VA/DoD Clinical Practice Guidelines

THE MANAGEMENT OF CHRONIC KIDNEY DISEASE

Provider Summary

Version 4.0 | 2019

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

Department of Veterans Affairs

Department of Defense

Provider Summary

QUALIFYING STATEMENTS

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

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

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

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

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Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "…on the use of clinical and epidemiological evidence to improve the health of the population…" across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.[1] This CPG is intended to provide healthcare providers with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients at risk for chronic kidney disease (CKD), thereby leading to improved clinical outcomes. In 2014, the VA and DoD published an updated CPG for the Primary Care Management of CKD (2014 CKD CPG), which was based on evidence reviewed through January 2013. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of CKD. Consequently, a recommendation to update the 2014 CKD CPG was initiated in 2018. The updated CPG includes objective, evidence-based information on the management of CKD. It is intended to assist healthcare providers in all aspects of patient care, including, but not limited to, screening, assessment, and management. The system-wide goal of evidence-based guidelines is to improve the patient's health and well-being by guiding health providers who are taking care of patients with CKD along management pathways that are supported by evidence. The expected outcome of successful implementation of this guideline is to:

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

Recommendations

The following recommendations were made using a systematic approach considering four domains as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach as detailed in the section on Methods and Appendix A in the full text CKD CPG. These domains include: confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient or provider values and preferences, and other implications, as appropriate (e.g., resource use, equity, acceptability).

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

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

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

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

[a] For additional information, please refer to the section on Grading Recommendations in the full text CKD CPG.

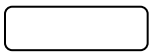
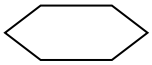
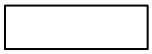
[b] For additional information, please refer to the section on Recommendation Categorization and Appendix D in the full text CKD CPG.

Algorithm

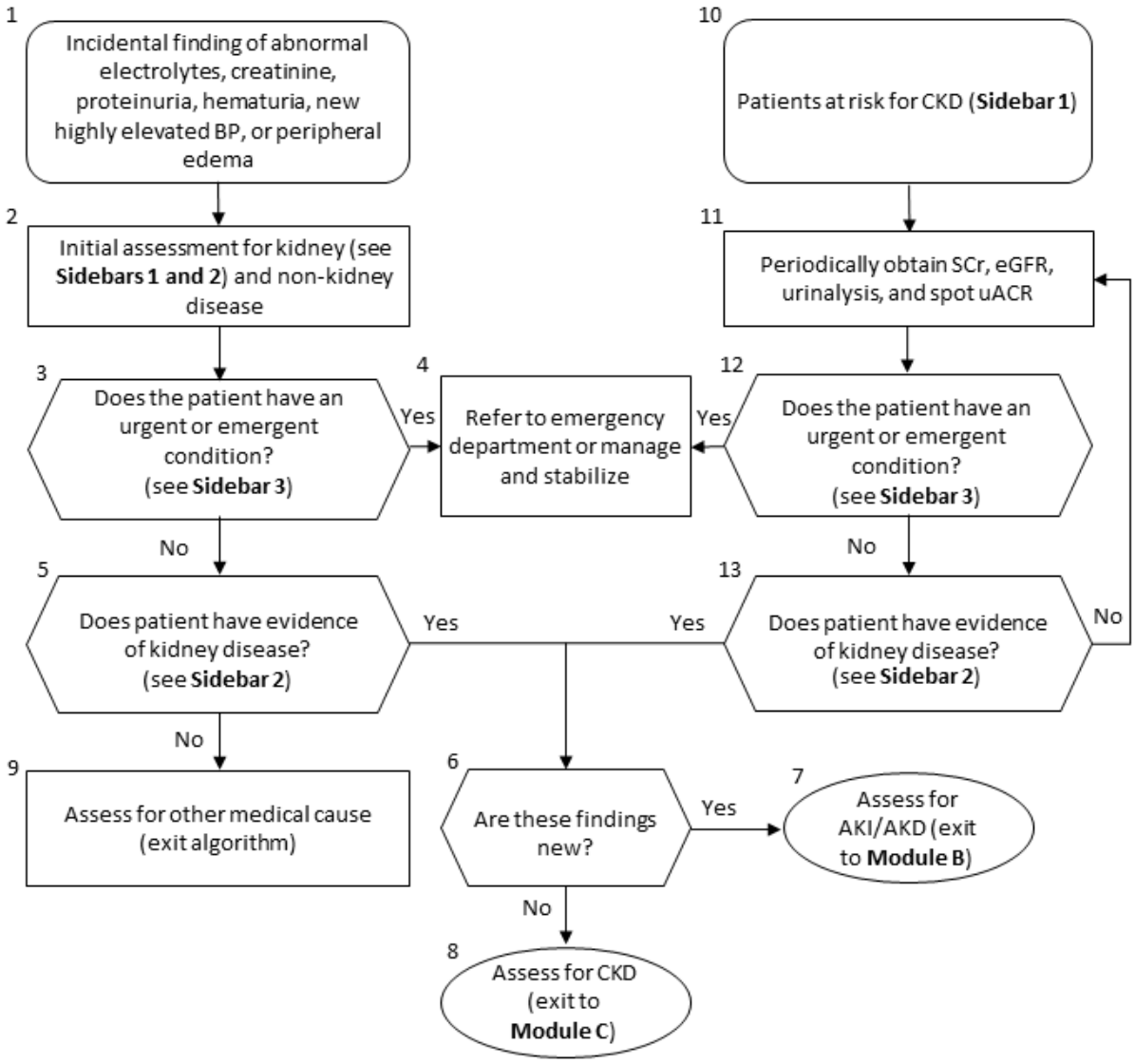
This CPG includes algorithms designed to facilitate understanding of the clinical pathways and decision-making processes used in managing patients with CKD. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format may promote more efficient diagnostic and therapeutic decision making; it also has potential to change patterns of resource use. Although the Work Group recognizes that not all clinical practices are linear, the simplified linear approach depicted through the algorithm and its format allows the provider to assess the critical information needed at the major decision points in the clinical process. It includes:

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

For each guideline, the corresponding clinical algorithm is depicted by a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[2]

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No
	Rectangles represent an action in the process of care
	Ovals represent a link to another section within the guideline

Module A: Screening for CKD and Initial Assessment



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

Sidebar 1: At-Risk Populations

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

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

Sidebar 2: Assessment for Kidney Disease

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

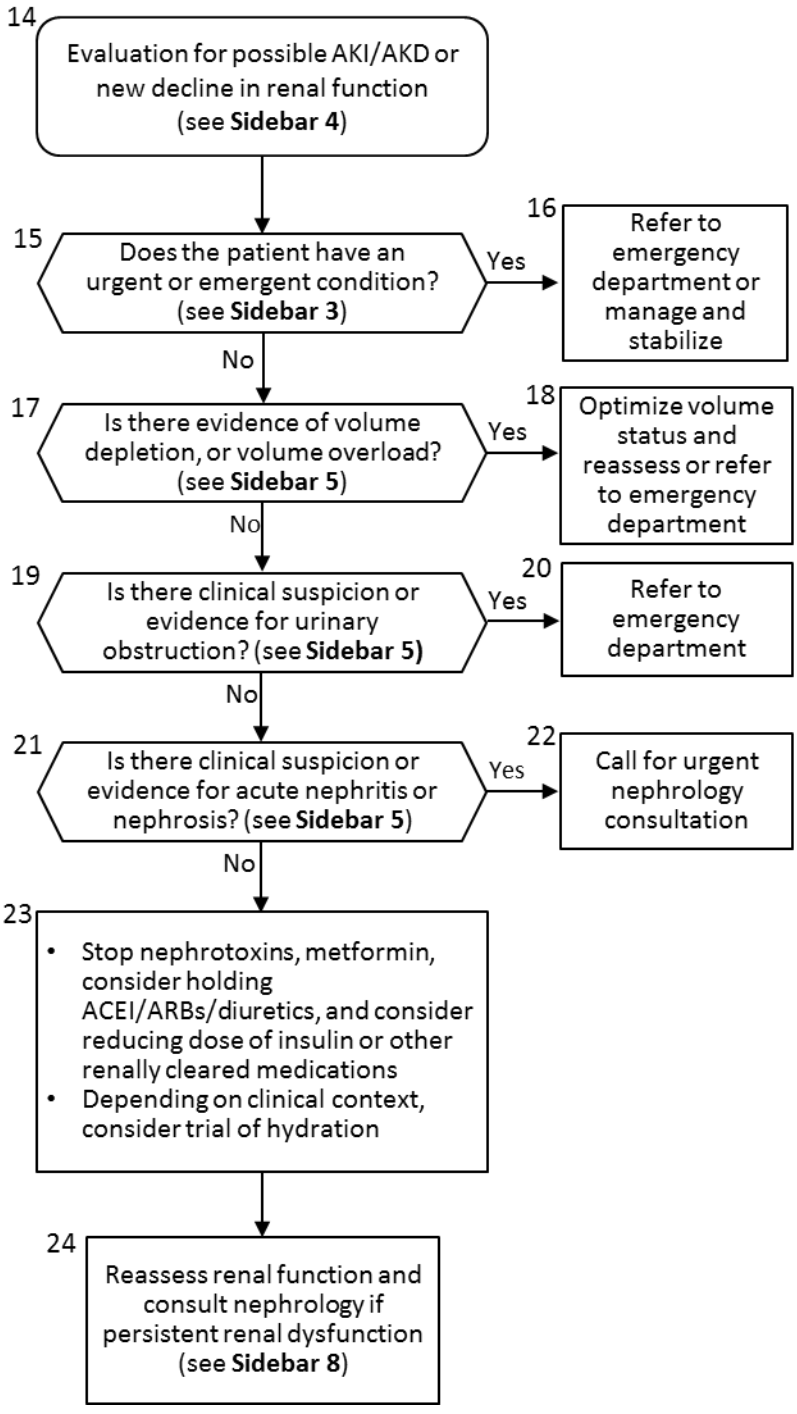
Abbreviations: BP: blood pressure; NSAID: non-steroidal anti-inflammatory drug

