000 patients who were either on HD or had a functioning kidney transplant and found that approximately 75% had been involved in modality selection, which appeared to be associated with higher levels of satisfaction with their selected treatment.

However, approximately half of respondents felt their choices had been limited for a variety of reasons, such as modality availability at their center, financial constraints, or the presence of medical or social contraindications for a given modality. The survey also found that patients were more satisfied when information was provided by health care professionals, though the level of satisfaction varied depending on modality (respondents were more often satisfied with information provided on ICHD [90%] and transplantation [87%] than with information provided on PD [79%] or home HD [61%]). However, 11% of respondents did not remember receiving any information, and 39% did not recall being informed of alternative modalities or given the option to change modality.(123)

Patient education and decision aids may improve SDM and enable patients to make better informed treatment choices. In an RCT by Easom et al., education increased patients' ability to select a dialysis modality and increased the likelihood of initiating KRT on a home modality (see discussion on Recommendation 5).(108) Outside the evidence base, Ladin et al. randomized 363 patients aged 70 years and older with stage G4 and G5 CKD in a multicenter RCT to assess the use of an online Decision-Aid for Renal Therapy (DART) tool, which provided literacy-sensitive education about available treatment choices. They found that the DART tool was associated with an improvement in knowledge regarding prognosis and treatment options, a decrease in uncertainty regarding treatment preferences, and a reduction in decisional conflict. Additionally, the number of patients choosing conservative management increased from 11.5% at baseline to 19.9% at 6 months while remaining stable in the control group. Overall, few patients changed their preference once a decision had been made. By 18 months, 14.8% had died, and 9.1% had entered hospice or palliative care (12.1% DART vs. 6.1% control).(124)

Optimal SDM regarding CKD requires collaboration between patients and their health care team. Some barriers to this process include varying levels of comfort among PCPs with KRT discussions and difficulty maintaining ongoing communication between PCPs and nephrology providers, which was emphasized by the patient focus group. Clinicians can facilitate SDM by being proactive, eliciting patient values and preferences at an early stage, and encouraging active patient participation in SDM. Additionally, patient engagement may promote self-management and adherence to medical recommendations, which should hopefully optimize patient outcomes. Providers should use easy terminology when having these discussions with patients and be aware of how their personal biases may influence patient decisions.(122) Because these conversations and decisions may be challenging, particularly for older patients, involving palliative care clinicians may be helpful in these complex goals of care decisions.

The evidence base from the 2019 VA/DOD CKD CPG regarding the choice of dialysis versus conservative management included data from one comprehensive SR,(125) two retrospective studies,(126,127) and one prospective cohort observational study.(128) Because of the complexity of the patient population, the variability of patient values and preferences regarding ESKD management and ethical issues, RCTs comparing outcomes of KRT versus conservative management are not possible, and there was significant heterogeneity in study design and outcomes in the evidence base. A meta-analysis of 89 studies that examined a primary outcome of survival among 294,921 patients with ESKD ranging in age from 60.5 to 92 years showed that one-year survival was higher in patients choosing dialysis (6 studies, 84.2% dialysis vs. 72.7% supportive care) and no difference in survival was demonstrated between different dialysis modalities; however, individual studies in the meta-analysis were limited by presence of

unadjusted confounders and lack of clarity on missing data. Thus, results may not be applicable across populations. In a retrospective review of 838 ESKD patients aged 65 years or older, Tam-Tham et al. demonstrated statistically significant lower mortality favoring dialysis for the first 3 years of follow-up.(126) Brown et al. found a survival benefit of approximately 13 months in a prospective cohort study (33 months for patients assigned to pre-dialysis clinic vs. 20 months for those followed in conservative management clinic).(128) Though outside the 2019 evidence base, a retrospective study of 73,349 Veterans also demonstrated a higher median life expectancy for patients on dialysis, which decreased with increasing age (difference in median life expectancy of 54, 26, 25, and 17 months for patients 60, 65, 75, and 85 years, respectively, when dialysis initiated at eGFR <6 compared to those choosing conservative management).(129) Results were attenuated on covariate analyses when co-occurring conditions, impaired functional status, and advanced age (over 80 years) were considered.(125,128,130) While studies consistently show that dialysis is associated with prolongation of life, the difference in survival for older patients is modest, typically measured in terms of months.

Comparative analyses for hospital utilization and end-of-life care outcomes are available for elderly patients electing to pursue dialysis. Tam-Tham et al. conducted a retrospective cohort study of 838 ESKD patients (126) aged 65 years or older with an eGFR below 10 mL/min/1.73 m^2 and found a survival benefit of up to three years in the dialysis group. However, these patients also experienced a 40% increased risk of hospitalization. Wong et al. conducted a retrospective cohort study of 14,701 VA patients aged 65 to 84 years with an eGFR below 15 mL/min/1.73 m^2 and found that patients who elected not to pursue dialysis had significantly lower rates of hospital admission, intensive procedures defined as cardiopulmonary resuscitation (CPR), mechanical ventilation, total parenteral nutrition, and death occurring in the hospital.(127) Additionally, patients in the non-dialysis group were more likely to use palliative care and hospice services (38.7% non-dialysis vs. 18.2% dialysis) and had significantly fewer hospital days. While not part of the previous SR, Montez-Rath et al. used target trial emulation in a cohort of 20,440 Veterans aged 65 and older with an eGFR <12 mL/min/1.73m^2, finding that survival was 78 days longer but time at home was shorter by 15 days among those starting dialysis compared to the group continuing medical management and forgoing dialysis.(131) Thus, while dialysis may be a life-sustaining treatment, the corresponding increase in life expectancy associated with dialysis may not outweigh the burden of therapy in older patients.

There is emerging interest in the concept of “palliative dialysis,” which is the provision of dialytic therapy with the intention of easing symptoms of ESKD and prioritizing QoL over longevity and traditional treatment benchmarks. Though studies consistently show that dialysis extends life, there is insufficient evidence to recommend for or against dialysis to improve QoL in patients with high comorbidities/low functional status approaching the need for dialysis. A prospective observational study examined QoL as assessed by the 36-Item Short Form Survey (SF-36) in 467 patients with CKD stages G4 and G5 attending a pre-dialysis clinic, compared to those enrolled in a renal supportive care clinic.(128) At time of enrollment, patients in the renal supportive care clinic were significantly older and reported lower SF-36 physical composite scores than those in the pre-dialysis clinic. While there was a statistically significant survival advantage in the pre-dialysis clinic cohort, there was no significant difference in QoL and symptom indices between these two groups. That said, when commensurate with the patient’s goals of care, providers could consider shorter or less frequent dialysis, as well as loosened

targets for dialysis adequacy and control of metabolic derangements. While this approach reflects respect for patient autonomy, the indications and infrastructure to support palliative dialysis have not been established in the U.S.(132) For example, there is currently no mechanism to separate quality and outcomes data for palliative dialysis patients in the assessment of dialysis unit quality benchmarks. Consequently, palliative dialysis is not universally offered at this time, and further study and development of policy to support this approach is needed.

The evidence on the impact of SDM and the outcomes associated with KRT compared to conservative medical management had significant limitations. Differences in baseline characteristics between patients electing to pursue dialysis versus supportive care may confound the survival benefit of dialysis, since healthier patients may choose dialysis over conservative management. Decisions regarding KRT may be influenced by cultural or socioeconomic factors, and these factors may also limit the applicability of studies across populations. Limited-to-no ability to randomize patients, as well as difficulty with balancing cohorts in treatment arms, present challenges to conducting randomized and/or controlled trials; thus, the available evidence consists of observational or retrospectively collected survey data. Further, the body of evidence is limited by variability between comparator groups and lead time bias (i.e., apparent survival advantage related to early treatment, rather than true benefit of treatment).

As kidney function declines, decisions regarding KRT versus conservative medical management must be made. For patients whose first priority is prolongation of life, early referral with sufficient time for clinical evaluation, patient education, SDM for modality selection, and dialysis preparation to include access planning, placement, and maturation is suggested. Given the complexity and logistics, up to a year may be required to address these issues and adequately prepare patients for dialysis. On the other hand, a conservative approach to ESKD management (over dialysis) may better match the goals of care for patients with high co-occurring conditions/low functional status who prioritize the avoidance of hospitalization and aggressive medical interventions.

Initial nephrology referral at the time of dialysis initiation is associated with poorer clinical outcomes.(133,134) A narrative review by Mutatiri et al. (135) summarized the benefits of early referral, such as lower mortality risk, lower hospitalization rates, higher likelihood of initiating KRT with PD or obtaining permanent vascular access prior to initiating HD, and lower treatment costs. While it is not always possible to accurately predict when patients are likely to require dialysis, validated risk prediction models can be utilized to guide management (see Recommendation 4, Algorithm Module C, and Sidebar 8). When the eGFR is below 30 mL/minute/1.73 m^2 or risk of ESKD calculated by validated risk prediction model exceeds 40% over 2 years,(136) multidisciplinary care that includes nephrology providers should be considered for co-management of CKD complications that could postpone the need for dialysis, optimize symptom control to improve QoL, and provide adequate modality education and preparation for dialysis, depending on patients' values and preferences.(125)

There is significant variability in patient preferences regarding goals of care, including dialysis, in the frail and elderly populations. Patient values and preferences are influenced by many factors including age, cultural background, underlying co-occurring conditions, socioeconomic

factors, and prior experience with dialysis. Moreover, provider and caregiver beliefs and values may also impact patient decisions. Providers, including nephrologists, should 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.(122,123) Respect for patient autonomy in the decision to pursue or decline life-sustaining treatment with dialysis, the potential harms to patient independence, and impact to QoL should also be considered. Potential survival benefits of dialysis must be balanced against the risks of more intensive medical interventions (125-127) and loss of functional capability and independence, all of which may impact patient QoL.(137) Shared decision-making enables patients to make informed decisions about their care, and ensures that their values and preferences are reflected in their treatment decisions.

Based on the available evidence and the need for individualized management, the Work Group suggests utilizing SDM and referral to Nephrology with sufficient time for comprehensive preparation for either KRT or conservative management. Dialysis is a life-sustaining treatment. However, in frail and elderly patients, where survival benefit is less clear and the impact to QoL may be significant, the decision to pursue dialytic therapy should not be assumed to be a matter of course; instead, goals of care must be individualized to the preferences, values, and capabilities of the patient and their caregivers.(138) Involvement of geriatric and/or palliative care services to assist in SDM conversations and symptom management may be helpful. In situations where providers, patients, and caregivers are undecided regarding whether dialysis will be beneficial or when there is concern about whether a patient will tolerate KRT, palliative dialysis or a time-limited trial of KRT followed by re-engagement of the patient and caregivers in an SDM discussion may be appropriate.

Recommendation 8 is *Not reviewed, Not changed*, while Recommendations 9 and 10 are *Not reviewed, Amended*; hence, the Work Group did not conduct an updated evidence review but reviewed the evidence identified in the 2019 VA/DOD CKD CPG.(122,123,125-128,130,133,134,137) The Work Group believes that the benefits of SDM in the care of patients with progressive kidney disease outweigh the harms/burdens. Timely education for patients with progressive CKD is essential so that they can articulate their goals of care and make an informed decision about the direction of their treatment. Early referral facilitates adequate preparation for whichever treatment option the patient chooses (i.e., vascular access placement or palliative care referral). The Work Group decided to carry forward three *Weak for* recommendations, two of which were combined into 2025 Recommendation 9, and one *Neither for nor against* recommendation, suggesting the utilization of SDM involving the patient, caregivers, the PCP, and the nephrology team to achieve patient-centered treatment goals.

For additional considerations in the management of elderly patients with CKD, see Appendix P.

Recommendation

11. We suggest intensive blood pressure management to reduce mortality and major adverse cardiovascular events in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 m².
(Weak for | Reviewed, Amended)

Discussion

The Work Group sought evidence to make recommendations about the impact of BP control on clinical outcomes and determine the appropriate BP target for patients with CKD. The evidence suggests that treating high BP in patients with CKD with a more intensive systolic blood pressure (SBP) goal of <140 mmHg results in a reduction in all-cause mortality and MACE, though there is insufficient evidence to recommend a specific target. In the current evidence base, an SR by Zhang et al. (139) reported a benefit in all-cause mortality with a small effect size (number needed to treat [NNT]=50 for approximately 3 years), while an SR by Ku et al. did not find a statistically significant benefit in reducing death (140) with more intensive BP control.(141-145) Zhang et al. (139) also found that intensive BP control, with different targets of <120 mmHg, <130 mmHg, and <140 mmHg, resulted in a reduction in MACE with a small effect size (NNT=50 for approximately 3 years).

The evidence base included three SRs assessing progression to ESKD or a validated surrogate marker for progression to ESKD (e.g., >50% decline in GFR, GFR <15 mL/min/1.73 m^2),(139,143,146) and no difference in intensive versus standard BP control was evident. Also similar to the 2019 VA/DOD CKD CPG, evidence regarding adverse events was variable, with one SR (139) suggesting no difference and another SR (146) suggesting a small degree of harm (number needed to harm [NNH]=100 for hypotension; NNH >100 for syncope) associated with more intensive BP control.(147)

There is some variation in patient preferences regarding antihypertensive treatment. Specifically, while intensive BP control reduces MACE/death, it may also result in increased pill burden and a risk, albeit slight, of serious side effects. Other implications of this intervention include some resource impacts (e.g., cost of medications, monitoring requirements), variable patient and clinician acceptance (e.g., clinical inertia), lower intervention rates in minority and rural populations, and uncertain generalizability to patient populations not included in the evidence base (e.g., late-stage CKD, non-ambulatory, limited life-expectancy).

The Work Group systematically reviewed the evidence related to this recommendation, and as such, it is a *Reviewed, Amended* recommendation. There was insufficient evidence to alter the strength or direction of the 2019 recommendation,(141-145) but the Work Group altered the recommendation to highlight the finding that more intensive BP control in patients with CKD reduced death and MACE. These benefits slightly outweigh the small potential for drug-related adverse effects. Patient values and preferences about taking additional pills and the associated need for increased monitoring vary somewhat. Per the patient focus group discussion, patients may place a higher value on avoidance of dialysis, which is not as affected by intensive BP control as reduction of MACE or mortality events. The Work Group's confidence in the overall quality of the evidence was Low because the evidence base was limited to SRs that utilized post-hoc and subgroup analysis. The most significant limitation for this current evidence base is that the SPRINT trial,(148) which excluded patients with late-stage CKD or significant

proteinuria, represented approximately half of the patients included in the SRs reviewed. The Work Group did not feel there was sufficient evidence to select a specific SBP target given the variability in enrolled populations studied, how BP measurements were conducted, and goal SBP assignment versus SBP achieved from the individual trials contained within the SRs. Providers may refer to the VA/DOD CPG for the Management of Hypertension in Primary Care (147) for further discussion of BP targets. Further research is needed to determine the impact of BP control in patients with advanced CKD or significant proteinuria, as well as to define the optimal BP target. Given the current body of evidence, the Work Group decided on a *Weak For* recommendation.

Recommendation

12. In patients with hypertension and albuminuria (i.e., urine albumin-to-creatinine ratio [UACR] >30 mg/g), we recommend the use of either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker to slow the progression of chronic kidney disease.
    (Strong for | Reviewed, Amended)

Discussion

This recommendation is revised from the 2014 VA/DOD CKD CPG, which was carried forward in the 2019 VA/DOD CKD CPG following an updated review of the evidence. The 2019 VA/DOD CKD CPG included multiple recommendations (2019 recommendations 21, 22, and 23) for the use of ACEI or ARB in patients with hypertension, albuminuria, and either diabetic or non-diabetic kidney disease to prevent the progression of CKD. In addition, ACEI has been reported to be beneficial in patients with type 1 diabetes with albuminuria to reduce the combined risk of death, dialysis, or transplantation.(149) Multiple trials and SRs support the use of ACEI or ARB as the initial hypertension treatment regimen based primarily on their beneficial effects on slowing CKD progression.(149-159)

The evidence that ARB or ACEI slow the progression of CKD in patients with CKD and diabetes mellitus with albuminuria was previously based on the Irbesartan Diabetic Nephropathy Trial (IDNT),(154) the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus (NIDDM) with the Angiotensin II Antagonist Losartan (RENAAL) trial,(150) and the Collaborative Study Group.(160) Data from the (Ramipril Efficacy In Nephropathy) REIN-2 (161) and the African American Study of Kidney Disease (AASK) trials,(162) which were reviewed as part of the evidence for BP target recommendations in the 2014 VA/DOD CKD CPG, showed that ACEI therapy slows progression in the setting of non-diabetic CKD with proteinuria. The evidence review for the 2014 VA/DOD CKD CPG included a meta-analysis by Nakamura et al.,(157) which showed that ACEIs or ARBs are equally effective in controlling BP in CKD, but the data at that time were limited regarding cardiovascular benefits of ACEIs or ARBs compared to other antihypertensive agents in patients with CKD. An SR included in the 2008 VA/DOD CKD CPG showed that treatment with an ACEI reduced the composite outcome of doubling sCr and ESKD by 30% compared to treatment without an ACEI.(153) The 2019 VA/DOD CKD CPG carried forward the 2014 recommendation for ACEI use in diabetic or non-diabetic CKD with albuminuria and use of ARB if ACEI were not tolerated. The Work Group concurred that the strength of evidence was Strong.

The Work Group systematically reviewed evidence related to this recommendation.(157,163,164) Therefore, it is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was High. The benefits of using either an ACEI or ARB to slow the progression of CKD outweighed the potential harm of cough, angioedema, or hyperkalemia. ACEI and ARB should not be combined due to an increased risk of AKI (164) and hyperkalemia, and clinicians should counsel patients about the possible teratogenic effects of ACEI and ARB. Patient values and preferences were similar because the treatment can slow the progression of CKD, thereby delaying the need for dialysis and mortality. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

13. We suggest the addition of a thiazide diuretic or calcium channel blocker to reduce blood pressure in patients with chronic kidney disease and hypertension not controlled on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.
(Weak for | Reviewed, New-added)

Discussion

Hypertension affects the majority of patients at all stages of CKD, and most require more than one medication to achieve BP control. The 2019 VA/DOD CKD CPG preferentially recommended ACEI or ARB as a first-line BP-lowering agent in patients with albuminuria. However, the previous CPG did not suggest a specific second-line agent if BP is not controlled with an ACEI or ARB or provide guidance for patients without albuminuria, leaving the choice of other BP-lowering medication classes based on potential cardiovascular benefits, co-occurring conditions, and patient preference. This CPG recommends ACEI or ARB as first-line agents for BP control in the setting of albuminuria and suggests addition of either a thiazide diuretic or calcium channel blocker (CCB) if a second agent is needed. This suggestion by the Work Group is based on low-quality evidence from the current evidence review and the prior evidence reviews.

The current evidence review provided data to support the use of thiazide diuretics in combination with ACEI or ARB. Historically, thiazide diuretics were felt to be ineffective in CKD stage G3b or higher.(165) Those with advanced CKD have an impaired ability to excrete dietary sodium, and thiazide diuretics are less effective for natriuresis. However, a meta-analysis of five small trials with a total of 214 participants with CKD stage G3b-G5 not on dialysis found that the addition of thiazide and thiazide-like diuretics effectively reduced BP.(166) The largest trial in this meta-analysis was the CLICK trial,(167) which randomized 160 individuals with uncontrolled BP and CKD stage G3b-5 not on dialysis to either placebo or chlorthalidone added to existing BP-lowering medications. Almost all trial participants were taking ACEI or ARB and 60% were taking loop diuretics. The reduction in 24-hour BP after 12 weeks was -11.0 mmHg (95% confidence interval [CI]: -13.9 to -8.1) in the chlorthalidone group and -0.5 mmHg (95% CI: -3.5 to 2.5) in the placebo group. The evidence review for the 2020 VA/DOD Hypertension CPG included data that thiazide-type diuretics were superior to other drug classes for preventing heart failure outcomes. Using a thiazide diuretic may also reduce the risk of hyperkalemia associated with ACEI or ARB, enabling continuation of these kidney protective agents (see Recommendation 14). Thus, thiazide diuretics may be beneficial in advanced CKD for multiple reasons.

While not part of the evidence base, the ACCOMPLISH trial, conducted in 2008, randomized 11,506 patients with hypertension at high risk for CVD events to treatment with either benazepril

plus amlodipine or benazepril plus hydrochlorothiazide and followed them for a mean of 36 months.(168) The primary endpoint was a composite of death from CVD, nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Blood pressure reduction was similar between the two groups over the course of the trial. The benazepril/amlodipine combination was superior to the benazepril/hydrochlorothiazide combination for reducing CVD events (9.6% vs. 11.8%; p<0.001), though it should be noted that heart failure was not included in the CVD composite definition. Progression of CKD was a prespecified endpoint and defined as doubling of serum creatinine concentration or need for dialysis. Progression of CKD was lower in the benazepril plus amlodipine group versus the benazepril plus hydrochlorothiazide group (2.0% vs. 3.7%; p<0.001).(169)

The Work Group found additional Moderate quality evidence for use of either ACEI or ARB with a CCB (ACEI+CCB or ARB+CCB) for lowering BP and reducing CVD events. One small RCT in the 2014 VA/DOD CKD CPG evidence base (170) showed no difference in eGFR decline among trial participants receiving a dihydropyridine CCB versus an ACEI for BP control in adults with non-diabetic CKD. However, the evidence review for the 2020 VA/DOD Hypertension CPG showed that CCB was superior to other drug classes for reducing all-cause mortality but inferior to other drug classes for preventing heart failure.(171) The current evidence review included a network meta-analysis of 16 head-to-head RCTs (172) that examined a variety of dual antihypertensive regimens versus monotherapy in adults with non-dialysis dependent CKD. Blood pressure control was better with combination ARB+CCB versus monotherapy with ACEI, ARB, or CCB. No difference in BP control was noted between ARB+CCB versus ARB+thiazide diuretic or ACEI+CCB. The combination of ARB+CCB showed lower odds of MACE versus ACEI monotherapy, combination ACEI+spironolactone, or ARB monotherapy. However, no difference in CVD events was noted between ARB+CCB combination therapy versus CCB monotherapy, CCB with a beta-blocker (BB), or CCB+thiazide diuretics. No difference in all-cause mortality was noted across drug combinations versus monotherapy with different agents in this SR.(171,172)

Another meta-analysis included in the current review examined the efficacy and safety of eplerenone, a mineralocorticoid antagonist, versus other drug classes in adults with CKD.(173) Compared to eplerenone, no difference in BP lowering was noted with ACEI/ARB or CCBs versus eplerenone, but greater BP lowering was noted with thiazide diuretics versus eplerenone.(173) At this time, evidence was insufficient to suggest the superiority of mineralocorticoid receptor antagonists (MRAs) over other drug classes for BP control or other clinical endpoints. However, data suggested a benefit with the use of finerenone, a non-steroidal MRA, on CKD progression and reduction in MACE (see Recommendation 18). There was limited data regarding the efficacy and outcomes associated with other combinations of antihypertensives, which represents an area for further research.

The Work Group systematically reviewed evidence related to this recommendation.(165-167,170,172,173) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Low. The benefits of using an ACEI or ARB in combination with a thiazide diuretic or CCB, including improved BP control and reduced risk of MACE, outweigh the potential harm of side effects, such as increased risk for gout, hypokalemia, diabetes, edema, and hyponatremia. Patient values and preferences vary because patients want to control BP to avoid complications associated with uncontrolled hypertension but may prefer

non-pharmacologic interventions and be disinclined to add to their pill burden or risk side effects. Use of single pill combinations is associated with higher medication adherence.(174) The VA and DOD have single pill combinations of ACEI+thiazide diuretic and ACEI+CCB, which may overcome patient reluctance to add another medication. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

14. In patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) currently on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, we suggest continuing therapy, unless there is drug intolerance or adverse event.
    (Weak for | Reviewed, New-added)

Discussion

There is strong evidence for the renoprotective benefit of ACEI and ARB (see Recommendation 12). Despite the high prevalence of hypertension and albuminuria in patients with advanced CKD in whom ACEI or ARB use is recommended, withdrawing RAASi is common due to concerns for increased risk of AKI and hyperkalemia.(175-177) In addition, it has been suggested that cessation of RAASi in late stage CKD may delay the need for dialysis initiation.(178,179) The 2019 VA/DOD CKD CPG, however, did not have randomized trial data available to make a determination regarding RAASi use in patients with advanced CKD (stage G4 or G5). The Work Group reviewed evidence available after 2019 regarding kidney outcomes in patients with advanced CKD on RAASi therapy. Evidence reviewed included the STOP-ACEI RCT (180) and two SRs with meta-analysis.(163,181)

The STOP-ACEI trial included 411 patients with stage G4 or G5 CKD (eGFR <30 mL/min/1.73m^2) not on dialysis, who had a decrease in eGFR >2 mL/min/1.73m^2 per year in the 2 years prior to trial enrollment and who had been taking either an ACEI or ARB. They were randomized to either continue or discontinue RAASi and followed for three years to assess the primary outcome of eGFR, secondary outcome of ESKD development, and a composite outcome which included ESKD events, need to start dialysis, and death, among others. There was no significant difference in eGFR at 3 years of follow-up in the RAASi continuation group versus the discontinuation group (-0.7; 95% CI: -2.5 to 1.0; p=0.42). In addition, no significant differences were found between the study groups with respect to ESKD events, the need to start dialysis, adverse cardiovascular events, and mortality.(180) Thus, STOP-ACEI provides evidence that ACEI use does not hasten CKD progression and that discontinuation does not delay need for dialysis initiation.

Vendeville et al. included the STOP-ACEI RCT in their 2024 SR/meta-analysis, as well as eight earlier RCTs and nine observational studies that compared the use of RAASi against other classes of anti-hypertensives (CCBs and BBs), to determine if choice of anti-hypertensive had an impact on the progression of CKD, need to start dialysis (ESKD events), and mortality. Their analysis suggested that the use of RAASi was associated with a 16% reduction in progression to ESKD, but the RCTs reviewed showed no benefit regarding MACE or all-cause mortality. Interpretation of the results from the observational studies was limited by high heterogeneity, residual confounding, and low evidence quality.(181) One retrospective propensity score matched cohort study described potential cardiovascular benefit without increased risk of

progression to ESKD in over 3,900 patients who experienced eGFR <30 mL/min/1.73 m^2 on RAASi therapy. This study was not included in the evidence base reviewed by the Work Group due to having an excluded study design.(182)

The meta-analysis of trials of ACEI or ARB in adults with CKD stage G3b-G5 by Cooper et al. (163) examined outcomes of validated markers of CKD progression, progression to ESKD, hypertension control, and major CVD events. Review of these trials showed no difference in BP control or CKD progression with use of ACEI versus ARB, and there was very low-quality evidence showing patients taking ACEI had lower rates of proteinuria.

While not included in the current evidence base, an additional recently published SR and meta-analysis (176) synthesized data from 18 RCTs with 1,739 participants who had baseline eGFR <30 mL/min/1.73m^2. Authors examined the association of ACEI or ARB treatment versus a comparator (placebo or antihypertensive drugs other than ACEI or ARB) with a primary outcome of rate of kidney failure requiring dialysis and secondary outcome of death. Overall, ACEI or ARB therapy was associated with an approximately 40% lower risk of kidney failure requiring dialysis (adjusted HR: 0.66; 95% CI: 0.55 to 0.79) but no benefit on mortality (HR: 0.86; 95% CI: 0.58 to 1.28) at a median follow-up of 34 months.(176) The benefits of ACEI or ARB on kidney failure outcomes did not differ with drug type (ACEI or ARB), GFR, or age group. This SR/meta-analysis provided additional evidence that RAASi may provide a protective effect against CKD progression and the need for dialysis initiation, not hasten it.

Caution with ACEI or ARB should be used in a few clinical scenarios. Use of ACEI or ARB may increase sCr (up to 30% within the first two weeks after initiation) and serum potassium, so patients with CKD on RAASi require monitoring.(183) Given the benefit of ACEI and ARB in the CKD population, the Work Group suggests implementing measures to manage persistent hyperkalemia, rather than stop ACEI or ARB therapy. If potassium becomes elevated, then measures to reduce hyperkalemia that may be considered include discontinuation of concomitant medications that may increase potassium, implementation of a low potassium diet, and addition of a diuretic or potassium binder. If efforts to control hyperkalemia are not effective, then reducing the dose or discontinuing RAASi may be considered after discussing the risk, benefits, and preferences with the patient (see Recommendation 21 and Appendix M on the management of hyperkalemia). ACEI and ARBs are teratogenic and should be avoided during pregnancy, including the first trimester. Thus, counseling about fetal risks is needed in women who are capable of pregnancy, and reliable contraception should be used if ACEI or ARB are used in sexually active non-menopausal women. ACEI/ARBs should be discontinued immediately in patients who become pregnant while taking these agents. Information on use of ACEI or ARB with lactation remains limited and an up-to-date reference should be consulted in this circumstance.

The Work Group felt that the benefit of delaying CKD progression associated with ACEI and ARB use, along with evidence that continuing RAASi is safe in late-stage CKD, slightly outweighs potential harms. The clinical decision to continue RAASi must be balanced against the need to follow these patients closely and manage adverse effects, such as hyperkalemia. Patients will likely care about lowering their risk for CKD progression, needing to take additional medications, and obtaining lab monitoring while on these medications. No implications

regarding access to care were identified since RAASi are easily accessible and inexpensive, especially compared to newer agents that have shown benefit at slowing CKD progression.

The Work Group acknowledged that the evidence reviewed for this guideline heavily relied on the STOP-ACEI trial and that the overall strength of evidence reviewed was Very low. However, the evidence suggested that there is no significant risk of worsening CKD progression or pushing patients with late stage G4 or G5 CKD into dialysis by continuing RAASi. Instead, RAASi therapy may confer a protective benefit against CKD progression and the need for dialysis in this population. In addition, large, randomized trials examining long-term progression of CKD in patients on SGLT2i, GLP-1 RA, and finerenone were completed on a background of patients maintained on RAASi with no direct adverse CKD progression described due to RAASi.(82,184,185) More highly-powered randomized trial data are needed to determine the cardiovascular benefit with an ACEI or ARB in patients with CKD.