Sidebar 3: Urgent/Emergent Conditions

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

Abbreviations: L: liter; mEq: milliequivalent

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



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

Sidebar 4: Definition of AKI and AKD

- Definition of AKI (presence of any of the following):
  - Increase of SCr of >0.3 mg/dL over not more than 48 hours
  - Increase in SCr of >50% as compared to baseline, presumed to have occurred over not more than 7 days
  - Urine output of <0.5 mL/kg/hr over 6 hours
- Definition of AKD (presence of any of the following):
  - GFR <60 mL/min/1.73 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

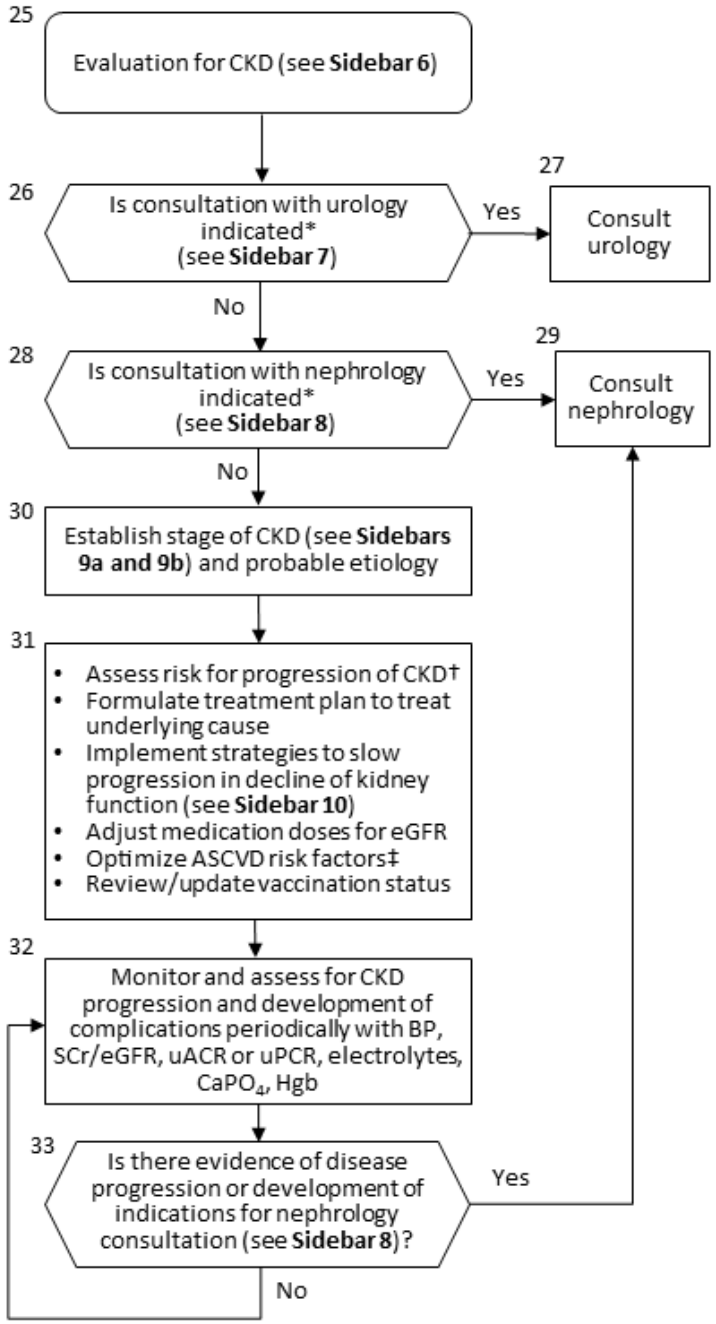
Abbreviations: AKD: acute kidney disorder; AKI: acute kidney injury; dL: deciliter; GFR: glomerular filtration rate; hr: hour; kg: kilogram; m: meter; mg: milligram; min: minute; mL: milliliters; SCr: serum creatinine

Sidebar 5: Assessment for AKD

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

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

Module C: Evaluation for CKD



Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; $CaPO_4$: calcium orthophosphates; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hgb: hemoglobin; hr: hour; kg: kilogram; mL: milliliters; SCr: serum creatinine; uACR: urinary albumin to creatinine ratio; uPCR: urine protein-to-creatinine ratio

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

†See Table 2: Risk Prediction Equations Developed for Patients with CKD in the full CKD CPG for more information

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

Sidebar 6: Criteria for CKD

Sustained abnormality for ≥3 months of <u>either</u>:

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

<u>or</u> any of the following:

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

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

Sidebar 7: Indications for Urology Consultation

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

Sidebar 8: Potential Indications for Nephrology Consultation*

- eGFR <30 ml/min/1.73m^2
- Rapid decline of eGFR (>5 mL/min/1.73m^2 per year)
- Non-diabetics with heavy proteinuria (24 hr urine protein >500 mg, uPCR >0.5, uACR >300)
- Diabetics with >3 g proteinuria (uPCR >3) or hematuria
- Unclear cause of CKD, hematuria, or proteinuria
- Complications of CKD (e.g., anemia, acidosis, hyperphosphatemia, hyperparathyroidism)
- ADPKD
- Renal transplant
- Metabolic management (prevention) of kidney stone disease
- Electrolyte abnormalities (e.g. hyperkalemia, hyponatremia)
- Patient's level of disease exceeds the level of comfort of the primary care provider

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

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

Sidebar 9a: Stage of CKD* – GFR Categories		
Category	**eGFR Range (mL/min/1.73 m^2)**	**Description**
G1	≥90	Kidney damage with normal or increased GFR
G2	60 - 89	Kidney damage with mildly decreased GFR
G3a	45 - 59	Mildly to moderately decreased GFR
G3b	30 - 44	Moderately to severely decreased GFR
G4	15 - 29	Severely decreased GFR
G5	<15 or dialysis	Kidney failure

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

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

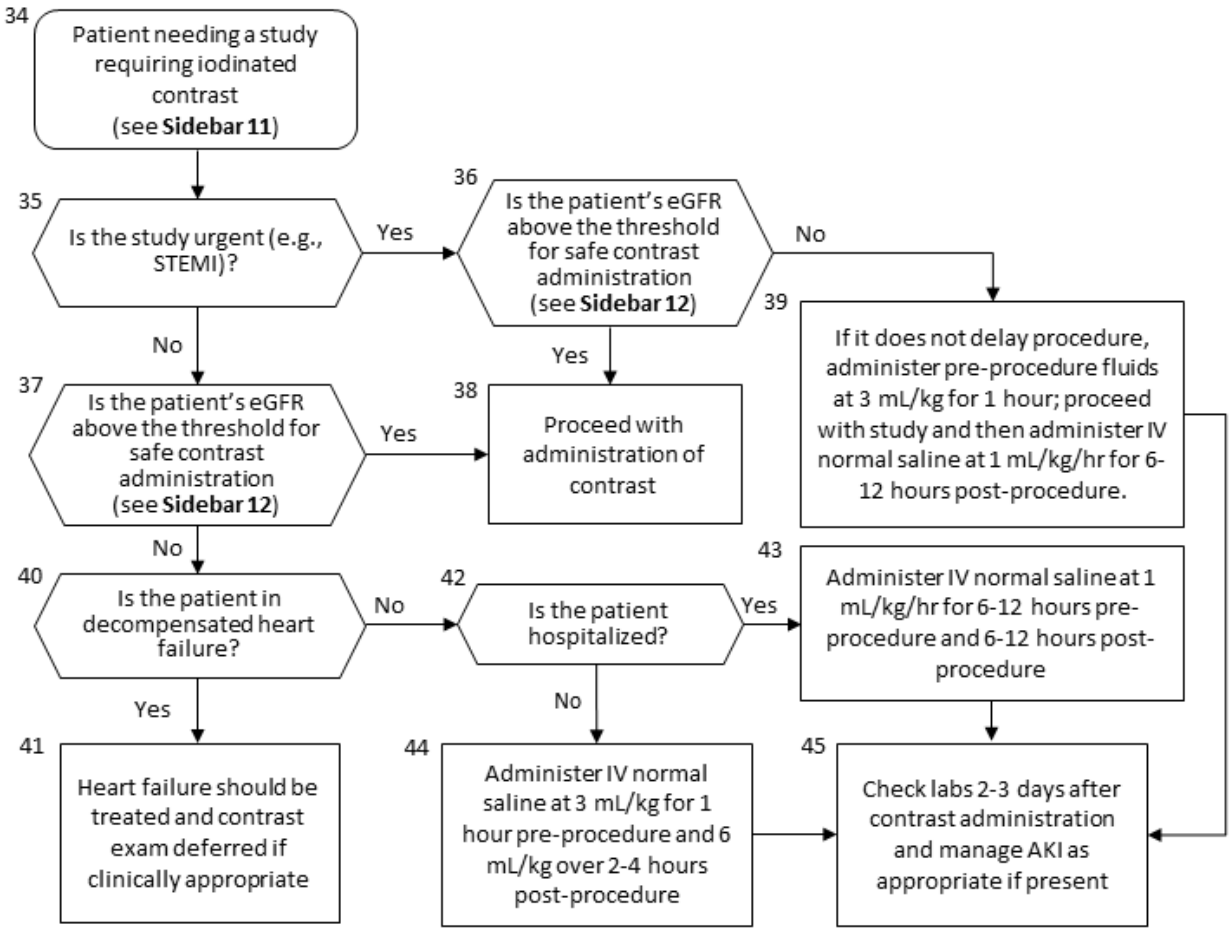
Abbreviations: uACR: urine albumin-to-creatinine ratio; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; g: gram; GFR: glomerular filtration rate; hr: hour; m: meter; min: minute; mg: milligram: mL: milliliter

Sidebar 10: Strategies to Slow Progression of CKD

- Control of hypertension with preferential use of either ACEI or ARB in patients with albuminuria/proteinuria
- Individualized control of diabetes
- Use of SGLT2 inhibitors in patients with type 2 DM and an eGFR > 30 mL/min/1.73m^2
- Eliminate/avoid nephrotoxic agents whenever possible (e.g., NSAIDs, iodinated contrast)
- Refer to dietitian for medical nutrition therapy (e.g., protein intake, sodium restriction, weight loss)

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

Module D: Management of Patients with CKD Requiring Iodinated Contrast



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

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

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

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

Sidebar 12: eGFR Cutoffs for Contrast

Venous Contrast:

- Patients should have eGFR >30 mL/min/1.73 m^2
- Or, if patient has DM, eGFR >45 mL/min/1.73 m^2

Arterial Angiography

- Patients should have eGFR >45 mL/min/1.73 m^2
- Or, if patient has diabetes, eGFR >60 mL/min/1.73 m^2

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

Scope of the CPG

Regardless of setting, any patient in the healthcare system should ideally have access to the interventions that are recommended in this guideline after taking into consideration the patient's specific circumstances.

Guideline recommendations are intended to be patient centered. Thus, treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient is essential and should be supported by evidence-based information tailored to the patient's needs. Use of an empathetic and non-judgmental approach facilitates discussions sensitive to sex, cultural, ethnic, and other differences. The information that patients are given about treatment and care should be culturally appropriate and available to people with limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory, or learning disabilities. Family involvement should be considered, if appropriate.

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

Methods

The 2019 CKD CPG is an update to the 2014 CKD CPG. The methodology used in developing the 2019 CPG follows the *Guideline for Guidelines*, an internal document of the VA and DoD EBPWG.[3] The *Guideline for Guidelines* can be downloaded from http://www.healthquality.va.gov/policy/index.asp. The guideline development process for the 2019 CPG update consisted of the following steps: formulating and prioritizing key questions (KQs); convening a patient focus group; conducting the systematic evidence review; convening a face-to-face meeting with the CPG Champions and Work Group members; and drafting and submitting a final CPG on the management of CKD to the VA/DoD EBPWG.

The Champions and Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence 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: 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).[4] Using this system, the Champions and Work Group determined the relative strength of each recommendation ("Strong" or "Weak"). A "Strong" recommendation generally indicates that the Work Group is highly confident that the desirable effects of an intervention outweigh undesirable effects. If the Work Group is less confident that the desirable effects of an intervention outweigh undesirable effects, they give a "Weak" recommendation. It is important to note that the GRADE terminology used to indicate the assessment across the four domains (i.e., "Strong" versus "Weak") should not be confused with the clinical importance of the recommendation. A "Weak" recommendation may be just as important to the clinical care of a patient as a strong recommendation.

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

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

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

The grade of each recommendation made in the 2019 CPG can be found in the section on Recommendations. Additional information regarding the use of the GRADE system can be found in Appendix A in the full CKD CPG.

The Work Group developed both new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition, the Work Group considered, without complete review of the relevant evidence, the current applicability of other recommendations that were included in the 2014 CKD CPG, subject to evolving practice in today's environment. A set of recommendation categories was adapted from those used by National Institute for Clinical Excellence (NICE).[5,6] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2014 CKD CPG and can be found in Table 1.

Table 1. Recommendation Categories and Definitions*

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

*Adapted from the NICE guideline manual (2012) [5] and Garcia et al. (2014) [6]

Abbreviation: CPG: clinical practice guideline

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Patient-centered Care

VA/DoD CPGs encourage providers to use a PCC approach that is individualized based on patient needs, characteristics, and preferences. Regardless of setting, all patients in the healthcare system should be able to access evidence-based care appropriate to their specific needs or condition. When properly executed, PCC may decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.[7-9] Improved patient-clinician communication and a PCC approach conveys openness and supports disclosure of current and future concerns.

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

Shared Decision Making

Throughout this VA/DoD CPG, the authors encourage clinicians to focus on SDM. The SDM model was introduced in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now called the National Academy of Medicine [NAM]) report, in 2001.[10] It is readily apparent that patients should make decisions regarding their plan of care and management options together with their clinicians. The unique role of SDM in nephrology care has been previously recognized in CPGs published by the Renal Physicians Association.[11] Clinicians must be adept at presenting information to their patients regarding individual treatments, expected outcomes, and levels and/or settings of care, taking into account the patient's learning needs and information they want to know. Through SDM, treatment plans are individualized based on patient capabilities, needs, goals, and preferences.

Diagnosis Assessment and Lab Monitoring

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

    - There is a rational expectation that screening high-risk populations for kidney disease may be helpful. Optimally, to make a recommendation on screening, there would be evidence such as a randomized controlled trial (RCT) with clinical endpoints that randomly assign patients, providers, or practices to either screening or usual care strategies. However, there is a paucity of available evidence. Thus, this current recommendation is based on very low quality evidence on interventions to reduce the risk of cardiovascular disease (CVD) events from the 2018 evidence review [12] and evidence carried forward from the 2008 and 2014 versions of the CKD CPG.[13]
    - The decision to screen for CKD should be individualized, based on SDM with the patient.
    - The Work Group recommends that future research be prioritized to identify the most promising population(s) and the optimal method for CKD screening and to evaluate the impact of screening interventions on important clinical outcomes.