The Work Group systematically reviewed the evidence related to this recommendation. (163,180,181) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Very low. The benefits of continued ACEI and ARB therapy, such as delayed progression to ESKD, slightly outweighed the potential harm/burdens of hyperkalemia and the requirement for close follow-up. Patient values and preferences were similar because patients care about CKD progression and taking medications when required. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

15. We recommend the addition of sodium-glucose co-transporter 2 inhibitors to maximally tolerated angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, in patients with chronic kidney disease who have one or more of the following:
    - Type 2 diabetes
    - Albuminuria (UACR >200 mg/g)
    - Heart failure

    to reduce the risk of major adverse cardiovascular events, heart failure, progression of kidney disease, and mortality, and continuing sodium-glucose co-transporter 2 inhibitors until start of dialysis.
    (Strong for | Reviewed, New-replaced)

Discussion

The evidence review identified 3 SRs/meta-analyses examining the impact of SGLT2i in patients with CKD. The evidence base included Mavrakanas et al. 2023 (SR of 12 RCTs, including 39,000 patients with CKD),(186) Chalmoukou et al. 2022 (SR of 27 RCTs),(187) and Drake et al. 2024 (SR of 84 RCTs).(188) One additional SR by Liu et al. 2022 (SR of 10 RCTs specifying a background of RAASi)(189) reported similar outcomes. All trials showed that SGLT2i were associated with decreased risk of a composite kidney outcome (worsening kidney function, ESKD, and renal death) by 23-36% (186-189) and albuminuria reduction in all groups. Those that examined cardiovascular outcomes showed that SGLT2i use was associated with a 34% reduction in hospitalization for heart failure.(188) The strength and consistency of heart failure benefit led to the recommendation for use in heart failure independent of diabetes and albuminuric kidney disease. Furthermore, use of SGLT2i was associated with decreased MACE (cardiovascular death, non-fatal MI, or stroke) by 10-26%, which was predominantly driven by

reduction in hospitalization for heart failure as well as all-cause mortality by 13-14%.(186,188) Outside of the evidence base, a study performed by Gregg et al. (37) showed that 37% of 96,345 Veterans prescribed SGLT2i discontinued use, though reasons for discontinuation were not cited, and SGLT2i discontinuation was associated with increased mortality and heart failure hospitalizations.(190,191)

While there was low variability between RCTs included in the SRs and low risk of bias, a limitation in the evidence base was low numbers of patients with CKD, advanced CKD, and heavy proteinuria in the RCTs that were evaluated in the SRs. Despite this, there was greater benefit seen in studies with a higher level of proteinuria in subgroup analysis, strongly suggesting additional benefit in this higher-risk population. Subgroup analyses in the RCTs included in the SR showed benefits in non-diabetic, non-albuminuric kidney disease and lesser degrees of proteinuria (UACR <200mg/g), indicating a need for additional clinical trials in these patient populations. A few of the included RCTs did not report RAASi use, but many study protocols were designed such that SGLT2i was added to maximally tolerated ACEI or ARB. Further studies to compare the effect of SGLT2i alone versus the combination of SGLT2i+RAASi may be informative, especially since some patients may not tolerate RAASi due to hypotension or other side effects. Since SGLT2i has typically been used as add-on therapy to usual care with metformin, there were no studies directly comparing outcomes between combination SGLT2i+metformin versus SGLT2i alone in diabetes, which may be an area for future research.

As this is a newer therapy, there will be a need for educating medical providers who may be unfamiliar with its use. SGLT2i treatment is contraindicated for type 1 diabetes, and caution should be taken when titrating down insulin doses in patients with type 2 diabetes on insulin at initiation of SGLT2i therapy due to risk of diabetic ketoacidosis. Multiple perioperative guidelines suggest holding SGLT2i during times of prolonged fasting, surgery, or critical illness to minimize the risk of ketosis, with reinitiation of SGLT2i treatment after an acute event has passed.(190,191) With SGLT2i initiation, there is an expected, reversible decrease in eGFR. Other guideline development groups (e.g., KDIGO)(3) have deemed this reversible decrease in eGFR safe enough to recommend not reassessing eGFR following the initiation of SGLT2i therapy. The lowest eGFR for initiation of SGLT2i was 20 mL/min/1.73m^2 in the evidence review, and the reversible decrease in eGFR on initiation of therapy did not cause any significant harm.(192) In fact, discontinuation of therapy was more common in the placebo arm than in the treatment arm of studies, suggesting SGLT2i was well tolerated. Most studies did not specify a threshold for discontinuing SGLT2i therapy; however, two studies specified discontinuation when eGFR was <15mL/min/1.73m^2, and one study specified discontinuation at the start of hemodialysis. There appeared to be continued efficacy when SGLT2i was continued until the initiation of dialysis, so the Work Group suggests continuation of SGLT2i treatment until patients are started on dialysis. Some Work Group members raised concerns that SGLT2i may potentiate volume depletion in patients taking loop diuretics, which is commonly prescribed in advanced CKD. Additional monitoring might be indicated in this situation. Depending on volume status, a decrease in diuretics at time of SGLT2i initiation might be warranted.

The patient focus group did not have any opinions on SGLT2i, but there is likely some variation in patient preferences regarding this treatment. Some patients may be bothered by the increased risk of genital mycotic infection or increased urination. Studies in the VA population

showed that SGLT2i prescriptions were lower in Black and women patients.(34) Some providers may be hesitant to prescribe SGLT2i for fear of reduced eGFR on initiation of therapy. Furthermore, use may be limited by clinical inertia and provider familiarity with older treatments for diabetes mellitus. Resource use must also be considered since the medication is expensive even with negotiated discount rates in the VA and DOD.

The Work Group systematically reviewed evidence related to this recommendation.(186-189) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was High. The body of evidence had some limitations, including a lower proportion of patients with established CKD, particularly advanced CKD and albuminuria. The benefits of adding SGLT2i to ACEI or ARB, including reduced risk of mortality, MACE, and CKD progression, greatly outweigh the small potential risk of genital infections and increased urination. Patient values and preferences have some variability regarding pill burden and side effects; however, treatment is generally well tolerated, and patients desire greater control of diabetes mellitus, CKD, and heart failure. Thus, the Work Group decided upon a *Strong For* recommendation.

Recommendation

16. We recommend adding a glucagon-like peptide-1 receptor agonist to an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in patients with type 2 diabetes and albuminuric chronic kidney disease to reduce the progression of chronic kidney disease, major adverse cardiovascular events, and all-cause mortality. **(Strong for | Reviewed, New-replaced)**

Discussion

Evidence on the use of GLP-1 RA included one SR/meta-analysis looking specifically at kidney outcomes,(187) one SR/meta-analysis assessing cardiovascular outcomes,(188) and one RCT evaluating both kidney and cardiovascular outcomes.(185) This body of evidence comparing addition of GLP-1 RA to standard of care with maximally tolerated ACEI/ARB and metformin, found GLP-1 RA reduced the progression of CKD compared with placebo by 8% in the SR and 23% in the RCT.(185) Both Drake and Perkovic found a reduction in MACE by 9-18% and all-cause mortality by 12-20% (185,188) when compared with placebo. While this body of evidence is of High quality, limitations include low numbers of patients with albuminuric or advanced CKD in the individual trials included in the SRs/meta-analyses. This limitation was mitigated by including evidence from the FLOW trial, an RCT evaluating GLP-1 RA use specifically in 3,533 participants with albuminuric (UACR >100 mg/g in those with eGFR 25-49 mL/min/1.73 m^2 and UACR >300 mg/g in those with eGFR 50 to 75 mL/min/1.73 m^2) and advanced kidney disease. The FLOW trial also demonstrated a significant reduction in CKD progression (HR: 0.76; 95% CI: 0.66 to 0.88), MACE (HR: 0.82, 95% CI: 0.68 to 0.98), and all-cause mortality (HR: 0.80, 95% CI: 0.67 to 0.95).(185) The Work Group was not able to recommend GLP-1 RA for the reduction in CKD progression in non-albuminuric kidney disease due to the lack of evidence in this patient population.

A study outside of the evidence base (193) evaluated a statistical model of additive cardiovascular and kidney benefit of GLP-1 RA to SGLT2i in patients with type 2 diabetes and albuminuric CKD with the assumption of 50% added benefit and 2% decrease in efficacy over time. This trial showed an additive benefit of combination therapy with SGLT2i, GLP-1 RA, and non-steroidal

MRAs, and was consistent with multiple other guidelines (e.g., KDIGO, American Diabetes Association, European Association for the Study of Diabetes, NICE, etc.).

While the Work Group believed the benefits of GLP-1 RA to be a class effect, there appeared to be significant heterogeneity in the effect of individual drugs within the GLP-1 RA class, with more recent trials predominantly set up to evaluate cardiovascular outcomes showing greater effect on primary outcomes. In the FLOW trial subgroup analysis, the concurrent use of SGLT2i caused the cardiovascular and CKD benefit of GLP-1 RA to lose statistical significance because the trial was not powered to detect a benefit in this population.(185) Further trials adding a GLP-1 RA to a baseline population taking metformin and SGLT2i are needed. As noted above (see Recommendation 15), there is consistent, strong evidence for the reduction of all-cause mortality with SGLT2i when added to ACEI or ARB. Thus, the Work Group suggests SGLT2i as add-on therapy to ACEI or ARB before considering GLP-1 RA for the management of diabetic kidney disease, consistent with patients' values and preferences.

There is a large variation in patient preferences regarding GLP-1 RA treatment. Because these drugs are administered by subcutaneous injections, some patients may have an aversion to needles or difficulty with administration because of dexterity, vision, or confusion. Some may lack the ability to properly store the medication in a refrigerator. A desire to manage weight might also play into patient preferences since GLP-1 RA are associated with 5-15% weight loss in the studies included in this evidence base.(185,187,188) Weight management medications should be paired with a comprehensive lifestyle intervention (see VA/DOD Overweight/Obesity CPG).

The benefits of GLP-1 RA treatment, including delaying progression of CKD, reducing all-cause mortality, improving glycemic control, and losing weight, outweigh the potential harms, including gastrointestinal (GI) side effects (e.g., nausea, vomiting, diarrhea) and injection site reactions. Acceptability by patients may be limited by a desire to avoid injectable medications. There are concerns about resource use with increased costs and availability of the medication due to production shortages. There are also concerns about access since these medications for medical weight loss are costly and may not be available to those in different demographic socioeconomic populations. GLP-1 RA medications may require prior authorization and the completion of medical necessity forms in the VA and DOD, which may limit their availability.

The Work Group systematically reviewed evidence related to this recommendation.(185,187,188) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was High. The body of evidence had some limitations, including a lower proportion of patients with established CKD, especially those with advanced CKD and albuminuria. The benefits of GLP-1 RA on CKD progression, MACE, and all-cause mortality outweigh the potential harm of adverse events such as GI side effects. Patient values and preferences vary largely because some patients favor the treatment for the added weight loss benefit while others prefer non-injectable treatments. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

17. In patients with chronic kidney disease and heart failure, we suggest sacubitril/valsartan as an alternative to monotherapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.
    (Weak for | Reviewed, New-added)

Discussion

Heart failure is a common co-occurring condition in patients with CKD. RAASi reduces mortality in patients with heart failure with reduced ejection fraction (HFrEF) and slows progression of proteinuric CKD. However, declining kidney function and adverse kidney events (e.g., AKI, hyperkalemia) may complicate RAASi therapy. Angiotensin receptor-neprilysin inhibitors (ARNIs) work by blocking angiotensin II at the receptor and increasing the concentration of natriuretic peptides and bradykinin, which promotes sodium excretion. In patients with stable New York Heart Association (NYHA) class II to IV heart failure, sacubitril/valsartan reduces the risk of mortality compared to monotherapy with an ACEI.(194)

There is data to suggest that combination sacubitril/valsartan may have renoprotective benefits over ACEI or ARB monotherapy. Evidence from a pre-specified secondary analysis in the PARAGON-HF trial in patients with heart failure and preserved ejection fraction (HFpEF) suggests that sacubitril/valsartan slows the progression of CKD when compared to valsartan alone.(195) Among 4,796 participants, the risk of the kidney composite outcome of 50% decline in eGFR or ESKD was reduced by half in the group assigned to sacubitril/valsartan compared to the group assigned to valsartan alone. A similar 50% reduction in the kidney composite outcome was noted in the subgroup of 2,341 participants with baseline CKD. An SR and meta-analysis of participants with baseline CKD included 3,159 participants from two RCTs of sacubitril/valsartan: PARADIGM, a trial of sacubitril/valsartan versus enalapril in heart failure; and UK-HARP III, a trial of sacubitril/valsartan versus irbesartan to prevent CKD progression.(196) Evidence from this review indicates that patients treated with sacubitril/valsartan had a slower decline in eGFR but no difference in the incidence of kidney dysfunction or ESKD, compared to those who received ACEI or ARB monotherapy. While additional ARNI trials evaluated kidney endpoints, these studies did not provide a subgroup analysis of participants with CKD, and therefore were not considered in the evidence review.(196)

Most studies indicate that the risk for adverse events is comparable between sacubitril/valsartan and monotherapy with either ACEI or ARB. Sacubitril/valsartan is generally not considered for patients with potassium >5.0 mEq/L or SBP <100 mmHg. In the PARAGON-HF analysis, participants assigned to sacubitril/valsartan had no difference in the incidence of hyperkalemic events. However, there were more hypotensive events in the sacubitril/valsartan arm.(195) Transition to sacubitril/valsartan from monotherapy with an ACEI should be delayed at least 36 hours after the last dose of ACEI to reduce the risk of angioedema, while a washout period is not necessary when converting from ARB monotherapy. Safety and efficacy data are limited for patients with eGFR <20 mL/min/1.73m^2.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, such as the assessment of

CKD progression as a secondary endpoint and the lack of data in individuals with proteinuria. The benefits of ARNIs, including reduced mortality in patients with heart failure and favorable effects on the progression of CKD, outweighed the potential harm of hypotension. Patient values and preferences were assessed as being similar. Other considerations included the high cost of ARNIs relative to RAASi monotherapy and limited access to this medication in resource-restricted settings. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

18. We suggest the addition of a non-steroidal mineralocorticoid receptor antagonist (e.g., finerenone) in individuals on maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker who meet **all** the following criteria:
    - Type 2 diabetes
    - Albuminuria >30 mg/g
    - eGFR ≥25 mL/min/1.73 m^2
    - Potassium <4.8 mEq/L

    for the purpose of decreasing major adverse cardiovascular events and slowing progression of chronic kidney disease.
    (Weak for | Reviewed, New-added)

Discussion

Mineralocorticoid receptor antagonists have been evaluated in patients with CKD and diabetes. Systematic reviews and meta-analyses (197-199) of the effect of MRAs on slowing progression of CKD and decreasing MACE show benefit for both outcomes. While steroidal MRAs show consistent evidence for UACR reduction,(199) the evidence for their impact on cardiovascular events and CKD progression is conflicting.(199,200) In the BARACK trial, an open-label study of patients with CKD and eGFR 30-49 mL/min/1.73 m^2 and albuminuria <618 mg/g, addition of spironolactone 25 mg daily showed no benefit on cardiovascular or CKD progression outcomes. Additionally, spironolactone was not well-tolerated, with two-thirds of patients in the spironolactone arm discontinuing treatment within six months, most frequently due to a decline in kidney function or hyperkalemia.(201)

Yuan et al. (199) found that MRAs significantly reduced the risk of developing kidney failure (risk ratio [RR]: 0.86) and cardiovascular events (RR: 0.84). However, these findings were driven by two RCTs of finerenone, the only currently approved non-steroidal MRA. FIDELIO-DKD (184) and FIGARO-DKD (202) enrolled patients with diabetes, eGFR >25 mL/min/1.73m^2, and albuminuria >30 mg/g. In these studies, patients were treated with maximally tolerated doses of ACEI or ARB before randomization and were required to have a serum potassium level of 4.8 mmol/L or less at the time of screening (after the run-in period to titrate ACEI or ARB). The primary outcome in FIDELIO-DKD was CKD progression, while the primary outcome in FIGARO-DKD was a composite cardiovascular endpoint. A prespecified pooled analysis of the two trials by Agarwal et al. and Singh et al. found that, at a median follow-up of 3 years, there was a reduction in the composite cardiovascular endpoint (HR: 0.86) and a reduction in a composite CKD progression endpoint (HR: 0.77) with finerenone.(197,203) Of note, the cardiovascular benefit was largely driven by a decrease in hospitalization for heart failure.

While finerenone was generally well-tolerated by patients in the FIDELIO-DKD and FIGARO-DKD trials, the population studied was limited to those with potassium <4.8 mmol/L prior to finerenone initiation. Despite this prerequisite, hyperkalemia-related adverse events (14.0% vs. 6.9%) and hyperkalemia leading to permanent treatment discontinuation (1.7% vs. 0.6%) were more frequent with finerenone.(197) In addition, at baseline, less than 10% of patients in both trials were treated within an SGLT2i. Thus, further research is needed to assess the effectiveness of finerenone versus SGLT2i, either as monotherapy or in combination. Because the evidence base supporting SGLT2i is stronger than the current evidence base for finerenone, the Work Group felt that initiation of an SGLT2i should be prioritized over an MRA in most patients who meet indications for both agents.

Patients likely have similar preferences regarding this treatment. However, the medication is currently very expensive (to the healthcare system, DOD or VA) and requires frequent bloodwork monitoring. Use is limited to those with potassium less than 4.8 mmol/L at initiation, and some patients will not tolerate this medication due to the development of hyperkalemia. Currently, there are no available data on finerenone use in pregnancy.(204)

The Work Group systematically reviewed evidence related to this recommendation.(197-200) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Moderate. The Work Group considered whether there was evidence of a class effect of MRAs in CKD. There was insufficient evidence to determine whether there was a beneficial effect of steroidal MRAs to prevent CKD progression. However, we found Moderate certainty evidence that among patients with type 2 diabetes, albuminuric CKD, and baseline potassium <4.8 mmol/L, finerenone reduces the risk of MACE and slows progression of CKD, based on consistent benefits in two RCTs that were incorporated in meta-analyses in the evidence base. The body of evidence had some limitations, including being driven by two RCTs conducted by the same research group. The benefits of reduction in MACE and CKD progression outweighed the potential harm (e.g., hyperkalemia) and the need for frequent monitoring. Patient values and preferences are likely to have some variation. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

19. In patients with chronic kidney disease not on dialysis, we recommend the initiation of statins to reduce major adverse cardiovascular events and mortality.
(Strong for | Reviewed, New-added)

Discussion

Patients with CKD are at high risk of CVD events and mortality, with lower eGFR and more severe albuminuria each associated with higher rates of adverse cardiovascular outcomes and mortality.(85) In fact, people with CKD not on dialysis experience risks of CVD events or death similar to people with coronary artery disease (CAD).(205-207)

An SR and meta-analysis by Tunnicliffe et al. (208) compared the use of statins to placebo, no treatment, standard of care, or another statin among adults with CKD not requiring dialysis. In a meta-analysis, compared to placebo or standard of care, statins reduced MACE (RR: 0.72), cardiovascular death (RR: 0.77), MI (RR: 0.55), and all-cause mortality (RR: 0.83); between 8-14

studies contributed to the meta-analysis, depending on the outcome. The evidence for MACE and all-cause mortality was of High certainty while the evidence for cardiovascular death and MI was of Moderate certainty. Findings were consistent across subgroups, including those with and without CVD at baseline, those with and without diabetes, and patients <55 years versus >55 years old. The meta-analysis did not report outcomes stratified by baseline cholesterol levels. The authors estimated that statins given to 1,000 people with CKD for one year might be expected to prevent 32 major CVD events and 10 deaths from any cause, among other outcomes. Further, the absolute benefits of statins in people with CKD were found to be similar to people with a 20% or greater 10-year absolute cardiovascular risk. There was Moderate certainty evidence that statins have little or no protective effect on progression to ESKD.

A meta-analysis of 28 trials examining the effects of statin therapy on vascular events and mortality, outside of this evidence review, found that relative reductions in major vascular events (including cardiovascular events and stroke) and vascular mortality seen with statin treatment became smaller as eGFR declined, with little evidence of benefit in patients on dialysis.(209) For this reason, and because the evidence base was limited to patients with CKD not on dialysis, the Work Group limited the recommendation on the initiation of statins to patients with CKD not on dialysis.

In the Tunnicliffe et al. meta-analysis, the median statin dose was equivalent to simvastatin 20 mg daily, which is moderate intensity. There was limited evidence regarding the most effective dose or type of statin among patients with CKD, due to few trials comparing different types or intensities of statin therapy. It was unclear if benefits depended on treatment-related reductions in serum cholesterol. Therefore, the Work Group could not make a recommendation regarding intensity of statin therapy. Similarly, the Work Group recommends treatment with a statin regardless of the baseline cholesterol profile.

There was limited reporting of adverse events, though statins did not seem to have a significant effect on liver enzymes, withdrawal due to adverse events, and cancer compared to placebo (all with Low certainty of evidence). Statins may be associated with muscle-related side effects,(210) but few studies reported elevated creatinine kinase or rhabdomyolysis.

There is some variation in patient preferences regarding treatment with statins. Benefits regarding mortality and MACE are meaningful and highly desirable. As noted previously, benefits are consistent across subgroups (primary and secondary prevention, diabetic and non-diabetic patients, those 55 years and older and younger than 55 years).(208) However, there is less data regarding benefits and harms of statins at extremes of age (i.e., patients less than 40 years and elderly patients). Additionally, some patients may be concerned about side effects, perhaps in part due to statin-related misinformation, and pill burden.(211) There are concerns regarding statin use in pregnancy and lactation; the FDA recommends that most patients should stop statins during pregnancy and that patients should not breastfeed while they are taking a statin.(212)

Our guidance is concordant with other relevant guidelines. The VA/DOD CPG for the Management of Dyslipidemia for Cardiovascular Risk Reduction (213) applies only to patients aged 40 or older and notes that the benefits of statins extend to people with CKD. For primary prevention, they recommend offering a moderate-dose statin in patients with >12% 10-year cardiovascular risk and suggest offering a moderate-dose statin in patients with a 6-12% 10-

year cardiovascular risk using SDM. Almost all patients with CKD would fall into these categories.

The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (3) makes the following lipid management recommendations for adults with CKD not treated with chronic dialysis or kidney transplantation: For adults aged >50 years, they recommend treatment with a statin or statin/ezetimibe combination. In adults aged 18-49 years, they suggest statin treatment in patients with known coronary disease, diabetes, or stroke or 10-year cardiovascular risk >10%. In a "Practice Point" (based on expert consensus rather than evidence review), they encourage "statin-based regimens to maximize the absolute reduction in LDL [low-density lipoprotein] cholesterol to achieve the largest treatment benefits."

The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (214) recommends statin therapy for primary prevention in adults aged 40-75 years with diabetes and those with LDL-C of 190 mg/dL or higher. In those without these conditions, estimation of 10-year ASCVD risk is recommended, with statin therapy recommended in those at >20% 10-year cardiovascular risk. Statin therapy is also recommended in the context of SDM for those at intermediate (>7.5% to <20%) risk, and the presence of risk-enhancing factors favor initiation or intensification of therapy for those at borderline risk (5% to <7.5%). They note that CKD is a risk-enhancing factor and that most patients with CKD have a 10-year ASCVD risk >10%. There is limited data on the performance of 10-year risk estimation tools for adults 20-39 years, and with some exceptions, most patients in this age range are unlikely to have a sufficiently elevated 10-year risk to warrant statin therapy.

When discussing the recommendation for statins with patients, it may be helpful to note that CKD is a risk-enhancing factor and that patients with CKD experience risks of cardiovascular events or death similar to people with CAD.(205-207) As previously noted, the risk of CVD events and cardiovascular mortality increases with decreasing eGFR and increasing levels of albuminuria. Multiple calculators have been developed to estimate CVD risk; however, the PREVENT Equations (106) provide risk estimates for CVD in patients aged 30-79 years, include eGFR as a predictor in the base model, and offer UACR as an add-on predictor, allowing for personalization of cardiovascular risk assessment in patients with CKD.

The Work Group systematically reviewed evidence related to this recommendation.(208) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was High due to consistent findings in many studies incorporated in the meta-analysis. In patients with CKD not on dialysis, the benefits of reduced MACE and mortality outweigh the potential harm of adverse events. Patient values and preferences vary somewhat, as benefits regarding cardiac events and mortality are highly desirable, but some patients may be concerned about side effects or pill burden. Statins are inexpensive and widely available. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

20. In patients with autosomal dominant polycystic kidney disease, we recommend referral to a nephrology provider* for evaluation and assessment of appropriateness of treatment with tolvaptan.
    (Strong for | Reviewed, New-replaced)

    *2019 VA/DOD CKD CPG Recommendation #32 was amended based on support of nephrology subspecialty referral, Risk Evaluation and Mitigation Strategies (REMS) requirements (approval by a REMS trained nephrologist), and clinical ramifications of early referral.

Discussion

Tolvaptan is FDA-approved to slow kidney function decline in adults with CKD due to autosomal dominant polycystic kidney disease (ADPKD) at risk for rapid progression. Tolvaptan has been found to slow decline in eGFR by about 1 mL/minute/1.73 m^2 per year in high-risk patients, 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 kidney outcomes, such as need for dialysis or transplant, have yet to be established.(215-217)

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial in patients with ADPKD showed that treatment with tolvaptan was associated with a slower decline in eGFR compared to placebo (mean change in eGFR of -2.72 mL/min/1.73 m^2 per year with tolvaptan vs. -3.7 mL/minute/1.73 m^2 per year with placebo over 36 months).(215) Predicted benefit in delay of eGFR decline was greater for young patients who start tolvaptan at earlier CKD stages.(218) According to baseline eGFR at time of treatment initiation, tolvaptan may delay reaching CKD stage G5 by 7.3, 4.4, 2.9, or 1.5 years if baseline eGFR was 90, 60, 45, or 30 mL/min/1.73 m^2, respectively, based on data extrapolation using the average decline in eGFR between placebo (-3.7 mL/min per year) and tolvaptan (-2.72 mL/min per year) groups in the TEMPO 3:4 RCT.(217,218) 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 m^2 with tolvaptan compared to 3.61 mL/min/1.73 m^2 with placebo over a one year period.(216)

An SR and meta-analysis (219) examining the efficacy and safety of tolvaptan versus ACEI or ARB that included RCTs, cohort studies, and prospective and retrospective studies, was reviewed for this 2025 VA/DOD CKD CPG update.(219) This SR and meta-analysis was determined to have Moderate quality evidence and included 10 studies with data on 6,328 patients and follow-up from 2 to 36 months. Use of tolvaptan was associated with a slower increase in annual total kidney volume (TKV), which has been used as a surrogate marker of disease progression, and reduced rate of eGFR decline. Patients on tolvaptan also reported less kidney pain, and there was no significant difference between groups in reported adverse hepatic events.(219)

Despite the beneficial effect of slowing CKD progression in high-risk ADPKD patients, long-term tolerability of tolvaptan might be difficult and not without risk. In TEMPO 3:4, more patients on tolvaptan discontinued study treatment (23% of Tolvaptan group vs. 14% of placebo) due to adverse events, particularly aquaretic side effects, such as thirst, polyuria, nocturia, and urinary frequency. REPRISE reported a lower overall incidence of withdrawal due to adverse events

(9.5% in the tolvaptan group vs. 2.2% in the placebo group); however, only patients who tolerated tolvaptan during an 8-week screening phase, in which 6.8% withdrew due to inability to tolerate the drug, were randomized to the active portion of the trial. Patients in this pre-selected group receiving tolvaptan again reported higher rates of aquaretic side effects, diarrhea, and fatigue.

In addition to the 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 vs. 5.3% in the placebo group; HR: 4.91) was observed in REPRISE.(216) Most cases of elevated hepatic enzymes improved with interruption or discontinuation of tolvaptan, and the risk of irreversible liver toxicity may be mitigated with monthly monitoring of liver function tests to facilitate 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.(220) Given the significant concern for hepatotoxicity, the FDA requires a certification process for prescribers and a patient registry to limit access for tolvaptan to those registered in the REMS program.(221)

Since tolvaptan is more likely to benefit patients in earlier stages of CKD, the Work Group suggests early referral of ADPKD patients to a nephrology provider to identify those most likely to benefit from tolvaptan therapy. It may be challenging to identify those who would most benefit because ADPKD has variable penetrance and rates of kidney function decline vary widely. Appropriate patient selection regarding the patient's ability to tolerate side effects, maintain adequate hydration, comply with frequent lab monitoring, and retain uninterrupted access to the medication, with the support of a committed nephrology provider experienced in managing tolvaptan, are preferred. Risks for significant harm of treatment must be weighed against the potential benefit (approximately 1 mL/min/1.73 m^2 per year slower decrease in eGFR). Other potential benefits to early referral for ADPKD include risk mitigation for other ADPKD complications (e.g., subarachnoid hemorrhage, cyst rupture, cyst hemorrhage, cyst infection, nephrolithiasis), opportunities for genetic testing which may be important in pre-conception counseling, determination of which patients would benefit from care by multidisciplinary PKD clinics, and improvement in pre-emptive kidney transplantation. Primary care providers can play a critical role in facilitating early nephrology referral for high-risk ADPKD patients to optimize potential therapeutic benefit.

Significant variability in provider and patient preferences, as well as variability in acceptance and tolerance of this treatment, are anticipated. The benefits of referral for nephrology assessment and possible tolvaptan therapy which, if indicated, may slow CKD progression and reduce PKD associated pain, must be weighed against the risk of adverse effects, the importance of maintaining adequate hydration, and close monitoring of liver function tests. Other implications that must be considered include access to nephrology subspecialty care, high medication cost, and resource use due to the need for frequent monthly labs.

The Work Group systematically reviewed available, relevant evidence for this *Reviewed, New-replaced* recommendation.(215-217,219) While overall confidence in the quality of the evidence was Moderate, data weaknesses included reliance on surrogate outcomes (e.g., TKV assessment), limitations in data extrapolation and modeling systems for data analysis, as well as an absence of long-term data demonstrating a reduction in CKD progression beyond 36 months or progression to ESKD. Despite tolerability and safety concerns, there is currently no other

primary therapy available for patients with rapidly progressive ADPKD. Finally, it must be emphasized that the benefits reported in slowing CKD progression remain greatest in early-stage CKD, highlighting the need for early nephrology subspecialty referral for evaluating the safe and appropriate initiation of tolvaptan. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

21. In patients with chronic kidney disease, we suggest using potassium binders in the management of persistent, non-life-threatening hyperkalemia.
    (Weak for | Reviewed, New-added)

Discussion

Patients with CKD may develop electrolyte abnormalities, such as hyperkalemia, particularly as kidney function declines. Additionally, ACEI/ARB and MRA, which may cause hyperkalemia, are indicated for many patients with CKD. Correction of hyperkalemia using older and newer potassium binding agents is superior to placebo in patients with CKD. In three studies cited in the evidence base,(222-224) the newer potassium binding agents, sodium zirconium cyclosilicate (SZC/ZS-9) and patiromer, significantly reduced mean potassium levels compared to placebo. Two older potassium binding agents, sodium polystyrene sulfonate (SPS) and Calcium Polystyrene Sulfonate (CPS), were shown in two studies in the evidence base to significantly reduce mean serum potassium when compared to placebo.(223,224) While not included in the evidence base, one study suggests that use of potassium binders is effective at controlling hyperkalemia, which allows continuation of RAAS blockade in patients with CKD or heart failure.(225)

Overall, the evidence comparing various strategies and interventions to manage CKD associated hyperkalemia for improvement of long-term complications is mixed and varies depending on the outcomes assessed and period of follow-up. The overall strength of the evidence for the outcomes assessed in the evidence base is Low to Very low due to the limitations in the methodological quality of the included RCTs. Prior studies not in the current evidence base showed that the use of potassium binders prevented mortality and complications of hyperkalemia, such as arrhythmia, but the current evidence did not show that potassium binders decreased hospitalizations or prolonged survival. Natale et al. indicated no difference in cardiovascular death or hospitalization between the newer potassium binding agents versus placebo. In addition, there were no hospitalizations noted with the older potassium binding agents or placebo groups.(224) In Dong et al., there were no recorded deaths with SPS or CPS.(223) Two deaths, one of which was cardiovascular, were reported in the SZC/ZS-9 group and none in the other studied groups. The authors did not specify whether the deaths were related to bowel necrosis or hyperkalemia. Despite the quality of these studies, the treatment of hyperkalemia with potassium binders is appropriate in CKD to reduce the risk of life-threatening hyperkalemia and permit the use of medications to slow the progression of CKD (e.g., ACEI/ARB, non-steroidal MRA).

Patient preference for using potassium binders likely varies. The side effect profile of potassium binders consists primarily of GI side effects, including nausea, vomiting, diarrhea, and constipation. With SPS, there is a rare side effect of bowel necrosis seen with older formulations that should be noted, although this medication has previously been widely used as a first-line

agent for hyperkalemia. Additionally, palatability of the potassium binders may be an issue for some patients. However, patients may find following a low-potassium diet challenging. Finally, patients would want to continue RAASi, which has been shown to slow CKD progression.

The Work Group systematically reviewed evidence related to the recommendation.(222-224) Therefore, the recommendation is categorized as *Reviewed, New-added*. The Work Group's overall confidence in the quality of evidence was Low to Very low due to the methodological quality of the included RCTs. The potential benefits of decreased mortality and prevention of hyperkalemia complications, such as arrhythmia, outweigh the potential harms of GI side effects, including bowel necrosis that has been described with SPS. Control of hyperkalemia may permit continued use of medications (e.g., ACEI/ARB, non-steroidal MRA) to slow progression of CKD. Patient values and preferences vary somewhat as patients may be reluctant to take additional medication, may have side effects or find the medication unpalatable. Alternative interventions may be helpful in controlling potassium levels (see Appendix H and Appendix M). Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

22. For patients with chronic kidney disease undergoing imaging utilizing iodinated contrast media who are at increased risk for iodinated contrast-associated acute kidney injury, we recommend intravenous volume expansion with isotonic crystalloid (see Algorithm Module E and Appendix Q for additional information).
    (Strong for | Reviewed, New-replaced)

Discussion

The following studies show best evidence to suggest that providers should assess contrast-associated AKI (CA-AKI) risk before performing contrast-enhanced diagnostic studies and employ interventions to reduce the CA-AKI risk. In a cohort of more than 20,000 propensity-matched patients undergoing computed tomography (CT) with or without IV contrast, Davenport et al. (226) 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 to 1.89; p=0.007). In a separate analysis, the same investigators found that CA-AKI risk increased with decreasing renal function, such that IV iodinated contrast administration was associated with a 40% increase in CA-AKI (OR: 1.40; 95% CI: 1.00 to 1.97) in patients with an eGFR of 30-44 mL/min/1.73 m^2 and almost 3-fold higher risk (OR: 2.96; 95% CI: 1.22 to 7.17) for patients with an eGFR of <30 mL/minute/1.73 m^2.(227)

Other studies have questioned the risks associated with iodinated contrast administration and CKD. While not included in the body of evidence, one meta-analysis found that IV infusion of contrast associated media did not show an increased risk of renal deterioration in individuals with CKD compared to those without CKD (OR: 1.07; 95% CI: 0.98 to 1.17; I^2=35.3%).(228) McDonald et al. (229) found no difference in rates of AKI among more than 20,000 propensity-matched patients undergoing CT with or without contrast enhancement (OR: 0.94; 95% CI: 0.83 to 1.07; p=0.38). In another analysis, the same investigators found no difference in the risk of AKI associated with contrast exposure after stratifying by level of eGFR.(230)

Administration of IV volume expansion before and after contrast imaging is recommended for high-risk patients with CKD. While not included in the evidence base for the 2019 VA/DOD CKD CPG, in one study of 216 patients undergoing percutaneous coronary intervention (PCI), the incidence of CA-AKI was lower in those receiving IV hydration compared to the control group. However, subgroup analysis further showed no difference in CA-AKI incidence in the low-risk group and significant reductions in CA-AKI in the moderate-risk groups who received IV saline following PCI.(231) Since the 2019 VA/DOD CKD CPG evidence review, Nijssen et al. (2017)(232) compared patients with stage G3-G5 CKD undergoing either contrast-enhanced CT or angiography who were randomized to IV isotonic saline or oral fluids. 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). In addition, the study observed that 5.5% of patients who received IV fluids also had complications from the IV. Although, the study excluded patients if they had an eGFR of less than 30 mL/min/1.73 m^2, previous dialysis, or no referral for IV hydration volume expansion. However, the majority of individuals included in this study were at low risk for CA-AKI, as evidenced by the overall incidence of less than 3%, for whom we do not recommend any prophylactic intervention.

Brar et al. (2014)(233) 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]) versus a standard regimen (3 mL/kg over one hour followed by 1.5 mL/kg/hr over four hours) in 396 patients with an eGFR <60 mL/minute/1.73 m^2 and decreased left ventricular function undergoing coronary angiography. 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 to 0.79; p=0.005). Newer research suggests that guided hydration may lower the incidence of CA-AKI; however, the strength of evidence is Low to Very low.

Based on these data, the 2019 VA/DOD CKD CPG Work Group concluded that patients with underlying kidney disease with reduced eGFR are at increased risk of CA-AKI following IV contrast administration and recommended that patients at increased risk of CA-AKI receive volume expansion with IV isotonic crystalloid solutions prior to and following contrast administration.

The risk of AKI associated with contrast exposure should not prevent the performance of medically necessary contrast-enhanced tomography. The Work Group concurs with the consensus statement by the American College of Radiology (ACR) and the NKF that the risks associated with IV iodinated contrast, as used in current practice, are lower than previously thought; that clinically indicated contrast-enhanced imaging should not be avoided solely on perceived risk of CA-AKI; and that, in general, prophylactic IV fluid expansion is only required for individuals with an eGFR <30 mL/min/1.73 m^2.(234) Prophylaxis should also be considered for individuals with an eGFR between 30-44 mL/min/1.73 m^2,(235) depending on the presence of other risk factors. Thus, the Work Group suggests that providers weigh the benefits of IV fluid volume expansion with the risks associated with delaying urgent or emergent imaging and procedures. The benefits of timely diagnostic imaging or procedures may outweigh the risk of CA-AKI, in which case providers should forgo IV fluid expansion rather than delay medically necessary imaging or procedures.

Other factors may contribute to CA-AKI risk. Besides eGFR, co-occurring conditions may also impact a patient's risk of CA-AKI; thus, patients with co-occurring diabetes mellitus are thought to be at increased risk if they have an eGFR <60 mL/min/1.73 m^2, while non-diabetic patients are considered higher-risk when their eGFR <45 mL/min/1.73 m^2. Previous guidelines suggest reducing CA-AKI risk by considering the use of the least nephrotoxic contrast media (low-osmolar or iso-osmolar contrast media), minimizing the volume of administered contrast media, and avoiding concomitant nephrotoxins, particularly NSAIDs. 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.(227,236,237) The 2025 VA/DOD CKD CPG Work Group recommends these other factors to be considered with the coordination between the ordering provider and specialists (e.g., radiologists, cardiologists, nephrology providers).

The Work Group suggests that IV isotonic crystalloid be administered to reduce the risk of CA-AKI in high-risk patients (see Algorithm Module E), unless IV fluid administration is contraindicated or would delay emergency imaging or procedures. 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 higher volumes of administered isotonic fluids. The Work Group agrees with IV fluid regimens suggested by the 2019 VA/DOD CKD CPG for patients with CKD undergoing contrast-enhanced CT procedures. For more urgent studies, patients can 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 at a rate of 1-3 mL/kg/hour post-procedure. For routines studies in hospitalized patients, 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.

Moroni et al. (2021)(238) compared tailored hydration to fixed hydration and found there was no difference between AKI rates between patients receiving fixed fluid hydration and those receiving LVEDP-guided hydration or Bioimpedance-Guided (BIVA) Hydration. The study found urine flow rate (UFR)-guided and central venous pressure (CVP)-guided hydration were more efficacious in preventing CA-AKI than fixed-hydration (UFR: OR: 0.32; 95% CI: 0.19 to 0.54; CVP: OR: 0.45; 95% CI: 0.21 to 0.97). One SR and meta-analysis with 5 relevant RCTs compared RenalGuard, a device that administers IV hydration based on diuresis, to oral and IV hydration, and found a 46% reduction in CA-AKI using RenalGuard (RR: 0.54; 95% CrI: 0.31 to 0.86).(239) However, these results may not be generalizable to patients undergoing diagnostic contrast procedures with IV contrast since the study was done in patients undergoing percutaneous cardiovascular procedures.(227,236,237)

Based on the results of RCTs published since the 2014 VA/DOD CKD CPG evidence review, the 2019 Work Group concluded that there is no evidence to support an added benefit to sodium bicarbonate administration compared to isotonic saline. Solomon et al. found no difference in either CA-AKI (14.5% with sodium bicarbonate vs. 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 vs. 16.3% with saline; p=0.78) among 391

patients with an eGFR <45 mL/minute/1.73 m^2 undergoing coronary or non-coronary angiography.(240)

The Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial evaluated 4,993 patients with diabetes mellitus with an eGFR <60 mL/minute/1.73 m^2 or without diabetes mellitus and an eGFR <45 mL/minute/1.73 m^2 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.(241) In the comparison of isotonic sodium bicarbonate to isotonic saline, CA-AKI occurred in 9.5% of patients assigned to sodium bicarbonate compared to 8.3% of patients assigned to isotonic saline. 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. Additionally, one RCT showed no difference in CA-AKI incidence in patients receiving IV balanced salt solution and IV isotonic saline.(241) The 2019 Work Group concluded that there was a potential risk of harm associated with sodium bicarbonate administration as well as risk of compounding errors and increased cost without evidence of benefit. Thus, the Work Group concluded that there was no benefit to sodium bicarbonate and recommends volume expansion with IV isotonic crystalloid solutions, when appropriate.

IV volume expansion reduces the risk of AKI but oral fluid administration does not. The evidence base contained a single meta-analysis of 513 patients in 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.(242) Detailed analysis of the included trials revealed marked heterogeneity in the oral fluid administration arms. Three of the six studies included administration of IV saline post-procedure, and two involved the administration of water plus either oral sodium bicarbonate or oral sodium chloride. In the only study that compared IV isotonic saline to unrestricted oral fluids,(243) 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. The strength of evidence was Very low and showed no change in incidence when comparing IV isotonic saline to oral mineral water, IV sodium bicarbonate, oral sodium bicarbonate, and water.(244) In one non-inferiority trial comparing a small sample of patients receiving oral sodium chloride to IV isotonic saline, there was no significant difference in AKI incidence 2-5 days after receiving contrast (Oral: 4.8% vs. IV: 3.1%; 95% CI: -4.2 to 7).(245) Based on this data, neither oral hydration nor oral sodium loading should be considered adequate as the primary means of prophylaxis in individuals at high-risk for CA-AKI.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed the evidence identified in the evidence review conducted for this CPG update (238,239,244-246) and considered the assessment of the evidence put forth in the 2014 and 2019 CKD CPGs. The Work Group determined that the 2025 evidence base was not as relevant since the retrieved evidence was outside of the focus of the recommendation (e.g., types of contrast agents used), investigated patients undergoing contrast-associated procedures rather than diagnostic studies, did not include high-risk patients, or did not categorically add or detract from current recommended interventions. The Work Group determined that the previous CPG strength of evidence favoring the administration of isotonic IV crystalloid was Low due to conflicting data

from poor quality studies. However, the data suggested an evident dose-response relationship in that larger volumes of IV fluids were associated with greater benefit and patients with more advanced CKD were more likely to benefit. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

23. We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury.
(Strong against | Reviewed, Not changed)

Discussion

Initial studies evaluating the benefit of N-acetylcysteine for the prevention of CA-AKI were inconsistent, but more recent studies consistently show lack of benefit. An AHRQ Comparative Effectiveness Review identified 67 RCTs and 11 observational studies, 54 (N=4,749 patients) of which were included in a pooled meta-analysis (247) that showed no difference between high-dose (>1200 mg/day) and low-dose (≤1200 mg/day) N-acetylcysteine. In a previous meta-analysis, N-acetylcysteine was not effective in preventing AKI following cardiac surgery.(248) The PRESERVE trial evaluated 4,993 patients with diabetes mellitus and an eGFR <60 mL/min/1.73m^2 or without diabetes and an eGFR <45mL/min/1.73m^2 undergoing coronary or non-coronary angiography, finding that N-acetylcysteine did not prevent CA-AKI, death, need for dialysis, or a persistent 50% increase in sCr at Day 90.(241) The Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT) showed that N-acetylcysteine was not effective for preventing CA-AKI in 1,172 patients undergoing angiographic procedures.(249) While no direct patient harm was associated with oral N-acetylcysteine, IV administration was associated with a risk of anaphylaxis. Additionally, use of N-acetylcysteine is associated with potential side effects and increased costs.

The Work Group systematically reviewed the evidence from the 2019 report as well as studies related to this recommendation.(241,247,248) Since the 2019 VA/DOD CKD CPG was published, there has not been adequate evidence published to deviate from the previous Work Group's recommendation, leading to a *Reviewed, Not changed* recommendation. The evidence considered from the 2019 VA/DOD CKD CPG had a Low quality of evidence, and the current review had a Very low strength of evidence and similar findings. Although the collective strength of evidence was Low, this recommendation is predicated on the findings of both PRESERVE and ACT.(241,247) In addition to inefficacy, N-acetylcysteine was associated with increased costs and risk of adverse effects, including anaphylaxis with the IV formulation. The harms/burdens slightly outweigh benefits, with the most serious harms being the potential for anaphylactic reaction with IV administration and potential delay of care. The Work Group determined that patient values and preferences are similar. Given the sparsity of new evidence, the Work Group agreed to carry forward a *Strong against* recommendation.

X. Research Priorities

There are several areas that require more focused research to provide stronger evidence for further recommendation development across the spectrum of care. In summary, the Work Group recommends further research on testing and risk assessment/reduction, interdisciplinary care, the comparative effectiveness of pharmacotherapies and non-pharmaceutical interventions, the efficacy and safety of interventions in different patient subpopulations, and long-term CKD progression and safety outcomes.

A. Testing and Risk Assessment/Reduction

Several research priorities were identified related to risk prediction equations, including the need for studies comparing the predictive ability of various equations and their impact on referral rates (total and appropriate) to nephrology. Clarifying testing strategies in individuals without common co-occurring conditions (i.e., diabetes mellitus, hypertension, CVD, heart failure), establishing a threshold for concern for elevated potassium levels, and optimizing patient follow-up for scheduling and testing were also highlighted. Additionally, the Work Group identified concerns related to CA-AKI, namely the risk of CA-AKI with newer technologies/protocols for contrast-guided diagnostics that impact the volume of contrast dispensed, as well as new patient categories that may be considered for interventions to reduce CA-AKI risk. Other topics of interest included whether SGLT2i prevents CKD development and whether prevention of AKI/AKD slows CKD progression. Regarding PICC lines, better quantification of the risk of vascular injury and strategies to mitigate the risk of injury were desired. There was a call to develop vascular access devices constructed of newer materials or impregnated with medications that could decrease the risk of infection, thrombosis, and vascular injury for future dialysis access.

B. Interdisciplinary Care and Self-Management Support

Research priorities focused on interdisciplinary care include identifying which health care professionals should comprise an IDT, for which purpose or outcome an IDT is warranted, and which IDT components are most beneficial to patients (e.g., education, case management, self-management support). Research questions about using IDTs via telehealth and/or mobile technology in urban and rural areas to eliminate barriers to care (e.g., distance, access to transportation, low socioeconomic resources, age, health literacy) and improve self-management, lifestyle management, medication adherence, patient engagement, satisfaction, and overall understanding of CKD were suggested. The Work Group also emphasized the need for a nationwide cost-benefit analysis comparing IDT and current clinical management approaches. Several members recognized an opportunity to evaluate the effects of IDTs on CKD detection and management using data from the VA CKD Cascade of Care Initiative's research on PACTs, as well as the Million Veterans Program Research Initiative.

C. Comparative Effectiveness Studies

There was a strong desire for future comparative effectiveness studies for a variety of interventions, including:

General Management Strategies

- Face-to-face vs. telehealth CKD education to assist patients in decision-making regarding in-center vs. home-based hemodialysis and peritoneal dialysis, transplant or conservative care, medication and diet adherence, self-management of CKD, and patient satisfaction

Medications to Decrease CVD and Improve Kidney Outcomes

- Different first-line therapies for CKD with diabetes mellitus
- Different agents of the SGLT2i drug class
- Nonsteroidal vs. steroidal MRAs
- Combination therapy with SGLT2i, GLP-1 RA, and non-steroidal MRAs
- GLP-1 RA vs. SGLT2i vs. Both as the primary or initial treatment for cardiovascular outcomes
- ARNIs vs. monotherapy with an ACEI or ARB in a CKD population
- Type and intensity of statin therapy in patients with CKD
- Various non-statin medications (e.g., proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, ezetimibe, bempedoic acid) in a CKD population

Pharmacologic Management of Other Kidney Disease Related Complications

- Bicarbonate goals at varying thresholds
- Various interventions for managing RAASi-related hyperkalemia

Contrast-Associated Kidney Injury Management

- Different interventions to prevent AKI and/or AKD

D. Studies Assessing Patient Subpopulations

Data on the efficacy and safety of several interventions within a CKD population or CKD subgroup was a commonly observed evidence gap within the reviewed literature. The Work Group highly prioritized the need for trials testing the efficacy of finerenone when added to RAASi and SGLT2i in understudied populations, such as patients with non-diabetic albuminuric kidney disease and those with eGFR <25 mL/min/1.73 m^2. There was a call for studies examining the adoption of goal-directed medical therapy among high-risk populations identified by risk prediction equations, as well as those evaluating optimal treatment goals for non-dialysis CKD patients. Moreover, future studies testing the effects of ARNIs in a CKD population within the context of newer therapeutic agents for Cardiovascular-Kidney-Metabolic Syndrome (e.g., SGLT2i, nonsteroidal MRA) were highlighted. Within a CKD population, other research priorities included future studies on the benefits and safety of various statin formulations in individuals with moderate to severe CKD, whether SGLT2i have similar benefits in a non-albuminuric CKD population, and the benefits of intensive BP control for patients with late-stage CKD and albuminuria. There was also an interest in RCTs within different etiologies of AKI and AKD.

E. Long-term Studies Assessing CKD Progression and Safety

The need for longer-term studies was identified as a strong research priority. Studies assessing CKD progression were emphasized, particularly those evaluating interventions for AKI and AKD prevention. Another area of interest included long-term studies to determine whether the chronic use of binders decreases emergency room visits, hospitalizations, and healthcare utilization. Finally, the Work Group highlighted the need for long-term studies assessing tolvaptan's safety and efficacy in reducing hard kidney outcomes (e.g., need for dialysis, kidney transplant).

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DOD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by AHRQ (see Table A-1).

Table A-1. PICOTS (250)

P	Patients, Population, or Problem	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.
I	Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic/screening test used with the patient or population.
C	Comparison	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
O	Outcome	Results of interest (e.g., mortality, morbidity, quality of life, complications). Outcomes can include short, intermediate, and long-term outcomes.
(T)	Timing, if applicable	Duration or follow-up of interest for the particular intervention and outcome to occur (or not occur).
(S)	Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

The Champions, Work Group, and Evidence Review Team carried out several iterations of this process, each time narrowing the scope of the CPG and literature review by prioritizing the topics of interest. Due to resource constraints, not all developed KQs could be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority to include in the review. Table A-4 contains the final set of KQs used to guide the systematic evidence review for this CPG.

a. Population(s)

The clinical population considered in this SR are adults (aged 18 years or older) with CKD, with the exceptions specified below:

- KQ1: Adults without a CKD diagnosis.
- KQ7: Adults with or at risk for CKD, undergoing imaging with contrast media.
- KQ11: Adults with type 1 or type 2 diabetes mellitus, with or without known CKD.

b. Interventions and Comparators

KQ	Intervention(s)	Comparator(s)
1	▪ Urinalysis ▪ Incidental discovery of kidney abnormality via imaging, congenital anomalies of the kidney and urinary tract (CAKUT)	N/A

KQ	Intervention(s)	Comparator(s)
	▪ Medical history (i.e., medication profile, history of AKI events, infections) ▪ Patient characteristics and demographics (e.g., family history of kidney disease) ▪ Patient signs and symptoms (e.g., diabetes, hypertension, cardiovascular disease, atrial fibrillation, kidney stones) ▪ History of chemotherapy, urinary tract infections, prematurity or low birth weight, congenital abnormalities of urinary tract, obesity, Vesicoureteral reflux	
2	▪ Risk calculators (e.g., CKD-prognosis consortium risk models, KindeyIntelX, KD Predict, Klinrisk model) ▪ Specific equations (e.g., KFRE) ▪ Kidney-specific tools for cardiovascular risks (e.g., CKD-PC Risk model)	Another risk prediction tool/model or cut point within the same tool
3	▪ In person ▪ App based ▪ Website/Internet based ▪ Written materials ▪ Group education ▪ Individual education	Usual care
4	One or more episodes of AKI/AKD	No AKI/AKD or a different number of episodes of AKI/AKD
5	Aggressive blood pressure treatment for lower blood pressure goals/lower blood pressure (e.g., treatment from 120/80 to 110/70)	Treatment to less intensive or standard blood pressure goals
6	Standard list of antihypertensives, alone or in combination	Another hypertensive
7	**Contrast agents:** ▪ Gadolinium (groups 1, 2, 3) ▪ Iso-osmolar agents ▪ Low osmolar agents **Adjuvant interventions:** ▪ Oral hydration ▪ Isotonic sodium bicarbonate (IV or oral) ▪ Isotonic saline (IV) ▪ N-acetylcysteine ▪ Kidney replacement therapy ▪ Sodium chloride (oral) ▪ Statins ▪ Other (e.g., ascorbic acid, fenoldopam, furosemide, dopamine, inorganic nitrate, mannitol, RenalGuard, theophylline) ▪ Ischemic preconditioning	Another contrast agent, dosing schedule, or adjuvant intervention

KQ	Intervention(s)	Comparator(s)
	▪ Dialysis (any type) **Dosing schedules:** ▪ Regimen for IV or oral fluid administration	
8	▪ Standard list of antihypertensives ▪ Discontinuation of ACEI ▪ DPP4 inhibitors (“gliptins”) ▪ Endothelin antagonists (e.g., Atrasentan) ▪ Statins ▪ Thiazolidinediones (TZDs) ▪ Tolvaptan ▪ Urate lowering therapies (e.g., allopurinol, febuxostat, verinurad) ▪ Veverimer (pending FDA approval)	▪ Placebo plus standard of care (SoC) as defined by study authors or SoC alone for ACEI discontinuation studies **Examples of SoC:** ▪ RAAS therapy (ACEI/ARB) ▪ ACEI/ARB titrated to max tolerated dose if hypertensive ▪ Lifestyle modification (e.g., diet, exercise, weight loss, tobacco cessation)
9	**Medications used for adverse cardiovascular events plus SoC:** ▪ Standard list of antihypertensives ▪ Anticoagulants (e.g., DOACs, warfarin) ▪ Aspirin ▪ Atrasentan ▪ Clopidogrel ▪ DPP4 inhibitors (“gliptins”) ▪ Statins/ other lipid lowering agents ▪ RAAS blockade	▪ Placebo plus standard of care (SoC) as defined by study authors **Examples of SoC:** ▪ RAAS therapy (ACEI/ARB) ▪ ACEI/ARB titrated to max tolerated dose if hypertensive ▪ Lifestyle modification (e.g., diet, exercise, weight loss to target BMI <25, tobacco cessation)
10	**Interventions for mineral/bone disease plus SoC:** ▪ Abaloparatide ▪ Aluminum hydroxide ▪ Bisphosphonates ▪ Calcimimetics (cinacalcet HCl, etelcalcitide) ▪ Calcium supplements ▪ Denosumab ▪ Ferric citrate ▪ Phosphate binders (calcium and non-calcium) (calcium acetate, calcium carbonate, calcium citrate, sevelamer, lanthanum carbonate) ▪ Phosphorus ▪ Raloxifene ▪ Romosozumab ▪ Tenapanor ▪ Teriparatide	▪ Placebo plus standard of care (SoC) as defined by study authors or SoC alone for RAAS discontinuation studies **Examples of SoC:** ▪ Diet restrictions (e.g., phosphorous reduction, Mediterranean diet, fruits/vegetables diet) ▪ Diuretics ▪ Exercise ▪ Weight training ▪ Calcium supplementation ▪ Vitamin D supplementation ▪ Fall guards ▪ denosumab, bisphosphonates, teriparatide, abaloparatide, romosozumab

KQ	Intervention(s)	Comparator(s)
	▪ Vitamin D analogs/Active Vitamin D analogs (e.g., Calcitriol, paricalcitol, doxercalciferol) ▪ Weight-bearing exercise **Interventions for hyperkalemia plus SoC:** ▪ Albuterol ▪ Bicarbonate ▪ Diuretics ▪ Insulin ▪ Patiromer ▪ Discontinuation of RAAS ▪ SGLT2i ▪ Sodium polystyrene sulfate ▪ SCZ/ZS-9 **Interventions for acidosis plus SoC:** ▪ Diuretics ▪ Fludrocortisone ▪ Sodium bicarbonate ▪ Veverimer ▪ Diet	

11	▪ nsMRAs (finerenone)
	▪ GLP1-RA
	▪ SGLT2i
	▪ Statins
	▪ Multifactorial interventions (e.g., lifestyle modification plus pharmacotherapy)
		▪ SoC for diabetes treatment plus placebo
		Examples of SoC:
		▪ Diet
		▪ Exercise
		▪ For Type 1 DM, any diabetic medication to get patient to A1c goal in a stepwise fashion:
		  ▪ Metformin + other oral meds (sulfonylureas, TZDs, SGLT2s, DPP4s)
		  ▪ Progression to injectables (GLP1a, insulin)
		  ▪ Insulin
		  ▪ Metformin
		▪ For Type 2 DM:
		  ▪ Metformin + other oral meds (sulfonylureas, TZDs, SGLT2s, DPP4s)
		  ▪ Progression to injectables (GLP1a, insulin)
		▪ RAAS blockade

12	**CIH plus SoC:** ▪ Acupuncture ▪ AST-120 ▪ Calcium	▪ SoC plus placebo **Examples of SoC:** ▪ RAAS therapy (ACEI/ARB)

KQ	Intervention(s)	Comparator(s)
	▪ Collagen ▪ Dietary fiber ▪ Exercise ▪ Fish oil / omega-3 fatty acids ▪ Glucosamine ▪ Lutein ▪ Mind-body (guided relaxation, meditation, mindfulness, tai chi, yoga) ▪ Probiotics ▪ Vitamins and minerals	▪ ACEI/ARB titrated to max tolerated dose if hypertensive ▪ Lifestyle modification (e.g., diet, exercise, weight loss to target BMI <25, tobacco cessation)

c. Standard Antihypertensive Pharmacotherapy List

Drug Class	Example Drugs
Alpha-blockers	▪ Doxazosin ▪ Prazosin ▪ Terazosin
Angiotensin-converting enzyme inhibitors (ACEI)	▪ Benazepril ▪ Captopril ▪ Enalapril ▪ Fosinopril ▪ Lisinopril ▪ Ramipril
Angiotensin II receptor blockers (ARB)	▪ Candesartan ▪ Losartan ▪ Olmesartan ▪ Telmisartan ▪ Valsartan ▪ Irbesartan
Beta-blockers	▪ Atenolol ▪ Carvedilol ▪ Metoprolol ▪ Labetolol
Calcium channel blockers (CCBs) - dihydropyridine	▪ Diltiazem ▪ Verapamil
Calcium channel blockers (CCBs) - non-dihydropyridine	▪ Amlodipine ▪ Felodipine ▪ Nifedipine
Carbonic anhydrase inhibitors	▪ Acetazolamide ▪ Methazolamide
Central alpha 2 agonists	▪ Clonidine ▪ Guanfacine
Diuretics - loop	▪ Bumetanide

Drug Class	Example Drugs
	▪ Furosemide ▪ Torsemide ▪ Ethacrynic acid (as an alternative for sulfa allergies)
Diuretics - potassium-sparing	▪ Amiloride ▪ Triamterene
Diuretics - thiazide	▪ Chlorthalidone ▪ Hydrochlorothiazide ▪ Metolazone ▪ Indapamide
Glucagon-like peptide-1 receptor agonists (GLP-1 RA)	▪ Dulaglutide ▪ Liraglutide ▪ Semaglutide
Mineralocorticoid receptor antagonists (MRAs) - steroidal and non-steroidal	▪ Eplerenone (steroidal) ▪ Finerenone (non-steroidal) ▪ Spironolactone (steroidal)
Renin inhibitors	▪ Aliskiren
Sodium-glucose transport protein 2 inhibitors (SGLT2i)	▪ Canagliflozin ▪ Dapagliflozin ▪ Empagliflozin
Dual SLGT1i/SGLT2i	▪ Sotagliflozin
Vasodilators	▪ Hydralazine ▪ Minoxidil
Phosphodiesterase-5 inhibitors	▪ Sildenafil ▪ Tadalafil ▪ Vardenafil
Other Vasodilatory drugs	▪ Dinitrate/Mononitrate ▪ Isosorbide

d. Outcomes

KQ	Critical Outcome(s)	Important Outcome(s)
1	Point prevalence of CKD by risk factor and patient demographics/characteristics	▪ Probability of decline in eGFR, incident/worsening of albuminuria, or kidney failure ▪ Incidence rates of CKD diagnosis ▪ CKD stage at diagnosis ▪ Kidney failure (treatment by dialysis or kidney transplant) ▪ CKD diagnosis rate at different predefined timepoints
2	▪ Risk of CKD progression to ESKD ▪ Validated surrogate markers/predictors of CKD progression	▪ Mortality ▪ Cardiovascular composite outcome (e.g., MACE)