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*)**

    - The combined impact of estimated glomerular filtration rate (eGFR) and albuminuria allow for a more complete evaluation of risk for CKD complications. Large patient-level meta-analyses demonstrated that albuminuria substantially improved risk prediction for CVD, mortality, and end-stage renal disease (ESRD) at all levels of eGFR.[14] The predictive value of urinary albumin to creatinine ratio (uACR) was much stronger and more progressive across worsening categories than the semi-quantitative measure of proteinuria assessed by dipstick.[15] These findings are based on spot uACRs and are well illustrated in Figure 7 of the Kidney Disease Improving Global Outcomes (KDIGO) CKD definition and classification article, which was not included in our systematic evidence review and did not contribute to the strength of this recommendation.[14]
    - Screening for albuminuria is considered standard of care for most patients with hypertension or diabetes mellitus (DM).
    - The Work Group recommends that uACR be measured in all patients with CKD, and clinicians should include the uACR for staging and classification of CKD, though there are no studies to guide the frequency of uACR measurement.
    - The Work Group's confidence in the quality of the evidence is moderate. The body of evidence had some limitations, including the potential for unmeasured confounders in the analyses.[15] The Work Group believes that the potential for improved prognostication of mortality outweighs the potential harm of adverse events, which was small.

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)***

    - Many patients are diagnosed, staged, and treated for CKD on the sole basis of an eGFR derived from serum creatinine (SCr). Use of SCr may be problematic since SCr reflects both urinary excretion as well as its production from muscle turnover and higher creatinine production is a marker of better overall health.[16] Cystatin C is an alternative method for estimating kidney function that is less biased by age, sex, race and muscle mass relative to creatinine.
    - In a patient-level meta-analysis that included 16 studies and 93,710 individuals that compared CKD staging and prognosis using SCr versus cystatin C,[17] a large proportion were re-classified to different CKD stages by cystatin C, and the re-classification improved risk stratification for clinically relevant outcomes at all eGFR categories.
    - As some providers may not be familiar with its use, it is essential that the cystatin C laboratory result be accompanied by an eGFR, and the CKD Epidemiology Collaboration (CKD-EPI) equation for cystatin C is appropriate in these populations.[18]
    - The body of evidence had some limitations, as the methods for measurement of creatinine and cystatin C varied across the studies included in the meta-analysis, as did the efforts to calibrate these measures to reference standards.[17]
    - The Work Group's confidence in the quality of the evidence is low. Feasibility and resource use should also be taken into account as cystatin C measurement is not currently offered at all

facilities, and there may be implementation challenges including upfront costs. However, the per assay cost of cystatin C is inexpensive.

4. **We suggest the use of a validated risk prediction model as a clinical decision support aid in the management of patients with chronic kidney disease. *(Weak for; Reviewed, New-added)***

5. **When assessing the risk of progression to end-stage renal disease, there is insufficient evidence to recommend a specific risk prediction calculator. *(Neither for nor against; Reviewed, New-added)***

   - Several CKD risk prediction calculators have been developed, some focusing on predicting the occurrence of CKD, and others on predicting the risk of CKD progression to ESRD for those with established CKD (see Table 2 in the full CKD CPG).[19]
   - Both the 4 -and 8-variable versions of the Kidney Failure Risk Equation (KFRE) model offers excellent discrimination as a prediction equation for adverse renal outcomes in a broad range of populations and has been externally validated.[20,21] Moreover, there is considerable evidence that its key variables, eGFR and albuminuria, are predictive of renal outcomes.[20] Lower variability in time to ESRD was found using the KFRE's one-year ESRD risk threshold of 5% compared with an eGFR threshold alone. Although limited by its observational study design and narrow cohort characteristics (non-diabetic African-American adults under 70 years of age), the study suggests that use of the KFRE prediction tool could be more informative for clinical decision making (e.g., timing of nephrology or transplant referral and vascular access planning) than an arbitrary eGFR threshold.[22]
   - A risk prediction tool for the progression of advanced CKD to ESRD was also developed by investigators in the VA using a 6-variable equation.[23] The VA equation is more complex, requiring repeated blood pressures (BPs), and the addition of comorbidities as well as demographic and laboratory variables. This equation yielded excellent discrimination in both the development and validation cohorts; however, the KFRE performed nearly as well.[23]
   - CKD progression risk models could cost effectively risk-stratify people and enable tailoring of disease modifying therapies, rational determination of frequency of follow-up, and inform timing of referral to specialty care.[19] Use of an ESRD risk prediction tool may be particularly useful to primary care providers in low health resource regions where subspecialty care is limited, thus enabling the primary care provider to begin patient counseling related to CKD progression.
   - While the use of risk prediction equations in other fields has been associated with improved patient outcomes,[24] the impact of estimating progression risk on the processes of ESRD preparation, slope of eGFR decline, and transition to ESRD has not been evaluated.[19]

General Management Strategies

A. Team Management and Education

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)***

   - One SR [25] and five observational studies [26-30] were identified which evaluate the impact of nephrology referral on outcomes. The findings suggest that nephrology referral may be associated with slower progression of kidney function decline, decreased mortality, and improved BP control.
   - There is currently insufficient evidence to recommend a specific threshold of risk, renal function, or proteinuria to refer patients for nephrology evaluation and management of CKD.
   - The Work Group's confidence in the quality of the evidence is low due to the heterogeneity in the definitions of "early" and "late" referral and the observational nature of the studies found.

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)***

   - The outcomes of utilizing an interdisciplinary team (IDT) to provide care to patients with CKD are not well established, and the studies identified in the evidence review had serious limitations and inconsistency with mixed results.[31-34]
   - An SR and meta-analysis of 21 studies with a mix of cohort and RCT designs by Shi et al. (2018) indicated that IDTs may reduce all-cause mortality, hospitalization rates, need for dialysis initiation with a catheter, and eGFR decline.[32]
   - The Work Group's confidence in the quality of the evidence is very low. Implications for resource use, equity with regard to availability and feasibility of IDT care, and time commitment from both patients and providers associated with IDT care must also be considered.

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)***

   - CKD health education supports the aim of maximizing PCC and SDM, consistent with the patient focus group findings.
   - Most clinical care includes informal patient education. While the benefits of patient education and self-care are often informally recognized by both patients and clinicians, the benefits of these specific interventions can be difficult to demonstrate in a study setting.
   - An SR of eight RCTs and three other trials were identified, which utilized different education modalities and programs, and results were inconclusive. [35-38]
   - The Work Group's confidence in the quality of the evidence is very low due to study design limitations. Future studies should focus on the impact of patient education on CKD outcomes,

feasibility, and effect of resource utilization on various healthcare systems and the most effective modality for formalized patient education.

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*)**

   - Mature arteriovenous fistulas (AVF) are associated with superior survival compared with arteriovenous grafts (AVG) or catheters in patients on hemodialysis, and are considered the gold standard for hemodialysis vascular access.[39]
   - Two observational studies were identified that found that peripherally inserted central catheter (PICC) lines were associated with increased risk of failure to achieve a working AVF or AVG.[40,41]
   - Clinicians should consider the patient's risk of requiring future hemodialysis prior to inserting a PICC line. In patients at high risk for ESRD, small-bore tunneled internal jugular catheters or ultrasound-guided peripheral intravenous (PIV) lines are acceptable options to avoid the risks a PICC line could pose on the success of future dialysis access.
   - The Work Group's confidence in the quality of evidence is moderate due to the limitations of the observational study design and potential for bias and confounding. The potential risk of failing to achieve adequate vascular access for hemodialysis must be balanced against the benefits of intravenous access with PICC lines.