KQ	Critical Outcome(s)	Important Outcome(s)
		▪ Functional status ▪ Healthcare utilization (i.e., hospitalization, length of stay, emergency department [ED] use, nursing home placement) ▪ Quality of life
3	▪ General CKD and transplant knowledge ▪ Perceived self-management and motivation	▪ Progression of CKD (includes validated surrogate markers and progression to ESKD) ▪ Quality of life/ Patient satisfaction ▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement) ▪ Adherence ▪ Cardiovascular composite outcome (e.g., MACE)
4	▪ Rate of CKD progression to ESKD ▪ Validated surrogate markers/predictors of CKD progression	▪ Cardiovascular composite outcome (e.g., MACE) ▪ Functional status ▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement) ▪ Mortality ▪ Quality of life
5	▪ Risk of CKD progression to ESKD ▪ Validated surrogate markers/predictors of CKD progression ▪ Cardiovascular composite outcome (e.g., MACE)	▪ Adverse events ▪ Mortality ▪ Hypertension control composite outcome* ▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement)
6	▪ Validated surrogate markers/predictors of CKD progression ▪ Cardiovascular composite outcome (e.g., MACE) ▪ Risk of CKD progression to ESKD ▪ Hypertension control composite outcome*	▪ Serious adverse events ▪ Functional status ▪ Polypharmacy
7	▪ AKI within 2-5 days (after contrast agent) ▪ Nephrogenic systemic fibrosis (for gadolinium)	▪ Kidney composite outcome (e.g., MAKE) ▪ Validated surrogate markers/predictors of CKD progression ▪ Failure to deliver indicated care due to fear of AKI (renalism) ▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement)
8	▪ Progression of CKD (includes validated surrogate markers and progression to ESKD)	▪ Adverse events (e.g., incidence of hyperK, falls, syncope) ▪ Toxicity ▪ Mortality

KQ	Critical Outcome(s)	Important Outcome(s)
		▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement) ▪ Quality of life ▪ Polypharmacy

9	▪ Cardiovascular composite outcome (e.g., MACE)	▪ All-cause mortality
		▪ Hospitalization
		▪ Polypharmacy
		▪ *Component cardiovascular outcomes abstracted if composite outcome unavailable*:
		  ▪ Stroke
		  ▪ Arrhythmia
		  ▪ Heart failure

10	▪ Laboratory findings - individual or combined (i.e., serum potassium [for hyperK], serum bicarbonate [for metabolic acidosis], PTH level, serum calcium, serum PO4, BMP/CMP) ▪ Fractures/falls/ mineralization (DEXA scan)	▪ Cardiovascular composite outcome (e.g., MACE) ▪ Progression of CKD (includes validated surrogate markers and progression to ESKD) ▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement) ▪ Mortality ▪ Quality of life
11	▪ Progression of CKD (includes validated markers/predictors and progression to ESKD)	▪ CKD diagnosis ▪ Cardiovascular composite outcome (e.g., MACE) ▪ Mortality ▪ Quality of life ▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement) ▪ Functional status
12	▪ Depression ▪ Functional status/physical function/exercise capacity	▪ Healthcare utilization (i.e., hospitalization, length of stay, ED use, nursing home placement) ▪ Anxiety ▪ Quality of life ▪ Blood pressure control ▪ Validated surrogate markers/predictors of CKD progression

*Data related to hypertension control was only abstracted if reported as a composite outcome

e. Timing

KQ	Timing
KQ1, KQs 3-12	Any
KQ2	Minimum 2 years

f. Setting(s)

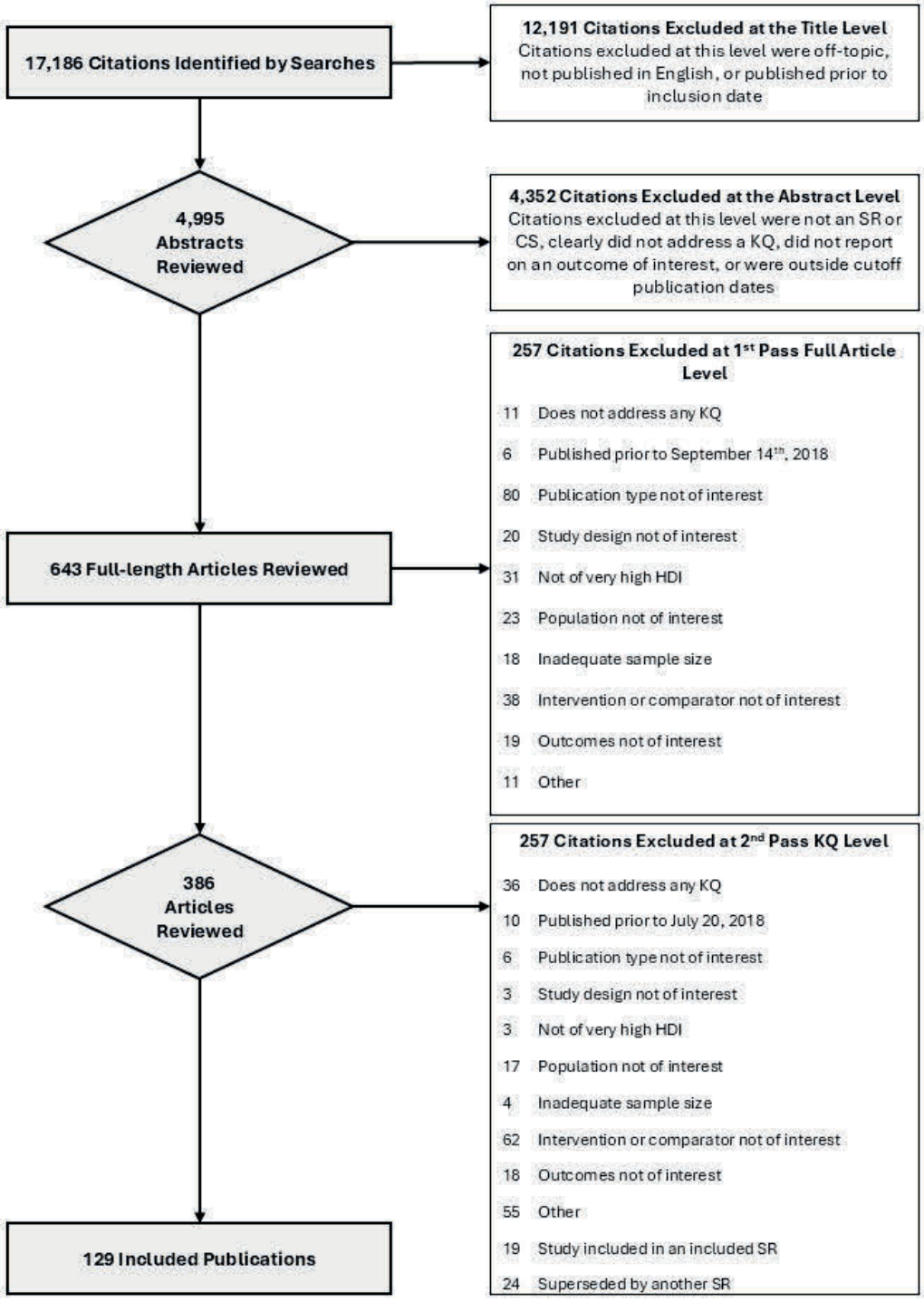
KQ	Setting(s)
KQs 1-6, 8-12	Primary care
KQ7	Any inpatient, emergency department, or outpatient setting

B. Conducting the Systematic Review

Extensive literature searches identified 17,186 citations potentially addressing the KQs of interest to this evidence review. Of those, 12,191 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 4,995 abstracts were reviewed with 4,352 of those being excluded for the following reasons: not an SR or clinical study, did not address a KQ of interest to this review, did not enroll a population of interest, published prior to September 14th, 2018, or did not otherwise meet eligibility criteria, such as lacking the population or comparator of interest, having an inadequate sample size, or not conducted in a very high HDI (Human Development Index) country. A total of 643 full-length articles were reviewed. Of those, 257 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 a clinical study or SR, not meeting inclusion criteria for any KQ, or being a duplicate reference. A total of 386 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 257 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below.

Overall, 127 studies in 129 publications 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 KQs.

Figure A-1. Study Flow Diagram



Abbreviations: CS: comparative study; HDI: Human Development Index; 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: 17,186 citations identified by searches.
    a. Right to Box 2: 12,191 excluded at the title level. Excluded citations were off topic, not published in English, or published prior to inclusion date.
    b. Down to box 3.
2. Box 3: 4,995 abstracts reviewed.
    a. Right to Box 4: 4,352 citations excluded at the abstract level. Citations excluded were not an SR or CS, clearly did not address a KQ, did not report an outcome of interest, or were outside cutoff publication dates.
    b. Down to Box 5.
3. Box 5: 643 full-length articles reviewed.
    a. Right to Box 6: 257 citations excluded at 1st pass full-article level.
        i. 11 doesn't address a KQ.
        ii. 6 published prior to September 14th, 2018.
        iii. 80 publication type not of interest.
        iv. 20 study design not of interest.
        v. 31 not of very high HDI.
        vi. 23 population not of interest.
        vii. 18 inadequate sample size.
        viii. 38 not an intervention or comparator of interest.
        ix. 19 no outcomes of interest.
        x. 11 other.
    b. Down to Box 7.
4. Box 7: 386 articles reviewed.
    a. Right to Box 8: 257 citations excluded at 2nd pass full-article level.
        i. 36 does not address any KQ.
        ii. 10 published prior to September 14th, 2018.
        iii. 6 publication type not of interest.
        iv. 3 study design not of interest.
        v. 3 not of very high HDI.
        vi. 17 population not of interest.

vii. 4 inadequate sample size.
viii. 62 intervention or comparator not of interest.
ix. 18 outcomes not of interest.
x. 55 other.
xi. 19 studies included in an included SR.
xii. 24 superseded by another SR.

b. Down to Box 9.

5. Box 9: 129 included studies.

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	What clinical factors increase the risk for CKD and identify patients who should be tested for CKD?	11 SRs and 24 observational studies
2	Which prediction tools/models should be used to optimize the risk prediction of CKD progression?	6 SRs and 11 observational studies
3	What models and modalities of patient education improve outcomes for CKD?	1 SR and 2 RCTs
4	In patients with CKD, how does prevention of acute kidney injury (AKI)/acute kidney disease (AKD) change the risk of CKD progression?	4 observational studies
5	What are optimal blood pressure goals for CKD patients?	5 SRs and 1 RCT
6	In patients with CKD, what are the optimal pharmacologic interventions for management of blood pressure that should preferentially be used?	5 SRs
7	What contrast agents, dosing schedules, and adjuvant interventions improve the safety profile for contrast in imaging?	5 SRs, 3 RCTs, and 4 observational studies
8	In patients with CKD, what is the safety and effectiveness of pharmacologic interventions for delaying, preventing, or reducing CKD progression?	12 SRs, 10 RCTs, and 1 RCT secondary analysis
9	In patients with CKD, what is the safety and effectiveness of pharmacologic interventions for delaying, preventing, or reducing adverse cardiovascular events?	6 SRs and 1 RCT
10	What strategies and interventions to manage mineral/bone disease and metabolic complications (e.g., acidosis, hyperkalemia) improve outcomes for CKD?	6 SRs, 7 RCTs, and 1 RCT extension study
11	For adults with type 1 or type 2 diabetes mellitus with or at risk for CKD, what interventions reduce the risk of developing CKD or CKD progression?	3 SRs and 2 RCTs
12	Which complementary and integrative health interventions improve health outcomes for CKD?	1 SR and 5 RCTs
Total Evidence Base		**127 studies (in 129 publications)***

*Some publications addressed more than one KQ, and some studies were reported in more than one publication. Therefore, the total number of publications in the evidence base is less than the added number of publications per KQ, as well as greater than the total number of studies included.

Abbreviations: CKD: chronic kidney disease; KQ: key question; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or SRs of RCTs published on or September 14, 2018, through June 30, 2024. If multiple SRs addressed a KQ, we selected the most recent and/or comprehensive review.
- Studies had to be published in English.
- Publication had to be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, research protocols, and other publications that were not full-length clinical studies were not accepted as evidence.
- Systematic reviews had to 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 Evidence-based Practice Centers of AHRQ). 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.
- RCTs must have had an independent control group. Randomized crossover trials were only included if data from the first period (prior to treatment crossover) was reported separately and an adequate washout period was used.
- Study must have enrolled at least 20 patients (10 per study group for RCTs and 20 for prospective non-randomized studies) unless otherwise noted.
- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older with CKD, or the population appropriate to the KQ. If the patient population fell below this threshold but the relevant population of patients with CKD was reported separately, then that study was included.
- To ensure applicability to the VA/DOD healthcare systems and consistency across the CPG program, inclusion of individual studies was limited to very high HDI, countries with an index ≥0.8 where standards of healthcare are comparable (e.g., U.S., Canada, United Kingdom, Western Europe, Israel, Japan, Hong Kong, Australia, and New Zealand). Inclusion of SRs was limited to those including more than half of the studies from eligible regions.
    - These regions of interest are listed in Table 1 of the Statistical Annex of the 2023/24 Human Development Report produced by the United Nations Development Program.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- If no RCTs were available to address KQs 1 (identifying patients who should be tested for CKD), 2 (prediction tools/models), or 7 (safety profile for contrast in imaging), prospective, non-randomized comparative studies were included. In the event there was no data identified for these KQs, we then looked at longitudinal cohort studies. Similarly,

if no SRs of RCTs were available for KQs 1, 2, or 7, then SRs of eligible non-RCT designs were used.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-5, below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix F.

Table A-5. Bibliographic Database Information

Name		Date Limits	Platform/ Provider
Bibliographic Databases	EMBASE	September 14, 2018, to June 30, 2024	Elsevier
	Medline/Premedline	September 14, 2018, to June 30, 2024	PubMed
	CINAHL	September 14, 2018, to June 30, 2024	EBSCO

d. Rating the Quality of Individual Studies and the Body of Evidence

Sigma Health Consulting assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(251)

Next, Sigma Health Consulting assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very Low.*

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Defense Health Agency's Clinical Quality Improvement Program, Sigma Health Consulting convened a 3.5 day in-person recommendation development meeting from October 7-10, 2024, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, Sigma Health Consulting finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting (see Determining Recommendation Strength and Direction).

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications.

a. Determining Recommendation Strength and Direction

Per GRADE methodology, to assess the quality of the evidence base and assign a grade for the strength for each recommendation, the GRADE system uses the following four domains to assess the strength of each recommendation (46):

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This 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 their strength. The evidence review used for the development of recommendations for this CPG was conducted by Sigma Health Consulting, who assessed the confidence in the quality of the evidence base and assigned a rating of "High", "Moderate", "Low", or "Very low".

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

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

2. Balance of Desirable and Undesirable Outcomes

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

3. Patient Values and Preferences

"Patient 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 wherein 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. This domain 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 patients' values and preferences?
- Are the assumed or identified relative values similar across the target population?

4. Other Implications

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility, and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions might not be effective and depending on the societal benchmark for willingness to pay, might 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-6) was used by the Work Group to guide discussions on each domain.

Table A-6. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgement
Balance of desirable and undesirable outcomes	▪ What is the magnitude of the anticipated desirable outcomes? ▪ What is the magnitude of the anticipated undesirable outcomes? ▪ Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	▪ Benefits outweigh harms/burdens ▪ Benefits slightly outweigh harms/burdens ▪ Benefits and harms/burden are balanced ▪ Harms/burden slightly outweigh benefits ▪ Harms/burden outweigh benefits
Confidence in the quality of evidence	▪ Among the designated critical outcomes, what is the lowest quality of relevant evidence? ▪ How unlikely is further research to change the confidence in the estimate of effect?	▪ High ▪ Moderate ▪ Low ▪ Very low
Patient values and preferences	▪ Are you confident about the typical values and preferences and are they similar across the target population? ▪ What are the patient's values and preferences? ▪ Are the assumed or identified relative values similar across the target population?	▪ Similar values ▪ Some variation ▪ Large variation
Other implications (e.g. resource use, equity, acceptability, feasibility, subgroup considerations)	▪ Are the resources worth the expected net benefit from the recommendation? ▪ What are the costs per resource unit? ▪ Is this intervention generally available? ▪ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ▪ Is there substantial variability in resource requirements across settings?	Various considerations

D. Recommendation Categorization

1. Recommendation Categories and Definitions

For use in the 2025 VA/DOD CKD CPG, a set of recommendation categories was adapted from those used by NICE.(51,52) These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2019 VA/DOD CKD CPG. The categories and definitions can be found in Table 3.

2. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether 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 are original, new recommendations that were not in the VA/DOD CKD CPG. "Reviewed, New-replaced" recommendations were in the previous version of the guideline but 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.

Recommendations could have also been designated as "Reviewed, Deleted." These are 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 suggested a shift in care, rendering recommendations in the previous version of the guideline obsolete.

3. 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 a review of the evidence. Due to time and budget constraints, the update of the VA/DOD CKD CPG could not review all available evidence on management of CKD. Instead, KQs were focused 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 review of the evidence. Thus, the support for these recommendations in the updated CPG was 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 into the updated version. The category of "Not reviewed, Amended" was used to designate recommendations that were modified from the 2019 VA/DOD CKD CPG with the updated GRADE language, as explained above.

Recommendations from the 2019 VA/DOD CKD CPG were 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 this updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2025 version of the guideline are noted in the Recommendations. Recommendations 6, 7, 8, 9, and 10 were carried forward from the 2019 VA/DOD CKD CPG using this method. The categories for the recommendations from the 2019 VA/DOD CKD CPG are noted in Appendix C.

E. Drafting and Finalizing the Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft narrative discussions to support each of the new recommendations. For the amended "carried forward" recommendation discussions, Work Group members could have opted to update the existing narrative discussions from the 2019 VA/DOD CKD CPG. The Work Group also considered tables, appendices, and other sections from the 2019 VA/DOD 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 revise the CPG. Once developed, the first two drafts of the CPG were posted on the CKD Wiki Website, an online common worksite for the guideline, 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 full Work Group, and appropriate revisions were made to the CPG. Finally, a third draft was circulated to pre-identified external reviewers for feedback, after which all feedback was reviewed and discussed by the full Work Group (see External Peer Review). Appropriate revisions were made, and the CPG was then finalized for EBPWG review.

Appendix B: Evidence Table

Table B-1. 2025 CKD Evidence Table [a, b, c, d]

#	2025 Recommendation	2019 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
1.	We suggest screening for chronic kidney disease (i.e., urine albumin/creatinine ratio and estimated glomerular filtration rate [eGFR]) in patients with one or more of the following associated risk factors: • Age over 60 years • Diabetes • Hypertension • Cardiovascular disease, including heart failure	Neither for nor against	(60-64) **Additional References** (65-80)	Weak for	Reviewed, Amended
2.	We recommend using urine albumin-to-creatinine ratio and estimated glomerular filtration rate for predicting chronic kidney disease progression.	Strong for	(62,85,86) **Additional References** (81-84)	Strong for	Reviewed, Amended
3.	In patients with an estimated glomerular filtration rate <60 mL/minute/1.73 m², we suggest estimating glomerular filtration rate with a combined creatinine and cystatin C formula for risk prediction.	Weak for	(85,93,94) **Additional References** (87-92)	Weak for	Reviewed, Amended
4.	We suggest the use of a validated end-stage kidney disease risk prediction model (e.g., kidney failure risk equation [KFRE]) for the management of stage G3-G5 chronic kidney disease.	Weak for	(96,97,99) **Additional References** (95,98,100)	Weak for	Reviewed, Amended
5.	When providing patient education about chronic kidney disease, there is insufficient evidence to recommend for or against any specific health education program or mode of delivery.	Neither for nor against	(108-110)	Neither for nor against	Reviewed, Amended

#	2025 Recommendation	2019 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
6.	We suggest interdisciplinary care (e.g., including dietitians, pharmacists, social workers, providers, nurses, and palliative care) for patients with chronic kidney disease.	Weak for	(111-114) **Additional References** (115)	Weak for	Not reviewed, Amended
7.	For patients who need long-term venous access and are at high risk for requiring kidney replacement, we suggest against peripherally inserted central catheter (PICC) lines to optimize success of future dialysis vascular access, while considering patient values and preferences.	Weak against	(118,119) **Additional References** (116,117,120)	Weak against	Not reviewed, Amended
8.	We suggest utilizing shared decision-making regarding kidney replacement therapy versus conservative management.	Weak for	(122,123,125-128,130,133,134,137) **Additional References** (108,121,124,129,131,132,135,136,138)	Weak for	Not reviewed, Not changed
9.	In patients with high co-occurring conditions/low functional status, we suggest nephrology referral with sufficient time for comprehensive preparation for conservative management or dialysis for treatment of kidney failure, depending on patient values and preferences.	Weak for		Weak for	Not reviewed, Amended
10.	In patients with high co-occurring conditions/low functional status approaching the need for dialysis, there is insufficient evidence to recommend for or against dialysis to improve quality of life.	Neither for nor against		Neither for nor against	Not reviewed, Amended
11.	We suggest intensive blood pressure management to reduce mortality and major adverse cardiovascular events in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 m².	Weak for	(139-146) **Additional References** (147,148)	Weak for	Reviewed, Amended
12.	In patients with hypertension and albuminuria (i.e., urine albumin-to-creatinine ratio [UACR] >30 mg/g), we recommend the use of either an angiotensin-converting enzyme inhibitor or	Strong for (2019 Recommendations 21 and 22); Strong	(157,163,164) **Additional References** (149-156,158-162)	Strong for	Reviewed, Amended

#	2025 Recommendation	2019 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
	angiotensin II receptor blocker to slow the progression of chronic kidney disease.	against (2019 Recommendation 23)			
13.	We suggest the addition of a thiazide diuretic or calcium channel blocker to reduce blood pressure in patients with chronic kidney disease and hypertension not controlled on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.	N/A	(165-167,170,172,173) **Additional References** (168,169,174)	Weak for	Reviewed, New-added
14.	In patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) currently on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, we suggest continuing therapy, unless there is drug intolerance or other adverse event.	N/A	(163,180-182) **Additional References** (82,163,175-179,182-185)	Weak for	Reviewed, New-added
15.	We recommend the addition of sodium-glucose co-transporter 2 inhibitors to maximally tolerated angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, in patients with chronic kidney disease who have one or more of the following: • Type 2 diabetes • Albuminuria (UACR>200 mg/g) • Heart failure to reduce the risk of major adverse cardiovascular events, heart failure, progression of kidney disease, and mortality, and continuing sodium-glucose co-transporter 2 inhibitors until start of dialysis.	Strong for	(186-189) **Additional References** (3,34,37,190-192)	Strong for	Reviewed, New-replaced
16.	We recommend adding a glucagon-like peptide-1 receptor agonist to an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in patients with type 2 diabetes and	Weak for	(185,187,188) **Additional References** (193)	Strong for	Reviewed, New-replaced

#	2025 Recommendation	2019 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
	albuminuric chronic kidney disease to reduce the progression of chronic kidney disease, major adverse cardiovascular events, and all-cause mortality.				
17.	In patients with chronic kidney disease and heart failure, we suggest sacubitril/valsartan as an alternative to monotherapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.	N/A	(195,196) **Additional References** (194)	Weak for	Reviewed, New-added
18.	We suggest the addition of a non-steroidal mineralocorticoid receptor antagonist (e.g., finerenone) in individuals on maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker who meet **all** the following criteria: • Type 2 diabetes • Albuminuria >30 mg/g • eGFR ≥25 mL/min/1.73m^2 • Potassium <4.8 mEq/L for the purpose of decreasing major adverse cardiovascular events and slowing progression of chronic kidney disease.	N/A	(197-200) **Additional References** (184,201-204)	Weak for	Reviewed, New-added
19.	In patients with chronic kidney disease not on dialysis, we recommend the initiation of statins to reduce major adverse cardiovascular events and mortality.	N/A	(208) **Additional References** (3,85,106,205-207,209-214)	Strong for	Reviewed, New-added
20.	In patients with autosomal dominant polycystic kidney disease, we recommend referral to a nephrology provider for evaluation and assessment of appropriateness of treatment with tolvaptan.	Weak for	(215-217,219) **Additional References** (218,220,221)	Strong for	Reviewed, New-replaced

#	2025 Recommendation	2019 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
21.	In patients with chronic kidney disease, we suggest using potassium binders in the management of persistent, non-life-threatening hyperkalemia.	N/A	(222-224) **Additional References** (225)	Weak for	Reviewed, New-added
22.	For patients with chronic kidney disease undergoing imaging utilizing iodinated contrast media who are at increased risk for iodinated contrast-associated acute kidney injury, we recommend intravenous volume expansion with isotonic crystalloid (see Algorithm Module E and Appendix Q for additional information).	Strong for	**2025 Evidence Base** (238,239,244-246) **Prior Evidence Base** (226,227,229,230,232,233,236,240,242,243,247) **Additional References** (228,231,234,235,237,241,252)	Strong for	Reviewed, New-replaced
23.	We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury.	Strong against	(241,247,248) **Additional References** (249)	Strong against	Reviewed, Not changed

[a] 2019 Strength of Recommendation column: “Not applicable” indicates that the 2025 VA/DOD CKD CPG recommendation was a new recommendation, and therefore does not have an associated 2019 strength of recommendation.

[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 a systematic evidence review carried out as part of the initial development or update of this 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 identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[c] 2025 Strength of Recommendation column: The 2025 VA/DOD CKD CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Grading Recommendations section for more information.

[d] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category

Appendix C: 2019 Recommendation Categorization

2019 CPG Recommendation #	2019 Recommendation Text[1]	2019 CPG Strength of Recommendation	2019 CPG Recommendation Category[2]	2025 CPG Recommendation Category[3]	2025 CPG Recommendation #
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	Reviewed, Amended	1
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	Reviewed, Amended	2
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	Reviewed, Amended	3
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	Reviewed, Amended	4
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	N/A – Deleted 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	N/A – Deleted 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	Not reviewed, Amended	6

[1] The 2019 Recommendation Text column contains the wording of each recommendation from the 2019 VA/DOD CKD CPG.
[2] The Recommendation Category column indicates the way in which each 2019 VA/DOD CKD CPG recommendation was updated.
[3] For recommendations that were carried forward to the 2025 VA/DOD CKD CPG, this column indicates the new recommendation(s) to which they correspond.

2019 CPG Recommendation #	2019 Recommendation Text[1]	2019 CPG Strength of Recommendation	2019 CPG Recommendation Category[2]	2025 CPG Recommendation Category[3]	2025 CPG 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	Reviewed, Amended	5
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	Not reviewed, Amended	7
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	Not reviewed, Not changed	8
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	Not reviewed, Amended	9
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	Not reviewed, Amended	10
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	N/A – Deleted recommendation	

2019 CPG Recommendation #	2019 Recommendation Text[1]	2019 CPG Strength of Recommendation	2019 CPG Recommendation Category[2]	2025 CPG Recommendation Category[3]	2025 CPG 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	N/A – Deleted 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	N/A – Deleted 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	Reviewed, New-replaced	15
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	Reviewed, New-replaced	16
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	N/A – Deleted 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	Reviewed, Amended	11
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	Reviewed, Amended	12

2019 CPG Recommendation #	2019 Recommendation Text[1]	2019 CPG Strength of Recommendation	2019 CPG Recommendation Category[2]	2025 CPG Recommendation Category[3]	2025 CPG Recommendation #
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		
24	We suggest initiation of oral iron therapy to support iron requirements in patients with chronic kidney disease.	Weak for	Not reviewed, Amended	N/A – Deleted 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	N/A – Deleted recommendation	
26	We recommend against initiating erythropoiesis-stimulating agents at a hemoglobin level greater than 10 g/dL.	Strong against	Not reviewed, Not changed	N/A – Deleted 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	N/A – Deleted 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	N/A – Deleted 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	N/A – Deleted recommendation	

2019 CPG Recommendation #	2019 Recommendation Text[1]	2019 CPG Strength of Recommendation	2019 CPG Recommendation Category[2]	2025 CPG Recommendation Category[3]	2025 CPG 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	N/A – Deleted 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	N/A – Deleted 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	Reviewed, New-replaced	20
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 E for additional information).	Strong for	Reviewed, Amended	Reviewed, New-replaced	22
34	We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury.	Strong against	Reviewed, New-replaced	Reviewed, Not changed	23
35	We recommend against the use of renal replacement therapy for iodinated contrast-associated acute kidney injury prophylaxis.	Strong against	Reviewed, Amended	N/A – Deleted recommendation	

Appendix D: Participant List

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Appendix E: Patient Focus Group Methods and Findings

A. Methods

VA and DOD Leadership recruited eight participants for the focus group with support from the Champions and other Work Group members as needed. The goal of recruitment for this Patient Focus Group was to have a group of engaging, diverse patients receiving VA or DOD healthcare services, who could cogently explain their experience with CKD. Participants were mixed in terms of receiving care from the VA and DOD, with one participant also receiving care from civilian providers. The time of CKD diagnosis ranged from childhood to midlife, with half of the participants receiving at least one kidney transplant. Participants reported receiving treatments for a variety of co-occurring conditions including diabetes mellitus, hypertension, and anxiety, which also integrated alternative treatments such as yoga, guided meditation, and mindfulness.

The Work Group, with support from Sigma Health Consulting, identified topics on which participants' input was important to consider in developing the CPG. Sigma Health Consulting developed an interview guide covering these topics, which the Work Group approved. The focus group facilitator who led the discussion used the guide to elicit participants' perspectives about their treatment and overall care. Not all questions included in the Moderator's Guide for the CKD Patient Focus Group were addressed by participants, but because the moderator encouraged conversation between the patient focus group members, most topics were covered.

B. Patient Focus Group Findings

a. Participants emphasized the importance of CKD screening and follow-up to ensure an accurate, timely diagnosis.

- Participants advocated for the proper use of laboratory tests to screen and accurately diagnose CKD.
- Participants urged providers to attentively follow up on test results to diagnose CKD in a timely manner.

b. Participants expressed the need for more information from providers on how to better prevent CKD progression and stabilize their disease.

- Participants stated that their desire to stabilize their kidney function is driven by a preference to avoid dialysis and prolong the life of their transplanted kidney.
- Participants asserted that providers could support them in taking control of their disease by supplying more information on how to better manage their CKD.

c. Participants valued effective patient-provider communication and emphasized the importance of direct and timely communication with providers.

- Participants appreciated a multidisciplinary team approach when creating treatment plans and advocated for using this approach to create consistent diet plans.
- Participants used a variety of delivery options to receive care, including telehealth and face-to-face visits.

- Providers should be intentional about communicating information in a timely manner, particularly during critical periods of treatment or illness.

d. Participants discussed the importance of offering education and training to providers on CKD.

- Emergency room providers and PCPs should be better educated on how to manage patients with kidney disease.
- Providers should be educated on the criteria for nephrology referral.
- Participants sometimes struggled with balancing treatments for CKD and other co-occurring conditions.
- More education and resources are needed for healthcare systems treating CKD patients in U.S. territories (Guam).

e. Participants discussed the value of non-pharmacologic interventions and lifestyle changes to manage anxiety and stress related to CKD.

- Some participants practiced yoga, guided meditation, mindfulness, and exercise to manage their CKD and stress.
- Intervention options vary based on age and physical activity level/ability.

f. Participants emphasized the importance of providers being empathetic when communicating with patients about sensitive, individual issues.