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

10. **We suggest utilizing shared decision making regarding renal replacement therapy (versus conservative management) in part to improve patient satisfaction *(Weak for; Reviewed, New-added)***

    - SDM is important in navigating the complex decisions that CKD poses for patients, their families and medical providers. SDM places patients at the center of their care process and ensures that their values and preferences are paramount in determining their treatment decisions.
    - Only two studies with very low quality evidence were identified regarding the impact of SDM in the management of patients with CKD.[42,43] Both studies demonstrated increased patient satisfaction with modality selection when patients were actively involved in decision making.
    - The Work Group's confidence in quality of the evidence was very low due to study design issues.[42,43]

11. **In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life is the priority, we suggest evaluation for renal replacement therapy with sufficient time for comprehensive preparation. *(Weak for; Reviewed, New-added)***

12. **In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom avoiding hospitalization, death in hospitals, or intensive**

procedures is the priority, we suggest offering conservative management over dialysis. *(Weak for; Reviewed, New-added)*

13. **In patients with high comorbidities/low functional status approaching the need for renal replacement therapy and for whom prolongation of life may not be the priority, there is insufficient evidence to recommend for or against dialysis to improve quality of life. *(Neither for nor against; Reviewed, New-added)***

- The decision to pursue renal replacement in the very elderly, frail, or medically complex CKD population is challenging for patients and providers alike. Because of the complexity of the patient population, the role of patient preferences in treatment decisions and ethical issues, it is not possible to conduct optimally designed clinical trials comparing renal replacement versus conservative (non-renal replacement) management.
- Evidence from one comprehensive SR and meta-analysis,[44] two retrospective studies,[45,46] and one prospective cohort observational study [47] demonstrated a survival advantage for patients electing to pursue dialysis versus supportive care.[45-47] However, these benefits attenuate on covariate analyses when comorbid features and age are considered.[44,47,48]
- Potential survival benefits of dialysis must be balanced against risks for more intensive medical care, invasive medical procedures including cardiopulmonary resuscitation,[44-46] death in hospital,[45] and loss of functional capability and independence, all of which may significantly impact patient quality of life.[49] Particularly in frail and elderly patients, the decision to pursue dialytic therapy should not be a foregone conclusion, and goals of care must be individualized to the preferences, values, and capabilities of the patient and their caregivers (see Recommendation 10 for further discussion of evidence for SDM).[11] In situations where providers, patients, and caregivers are undecided regarding whether or not to pursue renal replacement therapy (RRT), nephrology referral and a time-limited trial of dialysis followed by re-evaluation of goals of care may be appropriate. Referring providers and nephrologists should also thoughtfully consider the patient's frame of mind and capability to make complex decisions (including extent of any cognitive impairment), when pursuing goals of care discussions.[42,43]
- Recognizing that nephrology referral at the time of dialysis initiation is associated with poorer clinical outcomes,[25,28] as well as the complexity and logistics in preparing frail and medically complex patients for dialysis, nephrology referral up to a year in advance of anticipated need for dialysis initiation is suggested to allow adequate time for clinical evaluation, patient education, SDM, and preparation for dialysis including dialysis access evaluation. When consistent with the patient's goals of care, nephrology consultation for eGFR below 30 mL/minute/1.73m^2, as discussed elsewhere in this guideline (see Algorithm: Module C, Sidebar 8), supports the preparation process and allows for co-management of CKD complications that may also postpone the need for dialysis.[44]
- The Work Group's confidence in the quality of the evidence is low to very low. Significant limitations included limited ability to randomize patients, variability between comparator groups, observational data, lead time bias (i.e., apparent survival advantage related to early treatment, rather than true benefit of treatment), and cultural and socioeconomic factors.

Non-pharmacologic Management of CKD

A. Nutrition

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

- Dietary sodium restriction has been found to reduce proteinuria and improve BP control in patients with CKD.[50-52]
- The degree of sodium restriction required for benefit remains unclear. While prior studies have examined restriction levels between 50-80 mmol/day, more liberal restriction of 90-100 mmol (2070-2300 mg/day) may be similarly beneficial and more realistic for patients to follow.[51,52]
- The Work Group's confidence in the quality of the evidence is moderate. The three RCTs that compared dietary sodium restriction to other interventions (diet or medication) were limited by baseline differences in important patient characteristics and lack of an appropriate control group.[50-52] Additionally, blinding of dietary interventions was not feasible.

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)*

- Dietary protein restriction has been shown to slow the decline in GFR and the progression to ESRD, potentially by reducing intraglomerular pressure and reducing metabolic acidosis.[53,54]
- While dietary protein restriction may slow the progression of kidney disease, this intervention may also increase the risk for calorie malnutrition, particularly if patients are not educated and monitored appropriately.[54] Support from registered dieticians has been shown to improve BP control and reduce hospitalization in the later stages of CKD and is a valuable adjunct for providers and patients to facilitate adherence to a nutrition plan.
- The Work Group's confidence in the quality of the evidence is low. Individual patient acceptance of a low protein diet may be variable. The Work Group judged that the potential benefits of a modestly slower decline in GFR and longer time to initiate dialysis may slightly outweigh the potential harms, including malnutrition.

Pharmacologic Management of CKD and Associated Conditions

A. Diabetes Medications

16. We suggest offering metformin as a first-line therapy for the treatment of type 2 diabetes in patients with stage 1 to 3 chronic kidney disease to reduce all-cause mortality*. (Weak for; Reviewed, New-added)*

- Metformin is recommended in the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care (VA/DoD DM CPG)[1] as a first-line agent. In the 2014 CKD CPG, renal dysfunction, based on SCr, was recognized as a contraindication for the use of metformin

[1] 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

due to concern about metformin-associated lactic acidosis. However, the U.S. Food and Drug Administration (FDA) revised its warnings on the use of metformin in mild-to-moderate renal impairment based on eGFR in April 2016 after a review of the medical literature on the safety of metformin in patients with CKD.[55]

- The evidence review for the update of this guideline identified a single meta-analysis that included 17 observational studies, only six of which assessed the use of metformin in patients with CKD and type 2 DM. Although the quality of the evidence was low, metformin use was associated with a statistically significant decrease in all-cause mortality compared to treatment regimens that did not include metformin.[56]
- The Work Group's confidence in the quality of the evidence is low due to the observational study design, but the Work Group determined that the benefits of treatment with metformin outweigh the potential harms in patients with an eGFR >30 mL/minute/1.73m^2.

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)*

- Metformin is recommended as the first line agent based on mortality data. There are no data that metformin has any salutary benefit regarding the progression of CKD whereas the sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to slow the progression of CKD. However there are no head-to-head studies comparing outcomes with metformin to SGLT2 inhibitor monotherapy.
- For the purposes of this CPG, "add-on therapy" refers to use of medications as adjuncts to metformin for the treatment of type 2 DM in patients with CKD, if metformin is not contraindicated.
- A meta-analysis of three RCTs (n=34,322) showed that SGLT2 inhibitors were associated with decreased risk of CKD progression (composite of worsening renal function, ESRD, and renal death) in all groups stratified by CKD stage, but the effect was higher at increasing levels of renal function (33% risk reduction with baseline eGFR <60 mL/minute/1.73m^2, 44% risk reduction in group with eGFR 60-90 mL/minute/1.73m^2, and 56% risk reduction for those with eGFR >90 mL/minute/1.73m^2).[57]
- Another SR of nine studies comparing SGLT2 inhibitors with placebo (n=1,092) indicated that SGLT2 inhibitors improved uACR, heart failure, and BP. There was no significant difference in mortality or other major adverse cardiovascular events (MACE). Though SGLT2 inhibitors were associated with a 2.5-fold increase in genital infections, there was no difference in discontinuation due to adverse events compared to placebo.[58]
- Further data from the Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial, which did not meet the inclusion criteria for this CPG, demonstrated participants with a uACR > 300 and an eGFR of 30-90 mL/minute/1.73m^2, randomly assigned to canagliflozin experienced a 30% reduction in a composite outcome of the risk of ESRD, doubling of SCr, or renal or CVD mortality, compared with participants assigned to placebo.[59]

- The Work Group's confidence in the quality of the evidence is moderate to high, but the Work Group concluded that the significant risk reduction for the critical outcome of decreased CKD progression and CV morbidity markedly outweighs the harms, including risk of side effects.