- Providers should consider the mental health of patients during the diagnosis and treatment of CKD.
- Family planning and women's health issues should be considered when creating and communicating treatment plans.

Appendix F: Literature Review Search Terms and Strategy

A. Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table F-1. Search Concept for Population (EMBASE and Medline)

Concept	Controlled Vocabulary	Keywords
Problem **Chronic Kidney Disease** *Note: This search statement will be applied to all searches except for KQ7.*	**EMBASE (EMTREE)** 'chronic kidney failure'/exp **Medline (MeSH)** "Renal Insufficiency"[MeSH]	CKD chronic kidney disease chronic kidney failure chronic renal disease chronic renal failure kidney insufficiency renal insufficiency

Table F-2. Key Question Specific Search Concepts (EMBASE and Medline)

Key Question	Concept	Controlled Vocabulary	Keywords
KQ1: What clinical factors increase the risk for CKD and identify patients who should be tested for CKD?	**Clinical Factors**	**EMBASE (EMTREE)** diabetes mellitus'/exp 'heart disease'/exp 'hypertension'/exp **Medline (MeSH)** "Diabetes Mellitus"[Mesh] "Heart Diseases"[Mesh] "Hypertension"[Mesh] "Kidney Calculi"[Mesh]	acute kidney injury CAKUT chemotherapy congenital abnormality* diabetes family history genetic predisposition heart disease high blood pressure history hypertension imaging infection* kidney calculi kidney disease kidney stone* low birth weight medication history obesity premature birth renal abnormality urinalysis urinary tract urinary tract infection* vesicoureteral reflux atrial fibrillation

Key Question	Concept	Controlled Vocabulary	Keywords
			cardiovascular disease diabetes family history frequent urination genetic predisposition glomerulonephritis heart disease high blood pressure hypertension kidney calculi kidney cancer kidney disease kidney stone* lupus nephritis medication history
	Risk	**EMBASE (Emtree)** 'risk factor'/exp **Medline (MeSH)** "Risk Factors"[Mesh]	risk factor*
	Diagnosis	**EMBASE (Emtree)** 'diagnosis'/exp **Medline (MeSH)** "Diagnosis"[Mesh]	diagnosis
	Testing		testing
KQ2: Which prediction tools/models should be used to optimize the risk prediction of CKD progression?	**CKD**	Use standard set	
	Progression	**Embase (Emtree)** 'Disease exacerbation'/exp **Medline (MeSH)** "Disease Progression"[Mesh]	progression progressive
	Prediction		prediction predictor prognos* risk
	Tool		assessment calculator equation model score tool
KQ3: What models and	**Patient Education**	**EMBASE (Emtree)** 'patient education'/exp	patient education patient information

Key Question	Concept	Controlled Vocabulary	Keywords
modalities of patient education improve outcomes for CKD?			patient instruction
	Delivery		booklet* brochure" class* group hand-out* individual in-person internet app* one-on-one videoconference* website* workshop*
KQ4: In patients with CKD, how does prevention of acute kidney injury (AKI)/acute kidney disease (AKD) change the risk of CKD progression?	**Acute Kidney Disease**		acute kidney disease
	Acute Kidney Injury	**EMBASE (Emtree)** 'acute kidney failure'/exp **Medline (MeSH)** "Acute Kidney Injury"[Mesh]	acute kidney failure acute kidney injury acute renal failure acute renal injury
	Prevention	**EMBASE (Emtree)** 'prophylaxis'/exp **Medline (MeSH)** "Primary Prevention"[Mesh]	prevention health protection preventive prophylaxis risk reduction
KQ5: What are optimal blood pressure goals for CKD patients?	**CKD**	Use standard set	
	Blood Pressure	**EMBASE (Emtree)** 'blood pressure'/exp **Medline (MeSH)** "Blood Pressure"[Mesh]	blood pressure hypertension
	Goals		goal* guideline* optimal target*
KQ6: In patients with CKD, what are the optimal pharmacologic interventions for management of blood pressure that should preferentially be used?	**Pharmacological Interventions**		ace inhibitor* alpha-blocker* angiotensin converting enzyme inhibitor* angiotensin ii receptor blocker* angiotensin receptor-neprilysin inhibitor* beta-blocker* calcium channel blocker* carbonic anhydrase inhibitor* central alpha 2 agonist* diuretic*

Key Question	Concept	Controlled Vocabulary	Keywords
			dual slgt1 inhibitor* dual sglt2 inhibitor* glucagon-like peptide-1 receptor agonists mineralocorticoid receptor antagonist* phosphodiesterase-5 inhibitor* renin inhibitor* sglt2i sodium-glucose transport protein 2 inhibitors thiazide vasodilator*
	Management		management treatment
KQ7: What contrast agents, dosing schedules, and adjuvant interventions improve the safety profile for contrast in imaging?	**Kidney Injury (NOT CKD)**		kidney injury nephrotoxicity nephritis
	Safety		safety
	Imaging (including interventional procedures)	**EMBASE (Emtree)** 'angiography'/exp 'tomography'/exp 'interventional radiology'/exp 'fluoroscopy'/exp 'nuclear magnetic resonance imaging'/exp 'percutaneous coronary intervention'/exp **Medline (MeSH)** "Angiography"[Mesh] "Tomography, X-Ray Computed"[Mesh] "Fluoroscopy"[Mesh] "Radiology, Interventional"[Mesh] "Magnetic Resonance Imaging"[Mesh] "Percutaneous Coronary Intervention"[Mesh]	angiogra* cardiac catheterization ct computed tomography fluoroscopy interventional procedures interventional radiology magnetic resonance imaging mri percutaneous coronary intervention tumor embolization x-ray
KQ8: In patients with CKD, what is the safety and effectiveness of pharmacologic interventions for delaying, preventing, or reducing CKD progression?	**CKD**	**Use standard set**	
	Safety		adverse effect* adverse event* risk assessment safety side effect* tolerability toxicity
	Effectiveness	**Medline (MeSH)** "Treatment Outcome"[Mesh]	clinical response effectiveness efficacy

Key Question	Concept	Controlled Vocabulary	Keywords
			response rate
	Drug classes		ACE inhibitor* ACE angiotensin converting enzyme inhibitor* angiotensin ii receptor blocker* angiotensin receptor-neprilysin inhibitor* arni beta-blocker* calcium channel blocker* carbonic anhydrase inhibitor* central alpha 2 agonist* diuretic* discontinuation dpp4 inhibitors dual slgt1 inhibitor* dual sglt2 inhibitor* endothelin antagonist* glp1ra glucagon-like peptide-1 receptor agonists mineralocorticoid receptor antagonist* MRAs phosphodiesterase-5 inhibitor* renin inhibitor* sglt2i sodium-glucose transport protein 2 inhibitors statin* termination thiazolidinediones tolvaptan urate lowering therapies vasodilator* veverimer
KQ9: In patients with CKD, what is the safety and effectiveness of pharmacologic interventions for delaying, preventing, or reducing adverse	**Drug classes**		alpha-blocker* angiotensin converting enzyme inhibitor* angiotensin ii receptor blocker* angiotensin receptor-neprilysin inhibitor* anticoagulant* aspirin atrasentan beta-blocker* calcium channel blocker*

Key Question	Concept	Controlled Vocabulary	Keywords
cardiovascular events?			carbonic anhydrase inhibitor* central alpha 2 agonist* clopidogrel diuretic* dpp4 dual slgt1 inhibitor* dual sglt2 inhibitor* glucagon-like peptide-1 receptor agonists GLP1RA lipid lowering agent* mineralocorticoid receptor antagonist* MRAs phosphodiesterase-5 inhibitor* raas blockade renin inhibitor* SGLT2i sodium-glucose transport protein 2 inhibitors statin* thiazide vasodilator*
	Cardiovascular Disease	**EMBASE (Emtree)** 'angina pectoris'/exp 'cerebrovascular accident'/exp 'heart failure'/exp 'heart infarction'/exp **Medline (MeSH)** "Myocardial Infarction"[Mesh] "Stroke"[Mesh] "Angina, Unstable"[Mesh] "Heart Failure"[Mesh]	acute myocardial infarction cardiovascular death heart failure stroke unstable angina
KQ10: What strategies and interventions to manage mineral/bone disease and metabolic complications (e.g., acidosis, hyperkalemia) improve outcomes for CKD?	**CKD**	**Use standard set**	
	Mineral and bone disorder	**EMBASE (Emtree)** 'hypercalcemia'/exp 'hyperphosphatemia'/exp 'metabolic acidosis'/exp 'mineral and bone disorder'/exp **Medline (MeSH)** "Bone Diseases, Metabolic"[Mesh] "Hyperkalemia"[Mesh] "Hyperphosphatemia"[Mesh]	
Intervention			abaloparatide albuterol aluminum hydroxide

Key Question	Concept	Controlled Vocabulary	Keywords
			bicarbonate bisphosphonates calcimimetics cinacalcet hcl, etelcalcitide) calcium supplements denosumab diet diuretic discontinuation ferric citrate fludrocortisone insulin patiromer phosphorus abaloparatide bisphosphonates calcitriol calcium acetate calcium carbonate calcium citrate calcium phosphate binders denosumab doxercalciferol) exercise fall guards lanthanum carbonate non-calcium phosphate binders paricalcitol raloxifene romosozumab romosozumab sevelamer sglt2i sodium bicarbonate sodium polystyrene sulfate sodium zirconium cyclosilicate/zs-9 tenapanor teriparatide teriparatide veverimer vitamin d analogs vitamin d supplementation weight-bearing exercise
KQ11: For adults with type 1 or type 2 diabetes with or at risk for	**Diabetes**	**EMBASE (Emtree)** 'diabetes mellitus'/exp **Medline (MeSH)** "Diabetes Mellitus"[Mesh]	

Key Question	Concept	Controlled Vocabulary	Keywords
CKD, what interventions reduce the risk of developing CKD or CKD progression?	**Multifactorial Interventions**		multifactorial interventions
	Lifestyle Modifications		diet exercise lifestyle modifications tobacco cessation weight loss
	Pharmacological Interventions		alpha-blocker* angiotensin-converting enzyme inhibitor* ace inhibitor* angiotensin ii receptor blocker* angiotensin receptor-neprilysin inhibitor* injectible insulin beta-blocker* calcium channel blocker* carbonic anhydrase inhibitor* central alpha 2 agonist* diuretic* GLP1-RAs glucagon-like peptide-1 receptor agonists mineralocorticoid receptor antagonist* nsMRAs oral medication renin inhibitor*] sodium-glucose transport protein 2 inhibitors sglt2i statin dual slgt1 inhibitor* dual sglt2 inhibitor* vasodilator* phosphodiesterase-5 inhibitor*
KQ12: Which Complementary and Integrative Health (CIH) interventions improve health outcomes for CKD?	**Complementary and Integrative Medicine**	**EMBASE (Emtree)** 'alternative medicine'/exp 'integrative medicine'/exp **Medline (MeSH)** "Complementary Therapies"[Mesh] "Integrative Medicine"[Mesh]	alternative medicine complementary medicine integrative medicine

B. Search Limits

Table F-3. EMBASE

Concept	Query
EXCLUDE Publication Types	NOT 'editorial'/exp OR 'letter'/exp OR 'medical illustration'/exp OR 'book'/exp OR 'poster'/exp OR 'conference abstract'/exp OR 'conference paper'/exp OR 'conferences and congresses'/exp OR 'conference review'/exp OR 'erratum'/exp OR 'symposium'/exp OR 'short survey'/exp OR 'note'/exp OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR abstract:nc OR annual:nc OR conference:nc OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR meeting:nc OR sessions:nc OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR comment:ab,ti OR annual:ab,ti OR 'conference proceeding':ab,ti OR note:ab,ti OR meeting:ab,ti OR sessions:ab,ti OR 'short survey':ab,ti OR animal:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR goat:ab,ti OR goats:ab,ti OR pig:ab,ti OR pigs:ab,ti OR cadaver:ab,ti OR dog:ab,ti OR dogs:ab,ti OR monkey:ab,ti OR monkeys:ab,ti OR ape:ab,ti OR apes:ab,ti
EXCLUDE Population Types	NOT adolescen*:ti OR babies:ti OR baby:ti OR boy:ti OR boys:ti OR child*:ti OR girl*:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti
Humans	[humans]/lim
Language	[english]/lim
Date	[2018-2024]/py

Table F-4. PubMed

Concept	Query
EXCLUDE Publication Types	NOT comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Book Illustrations"[pt] OR congress[pt] OR annual[tiab] OR book[tiab] OR comment[tiab] OR chapter[tiab] OR note[tiab] OR review[tiab] OR symposium[tiab] OR poster[tiab] OR abstract[tiab] OR "conference paper"[tiab] OR "conference proceeding"[tiab] OR "conference review"[tiab] OR congress[tiab] OR editorial[tiab] OR erratum[tiab] OR letter[tiab] OR note[tiab] OR meeting[tiab] OR sessions[tiab] OR "short survey"[tiab] OR symposium[tiab] OR animal[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR goat[tiab] OR goats[tiab] OR pig[tiab] OR pigs[tiab] OR cadaver[tiab] OR dog[tiab] OR dogs[tiab] OR monkey[tiab] OR monkeys[tiab] OR ape[tiab] OR apes[tiab]
EXCLUDE Population Types	NOT adolescen*[ti] OR babies[ti] OR baby[ti] OR boy[ti] OR boys[ti] OR child*[ti] OR girl*[ti] OR infancy[ti] OR infant*[ti] OR juvenile*[ti] OR neonat*[ti] OR newborn*[ti] OR nurser*[ti] OR paediatric*[ti] OR pediatric*[ti] OR preschool*[ti] OR "school age*"[ti] OR schoolchildren*[ti] OR teen*[ti] OR toddler*[ti] OR youth*[ti]
Humans	Filter: Humans
Language	Filter: English
Date	Filter: 2018/9/18 – 2024/6/30

Appendix G. Alternative Text Descriptions of Algorithms

The following outlines narratively describe Module A, Module B, Module C, Module D, and Module E. 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: Initial Assessment of Kidney Disease

1. Module A begins with Box 1, in the shape of a rounded rectangle: “Concern for acute or chronic kidney disease (e.g., incidental lab abnormality, history, etc.)”
2. Box 1 connects to Box 2, 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 2, then Box 3, in the shape of a rectangle: “Refer to emergency department or manage and stabilize”
        i. Box 3 connects to Box 4, in the shape of hexagon, asks the question: “Does patient have risk factor(s) for CKD (e.g., DM, HF, CVD, HTN, age >60 years)? (see **Sidebar 1**)”
            1. If the answer is “Yes” to Box 4, then Box 5, in the shape of a rectangle: “Obtain sCr, eGFR, and spot UACR at least annually”
            2. If the answer is “No” to Box 4, then Box 6, in the shape of a rectangle: “Initial assessment for kidney and non-kidney disease (see **Sidebars 1 and 2**)”
    b. If the answer is “No” to Box 2, then Box 4, in the shape of a hexagon, asks the question: “Does patient have risk factor(s) for CKD (e.g., DM, HF, CVD, HTN, age >60 years)? (see **Sidebar 1**)”
        i. If the answer is “Yes” to Box 4, then Box 5, in the shape of a rectangle: “Obtain sCr, eGFR, and spot UACR at least annually”
        ii. If the answer is “No” to Box 4, then Box 6, in the shape of a rectangle: “Initial assessment for kidney and non-kidney disease (see **Sidebars 1 and 2**)”
3. Box 5 connects to Box 7, in the shape of a hexagon, asks the question: “Does patient have evidence of kidney disease? (see **Sidebar 2**)”
    a. If the answer is “Yes” to Box 7, then Box 9, in the shape of a hexagon, asks the question: “Are these findings new?”
        i. If the answer is “Yes” to Box 9, then Box 11, in the shape of an oval: “Assess for AKI/AKD (exit to **Module B**)”
        ii. If the answer is “No” to Box 9, then Box 12, in the shape of an oval: “Assess for CKD (exit to **Module C**)”
    b. If the answer is “No” to Box 7, then Box 5, in the shape of a rectangle: “Obtain sCr, eGFR, and spot UACR at least annually”
4. Box 6 connects to Box 8, in the shape of a hexagon, asks the question: “Does patient have evidence of kidney disease? (see **Sidebar 2**)”

a. If the answer is “Yes” to Box 8, then Box 9, in the shape of a hexagon, asks the question: “Are these findings new?”
    i. If the answer is “Yes” to Box 9, then Box 11, in the shape of an oval: “Assess for AKI/AKD (exit to **Module B**)”
    ii. If the answer is “No” to Box 9, then Box 12, in the shape of an oval: “Assess for CKD (exit to **Module C**)”
b. If the answer is “No” to Box 8, then Box 10, in the shape of an oval: “Assess for other medical cause (exit algorithm)”

Module B. Evaluation and Intervention for AKI/AKD or New Decline in Kidney Function

1. Module B begins with Box 13, in the shape of a rounded rectangle: “Evaluation for possible AKI/AKD or new decline in kidney function (see **Sidebar 4**)”
2. Box 13 connects to Box 14, 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 14, then Box 15, in the shape of a rectangle: “Manage and stabilize and/or refer to emergency department, as appropriate”
    b. If the answer is “No” to Box 14, then Box 16.
3. Box 16, in the shape of a hexagon, asks the question: “Is there evidence of volume depletion? (see **Sidebar 5**)”
    a. If the answer is “Yes” to Box 16, then Box 17, in the shape of a rectangle: “Optimize volume status and reassess or refer to emergency department”
    b. If the answer is “No” to Box 16, then Box 18.
4. Box 18, in the shape of a hexagon, asks the question: “Is there clinical suspicion or evidence for acute urinary obstruction? (see **Sidebar 5**)”
    a. If the answer is “Yes” to Box 18, then Box 19, in the shape of a rectangle: “Relieve obstruction and reassess; consider referral to emergency department”
    b. If the answer is “No” to Box 18, then Box 20.
5. Box 20, in the shape of a hexagon, asks the question: “Is there clinical suspicion or evidence for acute glomerular or interstitial disease? (see **Sidebar 5**)”
    a. If the answer is “Yes” to Box 20, then Box 21, in the shape of a rectangle: “Call for urgent nephrology consultation”
    b. If the answer is “No” to Box 20, then Box 22, in the shape of a rectangle:
        i. “Stop nephrotoxins
        ii. Consider trial of holding ACEI/ARBs/diuretics/SGLT2i
        iii. Stop metformin and consider reducing dose of medications cleared by the kidney (e.g., insulin)
        iv. Depending on clinical context, consider trial of volume expansion”

6. Box 22 connects to Box 23, in the shape of a rectangle: “Reassess kidney function and consult nephrology if persistent kidney dysfunction”

Module C. Evaluation and Management of CKD

1. Module C begins at Box 24, in the shape of a rounded rectangle: “Evaluation for CKD (eGFR and UACR) (see **Sidebar 6**)”
2. Box 24 connects to Box 25, in the shape of a rectangle: “Establish/confirm stage of CKD with eGFR and UACR (see **Sidebar 9, Recommendation 3, and Appendix J**) and probable etiology”
3. Box 25 connects Box 26, in the shape of a hexagon, asks the question: “Is consultation with urology indicated? (see **Sidebar 7**)
    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**)
        i. If the answer is “Yes” to Box 28, then Box 32, in the shape of a rectangle: “Consult nephrology”
        ii. If the answer is “No” to Box 28, then Box 29, in the shape of a rectangle: “Assess risk for progression of CKD (See **Sidebar 9**); formulate plan to treat underlying cause; implement strategies to slow progression in decline of kidney function (see **Module D**); 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 29 connects to Box 30, in the shape of a rectangle: “Monitor and assess for CKD progression and development of complications periodically (e.g., BP, sCr/eGFR, UACR or UPCR, electrolytes, Ca, PO_4, Hgb (See **Appendix I**)”
5. Box 30 connects to Box 31, 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 31, then to Box 32, in the shape of a rectangle: “Consult nephrology”
    b. If the answer is “No” to Box 31, then to Box 30, in the shape of a rectangle: “Monitor and assess for CKD progression and development of complications periodically (e.g., BP, sCr/eGFR, UACR or UPCR, electrolytes, Ca, PO_4, Hgb (See **Appendix I**)”

Module D. Pharmacologic Management of CKD in Patients Not on Dialysis

1. Module D begins with Box 33, in the shape of a rounded rectangle: “Confirmed CKD”
2. Box 33 connects to Box 34, in the shape of a rectangle: “Start Statin to reduce MACE and mortality (see **Recommendation 19**)”

3. Box 34 connects to Box 35, in the shape of a hexagon, asks the question: "Does patient have UACR>30 mg/g?"
    a. If the answer is "Yes" to Box 35, then Box 36, in the shape of a rectangle: "Start ACEI/ARB to slow progression of CKD (strongest evidence for kidney protection with ACEI/ARB is in UACR >300 mg/g); titrate to maximally tolerated dose (see **Recommendations 12 and 17**); in patients with HF, sacubitril/valsartan may be used as an alternative to ACEI/ARB"
    b. If the answer is "No" to Box 35, then Box 37.
4. Box 37, in the shape of a hexagon, asks the question: "Does patient have HTN?"
    a. If the answer is "Yes" to Box 37, then Box 38, in the shape of a rectangle: "Control BP to reduce CV events and mortality (see VA/DOD Hypertension CPG):
        i. Use ACEI/ARB and/or Thiazide and/or CCB (see **Recommendation 13**); then additional agents as needed (depending on co-occurring conditions).
        ii. Consider use of combination tablets."
    b. If the answer is "No" to Box 37, then Box 39.
5. Box 39, in the shape of a hexagon, asks the question: "Does the patient have type 2 DM or UACR >200 mg/g or HF?"
    a. If the answer is "Yes" to Box 39, then Box 40, in the shape of a rectangle: "Start SGLT2i to reduce MACE, HF, progression of CKD and mortality (see **Recommendation 15**)"
    b. If the answer is "No" to Box 39, then Box 43, in the shape of a rounded rectangle: "Continue to monitor/manage CKD and risk factors, consider nephrology referral as needed (see **Sidebar 8**)"
6. Box 40 connects to Box 41, in the shape of a hexagon, asks the question: "Does patient have type 2 diabetes?"
    a. If the answer is "Yes" to Box 41, then Box 42, in the shape of a rectangle:
        i. "Consider metformin if eGFR >30 mL/min/1.73^2 to reduce MACE (see VA/DOD Diabetes CPG)
        ii. Consider GLP-1 RA if UACR > 100 to reduce MACE, progression of CKD, and mortality (see **Recommendation 16**)
        iii. Consider finerenone if UACR >30 mg/g, eGFR ≥25, and Potassium <4.8 mEq/L, to decrease MACE and progression of CKD (see **Recommendation 18**)"
    b. If the answer is "No" to Box 41, then Box 43, in the shape of a rounded rectangle: "Continue to monitor/manage CKD and risk factors, consider nephrology referral as needed (see **Sidebar 8**)"
7. Box 42 connects to Box 43, in the shape of a rounded rectangle: "Continue to monitor/manage CKD and risk factors, consider nephrology referral as needed (see **Sidebar 8**)"

Module E. Management of Patients with CKD Requiring Iodinated Contrast

1. Module E begins at Box 44, in the shape of a rounded rectangle: “Patient needing intravenous iodinated contrast (arterial or venous) for imaging (see **Sidebar 10**)”
2. Box 44 connects Box 45, in the shape of a hexagon, asks the question: “Is the study urgent?”
    a. If the answer is “Yes” to Box 45, then Box 46, in the shape of a rectangle: “Proceed with contrast study”
        i. Box 46 connects to Box 50, in the shape of a rectangle: “Perform post-procedure volume expansion if indicated”
    b. If the answer is “No” to Box 45, then Box 47, in the shape of a hexagon: “Is the patient’s eGFR above the threshold for safe IV or IA contrast administration (see **table in footnote**)?”
        i. If the answer is “Yes” to Box 47, then Box 48, the shape of a rectangle: “Proceed with administration of contrast”
        ii. If the answer is “No” to Box 47, then Box 49, in the shape of a rectangle: “Perform pre-procedure volume expansion if indicated (see **table in footnote** and **Sidebar 10** for fluid regimens)”
            1. Box 49 connects to Box 50, in the shape of a rectangle: “Perform post-procedure volume expansion if indicated”

Appendix H. Management of CKD Table

Concerns:	Interventions:
Medications	• Adjust medication dose based on eGFR or CrCl if indicated • Eliminate/avoid nephrotoxic agents (see Appendix K) • Assess medication adherence • Assess for medication side effects since drug clearance may be reduced in patients with kidney dysfunction and side effects may contribute to non-adherence

Diabetes	• Optimize glycemic control
	  • Target HbA1c 7-8.5% in most patients with diabetes and CKD
	  • HbA1c <7% is appropriate for patients with life expectancy greater than 10-15 years and mild microvascular complications, if it can be safely done
	  • Target HbA1c 8-9% for patients with type 2 diabetes with life expectancy <5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self-management attributable to e.g., mental status, disability or other factors such as food insecurity and insufficient social support
	  • Metformin can be used if eGFR >30 mL/min/1.73m^2
	• Recommend participation in a Diabetes Self-Management Education and Support Program (see VA/DOD Diabetes CPG).
	• Recommend use of ACEI or ARB at maximally tolerated dose if UCR >30 mg/g – continue ACEI or ARB unless drug intolerance or other adverse events (see Recommendation 14)
	• Recommend use of SGLT2i or GLP-1 RA (see Recommendations 15 and 16, Module D and VA/DOD Diabetes CPG[a]) to slow progression of kidney disease
	• Recommend finerenone if UACR >30 mg/g despite maximal ACEI or ARB and potassium <4.8 mmol/L (see Recommendation 18)
	• Recommend avoiding sulfonylureas
	• Suggest more frequent blood sugar monitoring and/or use of continuous glucose monitor for patients at risk for hypoglycemia (e.g., those on insulin)

Hypertension	• Optimize blood pressure control (see Recommendations 11-13, Module D, and VA/DOD Hypertension CPG[b]) • Recommend use of ACEI or ARB as first-line especially in patients with albuminuria - continue ACEI or ARB unless drug intolerance or other adverse events (see Recommendation 12 and 14) • Recommend adding thiazide diuretics and/or calcium channel blockers, if blood pressure not controlled on ACEI or ARB (Recommendation 13) • Restrict dietary sodium to 2,300 mg/day (see VA/DOD Hypertension CPG) • Optimize volume status • Consider nephrology referral for resistant hypertension, defined as BP >140/90 mmHg despite optimal dose of 3 anti-hypertensives that include a diuretic
Albuminuria (urine albumin/creatinine >200mg/g in individuals without diabetes)	• Recommend use of ACEI or ARB at maximally tolerated dose – continue ACEI or ARB unless drug intolerance or other adverse events (see Recommendation 14) • Decrease other antihypertensives to maximize use of ACEI or ARB • Recommend adding SGLT2i for persistent proteinuria despite maximally tolerated dose of ACEI or ARB (see Recommendation 15 and Module D)

Vaccination	• Assess Hepatitis B status and vaccinate, if non-immune • Update pneumococcal vaccines • Update influenza and COVID vaccination annually • Provide age-appropriate vaccination (e.g., MMR, VZV, Tdap/Td, RSV) • Do not administer live vaccines (e.g., MMR, Zostavax) to kidney transplant recipients.
CV health	• Recommend placing a referral to an RD and/or a comprehensive lifestyle intervention program for weight management to achieve/maintain ideal body weight/BMI (e.g., VHA's MOVE! Weight Management). See the VA/DOD CPG for Management of Overweight and Obesity for further guidance on weight management. • Assess and treat dyslipidemia (see VA/DOD Dyslipidemia CPG[c]) • Recommend use of a statin (see Recommendation 19) • Assess risks/benefits of aspirin therapy • Recommend tobacco cessation • Encourage physical activity, considering the guidance of 150 min/week of moderate aerobic activity as appropriate
Pain	• Avoid NSAID use, including OTC and prescription (oral/topical), if possible • Use of Buprenorphine is preferred over other opiates for chronic pain (see Appendix N and VA/DOD Opioid Therapy for Chronic Pain CPG[d])
Education/behavior change support	• Review dietary habits and refer patient to an RD for individualized nutrition counseling on sodium, potassium, phosphorus, and fluid intake as indicated. • Offer education on diagnosis and prognosis of CKD, as well as measures to prevent progression to kidney failure • Develop sick day planning specifically addressing temporary cessation of sulfonylureas, ACEI, diuretics/direct renin inhibitors, metformin, ARBs, NSAIDs, and SGLT2i's (i.e., SADMANS) • Educate on KRT options to include dialysis, vascular access, and transplant when eGFR <20 mL/min/1.73 m^2 • Screen for depression or health-related mental illness
Anemia	• Evaluate for underlying cause of anemia • Assess for nutritional deficiency and replete iron, vitamin B12, and folate stores if levels low • Refer to nephrology if patient has CKD stage G3b or higher and persistent hemoglobin <10 for consideration of ESA • Refer for IV iron, if patient has persistent iron deficiency (transferrin saturation <20%, ferritin <100 mg/dl) despite trial of oral iron (after age-appropriate evaluation for etiology or if patient unable to tolerate oral iron)
Electrolytes	• Dietary management for hyperphosphatemia or hyperkalemia – consider referral to medical nutrition therapy • Manage persistent hyperkalemia with bicarbonate, adjustment of diuretics and potassium binders as indicated (see Appendix M). • Treat metabolic acidosis with bicarbonate
Mineral Bone Disease	• Modify diet for hyperphosphatemia (e.g., plant-based diet, avoidance of phosphorus additives/preservatives) • Consider vitamin D and active vitamin D
Iodinated contrast agents	• Use isotonic IV fluid to prevent CA-AKI, if indicated and time allows (see Recommendations 22-23 and Algorithm Module E)
Gadolinium	• Do not use group 1 gadolinium agents if eGFR <30 mL/min/1.73 m^2 or current AKI (see Appendix Q)

Nuclear medicine contrast	• No concerns for kidney toxicity so may use as clinically indicated
Kidney stones	• Recommend low-sodium diet and sufficient fluid intake to produce urine output >2.2 L/day • Dietary calcium restriction is not recommended even for calcium stones • Send stones for analysis when available • Manage symptomatic stones with analgesics, hydration, and alpha-blockers initially and refer to urology for persistent symptoms or obstructive nephrolithiasis • Refer to nephrology for metabolic evaluation/management of recurrent nephrolithiasis

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin II receptor blockers; BMI: body mass index; BP: blood pressure; CA-AKI: contrast-associated acute kidney injury; 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 RA: glucagon-like peptide-1 receptor agonist; IV: intravenous; KRT: kidney replacement therapy; L: liter; MMR: measles, mumps, and rubella; NSAID: non-steroidal anti-inflammatory drug; OTC: over-the-counter; RD: registered dietician; RSV: respiratory syncytial virus; SADMANS: sulfonylureas, other secretagogues, gliclazide, glimepiride, glyburide, repaglinide; SGLT2i: sodium-glucose cotransporter-2 inhibitor; Td: tetanus and diphtheria; Tdap: tetanus, diphtheria, and pertussis; VA: Department of Veteran Affairs; VZV: varicella zoster virus

[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

[e] Practice Point 4.3.2 -- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314. doi: 10.1016/j.kint.2023.10.018. PMID: 38490803.

Appendix I. Monitoring of CKD Table

Assessment	Frequency
Serum creatinine to estimate GFR, using the 2021 CKD-EPI creatinine equation	• At diagnosis and at least annually in patients at low or moderate risk of progression, at least 2-3x/year in those at high risk of progression and at least 4x/year in those at very high risk of progression (see Sidebar 9); more often when measurement will impact therapeutic decision-making. For example, within 2-4 weeks of initiation or increase in the dose of a RAASi.
Cystatin C	• At least once; repeat if more accurate assessment than can be provided by eGFRcr is needed (e.g., in extremes of creatinine generation such as high muscle mass, spinal cord injury, neuromuscular disease, or malnutrition; see Appendix J).
Spot urine ACR	• At diagnosis and at least annually; more often in patients at higher risk of progression (consider 2-3x/year in those at high risk of progression and 4x/year in those at very high risk of progression; see Sidebar 9) or when measurement will impact therapeutic decision-making.
Blood Pressure	• At diagnosis, at each visit, and as needed to ensure blood pressure is controlled to goal. • Strongly consider home blood pressure monitoring.
Potassium	• At diagnosis and at least annually; more often in patients with a history of hyperkalemia or at risk due to stage of CKD or medications. • Within 2-4 weeks of initiation or increase in the dose of a RAASi, depending on the current eGFR and serum potassium. • One month after initiation of a nonsteroidal MRA and then at least every 4 months.
Bicarbonate	• When measurement will impact therapeutic decision-making. Practically, bicarbonate is likely to be reported when eGFR or potassium are monitored.
Calcium, Phosphate, PTH, and 25-hydroxyvitamin D	• When measurement will impact therapeutic decision-making. Routine monitoring is unlikely to be needed in CKD stages G1-G3A. Practically, monitoring of calcium/phosphate/PTH is unlikely to impact therapeutic decision-making in patients who do not have an indication for nephrology consultation.
Hemoglobin	• At least annually in patients with CKD stage G3, at least twice per year in CKD stage G4, and at least 4x/year in CKD stage G5.
Kidney Failure Risk Prediction Calculation	• In CKD stages G3-G5, at diagnosis and periodically as eGFR and ACR change.
Cardiovascular Risk Prediction	• At diagnosis and when prediction will impact therapeutic decision-making (e.g., use of statins).
Medication reconciliation and review	• At diagnosis and each clinic visit or transition of care. • Assess the need for adjustments in drug dosing, for nephrotoxins (prescribed and over the counter medications and supplements), and for indicated medications that may have been held due to acute events.

Abbreviations: ACR: albumin-to-creatinine ratio; CKD: chronic kidney disease; CKD-EPI: CKD Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; eGFRcr: eGFR using creatinine; MRA: mineralocorticoid receptor antagonist; PTH: parathyroid hormone; RAASi: renin-angiotensin system inhibitor

Table I-2. Useful equations in CKD diagnosis, staging and risk assessment

Clinical Utility	Useful for	Equation (calculator website)	Required patient data	Comments
Predicts 2- and 5-yr risk of kidney failure in patients with CKD stage G3-G5	Patients with eGFR <60	Kidney Failure Risk Equation (KFRE) (95) (https://www.kidneyfailurerisk.com/)	Four-variable equation: age, sex, eGFR, UACR Eight-variable equation: age, sex, eGFR, UACR, serum calcium, phosphate, bicarbonate, albumin	• Validated in >2 million in >30 countries • Validated in pediatric, transplant and ethnically diverse populations • Incorporated in national/international guidelines including KDIGO CPG • Included in Clinical Decision Support Console in CPRS (VAMC)
Estimates 2- and 4-yr risk of ESKD, CVD, and death	Patients with eGFR <30	CKD G4+ (CKD-PC) risk calculator (101) (https://ckdpcrisk.org/lowgfrevents/)	Age, sex, race, eGFR, SBP, history of CVD, DM, UACR, smoking status	• Calculates competing risks of ESKD, CVD and death • May be useful in SDM since risk of CVD and mortality is higher than risk of ESKD in most older/frail patients
Predicts risk of 40% decline in kidney function or kidney failure	Patients with eGFR >60	40% decline in kidney function in 3-years (102) (https://ckdpcrisk.org/gfrdecline40/)	Age, sex, eGFR, UACR, SBP, antihypertensive medication use, diabetes, history of heart failure, history of coronary heart disease, history of atrial fibrillation, smoking status, BMI In diabetics: hemoglobin A1c, insulin use, use of oral diabetes medication	• 40% decline in kidney function is more applicable in those with early CKD • Used as surrogate marker for FDA/clinical trials • Overall lower C-statistic in Grams model (compared to Ferguson model) but Grams model developed/validated in larger population and Ferguson model developed/validated in Canadian patients; no online calculator available for Ferguson model
Estimates 5-year probability of eGFR <60 mL/min/1.73 m^2	Patients with CKD	Risk of Developing Reduced Kidney Function (103) (http://ckdpcrisk.org/ckdrisk)	Diabetes status, age, sex, race, eGFR, MCVD, BMI, smoking history, DM treatment, HgbA1c, UACR, HTN	

Clinical Utility	Useful for	Equation (calculator website)	Required patient data	Comments
Estimates probability of having eGFR <60 mL/min/ 1.73 m^2	Patients without known CKD	Screening for Occult Renal Disease (SCORED) score (104) (https://nccd.cdc.gov/ckd/Calculators.aspx)	Age, sex, anemia, HTN, DM, history CVD, history of CHF, PVD	
Conversion of UPCR or dipstick to UACR	Patients with or at-risk for CKD	Conversion of UPCR and dipstick to UACR (105) (http://ckdpcrisk.org/pcr2acr)	Crude equation: UPCR (mg/g) or urine dipstick protein Adjusted equation: sex, hypertension, and diabetes	• Many risk calculators include UACR but UACR data is not always available, so conversion enables clinicians to estimate UACR from other readily available measures of albuminuria • Urine dipsticks are low-cost and rapidly available, even in resource-restricted locations • Albuminuria is subject to intra-individual biological variability (first morning void thought to be most accurate) • Caution in non-albumin proteinuria (e.g., multiple myeloma, amyloidosis). • Similar estimates for KFRE calculated when using predicted vs. observed ACR (105)
Estimates 10-year and 30-year risk of CVD (composite CVD risk and individual risk of ASCVD and HF)	Patients without known CVD or HF, aged 30-79 years	AHA Predicting Risk of Cardiovascular Disease Events (PREVENT) equations (106) (https://professional.heart.org/en/guidelines-and-statements/prevent-calculator)	Age, sex, total cholesterol, HDL, SBP, BMI, eGFR, DM status, smoking status, use of antihypertensive medication, use of lipid-lowering medication Optional factors: UACR, A1C, zip code (for estimating SDI)	• Performed better than PCE (106,107) • 1% increase in PREVENT risk estimate associated with increased CVD mortality (HR: 1.09) (107)

Abbreviations: A1C: glycated hemoglobin; ACR: albumin-to-creatinine ratio; ASCVD: atherosclerotic CVD; BMI: body mass index; CHF: congestive heart failure; CKD: chronic kidney disease; CKD-PC: Chronic Kidney Disease Prognosis Consortium; CPG: clinical practice guideline; CPRS: computerized patient record system; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; FDA: Food and Drug Administration; HgbA1c: hemoglobin A1c; HDL: high density lipoprotein; HF: heart failure; HR: hazard ratio; HTN: hypertension; KDIGO: Kidney Disease: Improving Global Outcomes; MCVD: monogenic CVD; PCE: pooled cohort equation; PVD: peripheral vascular disease; SBP: systolic blood pressure; SDI: Social Determinants of Health Index;

SDM: shared decision-making; UACR: urine ACR; UPCR: urine protein-to-creatinine ratio; VAMC: Veterans Affairs Medical Center

Appendix J. Approaches for eGFR Calculation

In most kidney diseases, the excretory, endocrine, and metabolic functions of the kidney decline together. Glomerular filtration rate (GFR), a marker of excretory function, is widely accepted as the best overall index of kidney function. GFR is a measure of how quickly plasma is filtered each minute by the nephron, the fundamental unit of the kidney. Each nephron can be considered to have a single nephron GFR. The total GFR is a sum of the single nephron GFRs. Kidney disease is due to loss of nephrons. In young adults, the normal GFR is approximately 90-130 mL/min. GFR declines, on average, 0.8-1.0 mL/min/year after age 30, though this is variable.

Estimation of GFR

While there are methods to measure GFR, these methods are typically time-consuming and largely reserved for use in research. In clinical practice, GFR is estimated (eGFR) from validated equations using creatinine, cystatin C, or a combination of cystatin C and creatinine as filtration markers. An important caveat to estimation of GFR is that any estimate of GFR assumes that kidney function is in steady state. If kidney function is changing, such as in the setting of AKI or during recovery phase of AKI, the creatinine (or cystatin C) value is unstable, so the estimating formulas should not be used. If the creatinine or cystatin C levels are rising in a non-steady state condition, the formulas overestimate GFR. Conversely, if the levels are falling, the formulas underestimate GFR.

eGFR is used in screening for CKD (with urine albumin/creatinine assessment), determining severity of CKD, and monitoring progression of kidney disease. Knowing the level of GFR is important for medication prescribing.

Creatinine

Creatinine is an end-product of muscle metabolism and is filtered by the kidney and not reabsorbed. Creatinine is also secreted by the tubules into the urine, which accounts for 10-20% of creatinine elimination. Blood levels reflect creatinine generation (muscle mass and diet) and elimination (kidney filtration and tubular function).

Creatinine-based equations account for differences in creatinine generation due to age or sex. The creatinine eGFR equations assume that for a given age and sex that a person has an average muscle mass. In extremes of body weight/habitus or diseases that significantly affect muscle mass, the creatinine-based equations may be inaccurate. Vegetarian diets, high protein diets, or use of creatine supplements also affect creatinine generation and the accuracy of these equations. In addition, there are medications that can affect tubular secretion of creatinine and lead to higher creatinine levels that are not reflective of changes in GFR (see Table J-1).

Table J-1. Medications that block tubular secretion of creatinine

Generic Name	Common Brand Names	Use
Cimetidine	Tagamet	H_2 blocker
Trimethoprim,	Primsol, Priloprim, Trimpex	Antibiotic
Sulfamethoxazole/trimethoprim	Bactrim, Septa, Sulfatrim, SMZ-TMP	Antibiotic
Pyrimethamine	Daraprim	Antiparasitic
Dronedarone	MULTAQ	Antiarrhythmic
Dolutegravir	Tivicay	HIV
Cobicistat	Tybost	HIV
Olaparib	Lynparza	Cancer
Rucaparib	Rubraca	Cancer
Imatinib	Gleevac	Cancer
Bosutinib	Bosulif	Cancer
Sorafenib	Nexavar	Cancer
Crizotinib	Xalkori	Cancer
Gefitinib	Iressa	Cancer
Pazpanib	Votrient	Cancer
Phenacemide	Phenurone	Anticonvulsant

Abbreviation: HIV: human immunodeficiency virus

Cystatin C

Cystatin C is an alternative filtration marker that is a small protease inhibitor protein produced by all nucleated cells. It is filtered at the glomerulus and is then completely reabsorbed and degraded by the proximal tubule. Cystatin C is not as affected by muscle mass as creatinine. However, cystatin C levels are affected by fat mass (i.e., higher in obesity) and may be affected by inflammation, smoking, corticosteroids, or thyroid disease.(87) Cystatin C testing is becoming more widely available, though it currently is more expensive than creatinine.

Decreased kidney function is associated with an increased risk of mortality and cardiovascular disease. Prior research has found that cystatin C has a more linear association with adverse outcomes while creatinine has a U-shaped relationship, where both very low creatinine levels and high creatinine levels are associated with adverse outcomes.(3,90,91) This may reflect muscle mass loss which commonly occurs with chronic diseases.

Table J-2: Non-kidney factors affecting creatinine or cystatin C levels

Factors that increase serum creatinine	High protein or keto diets Medications that interfere with creatinine secretion (see Table J-1) Anabolic steroids Creatine supplements Very high muscle mass
Factors that decrease serum creatinine	Malnutrition Sarcopenia or weight loss with disease (e.g., cirrhosis, advanced heart failure, cancer) Vegetarian diet Neuromuscular diseases Spinal cord injury Above knee amputation

Factors that increase serum cystatin C	Hyperthyroidism Severe obesity Corticosteroids Cigarette smoking Chronic inflammation
Factors that decrease serum cystatin C	Hypothyroidism

eGFR equations

The most commonly used formula to estimate GFR is the CKD-EPI creatinine-based equation. It is used by the laboratory when creatinine is reported. Prior to 2021, the 2012 CKD-EPI equation, which estimated GFR using cystatin C only, was the only equation which incorporated terms for age and sex without race inclusion. In 2021, the NKF and ASN Joint Task Force recommended adoption of equations without race.(253) The newer 2021 CKD-EPI equations for creatinine and combination of creatinine and cystatin C that removed the adjustments for race were developed.(89) It is recommended that one of these validated, race-neutral equations be used to estimate GFR.

Creatinine or Cystatin C or both?

For most patients, the combined creatinine-cystatin C formula provides the most accurate estimate of GFR. It has been hypothesized that this is because the non-kidney determinants of creatinine and cystatin C balance each other, leading to a more accurate estimate.(87) In most circumstances, eGFR from creatinine is sufficient for screening, diagnosis and monitoring kidney function. When there is a concern about accuracy of creatinine-based equations, the combined creatinine-cystatin C formula should be used.

As noted above, there can be a number of non-GFR determinants of creatinine, so there are circumstances where the combined formula or the cystatin C formula alone should be used. In extremes of creatinine generation, such as spinal cord injury or neuromuscular disease, the cystatin C alone formula may be more appropriate. Similarly, weight loss with chronic diseases can lead to a decrease in creatinine generation and falsely high eGFR. In individuals with high muscle mass (e.g., body builders, athletes) and elevated creatinine (and normal urine albumin/creatinine), checking cystatin C could also rule out CKD. This is common in young military Veterans or Active-Duty personnel. In class 3 obesity (BMI >40 kg/m^2), the cystatin C formula may lead to falsely low eGFR, so the combined creatinine-cystatin C formula is most accurate. The combination creatinine-cystatin C equation can be used to confirm the diagnosis of CKD in the elderly when low eGFR has been present for >3 months and there are no other markers of CKD (i.e., normal imaging, normal urine albumin/creatinine level).(254)

Medication Dosing

There are a number of medications that require adjustments for kidney function and have narrow therapeutic windows.

For new medications, the recent Food and Drug Administration (FDA) guidance for industry recommends the use of eGFR over estimated creatinine clearance (Cockcroft-Gault).(255) For many older medications, dosing recommendations in kidney disease were based on estimated

creatinine clearance using the Cockcroft-Gault formula. However, there are a number of issues with this formula that can affect accuracy: it was developed using older serum creatinine assays, which typically give higher values than the currently used standardized isotope dilution mass spectrometry (IDMS) assays; it over-estimates clearance in obese individuals; and it has not been validated in different demographic patient populations.(256) Thus, eGFR is currently recommended. For most medications, eGFR creatinine is adequate. When there is a narrow therapeutic window or when there are concerns about creatinine-based formulas, the combined creatinine-cystatin C formula should be used.

When eGFR formulas are used to guide medication dosing, especially in individuals at extremes of body size, the eGFR should be de-indexed from its usual normalization to a standardized body surface area. This can be done by multiplying the eGFR value by the patient's body surface area and dividing it by 1.73.(257-259)

For additional considerations on nephrotoxic agents and medication dose adjustments in CKD, see Appendix K.

More Information

A useful resource on eGFR testing, as well as patient materials, can be obtained using the ASN eGFR toolkit: https://epc.asn-online.org/projects/egfr/

Appendix K. Nephrotoxic Agents and Medication Dose Adjustments in CKD

A. Background

It has been estimated that approximately 1 in 5 episodes of AKI in hospitalized patients are related to medication,(260) and during an inpatient episode of critical care, approximately a third of patients receive multiple potentially nephrotoxic medications.(261) In the outpatient environment of care, approximately half of patients with stage G3-G5 CKD are using a potentially inappropriate medication.(262) AKI/CKD states represent complex clinical conditions with often limited therapeutic alternatives. As such, this appendix is not intended to provide an exhaustive list of drugs that could be nephrotoxic or need adjustment with changing kidney function but rather, to provide the front-line clinician with a conceptual approach to the assessment of a drug's nephrotoxic potential and management of pharmacotherapy in patients with CKD.

B. Nephrotoxic Medications

The kidney is a relatively small organ but receives 20% of cardiac output and has a role in the filtration, secretion, reabsorption, and biotransformation of medications. As such, it has a greater exposure to the risk of toxic drug effects than other organ systems.(263) Despite the commonness of drug-related harm to the kidney, there is, interestingly, not an agreed upon nomenclature or specific definition of drug-induced nephrotoxicity. For this guideline targeted towards the PCP, we highlight the approach developed during the KDIGO 2019 Controversies in Acute Kidney Injury conference as it organizes drugs into two major categories by which they can cause harm: kidney dysfunction or kidney injury.(264) This allows the prescribing provider to consider any drug, or combination of drugs, as to its manner of causing direct kidney injury, dysfunction, both, or neither in the context of patient specific risk mitigation or exacerbating factors.(264)

Although the 2-grouping format of the KDIGO controversies model may have some affinity for the PCP, organizing drug-induced nephrotoxicity in this manner is not without limitations. First, all the systems are grounded with a focus on hospital-acquired AKI of which drug-induced kidney injury is a significant contributor. Unfortunately, there is a paucity of information on community acquired AKI, which is epidemiologically distinct.(265) Consequently, the ambulatory care provider must borrow from evidence obtained in the hospital setting and intuit risk factors for community-acquired drug-induced nephrotoxicity (see Table K-1). Also, while these models can help with risk versus benefit assessment for drug toxicity that accumulates with dose and duration of exposure, there is not a good means for estimating the risk of drug-induced nephrotoxicity that occurs idiopathic or immune-mediated mechanisms, such as acute interstitial nephritis (AIN) that may occur with proton pump inhibitors (PPI). Per the FDA Adverse Event Reporting System (FAERS) from 2019-2023, there were 77,000 reports of serious AKI suspected to be caused by a drug. Seven of the top 10 suspect generic drugs reported were in the PPI class representing 86% of all reported cases of serious, drug-induced AKI.(266) These findings are similar to global surveillance reports where the PPI class occupies 4 of 5 drugs suspected of causing nephrotoxicity.(267) Thus, the PCP must have a high degree of clinical suspicion of drugs may be causative when an acute decline in kidney function is detected, especially since cessation of the offending agent is the first step in reversing drug-induced AKI. While rapid detection and removal of the offending drug or nephrotoxin is important, prevention is key. Kurani et al. (2019)(262) demonstrated that patient knowledge of their having CKD was associated with a protective effect, reducing exposure

to potentially nephrotoxic medications. As such, patient education on their diagnosis of CKD and the risk of medications causing AKI or worsening CKD should not be underestimated as a risk mitigation strategy.

Table K-1. Possible Risk Factors for Community Acquired Drug Induced Nephrotoxicity in Adults

Possible Risk Factors for Community Acquired Drug Induced Nephrotoxicity in Adults	Actions to Mitigate Risk of Community Acquired AKI & Drug Induced Nephrotoxicity in At-Risk Patients
• Acute illness • Advanced age • Bacterial infection (e.g., pneumonia) • Black race • Cancer • Dehydration* • Diabetes • Increased health system utilization • Low systolic blood pressure • Nephrotoxic drug exposure* • Other organ dysfunction (e.g., HF, Liver disease, COPD) • Polypharmacy* • Pre-existing CKD/Prior AKI • Recent hospitalization and/or contrast dye exposure	• Recognize risk and educate patients about risk factors. • Address modifiable risks when possible
	• Conduct a Kidney Health Assessment (KHA)** at least annually, or after serious medical procedure/event, or if change in overall health status occurs
	• Conduct medication reconciliation (include OTC and herbal/dietary supplements) • Stop unnecessary medications • Avoid polypharmacy • Minimize nephrotoxic drugs • Collaborate with other providers regarding indication/dosing of specific medications
	• Include a clinical pharmacist for drug stewardship, especially if CKD is present
	• Develop “sick day” medication plans especially if reduced intake or GI losses occur

*There is no agreed upon list of risk factors for drug-induced nephrotoxicity. The above list is borrowed from risks of AKI from ADQI,(268,269) KDIGO guidelines,(3) retrospective VA (270) and non-U.S. health-system cohort studies,(271,272) and expert review.(273)

**Kidney Health Assessment is a term coined by ADQI which recommends assessment of ABCDs – history of AKI, Blood pressure, serum Creatinine, urine Dipstick (or other measure of albuminuria/proteinuria)

Abbreviations: ADQI: Acute Disease Quality Initiative; AKI: acute kidney injury; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; GI: gastrointestinal; HF: heart failure; KHA: Kidney Health Assessment; NSAID: non-steroidal anti-inflammatory drug; OTC: over-the-counter

C. Medication Management in CKD

Patients with CKD have altered pharmacokinetics and pharmacodynamics specifically because of reduced renal elimination of drugs (e.g., reduced filtration, secretion, and kidney metabolism). Although less well defined, bioavailability and non-kidney drug clearance may be altered as well,(274) especially in more advanced stages of CKD. Drugs that can be used in CKD should be dose-adjusted based on the degree of residual kidney function. The extent of dose reduction typically depends on the level of kidney function, and some medications may be contraindicated in those with severe kidney 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 (e.g., MicroMedex, American Hospital Formulary Service [AHFS] Drug information, The Renal Drug Handbook) with compiled drug information on recommended dosing based on kidney function; however, the information may vary among sources.

Optimizing the use of medications is important in patients with CKD. Drugs should only be used in CKD if the clinical benefits clearly outweigh the risks, and drugs should be avoided to minimize polypharmacy or discontinued if there is unclear benefit. Often, as CKD progresses, so do co-occurring conditions, so that the likelihood of both polypharmacy and inappropriate prescribing/dosing increases in patients with CKD.(275,276) Drug Stewardship principles are a means to optimize the safe and effective use of drug therapy. It is beyond the scope of this appendix to provide a detailed discussion of drug dosing and drug stewardship in CKD, but some key components are included in Table K-2. Collaborating with other providers and clinical pharmacists to ensure patients are on the correct combination of medications at the appropriate doses helps mitigate the risk of polypharmacy and drug toxicity. Additionally, ensuring patients are educated on the utility of maintaining an accurate medication list, the importance of medication adherence, and the side effects of medications, and empowering patients to ask questions are important strategies to enhance their care.

Table K-2. Drug Stewardship Activities in Patients with CKD*

Action	Discussion/Rationale
Ensure awareness of CKD diagnosis	• Given that patients with CKD are likely to receive care from multiple providers, electronic health records and decision support tools can be leveraged to highlight CKD diagnosis and stage
Assess both CKD stage and an estimate of kidney function (e.g., creatinine clearance or eGFR)	• Automatically reported eGFR using the CKD-EPI equation is common; consider use of combination creatinine-cystatin C equation when accurate eGFR is needed. Although results may vary based on the method of estimation used, some estimate of GFR or creatinine clearance is better than no assessment or serum creatinine only (see Appendix J for discussion about use of eGFR and limitations of different eGFR calculations).
Adjust drug and drug dose based on the estimated GFR or creatinine clearance	• Utilize the manufacturer's product labeling for recommendations. If kidney dosing information is not available, tertiary references (e.g., Micromedex, Lexicomp) can be utilized. In some cases, specialty consult may be necessary. When available, consider drug monitoring for medications with narrow therapeutic index (e.g., anticonvulsant drug levels).
Perform a medication review and reconciliation at regular intervals, at transitions of care, or if health status/GFR changes	• Regular medication review can detect drug-drug interactions, adverse effects, need for dose adjustment, and drugs for which an indication no longer exists. Patients with CKD may be more prone to adverse effects from any prescribed drug and are at risk of a "prescribing cascade." Additionally, OTC and herbal/natural products are commonly used and should specifically be queried during a medication review.
Educate Patients with CKD regarding the expected benefits and possible medication risks	• Patients with CKD have a key role in drug stewardship and should be comfortable informing all providers that they have kidney disease to ensure that, at point-of-care, treatment planning considers their degree of kidney function.

*Adapted from KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD: Chapter 4 practice points (3)

Abbreviations: CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated GFR; GFR: glomerular filtration rate; OTC: over the counter

Appendix L. List of Pharmacotherapies

Table L-1. Relevant Pharmacotherapy in Patients with CKD

Medication Class	Drug	Initial Dose	Dosing Range	Considerations
Angiotensin-converting enzyme inhibitors (ACEI)	Benazepril	5mg daily	5mg-40mg daily	• Teratogenic • Contraindications: Concurrent use with aliskiren, use within 36 hours of neprilysin inhibitor (e.g., sacubitril), • History of angioedema • May cause: Cough, angioedema, hyperkalemia, hypotension, increase in serum creatinine • Monitor: Blood pressure, potassium, kidney function
	Captopril	6.25mg 2-3 times daily	6.25mg -50mg 2-3 times daily	
	Enalapril	2.5mg once or twice daily	2.5mg-20mg 1-2 times daily	
	Fosinopril	10mg daily	10mg-40mg daily	
	Lisinopril	2.5mg daily	2.5mg-40mg daily	
	Moexipril	3.75mg daily	3.75mg-30mg daily	
	Quinapril	10mg daily	10mg-80mg daily	
	Ramipril	1.25mg daily	1.25mg-20mg daily	
Angiotensin receptor blockers (ARB)	Azilsartan	40mg daily	40mg-80mg daily	• Teratogenic • Contraindications: Concurrent use with aliskiren, • History of angioedema • ARBs do not require washout period with neprilysin inhibitor • May cause: Angioedema (less likely than ACEI), hyperkalemia, hypotension, increase in serum creatinine • Monitor: Blood pressure, potassium, kidney function
	Candesartan	4mg daily	4mg-32mg daily	
	Irbesartan	150mg daily	150mg-300mg daily	
	Losartan	25mg once daily	25mg-100mg daily	
	Olmesartan	20mg daily	20mg-40mg daily	
	Telmisartan	20mg daily	20mg-80mg daily	
	Valsartan	40mg-80mg divided into 1 or 2 doses daily	80mg-320mg divided into 1 or 2 doses daily	

Medication Class	Drug	Initial Dose	Dosing Range	Considerations
Angiotensin receptor blockers (ARB) + neprilysin inhibitor	Valsartan-sacubitril	24mg/26mg twice daily	24mg/26mg-97mg/103mg twice daily	• Teratogenic • Contraindications: Concurrent use with ACEI or ARB, or aliskiren, history of angioedema • 36-hour washout period necessary when transitioning from ACEI (washout not necessary with ARB) • May cause: Angioedema (less likely than ACEI), hyperkalemia, hypotension, increase in serum creatinine • Monitor: Blood pressure, potassium, kidney function
Calcium channel blockers (Dihydropyridine)	Amlodipine	2.5mg daily	10mg daily	• May cause: Hypotension, peripheral edema, flushing, headache, dizziness, palpitations, tachycardia • Monitor: Blood pressure, heart rate, evidence of peripheral edema
	Felodipine	2.5mg daily	10mg daily	
	Isradipine	2.5mg twice daily	5mg twice daily	
	Nifedipine ER	30mg daily	90mg daily	
	Nisoldipine	Geomatrix delivery system: 8.5mg daily	Geomatrix delivery system: 34mg daily	
		ER: 10mg daily	ER: 40mg daily	
	Nicardipine	IR: 20mg three times daily	IR: 30mg three times daily	
		SR: 30mg twice daily	SR: 60mg twice daily	
	Diltiazem	IR: 40mg four times daily	IR: 90mg four times daily	• Contraindications: Hypotension,

Medication Class	Drug	Initial Dose	Dosing Range	Considerations
Calcium channel blockers (non-Dihydropyridine)		12-Hour: 60mg twice daily	12-Hour: 180mg twice daily	cardiogenic shock, sick sinus syndrome or 2nd or 3rd degree AV block (unless the patient has a functioning artificial ventricular pacemaker), acute MI, pulmonary congestions • May cause: Hypotension, bradycardia, worsening heart failure, AV block, edema, constipation, dizziness • Monitor: Blood pressure, heart rate, electrocardiogram, evidence of peripheral edema
		24-Hour: 120mg once daily	24-Hour: 360mg once daily	
	Verapamil	IR: 40mg three times daily	IR: 160mg three times daily	
		ER: 120mg once daily	ER: 480mg daily	
Thiazide diuretics	Chlorthalidone	12.5mg daily	100mg daily (risks outweigh benefits at doses >25mg daily)	• Contraindications: Hypersensitivity to sulfonamide-derived drugs • May cause: Hypokalemia, hypomagnesemia, hyponatremia, hypercalcemia, hyperuricemia, elevated lipids (LDL, triglycerides) hyperglycemia (in diabetic patients), dizziness, hypotension • Monitor: Blood pressure, electrolytes, kidney function, fluid status
	Hydrochlorothiazide	12.5mg daily	100mg daily (risks outweigh benefits at doses >50mg daily)	
	Indapamide	1.25mg daily	5mg daily (risks outweigh benefits at doses >2.5mg daily)	
Non-Steroidal mineralocorticoid receptor antagonist	Finerenone	10mg daily	10mg-20mg daily	• Initial dosing determined by eGFR and subsequent dosing adjustments determined by eGFR and potassium levels • Contraindications: Hyperkalemia, concomitant use with

Medication Class	Drug	Initial Dose	Dosing Range	Considerations
				strong CYP3A4 inhibitors, renal insufficiency • May cause: Hyperkalemia, hypotension, hyponatremia • Monitor: Blood pressure, potassium, kidney function
Biguanide	Metformin	500mg twice daily	500mg-2550mg daily	• Boxed warning for increased risk of lactic acidosis with concurrent: dehydration, kidney impairment, age >65, intravascular iodinated contrast, excess alcohol intake, drug interactions • Contraindications: eGFR <30 mL/min/1.73m^2 (initiation not recommended in eGFR 30-45 mL/min/1.73m^2), metabolic acidosis • May cause: Nausea, vomiting, diarrhea, flatulence, abdominal cramping • Monitor: Kidney function, blood glucose, vitamin B12
Potassium binding medication	Patiromir	8.4g daily	8.4g-25.2g daily	• May cause: Decreased GI motility, peripheral edema, binding of other medications potentially reducing efficacy of other medications, hypokalemia • Monitor: Potassium • Can be used off-label in conjunction with
	Sodium polystyrene sulfonate	PO: 15g 1-4 times daily Rectal: 30g-50g every 6 hours daily	PO: 15g 1-4 times daily Rectal: 30g-50g every 6 hours daily	
	Sodium zirconium cyclosilicate	10g 3 times daily for up to	5g once every other day to 15g daily to maintain	