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)*

- Evidence on the use of glucagon-like peptide-1 receptor (GLP-1) agonists was limited to two studies with moderate-to-high quality evidence.[60,61]
- In a post hoc subgroup analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, liraglutide was found to reduce all-cause mortality and MACE compared to placebo in patients with eGFR <60 mL/minute/1.73m^2.[60]
- In the Dulaglutide Versus Insulin Glargine in Patients with Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease (AWARD-7) trial, dulaglutide was found to significantly reduce the decline of eGFR in patients with stage 3 and 4 CKD but had no significant effect on ESRD or kidney transplant. There was also no significant difference in all-cause or cardiovascular mortality, but AWARD-7 was not designed to assess mortality and MACE outcomes.[61]
- Both of these studies showed no significant difference in adverse events in comparison with the control groups.[60,61]
- In regards to semaglutide, two trials, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) [62] and Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (PIONEER-6) [63] did not meet the inclusion criteria. These studies showed favorable trends with the use of a GLP-1 agonist, but the target population was patients with DM. With no subgroup analysis and less than a quarter of the patients having CKD, these could not be used in supporting this recommendation.
- GLP-1 agonists are contraindicated in patients at increased risk for thyroid tumors.
- In weighing options for management of DM in the CKD population, GLP-1 agonists would not be considered first line given the mortality benefit seen with metformin and emerging evidence for the renoprotective benefit of SGLT2 inhibitors. The low overall risk of adverse effects and potential for weight loss make GLP-1 agonists an attractive option. The Work Group suggests offering liraglutide or dulaglutide as adjuncts to metformin or as an alternative to SGLT2 inhibitors.
- The systematic evidence review did not identify studies using other GLP-1 agonists that met inclusion criteria so it is unknown whether the observed benefits can be generalized to a class effect.

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)*

- The literature review for this update identified two SRs [64,65] related to the use of dipeptidyl peptidase 4 (DPP-4) inhibitors (also known as "gliptins") and one retrospective cohort study [66] on the use of thiazolidinediones (TZD) which provided low to very low quality evidence.

- In a pooled analysis of nine RCTs comparing saxagliptin to placebo, there was no statistically significant change in eGFR.[65] A second SR examined linagliptin versus placebo in a post hoc subgroup analysis of two RCTs and found no significant difference in cardiac failure, congestive heart failure, left ventricular failure, or other serious adverse events.[64]
- The systematic evidence review for this CPG identified one retrospective cohort study on TZD use which showed lower mortality and decreased need for long-term dialysis with TZDs. However, the study was of very low quality due to lack of randomization and blinding in the study design.[66]
- Given the low to very low quality of available literature, there was insufficient evidence for the Work Group to recommend for or against the use of either DPP-4 inhibitors or TZD in patients with DM and CKD to improve long-term kidney outcomes or mortality.

B. Hypertension Medications

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

- The evidence review for this CKD CPG update focused on the question of optimal BP goals in patients with CKD and consisted of two SRs,[67,68] one subgroup analysis of a multicenter RCT (Systolic Blood Pressure Intervention Trial [SPRINT]),[69] and extensions of two prospective cohort studies (African American Study of Kidney Disease [AASK] with a follow-up of 14.4 years [70] and Modification of Diet in Renal Disease [MDRD] trials with a follow-up of 19.3 years [71]), that compared treatment to more intensive or lower BP goals versus standard or usual BP targets. However, confidence in the overall quality of the evidence was low.
- Though there does not appear to be a benefit with regard to progression of CKD, treatment to more intensive BP targets has been reported to reduce mortality in patients with CKD.[67,69,71]
- Since the studies evaluated different patient populations as well as different BP targets, it is not possible to make a recommendation for a specific BP target for all patients with CKD. The Work Group suggests that a lower BP target (e.g., 120 to 130/<80 mmHg) as opposed to the previous BP goal of less than 140/90 mmHg could be considered for reducing mortality in patients with CKD, taking into consideration risk versus benefit on an individual basis, and after discussion of the treatment plan with the patient.

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

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

- The supporting evidence to recommend an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), if unable to tolerate an ACEI, in patients with non-diabetic

CKD, hypertension, and albuminuria [72-84] or an ACEI or ARB in patients with CKD, DM, hypertension, and albuminuria[85-91] are dated before 2008. The data for the use of ARBs in patients with non-diabetic CKD are primarily based on evidence from surrogate outcomes as reviewed in the 2008 CKD CPG. The Work Group acknowledges that the evidence for these recommendations is based primarily on data reviewed for the 2008 and 2014 CKD CPG, and therefore, used a different evidence grading system.

- Given the positive renal benefit with an ACEI in non-diabetic CKD and albuminuria and of an ACEI or ARB in diabetic patients with CKD and albuminuria, the Work Group carried forward these as "Strong for" recommendations for clinical practice from the 2014 CKD CPG without an updated review of the evidence.

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)*

- The evidence to recommend against the use of combination of an ACEI and ARB, or an ACEI or ARB with a direct renin inhibitor, are dated prior to 2014.[92-96] The Work Group concurs that the harms outweigh the benefit and support the 2014 CKD CPG strong recommendation against the use of combination renin-angiotensin-aldosterone system (RAAS) blockade with an ACEI and ARB, or ACEI or ARB in combination with a direct renin inhibitor in patients with CKD.

C. Anemia Medications

24. We suggest initiation of oral iron therapy to support iron requirements in patients with chronic kidney disease. *(Weak for; Not Reviewed, Amended)*

- The Work Group did not systematically review evidence related to this recommendation and instead carried forward evidence included in the 2014 CPG.[97,98] In addition to the evidence reviewed in 2014, recent studies not included in the evidence base also support this recommendation.[99-107]
- Iron deficiency is common in patients with CKD. Blood loss and medications that may decrease intestinal iron absorption may contribute to iron depletion.
- Diagnosing iron deficiency may be challenging in patients with CKD, and iron deficiency is a major cause of hyporesponsiveness to erythropoiesis-stimulating agent (ESA) therapy.
- Anemia may improve with iron supplementation in CKD patients with normal ferritin levels, reflecting "functional iron deficiency," so targeting higher ferritin targets may be necessary.[98] Correction of absolute or relative iron deficiency is an important part of anemia management in CKD patients. There is limited evidence to support specific ferritin and transferrin saturation levels to initiate iron therapy or to be used as targets.
- No studies have shown significant differences between most oral iron preparations with regard to efficacy and tolerability. Ferrous sulfate, which is the most commonly used oral iron preparation, is inexpensive and easily accessible; however, side effects (primarily gastrointestinal related), drug interactions, and pill burden may hinder adherence and limit use of oral iron.[100,101,107]

- Parenteral iron is effective at repleting iron stores and increasing hemoglobin,[97,102] and may be a more convenient option for selected patients. Newer intravenous (IV) iron preparations (e.g., iron sucrose, sodium ferric gluconate, ferric carboxymaltose, ferumoxytol) are associated with lower risk of severe adverse reactions, including anaphylaxis, compared to iron dextran. However, the potential for adverse reactions, need for infusion capabilities, increase in resource utilization/cost, and the need for IV access (which may be limited in patients who need to preserve blood vessels for future dialysis access) may make IV iron less advantageous.
- The Work Group's confidence in the quality of the evidence is low. While the body of evidence had some limitations, it supports the use of oral iron over IV iron; however, parenteral iron may be used based on patient preferences regarding side effects, prior response to treatment, and accessibility/feasibility of IV iron therapy.