Medication Class	Drug	Initial Dose	Dosing Range	Considerations
		48 hours, then 10g once daily	potassium in normal range	other therapies for emergent hyperkalemia
Sodium-glucose cotransporter-2 inhibitors (SGLT2i)	Bexaglifloxin	20mg daily	20mg daily	• May initiate if eGFR >20 and continue until KRT is initiated • May cause: Ketoacidosis, genital mycotic infections, volume depletion, increased sCr, increased urination, increased thirst • Monitor: Fluid status, signs/symptoms of ketoacidosis, signs/symptoms of urinary tract infection, blood glucose kidney function, blood pressure
	Canagliflozin	100mg daily	100mg-300mg daily	
	Dapagliflozin	5mg daily	5mg-10mg daily	
	Empagliflozin	10mg daily	10mg-25mg daily	
	Ertugliflozin	5mg daily	5mg-15mg daily	
Glucagon-like peptide-1 (GLP-1) agonists	Dulaglutide	0.75mg once weekly	1.5mg-4.5mg once weekly	• Boxed warning for risk of thyroid C-cell tumors • Contraindicated in patients with a personal or familial history of medullary thyroid cancer (MTC) or in patients with multiple endocrine neoplasiasyndrome type 2 (MEN 2) • May cause: diarrhea, nausea, vomiting, abdominal pain, decreased appetite, dyspepsia, dysgeusia, cholelithiasism cholecystitis, cholestasis, pancreatitis, hypoglycemia (higher incidence with
	Exenatide	IR: 5mcg twice daily ER: 2mg once weekly	IR: 5mcg-10mcg twice daily ER: 2mg once weekly	
	Liraglutide	Diabetes: 0.6mg daily Weight loss: 0.6mg daily	Diabetes: 1.2mg-1.8mg Weight loss:1.2mg-3mg daily	
	Semaglutide	Diabetes Inj: 0.25mg weekly Oral: 3mg daily	Diabetes: Inj:0.5mg-2mg weeky Oral:7mg-14mg daily	

Medication Class	Drug	Initial Dose	Dosing Range	Considerations
		Weight loss: 0.25mg weekly	Weight loss:0.5mg-2.4mg weekly	adjunctive insulin or sulfonylurea) • Monitor: kidney function, GI symptoms, signs/symptoms of pancreatitis, body weight, signs/symptoms of worsening diabetic retinopathy, blood glucose
	Tirzepatide	2.5mg weekly	5mg-15mg weekly	
Alkalinizing agents	Citric acid and sodium citrate	15mL 30mL in 2-3 divided doses	15mL-30mL in 2-3 divided doses, titrated until serum bicarbonate is in normal range	• Contraindications: Untreated Addison's disease; severe myocardial damage • May cause: Metabolic alkalosis, hyperkalemia, hypernatremia, diarrhea, nausea, vomiting, impaired drug absorption • Monitor: Potassium, sodium, bicarbonate, kidney function, liver function, urinary pH, drug interactions
	Citric acid, sodium citrate, and potassium citrate	15mL-30mL after meals and at bedtime	15mL-30mL after meals and at bedtime	
	Sodium bicarbonate	650mg daily 2-3 times daily	650mg daily 2-3 times daily, titrated until serum bicarbonate is in normal range	
Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors [Statins]	Atorvastatin	10mg daily	10mg-80mg daily	• Contraindications: Active liver disease, pregnancy/breastfeeding, concurrent use of strong CYP3A4 inhibitors (simvastatin, lovastatin) • May cause: Myopathy, rhabdomyolysis (increased risk with age >65, kidney impairment), hepatotoxicity • Monitor Lipid panel
	Fluvastatin	20mg daily	20mg-80mg daily	
	Lovastatin	20mg nightly	20mg-80mg nightly	
	Pitavastatin	1mg daily	1mg-4mg daily	
	Pravastatin	10mg daily	10mg-80mg daily	
	Rosuvastatin	5mg daily	5mg-40mg daily	
	Simvastatin	10mg daily	10mg-40mg daily	
Vasopressin V2 receptor antagonist	Tolvaptan	60mg daily (divided as 45mg	60mg-120mg daily divided as: 45mg/60mg/90 mg when	• Boxed warning for severe hepatotoxicity • Available through a restricted distribution

Medication Class	Drug	Initial Dose	Dosing Range	Considerations
		when waking up and 15mg 8 hours later)	waking up and 15mg/30mg/30 mg 8 hours later	program under a Risk Evaluation and Mitigation Strategy (REMS) • Contraindications: History of significant liver impairment or injury, concomitant use of strong CYP3A4 inhibitors, abnormal blood sodium concentrations, unable to sense or respond to thirst, hypovolemia, uncorrected urinary outflow obstruction, anuria, pregnancy, breastfeeding • May cause: Polyuria, nocturia, polydipsia, frequent urination, hepatotoxicity, dizziness, hypovolemia, dehydration • Monitor: Liver function tests, clinical signs/symptoms of hepatotoxicity, fluid status, potassium, sodium

Abbreviations: ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; AV: atrioventricular block; CYP3A4: cytochrome P450 3A4; eGFR: estimated glomerular filtration rate; ER: extended release; g: gram; GI: gastrointestinal; GLP-1: glucagon-like peptide-1; HMG-CoA: Hydroxymethylglutaryl-CoA; IR: immediate release; KRT: kidney replacement therapy; LDL: low density lipoprotein; mg: milligram; mL: milliliter; MEN 2: multiple endocrine neoplasiasyndrome type 2; MTC: medullary thyroid cancer; PO: by mouth; REMS: Risk Evaluation and Mitigation Strategy; sCr: serum creatinine; SGLT2i: sodium-glucose cotransporter-2 inhibitors; SR: sustained release

Appendix M. Management of Hyperkalemia

A. Background

Potassium is key to cell membrane electrophysiology, with abnormalities predisposing to abnormal cardiac conduction and arrhythmias.(3) The kidneys play a key role in regulating potassium, with decreased GFR associated with increased potassium concentration. In addition to decreased GFR, other risk factors for hyperkalemia include diabetes, hyperglycemia, constipation, and higher albumin-to-creatinine ratio. Drugs including ACEI/ARB, MRAs, potassium-sparing diuretics, NSAIDs, trimethoprim, and calcineurin inhibitors can also cause hyperkalemia, as can volume depletion.(3)

B. Definition

An acute episode of hyperkalemia is a potassium result above the upper limit of normal that is not known to be chronic. However, there is no consensus on the magnitude, duration, and frequency of elevated potassium values that define chronicity.(277)

C. Management

The aggressiveness of treatment of hyperkalemia depends on the degree of elevation and the presence or absence of electrocardiogram (EKG) findings. Observationally, the risk of death from a given level of hyperkalemia is lower in more advanced CKD, suggesting that there are adaptive mechanisms that allow tolerance of hyperkalemia.(3) The aggressiveness of treatment of hyperkalemia depends on the degree of elevation and the presence or absence of EKG findings. Outpatients with acute hyperkalemia who have a potassium concentration of >6.0 mmol/L or hyperkalemia with any new EKG changes should be referred to a facility with cardiac monitoring, usually an emergency department that can address this urgently.(277)

A KDIGO Controversies Conference on the management of potassium in kidney disease suggests classifying acute hyperkalemia as mild, moderate, or severe based on the potassium concentration and the presence or absence of EKG changes, as follows (277):

- Mild: 5.0*-5.9 mmol/L without EKG changes
- Moderate: 5.0*-5.9 mmol/L with EKG changes or 6.0-6.4 mmol/L without EKG changes
- Severe: 6.0-6.4 mmol/L with EKG changes or >6.5 mmol/L regardless of EKG findings

*or upper limit of normal range

They acknowledge that it is not known whether EKG changes are sensitive in the prediction of potentially lethal arrhythmia.

The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (3) recommends the following steps to manage hyperkalemia (potassium >5.5 mmol/L) in CKD:

First-line:

- Review non-RAASi culprit medications and discontinue when possible
- Consider appropriate moderation of dietary potassium intake

Second-line:

- Use diuretics (when appropriate and risk of volume depletion is low)

- Optimize serum bicarbonate levels
- Consider potassium-exchange agents

Third-line (Last resort):

- Reduce or discontinue RAASi/MRA; restart in future if patient condition allows

Providers may consider reducing or stopping ACEI/ARB when eGFR drops below a given eGFR threshold or when hyperkalemia develops. However, studies show that ACEI and ARB use in advanced CKD is safe (see Recommendation 14). Protocols for RCTs of finerenone held the medication at potassium >5.5 mmol/L; however, it may be appropriate to continue these medications in people with potassium of 5.5-6.0 mmol/L.(3) Hyperkalemia associated with use of ACEI/ARB can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping ACEI/ARB.(3) We recommend involvement of nephrology when there is consideration of continuing ACEI/ARB/MRA when potassium >5.5 mmol/L.

The International Society of Nephrology provides an Optimization of RAASi Therapy Toolkit that includes guidance for managing hyperkalemia in patients on RAASi.

D. Dietary Considerations

People with CKD and hyperkalemia are commonly advised to follow low-potassium diets. However, randomized evidence about whether this approach is effective is lacking.(277) An unintended consequence of this advice may be a shift toward less healthful diets. In the early stages of CKD, a high intake of foods naturally rich in potassium appears to be protective against disease progression, and dietary restriction of foods naturally containing potassium, such as fruits and vegetables, may be harmful to health.(3) Multiple observational reports in CKD have explored the association between dietary potassium intake and outcomes; in a majority, surrogates of high potassium intake were associated with a lower risk of death or progression of kidney disease. In addition, observational studies in persons with CKD or ESKD report weak associations between dietary potassium intake and potassium concentration.(277)

Although the advice to people with CKD has emphasized plant-based foods as causes of hyperkalemia, other healthy nutrients in plant-based foods affect potassium absorption and distribution; therefore, the net bioavailable potassium from plant-based foods may be lower. Conversely, highly processed foods (rich in potassium additives), meats, dairy products, juices, and salt substitutes made with potassium chloride are higher in absorbable potassium than many plant-based fresh foods.(3) Thus, the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (3) recommends, “Provide advice to limit the intake of foods rich in bioavailable potassium (e.g., processed foods) for people with CKD G3-G5 who have a history of hyperkalemia.” The involvement of a renal dietitian can be helpful, as can the use of teaching materials that emphasize the avoidance of processed foods with potassium additives (e.g., Potassium Management in Kidney Disease).

E. Use of Potassium Binders

Newer potassium exchange agents (i.e., patiromer and SZC) appear relatively safe when used long-term (278,279) and may facilitate the use of evidence-based medications such as ACEI/ARBs and non-steroidal MRAs.(3)

It is important to be aware of local availability and formulary restrictions regarding potassium exchange agents, and the involvement of nephrology consultants may be helpful. It is also important to be aware that drug interactions with potassium binders are common, resulting from direct binding (patiromer) and alteration in gastric pH (SZC). Thus, the manufacturers recommend taking all other oral drugs at least 3 hours before or after patiromer and at least 2 hours before or after SZC for drugs whose absorption is dependent on gastric pH.(3)

Appendix N. Chronic Pain Management in CKD

A. Overview and Conceptual Approach

Acute and subacute pain (e.g., <3 months duration) should be evaluated and treated as clinically indicated, with the natural history of acute pain being that it resolves as the acute process improves. Unlike acute pain which has a clear cause and time course, more than 90% of people seeking care for chronic pain have chronic primary pain syndromes (e.g., fibromyalgia, non-specific low back pain), where pain is a disease of its own rather than a symptom of tissue pathology or a physical disorder (e.g., osteoarthritis).(280-283) The International Association for Study of Pain (IASP) defines chronic primary pain as pain that has persisted for longer than 3 months that is not better accounted for by another diagnosis and is associated with significant emotional distress (e.g., anxiety, anger, frustration, or depressed mood) and/or interference in activities of daily life and participation in social roles.(284) Chronic primary pain is driven by biopsychosocial etiologies that often do not respond well to treatments that reduce nociceptive signal generation or conduction.(280-283) Thus, making this determination is crucial because it helps the provider select treatments that are likely to be helpful (e.g., functional gain-promoting behavioral strategies) and avoid interventions that are unlikely to be helpful and potentially harmful (e.g., repetitive application of anti-nociceptive treatments).

The available research, although limited, shows that patients with any stage of CKD report strikingly higher prevalences of chronic pain than the general population,(285) with pain prevalence estimated at 60%.(286) Co-occurring depression, anxiety, and sleep disturbance, which are also more common in patients with advanced CKD and ESKD than in the general population, contribute to the dysesthetic experiences (e.g., negative affect, fatigue, lost social roles, decreased physical activity, multi-site pain).(286) Additionally, post-traumatic stress disorder and substance use are common co-occurring conditions in both Veterans and Active-Duty Service Members with chronic pain. These conditions can both exacerbate pain perception and complicate management.

The overall approach to the management of pain in CKD is similar to management in general populations. The VA/DOD endorses a biopsychosocial stepped-care model of pain management, where the overarching primary focus is restoration of function important to the patient, rather than reductions in pain scores.(287) KDIGO suggests that the “choice of management should be based on shared decision making and should be individualized according to comorbid health conditions, existing medications, patient preferences, availability and accessibility, and other relevant factors.”(286)

The management of pain in patients with CKD, however, may be particularly challenging. In general populations, most biomedical treatments for chronic pain are only modestly beneficial, and benefits often do not persist. Patients may be reluctant to engage in behavioral or physical treatments for a variety of reasons, including burden of appointments. Pharmacologic options are limited due to concern for toxicity and side effects since many medications undergo renal elimination, and there is limited safety data available for the CKD population. In addition, PCPs may lack familiarity with dosing and safety in advanced CKD or ESKD, while nephrology providers may feel less comfortable with the management of pain. High pill burden and polypharmacy may lead to (appropriate) reluctance to add medications.(286) Finally, possibly because of the limited effectiveness of interventions intended to reduce pain and/or concerns about toxicity of alternative

medications, opioids are prescribed to patients with CKD/ESKD at rates several-fold higher than the general population (20% CKD, 30% dialysis vs. 4-7% general U.S. Population).(288,289) Use of opioids engenders its own risks (see 2022 VA/DOD Opioid CPG).

Table N-1: Conceptual approach to chronic pain management in patients with CKD

Concept	Strategies
Focus on function as primary target of intervention	• Emphasize functional outcomes (rather than pain scores) when assessing therapeutic interventions • Help patients identify self-management strategies that gradually increase engagement with both physical and social activities WITH their baseline level of pain • Promote restorative sleep (290) • Educate patients about stress reduction techniques (e.g., mindfulness, deep breathing, imagery)(291)
Address co-occurring conditions	• Treat co-occurring mental health conditions (e.g., PTSD, depression, anxiety) that impair patient engagement in a functional recovery plan - pain may improve as symptoms of depression, anxiety, or insomnia abate (292) • Optimize medical conditions that hinder patient participation in functional activities • Identify OUD or physiologic opioid dependence and treat with MOUD (e.g., buprenorphine, or referral for methadone) • Encourage functional activities that are meaningful to the patient since participation may improve both pain and mental health conditions.
Try non-pharmacologic interventions	• Add psychosocial or behavioral interventions (e.g., Cognitive Behavioral Therapy,(293) Acceptance and Commitment Therapy,(294) Pain Reprocessing Therapy,(295) Cognitive Functional Therapy (296)) based on availability and patient preference if self-management strategies are insufficient. • Consider acupuncture and chiropractic care if available and indicated • Be familiar with local resources for non-pharmacologic interventions
Prescribe pharmacologic intervention to increase engagement in functional recovery activities, when appropriate	• Select medications based on risk of nephrotoxicity, side effects, overdose and potential drug interactions • Assess risks and benefits of treatments on co-occurring conditions • Adjust dose of medication for patient's kidney function, optimally assessed using eGFR or using manufacturer's dose guidance, if available (see Appendix K) • Consider starting at lower dose and titrating slowly to mitigate risks • Use analgesics judiciously, short-term, to support functional activities • De-prescribe if no benefit is observed in the near-term (e.g., 3 months) to prevent polypharmacy • Consider patient-directed deprescribing if functional benefit has been achieved and stabilized (e.g., 9-12 months). • Assess risk of fall and fracture given possibility of underlying bone disease in patients with CKD and use caution when co-prescribing sedating medications (e.g., opioids, benzodiazepines, gabapentenoids)
Refer to pain specialist	• Consider referral when there is diagnostic uncertainty, limited uptake in functional aspects of the treatment plan, limited gains, or difficulties with medication management • Employ multidisciplinary/interdisciplinary approach (e.g., VA Pain Management Team) especially for patients with complex pain syndromes • Offer virtual options for patients who have barriers to travel (e.g., distance, appointment burden), when available

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; MOUD: medication for OUD; OUD: opioid use disorder; PTSD: post-traumatic stress disorder; VA: Veterans Affairs

B. Non-Pharmacologic Pain Management in Patients with CKD

Non-pharmacologic interventions for pain include psychosocial or behavioral interventions and physical therapy or exercise-based interventions. Acupuncture and chiropractic care can also be utilized if available and indicated (see VA/DOD Low Back Pain CPG). Recently, both cognitive functional therapy (CFT) and pain reprocessing therapy (PRT) have reported durable (e.g., 1 and 3 years) improvements in function/disability (CFT) and pain (PRT) in a non-CKD chronic primary back pain population.(295,297) In ESKD patients, there is a beneficial effect of exercise or physical activity interventions on Health Related QoL, although most studies have been limited by small sample sizes or other methodological limitations.(298) In the few studies reporting pain as an outcome, the effect is generally small. Non-pharmacologic treatments have largely been studied in general populations, so more research is needed to evaluate their effect in patients with CKD. From a practical standpoint, it is important to be familiar with local resources for non-pharmacologic treatment and to use similar principles regarding intent and duration as with pharmacologic interventions.

Two recent trials contribute to the understanding of non-pharmacologic therapy of chronic pain in ESKD:

- The HOPE trial randomized patients with ESKD and chronic pain to Pain Coping Skills Training (PCST), an intervention to increase self-efficacy for managing pain or usual care. PCST consists of weekly cognitive behavioral therapy (CBT) delivered by video or telephone (usually during dialysis) for 12 weeks, followed by interactive voice response sessions delivered by telephone for an additional 12 weeks. The primary outcome was pain interference. At 12 weeks, the PCST group had a larger reduction in the Brief Pain Inventory interference score; the effect persisted at week 24 but was diminished at week 36. A decrease in Brief Pain Inventory (BPI) Interference scores greater than the minimal clinically important difference occurred in 50.9% of patients in the PCST group versus 36.6% in the usual care group at 12 weeks. While the effect on the overall cohort was of modest magnitude, the intervention resulted in a clinically meaningful improvement in pain interference for a substantial proportion of patients.(234)
- The TACcare trial randomized patients with ESKD and fatigue, pain, and/or depression to a stepped collaborative care intervention versus attention control. The stepped care intervention consisted of 12 weekly sessions of CBT delivered via telehealth in the hemodialysis unit or home, and/or pharmacotherapy, using an SDM approach to treatment selection. The co-primary outcomes were change in fatigue, average pain severity, and/or depression. All patients in the intervention group chose to receive CBT; less than 10% of patients in the intervention group additionally selected medication initiation for pain or depression. Patients in the intervention group experienced significantly larger reductions in fatigue, pain severity, and depression at 3 months; the improvements in fatigue and pain severity were considered “modest” and on depression “small.” There were persistent effects on fatigue and pain at 6 months (but not 12 months).(299)

C. Pharmacologic Pain Management in Patients with CKD

Pharmacologic considerations in CKD include concerns about medications causing kidney impairment (e.g., NSAIDS) and the need to account for renal elimination of medications or their metabolic products, which may be associated with increased risk of side effects (e.g., morphine, hydrocodone). We will briefly highlight common challenges in managing medications for pain in CKD.

NSAIDs in CKD

NSAIDs may cause gastrointestinal, cardiovascular, and kidney adverse events. By blunting prostaglandin-associated regulation of renal hemodynamics, NSAIDs can induce renal ischemia.(298) NSAIDs can also increase blood pressure, cause edema and sodium retention (mostly mild), induce hyperkalemia, and contribute to heart failure.(300) Fortunately, NSAID-induced kidney injury is typically reversible with prompt discontinuation.(298)

What is the risk of NSAID induced kidney injury (AKI or CKD)?

Observational studies demonstrate that nephrotoxic risks of NSAIDs are modest, somewhat predictable, and may be less than risks associated with alternative medications. Patients at higher risk for AKI include those with heart failure, cirrhosis, CKD, or dehydration,(300) as well as those on medications that may alter kidney blood flow, such as RAASi, diuretics,(301) and calcineurin inhibitors.(302) In non-CKD populations, observational studies have revealed conflicting results regarding NSAID-induced kidney injury, with some finding no association with incident CKD (303) and others demonstrating an increase in relative risk with risk generally increasing based on intensity or duration of NSAID exposure.(304-307) While the trend towards increased risk of incident CKD in more recent larger population studies is consistent, the absolute risks are small when reported. Nelson et al. demonstrated an excess of 17 CKD events per 100,000 exposed Active-Duty U.S. service members.(306) There is even less information regarding the risk of developing NSAID-associated renal injury in patients with CKD, in part because those with kidney dysfunction are often excluded from prospective clinical trials. One meta-analysis supported an increased risk of NSAID-associated AKI with HR of 1.7 in patients with pre-existing CKD (308) and an absolute risk of 4% in NSAID exposed versus non-exposed individuals. However, the data reported within the individual trials in that meta-analysis varied by an order of magnitude (e.g., OR: 1.05 to 5.25), suggesting the presence of different populations with differing NSAID risks to a degree that pooled/average numbers should be interpreted with skepticism.

What is the risk of topical NSAID versus systemic NSAID?

Topical NSAIDs are recommended for use in knee osteoarthritis based on evidence of equivalent efficacy for improving pain and function and superior systemic adverse effect profiles compared to oral NSAIDs (see VA/DOD CPG for the Non-Surgical Management of Hip & Knee Osteoarthritis). Multiple meta-analyses of RCTs have shown that adverse effects of topical NSAIDs are similar to placebo, except for increased local adverse effects, mostly mild skin reactions.(309-311) Diclofenac is a topical NSAID approved in the U.S. for osteoarthritis. In a pooled safety analysis of 7 RCTs of topical diclofenac 1.5% use, among 138 patients using topical diclofenac for 4-12 weeks, no patients experienced a serious kidney adverse event; changes in BP and kidney function were similar between the diclofenac and placebo/control groups.(312) Studies with topical diclofenac have shown that the level attained in blood is 0.4-2.2% of the maximum serum

concentration achieved with oral diclofenac; however, concentrations in knee synovial tissue are 10-20 times higher than blood plasma concentrations.(313)

Lim and colleagues attempted to address the risk of NSAID-associated kidney injury, defined as AKI and/or hyperkalemia, within the first 30 days after a newly prescribed topical, short course (<14 days), or longer course NSAID in at-risk populations; these observational analyses of adults in Singapore attempted to control for potential confounders.(314-317) Among older adults prescribed topical or short-term oral NSAIDs, both topical (OR: 1.48) and short-course oral NSAIDs (OR: 1.59) were associated with increased risk of AKI and/or hyperkalemia at 30 days. Topical NSAIDs had a reduced odds of the outcome compared to short-course oral NSAIDs in those with diabetes mellitus, CKD, or CVD.(314) In a very similar observational analysis of older adults, topical NSAIDs (adjusted OR: 1.29), systemic NSAIDs of <15 days duration (adjusted OR: 1.43), and systemic NSAIDs of ≥15 days duration (adjusted OR: 1.84) were each associated with the outcome of AKI or hyperkalemia at 30 days, but with incrementally higher odds with oral and prolonged administration, suggesting greater nephrotoxicity with the oral route and longer duration of treatment.(316) Among patients with CKD, topical NSAIDs and oral NSAIDs (compared with no NSAID prescription) were both associated with AKI (OR: 1.38 and 1.77 respectively). Moderate and severe AKI were increased with oral NSAIDs but not topical NSAIDs.(317) While each of the analyses attempted to control for confounders, it is unclear how much residual confounding by indication remains. Overall, the literature suggests that the risk of adverse kidney outcomes is decreased (but likely not eliminated) by use of topical rather than oral NSAIDs.

Are opioids preferable to NSAIDs in CKD?

A prospective cohort study (318) compared outcomes in patients with CKD not requiring dialysis followed for a median of 6.8 years. Baseline full-agonist opioid and NSAID use were reported to be 9.9% and 15.5%, respectively. Baseline use of opioids was associated with increased risk for a kidney disease composite outcome, kidney failure requiring KRT, hospitalization, and death. Baseline use of NSAIDs was associated with increased risk for the kidney disease composite outcome and hospitalization, but the outcomes were not consistent among subgroups. Overall, opioid use had a stronger association with adverse effects than NSAIDs. It is unclear to what degree these findings are confounded by indication, where use of NSAIDs or opioids is a marker for other factors associated with poor kidney outcomes and mortality. Shifting from NSAIDs can lead to use of alternatives, such as full agonist opioids, gabapentinoids, and other agents with their own toxicities. Opioid receptors are expressed in the kidney, and it has been posited that prolonged opioid use and accumulation of toxic metabolites may lead to kidney damage via mechanisms including increased BP, podocyte dysfunction, urinary retention, decreased kidney blood flow, and sympathetic renal nerve stimulation.(319)

Given the effective anti-inflammatory and analgesic effects of NSAIDs, the predictable and modest risks of NSAIDs, and the limitations of alternative treatments, some reviews now recommend considering cautious time-limited use of NSAIDs with consideration of individual risk factors, SDM, and careful monitoring.(320,321)

Key Takeaways and Clinical Pearls regarding NSAID use in CKD:

- Reduced NSAID exposure (e.g., topical < short-term oral < long-term oral NSAID) is likely associated with reduced risk of AKI.

- Concomitant use of multiple agents that affect kidney hemodynamics (e.g., RAASi, diuretics, SGLT2i, finerenone) as well as volume depletion may further increase the risk of NSAID-induced AKI.
- Consider increasing frequency of eGFR monitoring with NSAID use, especially if prolonged or high-dose.
- Risks of NSAIDs are likely to outweigh benefits where there is evidence of little to no benefit (e.g., chronic primary musculoskeletal or wide-spread pain syndromes).
- Determine meaningful functional targets for the patient, using SDM, prior to a trial of NSAID therapy.
- Proactively educate the patients on risks of NSAIDs, both OTC and prescribed, and be cognizant that patients may use OTC NSAIDs without discussion with a provider.

Gabapentinoids in CKD

Gabapentinoids (i.e., gabapentin and pregabalin) are eliminated solely by the kidneys. They are approved for neuropathic pain, fibromyalgia, and seizures, but use requires balancing benefits with potential adverse effects. While effective for pain relief, a Cochrane Review meta-analysis of use in the general population revealed that dizziness, somnolence, edema, and gait disturbance were more common among those prescribed gabapentin.(322) In a study of VA patients, falls, fractures and altered mental status were increased among gabapentin users compared to matched non-users, with highest risk for falls or fractures among those prescribed ≥2400 mg/d.(323) Among older patients with eGFR <60, starting at a higher dose (gabapentin >300 mg/d or pregabalin >75 mg/d) was associated with a slightly higher risk (1.9% vs 1.5%) of hospital visit for encephalopathy, fall, fracture or respiratory depression within 30 days.(324) Among patients on dialysis, gabapentinoids are associated with altered mental status, falls, and fracture.(325) Concomitant use of gabapentinoids and an opioid was associated with increased risk of death compared to only opioids in one study of dialysis patients.(326) Thus, gabapentinoids should be prescribed only when benefits clearly exceed risks. Additionally, use of lower doses and avoidance of concurrent administration with opioids or other sedating medications is suggested in patients with CKD or ESKD.

Full-agonist opioids in CKD

The 2022 VA/DOD CPG for the Use of Opioids in the Management of Chronic Pain noted the evidence of ill effects of long-term full agonist opioid use, including opioid use disorder (OUD), overdose, and death. They concur with the 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain that opioids should not be considered routine therapy for chronic pain, outside of active cancer, palliative, and end-of-life care.(327) Further, the 2022 VA/DOD CPG for the Use of Opioids in the Management of Chronic Pain recommends against the initiation of opioid therapy for the management of chronic non-cancer pain, particularly in younger patients, as age is inversely associated with the risk of OUD and overdose. In observational studies, full-agonist opioid use in patients with CKD has been associated with kidney failure progression, hospitalization, and mortality.(298,318) Thus, non-pharmacologic options and optimization of non-opioid analgesics should usually be considered prior to opioid prescribing. However, closely monitored opioid therapy may be warranted in select patients after careful consideration of risks and benefits. When initiating opioids, a short duration prescription with reevaluation at 30 days or sooner to assess improvements in pain and functional status and adverse effects, is recommended. The lowest effective dose of opioids as indicated by patient-specific risks and

benefits should be prescribed, and concomitant use of other sedating medications should be avoided. The metabolites of agents, such as codeine, morphine, and tramadol, may be toxic and are eliminated by the kidneys, so use of opioids whose metabolites are less dependent on kidney function, such as oxycodone, hydromorphone, fentanyl, methadone, and buprenorphine, is preferred.(298) A drug reference (e.g., Micromedex) or review (e.g., Roy et al. 2020)(298) should be consulted for further details, and additional information is provided in Table N-2. Besides employing these risk mitigation strategies, patients should be provided with overdose education as well as a prescription for naloxone.

Buprenorphine in CKD

Buprenorphine is a partial opioid agonist available in several different formulations (e.g., patch, buccal, sublingual), which has a beneficial effect on pain intensity in the general population.(328,329) Due to its partial agonism, it has lower risk for respiratory sedation and overdose. Additionally, it is metabolized in the liver, requires no dose adjustment in CKD, and is not dialyzed.(298) In patients with CKD who have an indication for opioid initiation or are already on full agonist opioids, Buprenorphine may provide a safer alternative for pain management. Though use may be stigmatized, sublingual (but not buccal or transdermal) buprenorphine is also indicated for the treatment of OUD. Thus, for patients receiving daily opioids for the treatment of chronic pain, the 2022 VA/DOD CPG for the Use of Opioids in the Management of Chronic Pain suggests the use of buprenorphine instead of full agonist opioids due to lower risk of overdose and misuse. They note that "given the known risks of moderate to high dose full agonist therapy and the intrinsic ceiling effect on respiratory depression that buprenorphine provides, the Work Group determined that a specific recommendation should be made based on its benefit compared to moderate to high dose long-term opioid therapy for the critical outcomes of overdose, addiction, and mortality." Note that a waiver is no longer required for prescribing any formulation of buprenorphine.