25. We recommend against initiating erythropoiesis-stimulating agents in patients with chronic kidney disease for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension. *(Strong against; Not Reviewed, Amended)*

26. We recommend against initiating erythropoiesis-stimulating agents at a hemoglobin level greater than 10 g/dL. *(Strong against; Not Reviewed, Amended)*

- Anemia has been associated with fatigue, dyspnea, adverse effects on cardiac function as well as mental and cognitive decline. Common factors for anemia in CKD include lack of effective erythropoietin (EPO) production by diseased kidneys, shortened life of red blood cells in the uremic state, and chronic inflammatory state attributed to uremia resulting in altered iron absorption and decreased EPO responsiveness.
- Early diagnosis and treatment of anemia in patients with CKD are the cornerstones of clinical management, so regular surveillance for anemia in patients with CKD is recommended. The 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended the use of hemoglobin to define anemia and evaluation when hemoglobin falls below 13.5 g/dL in males and below 12 g/dL in females.[104]
- Blood transfusion can quickly correct anemia and furnish some iron. Risks associated with blood transfusion include allergic reactions, transfusion of blood-borne infection, hemolytic reactions, transfusion-related lung injury, and iron overload. Additionally, pre-transplant blood transfusions may cause allosensitization, which may be associated with longer wait times to transplantation and increased rejection and graft loss post-transplant. Thus, blood transfusion should be avoided in non-emergent situations whenever possible, particularly in potential transplant candidates.[103]
- The Work Group did not systematically review evidence related to these recommendations and instead carried forward evidence included in the 2014 CPG.[108-113] In addition to the evidence reviewed in 2014, more recent evidence also supports these recommendations.[55,104,105,114-120]
- Erythropoiesis-stimulating agent (ESA) treatment is effective in raising the mean hemoglobin and reduces the need for blood transfusions in patients with stage 3 to 5 CKD,[108-111] but treatment with ESAs has also been associated with potential harms and significant burdens. Controlled trials on ESA treatment in patients with CKD and anemia from previous versions of the CKD CPG used to support these recommendations, including the Correction of Hemoglobin

and Outcomes in Renal Insufficiency (CHOIR), Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE), and Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trials, showed greater risks for death, serious adverse cardiovascular reactions, and stroke with higher hemoglobin targets compared to lower hemoglobin targets.[111-113] Additionally, in patients with a history of malignancy, ESA use was associated with increased mortality from cancer, tumor progression, and thrombotic events.[114]

- Other burdens associated with ESA use for patients with CKD not on dialysis include cost, frequent clinic visits for injections, need for laboratory monitoring, increase in resource utilization for laboratory monitoring and staffing to dispense and administer medication, and ongoing surveillance of patient condition for prompt identification of critical findings requiring cessation of ESA treatment.
- ESA should be initiated after weighing the risks related to blood transfusion and ESA therapy with the benefits of alleviation of symptoms and avoidance of blood transfusions.
- Primary care providers should consider referral to nephrology or specialized clinic for ESA management.

D. Bone Health Medications

27. We suggest against offering calcitriol or active vitamin D analogs to patients with stage 3 and 4 chronic kidney disease and elevated parathyroid hormone levels *(Weak against; Not Reviewed, Amended)*

- The Work Group did not systematically review evidence related to this recommendation but reviewed the evidence from the 2014 CPG and amended the language of the recommendation.[121-127]
- Active vitamin D compounds effectively decrease parathyroid hormone (PTH) levels in all studies, but the effects of active vitamin D compounds on serum calcium and phosphate levels and other effects on bone histomorphometric changes were inconsistent.
- The Work Group's confidence in the quality of the evidence is low because data demonstrated inconsistent outcomes with use of active vitamin D compounds. Some studies showed significant increases in serum calcium and phosphate levels [121,122] while others noted no differences in serum calcium or phosphate values.[123-126] One SR reported changes in bone histomorphometry suggesting that oral calcitriol may slightly improve osteitis fibrosa, but may increase the risk of osteomalacia.[127] In one study of 25 patients, no significant differences were found in bone mineral density at femoral neck or lumbar spine after 12 months of oral calcitriol therapy. In another study of 38 patients calcitriol did not improve fracture rates.[127] While one study found significantly higher SCr levels in the paricalcitol group when compared to placebo,[122] differences in eGFR were not observed with cystatin C-based eGFR measurements.
- In the absence of consistent evidence pointing toward kidney, bone or cardiovascular benefit (other than reduction in PTH levels) and the potential for hypercalcemia and cost burden, we suggest not offering calcitriol or active vitamin D analogs to patients with stage 3 and 4 CKD. Active vitamin D analogs or calcitriol may be useful in the management of secondary hyperparathyroidism in patients with CKD stage 5 or patients on dialysis, but use should be managed by a nephrologist.

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)*

- The Work Group did not systematically review evidence related to this recommendation, but reviewed the evidence from the 2014 CPG and amended the language of the recommendation.[128] The Work Group's confidence in the quality of existing evidence is low because of small sample size.
- Calcimimetic agents (oral cinacalcet or IV etelcalcetide) are FDA approved for the control of secondary hyperparathyroidism in patients with ESRD.
- Cinacalcet effectively lowers PTH levels compared to placebo in patients with CKD not yet on dialysis; however, cinacalcet use was associated with development of hypocalcemia and an increase in serum phosphate.[128,129] The clinical significance of these biochemical changes is uncertain, but no studies have documented any bone/mineral or cardiovascular benefit of calcimimetic treatment in the CKD population.
- Due to lack of evidence of benefit and the risk of developing hypocalcemia and hyperphosphatemia with cinacalcet therapy, the Work Group suggests against the use of calcimimetics for the management of hyperparathyroidism in stage 3 and 4 patients.

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)*

- The evidence review for this update of the CKD CPG on the use of phosphate binders in patients with CKD included one SR and meta-analysis of three studies comparing sevelamer to placebo or usual care and three studies comparing lanthanum to placebo or usual care.[130] This meta-analysis concluded that treatment with these phosphate binders did not reduce mortality, myocardial infarction (MI), decline in renal function, or progression to ESRD.
- Although there is epidemiologic evidence not included in the evidence review that hyperphosphatemia is associated with increased mortality in patients on dialysis,[131-134] there is no evidence that the use of a phosphate binder will provide long-term outcome benefit.
- The Work Group's confidence in the quality of the evidence is very low due to the limited number of high quality trials and lack of long-term data.

E. Other Medications to Slow CKD Progression

30. We suggest the use of sodium bicarbonate supplementation in chronic kidney disease patients with metabolic acidosis to slow the progression of chronic kidney disease. *(Weak for; Not Reviewed, Not Changed)*

- The Work Group did not systematically review evidence related to this recommendation but reviewed the evidence from the 2014 CKD CPG and carried forward the recommendation.[135]
- An SR by Susantitaphong et al. (2012) of six studies with a total of 312 patients assessing the use of sodium bicarbonate as alkali therapy demonstrated that, for studies with a duration longer than two months, sodium bicarbonate therapy was associated with improvement in eGFR and a lower incidence of dialysis initiation.[135]

- An alternative form of alkali therapy is a diet rich in fruits and vegetables. While not included in the 2014 CKD CPG evidence review, Goraya et al. (2014) treated 108 patients with CKD stage 3 for three years with oral sodium bicarbonate, fruits and vegetables as alkali therapy, or usual care (n=36 in each arm).[136] Both the sodium bicarbonate and fruits and vegetables groups had improvement of metabolic acidosis and less of a decline in eGFR compared to usual care. While this additional study confirms the benefit of preserving kidney function with alkali therapy, the small number of patients and the pre-selection for not developing hyperkalemia prevents recommending fruits and vegetables as an alternative alkali therapy over sodium bicarbonate.
- The data supporting sodium bicarbonate therapy to improve the plasma bicarbonate therapy in patients with metabolic acidosis is consistent across the trials, but the total number of patients included is small. Therefore, confidence in the quality of evidence remains very low. Patients may have trouble tolerating the gas from oral sodium bicarbonate, and the large size and number of pills required may affect medication adherence.

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)*

- The systematic evidence review conducted for the 2019 CPG regarding the use of urate-lowering therapy in delaying CKD progression included one SR and meta-analysis,[137] two RCTs,[138,139] and one post hoc subgroup analysis of an RCT.[140]
- An SR and meta-analysis by Pisano et al. showed that use of allopurinol was associated with lower incidence of progression to ESRD in patients with stage 2-4 CKD compared to the control.[137] Several of the studies included in the meta-analysis had high risk of bias, and the authors did not include all studies that had sufficient data for analysis in the meta-analysis. Two RCTs compared febuxostat to placebo in CKD and found no difference in rates of change in renal function or cardiovascular events.[138,139] In a post hoc subgroup analysis of an RCT comparing febuxostat to allopurinol, there was no statistically significant difference in change in eGFR, but the trial was only six months in duration.[139,140]
- Confidence in the quality of the evidence is very low due to serious limitations in study quality, inconsistent outcomes, and variable follow-up range.