Table N-2: Select Pharmacologic Agents for Chronic Secondary Pain[a, b, c, d]

Pharmacologic Agent(s)	Risk in CKD	Dose Adjustment
Acetaminophen	Generally accepted as safe	GFR<60: 650mg q6 hours GFR <30: 650mg q8 hours
Duloxetine	Increased drug and metabolite exposure	GFR <30: Avoid use
Oral NSAID	↑↑ risk AKI (<14 days) ↑↑↑ risk AKI (>14 days)	Avoid long-term use, if possible. Short-term use after careful consideration of risks and benefits and use lowest dose for shortest period with monitoring of kidney function.
Topical NSAID	↑ risk AKI	
Topical capsaicin	N/A (no systemic exposure)	N/A
Topical lidocaine	Accumulation of CNS toxic metabolites, but clinical impact is uncertain	No specific recommendations based on the level of kidney function are provided.

Gabapentin or **Pregabalin**	Accumulation of drug, dose-related side effects	Reduce dose and dosing frequency based on estimated kidney function
Muscle relaxants	Accumulation of drug and/or metabolites with potential for dose-related side effects	**Baclofen / Tizanidine --** Avoid use except in spasticity (e.g., multiple sclerosis, spinal cord injury) and reduce dose and dosing frequency based on estimated kidney function **Cyclobenzaprine** / **Methocarbamol** – Use not recommended due to lack of evidence of benefit. No specific dosing recommendations are available.
Full agonist opioids	Accumulation of active or toxic metabolites (varies with each opioid). For example, Codeine, morphine, and tramadol metabolites may accumulate to a greater degree than other opioids	Guidance varies for each drug, but hydrocodone, hydromorphone, oxycodone, methadone and fentanyl all have renal dose adjustment guidance. Consult a reference or specialist.
Buprenorphine (patch, buccal, sublingual)	~70% fecally eliminated, impact of kidney disease on active metabolites is unknown.	Dose adjustments not required per manufacturer's guidance

[a] See the VA/DOD Clinical Practice Guideline for the Diagnosis and Treatment of Low Back Pain. Available at: https://www.healthquality.va.gov/guidelines/Pain/lbp/

[b] See the VA/DOD Clinical Practice Guideline for the Non-Surgical Management of Hip & Knee Osteoarthritis. Available at: https://www.healthquality.va.gov/guidelines/CD/OA/.

[c] See the VA/DOD Clinical Practice Guideline for the Management of Chronic Multisymptom Illness. Available at: https://www.healthquality.va.gov/guidelines/MR/CMI/

[d] See the VA/DOD Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain. Available at: https://www.healthquality.va.gov/guidelines/pain/cot/index.asp

Abbreviations: AKI: acute kidney injury; CNS: central nervous system; GFR: glomerular filtration rate; N/A: not applicable; N/A: not applicable; NSAID: non-steroidal anti-inflammatory drug

Appendix O. Military Occupation Exposures and CKD

Military personnel have unique environmental and occupational exposures, some of which have been associated with kidney disease. It is well documented that contact with tactical herbicides (i.e., Agent Orange in the Vietnam War or other dioxin-containing herbicides) are associated with the development of malignancy, including Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukemia, and other B-cell lymphomas. Exposure has also been linked to chronic conditions including diabetes mellitus and hypertension.(330) Kidney disease may be a secondary outcome of exposures because of malignancy or diabetes.

More recently, garrison exposures (i.e., exposure of personnel to environmental toxins occurring on U.S. military installations) have 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.(331) A Final Rule in 2017 went further to establish presumptive service-connection for Veterans with any of eight conditions, including kidney and/or bladder cancer.(331)

Military occupational exposure to airborne hazards includes particulate matter 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 identified as having potential for long-term health effects, including twelve that target the kidney, resulting in kidney cancer, kidney tubular degeneration, and nephropathy in animal studies.(330) Limited evidence exists to define military airborne hazard exposure and kidney disease; however, an observational cohort study of Veterans revealed an increase in CKD in areas where levels of particulate matter were high.(330,332) Therefore, a history of airborne exposures should be sought.

In addition to chemical exposures, military personnel are subject to prolonged exposure to elevated temperatures, commonly in conjunction with intense physical exertion. Heat-related illness can increase risk of hyperthermia, dehydration, and damage to the kidneys.(333) Increases in core body temperature, more so in the presence of dehydration, magnifies processes that may result in kidney related pathology such as acute kidney injury.(334) While uncertainty exists regarding the incidence of heat related illness during active military operations, it is well understood that heat related illnesses pose a threat to resources and mission effectiveness.(333) There is some data to suggest a decline in heat stroke incidence over the past 3 years, while incidence of heat exhaustion has increased within that same time span. Causality for these trends is not truly known; however, it is suspected that increased awareness of signs and symptoms, as well as prompt management of symptoms, is a key component for the prevention of heat exhaustion progression to heat stroke.(335) Although impact of heat-related illness is not clearly defined, heat-related illness should be considered as a potential contributor to historical or acute kidney injury, which may hasten development of CKD.

We suggest that providers take a detailed military occupational history from each patient newly diagnosed with CKD, perform an occupational and 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, extreme heat, 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 WRIISC may be warranted.

Appendix P. Special Considerations when Caring for Older Patients

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.(336) The majority of the 13,000 Veterans who transition to ESKD annually are >65 years old (median age 70.3 years).(337) 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 patients with CKD (Table P-1).

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. Among older individuals with evidence of muscle wasting or frailty, evaluation for CKD should include equation which combines serum cystatin C and creatinine to estimate kidney function.(3) Additionally, UACR may be falsely elevated due to diminished urine creatinine excretion.(338)

Table P-1. Relevance and Application of Geriatric Approach to Older Patients with CKD Using the 5 M's (339)

	Relevance to CKD	Approach
Mind	Cognitive impairment and depression are more prevalent at more advanced stages of CKD and increase the risk for poor outcomes.	• 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 ESKD.	• 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.	• 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 m^2, 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)	• 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. (See Recommendations 8-11)	• Assist patients in formulating and verbalizing goals of care when needed • Include patient preferences and priorities for SDM that support the patient's goals of care. • Complete life sustaining treatment directive (e.g., living will) • Conservative kidney management decision aids may be useful (e.g., Conservative Kidney Management).

Abbreviations: ADL: activities of daily living; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: end- stage kidney disease; m: meter; mL: milliliter; 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 and competing risk of mortality. 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/min/1.73 m^2 may live an additional seven years or more compared to the lowest quartile, who may live less than two years.(340) At the same time, many older adults with CKD are likely to die from other causes before they experience progression to kidney failure.(341) Consequently, the use of externally validated mortality and kidney failure risk prediction tools may help guide decisions about therapies to slow progression as well as those regarding kidney failure.(342,343)

Exclusion of older adults from clinical trials. Older adults or those with multiple chronic conditions are often excluded or have limited representation in clinical trials. Therefore, there is greater uncertainty about the effects of CKD interventions in this population.

Shared decision-making for KRT and role of conservative management. The 2019 VA/DOD CKD CPG provided four recommendations addressing SDM for KRT and the role of conservative management (versus KRT) in older adults. Without reviewing new evidence, one recommendation was carried forward unchanged in the current guidelines (see Recommendation 8),while the remaining recommendations were carried forward and amended (see Recommendations 9 and 10).

The incidence of kidney failure treated with KRT peaks between 75 and 84 years of age. 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.(138) 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 kidney failure management decisions are built and is accepted as the standard of care. Some barriers to this process of SDM include the varying levels of comfort among PCPs with KRT discussions and the difficulty of maintaining ongoing communication between primary care and nephrology providers. 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. Timely SDM allows 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).

The decision to pursue kidney 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, RCTs comparing kidney replacement versus conservative (non-kidney replacement) management are not possible.

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.(133,134) 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.

Comparative analyses for hospital utilization and end-of-life care outcomes are available for elderly patients electing to pursue dialysis. These studies demonstrate that dialysis initiation may lengthen life while increasing hospitalizations and intensive procedures.(126) For example, 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 m^2, identified between 2000 and 2009, and who died during that same time period.(127) Patients who elected not to pursue dialysis had significantly lower rates of hospital admission, intensive procedures defined as CPR, mechanical ventilation, and total parenteral nutrition, and death occurring in the hospital. The use of palliative care and hospice services significantly increased in the non-dialysis population. Significantly fewer hospital days and longer duration of hospice and palliative care services were also noted in this cohort. Montez-Rath et al. (2024)(131) emulated a target trial of dialysis versus medical management in patients aged 65 or older in the U.S. Veteran population who were not evaluated for transplant. Compared to patients who started dialysis when eGFR <12 mL/min/1.73m^2, patients who received medical management and did not start dialysis had shorter life expectancy but spent approximately 2 weeks more at home.

The prior evidence review concluded that the evidence has important limitations, because observational studies may be affected by lead time bias, confounding by indication, variability between comparator groups, as well as cultural and socioeconomic factors that influence treatment choices.

Based on this evidence, a conservative or symptom-driven approach to advanced kidney disease management may better match the goals of care for patients who prioritize the avoidance of aggressive medical treatment when compared with dialysis. Potential survival benefits of dialysis must be balanced against risks for more intensive medical care,(125-127) death in hospital,(127) and loss of functional capability and independence, all of which may impact patient QoL.(137) Particularly in frail and elderly patients, 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.(138) A kidney

management care plan that focuses on promoting quality of life without pursing dialysis or transplantation may be more suitable for some patients.(344) Conservative kidney management decision aids may be useful to guide discussion.(124,345)

Appendix Q. Gadolinium and Iodinated Contrast

Iodinated Radiocontrast Media

Iodinated radiocontrast media are used for contrast-enhanced CT and coronary and non-coronary angiography. Historically, iodinated contrast was one of the most common causes of nephrotoxic AKI, accounting for 11-12% of episodes of hospital-acquired AKI in two series, one published more than 40 years ago.(346,347) More recently, epidemiologic studies comparing the development of AKI in individuals undergoing contrast-enhanced CT with those undergoing non-contrast CT have suggested that the risk of CA-AKI is low. In one analysis of more than 10,000 individuals undergoing contrast-enhanced CT to an equal number of individuals undergoing non-contrast CT at the Mayo Clinic who were matched based on propensity for development of AKI, McDonald and colleagues found no increased risk for development of AKI associated with use of iodinated contrast.(229) However, in a similar analysis of over 17,500 propensity-matched individuals undergoing CT with or without contrast administration at the University of Michigan, Davenport and colleagues found a progressive risk of CA-AKI associated with reduced kidney function, with an OR increasing from 1.1 among individuals with an eGFR of 45-59 mL/min/1.73 m^2 to an OR of 3.0 among those with an eGFR <30 mL/min/1.73 m^2.(226) Multiple factors have likely contributed to the decreasing risk of CA-AKI including decreased toxicity associated with the currently used contrast agents (i.e., iso-osmolal and low osmolality agents as compared to the older high osmolality agents) and the need for lower volumes of contrast given improved imaging technology.

Based on current data, the ACR and the NKF have concluded that the risk of CA-AKI associated with IV contrast in individuals with an eGFR ≥45 mL/min/1.73 m^2 is minimal and prophylactic strategies to mitigate AKI risk are not indicated, but that such strategies should be used for individuals with an eGFR <30 mL/min/1.73 m^2.(235) Among individuals with an eGFR 30-44 mL/min/1.73 m^2, the ACR/NKF consensus suggests use of prophylaxis if patients have co-occurring conditions associated with heightened AKI risk, including diabetic nephropathy and heart failure.

The risk of CA-AKI following intra-arterial contrast administration/angiography is higher than after IV administration. Whether this is due to greater toxicity of iodinated contrast media when administered intra-arterially or due to other factors, including the potential risk of atheroembolic disease associated with vascular manipulation, is uncertain. There is evidence, however, of a dose-response relationship between the volume of contrast administered and the incidence of CA-AKI.(348) Because of the higher risk of CA-AKI associated with intra-arterial contrast administration, the threshold for utilizing prophylaxis to mitigate the risk of CA-AKI is generally higher than for IV contrast administration, with eGFR thresholds of 45 mL/min/1.73 m^2 for the majority of individuals and 60 mL/min/1.73 m^2 for higher-risk individuals, including those with diabetic nephropathy or heart failure.

Strategies to mitigate the risk of CA-AKI include use of the least nephrotoxic iodinated contrast media available (i.e., use of low osmolal or iso-osmolal contrast media), using the minimal volume of contrast media necessary to provide adequate imaging, and administering periprocedural IV isotonic crystalloid. No single regimen for periprocedural IV fluid administration has been demonstrated to be superior; however, administration of isotonic crystalloid at a rate of 1 mL/kg per hour for 6 to 12 hours pre- and post-procedure for hospitalized patients while administration of

3 mL/kg of isotonic crystalloid over one hour pre-procedure followed by 6 mL/kg over 2 to 6 hours post procedure for outpatients is often suggested.(241) Higher rates or larger volumes of fluid administration, protocols that use left-ventricular end diastolic pressure (233) and devices to match fluid administration to urine flow rate (e.g., Renal Guard® device)(349) have been utilized but are not clearly superior to simple fixed-volume fluid administration as suggested above. Similarly, the optimal IV fluid to be administered is also uncertain; while initially thought to be superior to 0.9% saline, the PRESERVE trial demonstrated that 1.26% sodium bicarbonate is not superior to 0.9% saline,(241) and other isotonic crystalloid solutions, such as lactated Ringer's solution, are likely equivalent to 0.9% saline but have not been rigorously evaluated. A variety of pharmacologic agents have been evaluated for potential benefits in mitigating the risk of CA-AKI including N-acetylcysteine,(241,350) dopamine,(351,352) fenoldopam,(353) mannitol,(354,355) furosemide,(354,355) ascorbic acid, and statins (356-358) have been evaluated, but none have been shown to be beneficial. Periprocedural hemodialysis or hemofiltration is also not effective.(359) The WG therefore recommends administration of 0.9% saline in high-risk patients but do not recommend administration of other agents for prophylactic purposes.

The failure to perform indicated medical procedures due to excessive concern regarding the development of iatrogenic AKI has been termed "renalism".(360) Studies have demonstrated that failure to perform otherwise indicated coronary angiograms and percutaneous coronary angiography are associated with an increased mortality risk.(360-362) Similarly, it has been suggested that failure to utilize iodinated contrast for imaging, when indicated, can lead to underdiagnosis of malignancies, aortic aneurysms, pulmonary emboli and other critical findings. **It is therefore recommended that indicated procedures be performed regardless of level of kidney function, with appropriate prophylactic interventions implemented to mitigate risks when possible.**

Gadolinium-Based Contrast Media

Gadolinium-based contrast media (GBCM) are used to enhance magnetic resonance imaging (MRI). Gadolinium (Gd) is a rare earth metal in the lanthanide series that is strongly paramagnetic, enhancing discrimination between tissues during an MRI. Gd as a free ion (Gd^{3+}) is highly toxic since it competes with ionized calcium (Ca^{2+}) in biological systems, leading to competitive inhibition of a range of biological processes, including inhibition of Ca^{2+}-binding enzymes and affecting voltage-gated calcium channels.(363,364) In addition, Gd^{3+} may have been demonstrated to be deposited in a variety of tissues, including brain, bone, and skin, even in individuals with preserved kidney function.

To mitigate the toxicity of gadolinium and enhance its solubility, GBCM complexes the Gd^{3+} ion with a carrier molecule. Before 2006, GBCM were thought to be entirely safe, and high doses of GBCM were used for MRI studies. GBCM were also used in place of iodinated contrast agents for radiocontrast enhancement to prevent CA-AKI in patients with CKD. However, in 2006, Grobner reported the association of gadolinium-based contrast agents (GBCAs) with nephrogenic systemic fibrosis (NSF), an irreversible systemic fibrotic disease, in dialysis patients.(365) NSF is a systemic fibrotic disease seen only in patients with kidney dysfunction who received GBCM.

The predominant risk factors for NSF are reduced kidney function (including dialysis dependence and severe acute or chronic kidney dysfunction) and the type and dose of GBCM. Advanced liver disease, including individuals post-liver transplant, have also been considered to be at increased

risk; however, it is likely that this reflects concomitant kidney dysfunction, often masked due to reduced generation resulting in blunted elevations in serum creatinine. The exact pathobiology of NSF is poorly understood as older data are limited to retrospective observational studies, animal models are limited, and there are no new cases with use of newer GBCMs. It is hypothesized that the initiating factor in the development of NSF is the dissociation of Gd^{3+} ions from the carrier molecules in exchange for endogenous metal ions, such as Fe^{3+}, Cu^{2+}, and Zn^{2+}, through a process of transmetallation. Since GBCM are normally rapidly excreted by the kidney, reduced kidney function results in increased retention of GBCM in the body, giving Gd^{3+} time to dissociate from the carrier molecule.

The risk of NSF increases with cumulative doses of GBCM and is associated with variation in the affinity between the Gd^{3+} ion and the carrier molecule. GBCM are now categorized into three groups: Group 1 GBCM (e.g., gadpdiamide, gadopentate dimeglumine, and gadoversetamide) are linear non-ionic molecules that have the lowest binding affinity and the highest association with development of NSF. Group 2 GBCM (e.g., gadobenate dimeglumine, gadobutrol, gadoteric acid, and gadoteridol) are linear ionic or macrocyclic agents with much higher binding affinity than the Group 1 GBCM. Gadoxetate disodium, the sole Group 3 GBCM, is an ionic linear molecule with both hepatic and renal excretion that has higher binding affinity than the Group 1 agents.

In an analysis of 4,931 patients with stage G4 or stage G5 CKD or ESKD on dialysis who underwent MRI with Group 2 GBCM, there were no cases of NSF. Across this entire population, the upper bound of the 95% CI of the risk of NSF was 0.07%.(366) In a subsequent analysis, breaking the risk down based on CKD stage and dialysis dependence, the upper bound of the 95% CI for the risk of NSF was 0.2% for stage G5 CKD on dialysis (n=1,849), 0.5% for stage G5 CKD not on dialysis (n=732), and 0.19% for stage G4 CKD (n=1,955).(367) Based on these data, a workgroup convened by the ACR and NKF concluded that the risk of NSF is very low for the standard dose (0.1 mmol/kg) of group 2 GBCM, even in patients with eGFR <30mL/min/1.73 m^2 or AKI.(368) They further recommend that dialysis should not be initiated, nor should dialysis schedule or frequency be altered following administration of group 2 GBCM.

An analysis done by the VA Evidence Synthesis Program identified no reported cases of NSF associated with use of Group 2 or Group 3 GBCM.(369) Across 12 studies that included over 18,000 patients with any degree of kidney disease, the upper 95% CI for the risk of NSF occurrence per exposure using Group 2 and Group 3 GBCM ranged between 0.0002 and 0.3085, with the highest bound associated with a study that only included 10 patients.(369) While they did not calculate a pooled upper bound of the 95% confidence limit, based on zero cases of NSF among more than 18,000 individuals with kidney disease, the value would be 0.0002, corresponding to a 97.5% probability that the risk of NSF is less than 1 in 5,000 exposures. In a second analysis of 12 studies that included 118,844 patients exposed to either Group 1 or Group 2 GBCM, there were 41 cases of NSF, of which 37 were associated with exposure to only Group 1 GBCM and 4 with exposure to Group 2 GBCM, although 3 of the 4 had likely confounding with prior exposure to Group 1 agents. In addition, they identified 18 cases of NSF after exposure to Group 2 or Group 3 GBCM in 10 case reports or small case series. Of the 18 cases, 9 described confounding with prior exposure to a Group 1 GBCM. Overall, they concluded that there are very few reported cases of NSF after exposure to Group 2 or Group 3 GBCM, and most reported cases are of uncertain value since they occurred in patients who had been exposed to Group 1 GBCM around the same time. Generally, they found little data to inform the care of patients who

are at risk for developing CKD or those with AKI, concluding that rare cases of NSF cannot be excluded in patients with significant kidney disease.

Based on these data, a precise risk of NSF after exposure to Group 2 or Group 3 GBCM cannot be given but is likely extremely low. While potential risks should be discussed with the patient during SDM, Group 2 GBCM can be utilized in individuals with an eGFR <30 mL/min/1.73 m^2 if other imaging techniques will not be adequate. The dose of GBCM used should be the minimum required to obtain satisfactory imaging. No prophylactic interventions are of benefit in minimizing the risk of NSF; for patients on hemodialysis, the procedure should be timed to immediately precede a dialysis session. However, dialysis should otherwise not be altered or initiated based on the use of group 2 GBCM.

Appendix R. General Medical and Lifestyle Management Recommendations to Improve Standard of Care in CKD Patients

Patients with CKD along with other advanced chronic disease patient populations benefit from lifestyle modification, which includes smoking cessation, improved sleep quality, increased physical activity, weight management, and diet modification. Outlined below are additional considerations for the CKD patient population.

Exercise

Patients with CKD are typically less active than sedentary individuals without CKD.(370-372) O'Hare et al. reported that sedentary dialysis patients had a higher risk of death within one year than those who reported participation in some form of physical activity.(373) Physical inactivity is also a strong predictor of cardiovascular mortality in patients with earlier stages of CKD (374) and represents a potentially modifiable risk factor. In addition to cardiovascular risks associated with physical inactivity, several studies have also highlighted the link between inactivity and poor physical functioning and fitness in patients with CKD.(370,373,375) Recent studies have shown that exercise is feasible and safe to perform among patients with CKD, including among patients with ESKD during dialysis. Both intradialytic exercise (IDE) and home-based exercise (HBE) enhance physical function, cardiopulmonary capacity, health-related QoL, and cognitive well-being. Some research proposed an indirect link between IDE and survival rates.(376-379) Given the strong association between physical inactivity and mortality in dialysis patients (373,380) and the potential improvements in physical functioning associated with increasing activity,(381) it is reasonable to recommend exercise among patients with CKD. T3recommends at least 150 minutes of moderate intensity physical activity every week (i.e., 30 minutes on at least 5 days), aligning with the same recommendation from the Surgeon General,(382) the Centers for Disease Control and Prevention,(383) and American Heart Association.384 For individuals who may be frail or for whom safety is a concern with exercise, a physical therapy referral prior to the discussion of implementing exercise is reasonable.

Dietary management of CKD

Recommending a generally healthy well-balanced diet, rich in fruits and vegetables is reasonable for all patients with chronic disease burden. The dietary evaluation and management of patients with CKD should be individualized with support from a registered dietitian to avoid a one-size-fits-all approach to dietary education. For example, a sodium restricted diet may mitigate proteinuria in patients with proteinuric CKD;(385) however, among CKD patients in whom salt wasting is a feature of the disease, these recommendations may not apply.

Additionally, the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets are recommended in the management of hypertension (see VA/DOD Hypertension CPG), and both are generally higher in potassium. However, fresh fruits and vegetables are typically higher in potassium,(386) which may be problematic in some patients who develop hyperkalemia as a result of their CKD; thus, adjustments may be needed. An unintended consequence of this advice may be a shift toward less healthful diets. In the early stages of CKD, a high intake of foods naturally rich in potassium appears to be protective against disease progression, and dietary restriction of foods naturally containing potassium, such as fruits and vegetables, may be harmful

to health.(3) Multiple observational reports in CKD have explored the association between dietary potassium intake and outcomes; in a majority, surrogates of high potassium intake were associated with a lower risk of death or progression of kidney disease. In addition, observational studies in persons with CKD or ESKD report weak associations between dietary potassium intake and potassium concentration.(277)

Finally, given the association of cardiovascular outcomes with CKD related mineral bone disease, it is also reasonable to recommend a low inorganic phosphorus (i.e., phosphorus additives in processed packaged foods) diet for patients with evidence of progressive CKD.

Individuals with multiple co-occurring conditions are at a higher risk for malnutrition particularly with pharmacologic treatment. The use of GLP-1 RA combined with SGLT2i in individuals with CKD may require careful monitoring for muscle wasting and the need for additional protein consumption.(387) Conversely, protein restriction may be reasonable for individuals whose protein consumption is deemed to be more than nutritional needs. Consider a referral to a renal dietitian for assessment and education regarding appropriate protein intake. Patients should be screened frequently for evidence of acute and/or chronic malnutrition using the six Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition (ASPEN) clinical criteria and further assessed and treated if screening is positive.(388,389)

Appendix S: Abbreviation List

Abbreviation	Definition
AASK	African American Study of Kidney Disease trial
ACEI	angiotensin-converting enzyme inhibitor
ACR	American College of Radiology
ACT	Acetylcysteine for Contrast-induced Nephropathy Trial
ACT	acceptance and commitment therapy
ADPKD	autosomal dominant polycystic kidney disease
ADQI	Acute Disease Quality Initiative
AHRQ	Agency for Healthcare Research and Quality
AIN	Acute Interstitial Nephritis
AKD	acute kidney disorder
AKI	acute kidney injury
APOL1	apolipoprotein L1
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
ASN	American Society of Nephrology
ASPEN	American Society for Parenteral and Enteral Nutrition
AV	atrioventricular block
AVF	arteriovenous fistula
AVG	arteriovenous graft
BIVA	Bioimpedance-guided
BMI	body mass index
BP	blood pressure
Ca	calcium
CA-AKI	contrast-associated acute kidney injury
CAD	coronary artery disease
CAKUT	congenital anomalies of the kidney and urinary tract
CBT	cognitive behavioral therapy
CCB	calcium channel blocker
CEAPIR	European Kidney Patients' Federation
CFT	cognitive functional therapy
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CO_2	carbon dioxide
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
COR	contracting officer's representative
CORETH	Choice of Renal Replacement Therapy
COX-2	cyclooxgenase-2
CPGs	clinical practice guidelines
CPR	cardiopulmonary resuscitation
CPS	calcium polystyrene sulfonate
CrCl	calculated creatinine clearance
CrI	credible interval
CT	computed tomography

Abbreviation	Definition
CV	cardiovascular
CVD	cardiovascular disease
CVP	central venous pressure
CYP3A4	cytochrome P450 3A4
DART	Decision-Aid for Renal Therapy
DASH	Dietary Approaches to Stop Hypertension
DEXA	dual-energy X-ray absorptiometry
dL	deciliter
DM	diabetes mellitus
DOD	U.S. Department of Defense
DPP-4	dipeptidyl peptidase-4
DVD	digital video disc
EBPWG	Evidence-Based Practice Work Group
EFMP	exceptional family member program
eGFR	estimated glomerular filtration rate
eGFRcr	eGFR using creatinine
ER	extended release
EKG	electrocardiogram
ESA	erythropoiesis-stimulating agent
ESKD	end-stage kidney disease
FAERS	U.S. Food and Drug Administration Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
g	gram
GBCA	gadolinium binding contrast agents
GBCM	gadolinium-based contrast media
Gd	gadolinium
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HA-AKI	hospital-acquired acute kidney injury
HbA1c	glycated hemoglobin
HBE	home-based exercise
HD	hemodialysis
HDI	Human Development Index
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HgB	hemoglobin B
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMG-CoA	hydroxymethylglutaryl-CoA
HR	hazard ratio
hr	hour
HTN	hypertension
IA	intra-arterial
IASP	International Association for Study of Pain

Abbreviation	Definition
ICD-10	International Classification of Diseases, 10th revision
ICHD	in-center hemodialysis
IDE	intradialytic exercise
IDMS	isotope dilution mass spectrometry
IDNT	Irbesartan Diabetic Nephropathy Trial
IDT	interdisciplinary team
IHS	Indian Health Service
IR	immediate release
ITT	intention-to-treat
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KFRE	Kidney Failure Risk Equation
kg	kilogram
KHA	Kidney Health Assessment
KQs	key questions
KRT	kidney replacement therapy
L	liter
LDL	low-density lipoprotein
LVEDP	left ventricular end-diastolic pressure
m	meter
MACE	major adverse cardiovascular event
MASLD	metabolic dysfunction-associated steatotic liver disease
MEN 2	multiple endocrine neoplasiasyndrome type 2
mEq	milliequivalent
mg	milligram
MI	myocardial infarction
min	minute
mL	milliliter
mmol	millimole
MMR	measles, mumps, and rubella
MOUD	medications for opioid use disorder
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NAM	National Academy of Medicine
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NIDDM	non-insulin-dependent diabetes mellitus
NKF	National Kidney Foundation
NNH	number needed to harm
NSAID	non-steroidal anti-inflammatory drug
NSF	nephrogenic systemic fibrosis
NYHA	New York Heart Association
OR	odds ratio
OTC	over-the-counter
OUD	opioid use disorder
PACTs	patient aligned care teams

Abbreviation	Definition
PCE	perchloroethylene
PCI	percutaneous coronary intervention
PCP	primary care provider
PCSK9	proprotein convertase subtilisin/kexin type 9
PCST	Pain Coping Skills Training
PD	peritoneal dialysis
PDE5	phosphodiesterase type 5
PICC	peripherally inserted central catheter
PICOTS	population, intervention, comparison, outcome, timing and setting
PIV	peripheral intravenous
PKD	polycystic kidney disease
PMT	pain management team
PO	by mouth
PO_4	orthophosphate
PPI	proton pump inhibitor
PRT	pain reprocessing therapy
PTH	parathyroid hormone
QoL	quality of life
RAAS	renin-angiotensin-aldosterone system
RAASi	renin-angiotensin-aldosterone system inhibitor
RBC	red blood cell
RCTs	randomized controlled trials
RD	registered dietitian
REIN-2	Ramipril Efficacy In Nephropathy trial
REMS	Risk Evaluation and Mitigation Strategy
RENAAL	Angiotensin II Antagonist Losartan trial
REPRISE	Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD
RR	risk ratio
RSV	respiratory syncytial virus
SADMANS	sulfonylureas, other secretagogues, gliclazide, glimepiride, glyburide, repaglinide
SBP	systolic blood pressure
SCAR	severe cutaneous adverse reactions
sCr	serum creatinine
SZC/ZS-9	sodium zirconium cyclosilicate
SDM	shared decision-making
SDOH	social determinants of health
SF-36	36-Item Short Form Survey
SGLT2i	sodium-glucose co-transporter 2 inhibitor
SPRINT	Systolic Blood Pressure Intervention Trial
SPS	sodium polystyrene sulfonate
SR	systematic review
SR	sustained release (in Appendix L only)
Td	tetanus and diphtheria
Tdap	tetanus, diphtheria, and pertussis
TCE	trichloroethylene
TEMPO	Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes trial

Abbreviation	Definition
TKV	total kidney volume
TZD	thiazolidinediones
UACR	urine albumin-to-creatinine ratio
UFR	urine flow rate
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
USRDS	U.S. Renal Data System
VA	U.S. Department of Veterans Affairs
VAMC	Veterans Affairs Medical Center
VC	vinyl chloride
VZV	varicella zoster virus
WRIISC	War Related Illness and Injury Study Center

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