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)*

- Tolvaptan has been found to slow the intermediate endpoint of decline in eGFR by about 1 mL/minute/1.73 m^2/year in patients with rapidly progressing autosomal dominant polycystic kidney disease (ADPKD), although use of tolvaptan has been associated with an increased incidence of adverse effects. The long-term safety and efficacy for the reduction of hard renal outcomes, such as need for dialysis or transplant, have yet to be established.[141-143]
- The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial and The Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial suggested that treatment with tolvaptan was associated with a slower decline in eGFR compared to

placebo.[141,142] However, in TEMPO 3:4 more patients on tolvaptan discontinued study treatment due to adverse events, including increases in hepatotoxicity and aquaretic side effects such as thirst, polyuria, nocturia, urinary frequency.[141] A lower overall incidence of adverse events was noted in REPRISE; however, only patients who tolerated tolvaptan during an 8-week screening phase were randomized to the active portion of this trial.[142] Patients in this selected group receiving tolvaptan again reported a 7% absolute increase of adverse effects including aquaretic side effects, diarrhea, and fatigue

- Besides the more common side effects noted above, significant concerns for the safety of tolvaptan have been identified with respect to hepatotoxicity. An increased risk of hepatic adverse events was observed in REPRISE.[144] Most cases of elevated hepatic enzymes improved with interruption or discontinuation of tolvaptan, and the risk for liver toxicity may be mitigated with monthly monitoring of liver function tests facilitating early identification of hepatotoxicity. However, a 2018 FDA post-marketing review of tolvaptan reported a single case of liver failure requiring transplantation, despite monthly monitoring.[145]
- Patients with ADPKD who are expected to benefit the most from tolvaptan include those with eGFR over 30 mL/minute/1.73 m^2 with rapidly progressing disease. As ADPKD presents with a wide range of penetrance and rates of decline in renal function and significant toxicity may result from the agent, the Work Group strongly advises consultation with a nephrologist to identify patients likely to benefit from tolvaptan prior to initiation of therapy. Appropriate patient selection with regard to the patient's ability to tolerate side effects, maintain adequate hydration, and comply with frequent lab monitoring, as well as retain uninterrupted access to the medication and a committed nephrologist experienced in managing tolvaptan, must be carefully considered prior to offering therapy and be weighed against the potential benefit of a 1 mL/minute/1.73 m^2/year slowing of the decrease in eGFR.
- While overall confidence in the quality of the safety data evidence is moderate, it is lower for the efficacy data due to reliance on surrogate outcomes.[136] Limitations of the current body of evidence include reliance on the use of surrogate outcomes and modeling systems for data analysis as well as an absence of long-term data demonstrating a reduction in ADPKD progression to ESRD.

Contrast-Associated Kidney Injury Management

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

- Although widely perceived as a common risk for acute kidney injury (AKI), recent epidemiologic studies, particularly among patients receiving IV contrast for computed tomography, have questioned the risks associated with contrast administration.
- The Work Group systematically reviewed the evidence identified in the evidence review conducted for this CPG update [146-150] and considered the assessment of the evidence put forth in the 2014 CKD CPG.[151]
- The 2014 evidence review identified a meta-analysis of 513 patients of six trials comparing IV saline with various regimens of "oral fluid" administration.[151] In a study comparing IV isotonic

saline to unrestricted oral fluids, only one patient (3.7%) in the saline group developed contrast associated acute kidney injury (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.[152] Based on this data, oral hydration should not be considered adequate for prophylaxis for CA-AKI.

- Since the 2014 evidence review, an RCT has compared IV isotonic saline (3-4 mL/kg/hr for four hours pre- and post-contrast exposure or 1 mL/kg/hr for 12 hours pre- and post-contrast exposure) to no IV fluids among 660 patients with an eGFR of 30-59 mL/minute/1.73 m^2 undergoing either contrast-enhanced computed tomography (52%) or angiography (48%) with a mean administered contrast volume of 90 mL. 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).[150]
- The Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial 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]) to a standard regimen of 3 mL/kg over one hour followed by 1.5 mL/kg/hour over four hours in 396 patients with an eGFR <60 mL/minute/1.73 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 controls (total saline volume 812±142 mL) (RR 0.41; 95% CI: 0.22-0.79; p=0.005).[148]
- The Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial evaluated 4,993 patients with DM and an eGFR <60 mL/minute/1.73 m^2 or without DM 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. In the comparison of isotonic sodium bicarbonate to isotonic saline, CA-AKI occurred in 9.5% of patients assigned to sodium bicarbonate as compared to 8.3% of patients assigned to isotonic saline (OR: 1.16; 95% CI: 0.96-1.41; p=0.13). The primary study endpoint of death, need for dialysis, or a persistent 50% increase in SCr at day 90 occurred in 4.4% of patients in the sodium bicarbonate arm and 4.7% of patients in the saline arm (OR: 0.91; 95% CI: 0.72-1.22; p=0.62).[149] Thus, the Work Group concluded that there was no benefit to sodium bicarbonate compared to saline. Additionally, the Work Group concluded that there is a potential risk of harm associated with sodium bicarbonate administration based on the risk of compounding errors and an increased cost.
- The Work Group determined that the strength of evidence favoring the administration of isotonic IV crystalloid was low with conflicting data from poor quality studies, but evidence suggests that larger volumes of IV fluids were associated with greater benefit and those with more advanced CKD were more likely to benefit.
- The Work Group suggests that IV isotonic crystalloid be administered to reduce the risk of CA-AKI in high-risk patients (i.e., patients with DM and an eGFR <60 mL/minute/1.73 m^2 or non-diabetic patients with an eGFR <45 mL/minute/1.73 m^2 undergoing angiography with intra-arterial contrast administration or patients with an eGFR <30-45 mL/minute/1.73 m^2 undergoing contrast-enhanced computed tomography), if there is no medical contraindication.

- The Work Group suggests that patients with CKD undergoing outpatient angiographic or contrast-enhanced computed tomographic procedures be given at least 3 mL/kg of isotonic saline over one hour pre-procedure continued at a rate of 1-1.5 mL/kg per hour during the procedure, and at least an additional 6 mL/kg of isotonic saline over 2-6 hours (rate of 1-3 mL/kg per hour) post-procedure. For inpatients, the Work Group suggests the administration of isotonic saline at 1 mL/kg per 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.

34. We recommend against the administration of N-acetylcysteine for prevention of iodinated contrast-associated acute kidney injury. *(Strong against; Reviewed, New-replaced)*

- The Acetylcysteine for Contrast-induced Nephropathy Trial (ACT) [146] and PRESERVE[149]) randomized a total of more than 7,300 patients to N-acetylcysteine or placebo. These RCTs provide strong evidence that N-acetylcysteine is ineffective in the prevention of CA-AKI. The quality of the evidence was low, but the use of N-acetylcysteine is associated with potential side effects and increased costs.

35. We recommend against the use of renal replacement therapy for iodinated contrast-associated acute kidney injury prophylaxis. *(Strong against; Reviewed, Amended)*

- The Work Group systematically reviewed the evidence identified for this CPG update [146] and considered the assessment of the evidence put forth in the 2014 CKD CPG.[153]
- There are limited data on the benefit of RRT for the prevention of CA-AKI. In a meta-analysis of six trials of hemodialysis not included in the evidence base, Cruz et al. found a pooled risk ratio of 1.61 (95% CI: 1.13-2.28) for the development of AKI with hemodialysis compared to standard management. A pooled risk ratio of 0.46 (95% CI: 0.12-1.70) was reported in three trials of hemofiltration and hemodiafiltration, but two of these three trials demonstrating benefit used change in SCr as the primary outcome.[154] In an Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review, Subramaniam et al. concluded that the evidence was insufficient to support a clinically important benefit of RRT.[146]
- The proposed mechanism of benefit for this intervention, rapid removal of the administered dye load, lacks biological plausibility as it would take 8-12 hours of intermittent hemodialysis and a longer duration of continuous RRT to remove >90% of the administered dye load.
- Although the confidence in the quality of the evidence is very low, given the potential for harm and the burden of therapy, including the need for insertion of large-bore central venous catheters to provide dialysis, the need to transfer patients to intensive care units to provide continuous hemofiltration, and the expense of treatment, the Work Group recommends against the use of RRT for prevention of CA-AKI.

Additional Resources

- VA Kidney Program Website: https://www.va.gov/health/services/renal/learn.asp
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): https://www.niddk.nih.gov/health-information/kidney-disease
- The National Kidney Disease Education Program (NKDDEP): http://nkdep.nih.gov/
- The Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf

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https://www.healthquality.va.gov/guidelines/CD/ckd/