



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

**Department of Veterans Affairs**  
**Department of Defense**

## Clinician Guideline 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 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 recommendations.

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

**Version 3.0 – 2014**

## Summary

Chronic kidney disease (CKD) is one of the most common serious medical conditions affecting adults in the United States (US). The Centers for Disease Control and Prevention (CDC) estimate that more than 10% of adults in the US—over 20 million people—have CKD, [1] which is defined as having an estimated glomerular filtration rate (eGFR) of  $<60 \text{ mL/min}/1.73\text{m}^2$  or albuminuria (albumin excretion rate [AER] of  $\geq 30 \text{ mg}/24 \text{ hours}$  or albumin:creatinine ratio [ACR] of  $\geq 30 \text{ mg/g}$ ), kidney transplantation, or any of several other less common reasons (e.g., urine sediment abnormalities, electrolytes and other abnormalities due to tubular disorders, histologic abnormalities, structural abnormalities identified by imaging). [2] Patients may suffer from mild illness without symptoms to severe illness associated with increased risk of death or progression to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation. The risk of developing CKD increases among people over 50 years of age and peaks after 70 years of age. [1] In many patients the disease is caused by, or associated with, other conditions including diabetes, hypertension, cardiovascular disease, malnutrition, and anemia. Early intervention and management is important to stabilize, or at least slow down, progressive kidney damage, which worsens the prognosis of patients with CKD. The stages of CKD are described in Table 1 below. For a given stage of CKD, the categories A1-A3 will increase the risk of CKD progression.

**Table 1. Stages of CKD [2-4]**

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

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

The Department of Veterans Affairs (VA) and Department of Defense (DoD) have an obligation to ensure that all patients with CKD receive a full range of high quality care. This clinical practice guideline (CPG) is designed to assist primary care providers in managing patients with CKD Stages 1-4. Additionally, the CPG provides evaluation considerations and treatment options, including pharmacological and non-pharmacological interventions.

Topics discussed in this CPG include:

- Evaluation for CKD
- Strategies for acute kidney injury (AKI) avoidance
- Self-management strategies
- Clinical management strategies

### Evaluation for CKD

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

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

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

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

### Acute Kidney Injury Avoidance

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

## **Self-Management Strategies**

The role of the patient in management of CKD is being increasingly emphasized. We reviewed the literature for evidence of self-management strategies that might reduce CKD progression. The guideline panel suggests the use of dietary sodium restriction and dietary protein restriction as these interventions may slow CKD progression. The guideline panel also encourages weight loss, exercise, health education and smoking cessation interventions for patients with CKD as these are useful strategies to improve overall patient health.

More broadly, evidence suggests that patient self-management plays an essential role in the management of any chronic disease.

### **Additional Resources for Smoking Cessation**

The VA smoking quit line, 1-855-QUIT-VET, offers callers counseling, help building a quit plan, and strategies to prevent relapse.

SmokefreeVET is a free mobile text messaging service that sends tips, support, and encouragement for up to eight weeks during the quitting process. Veterans can sign up by visiting <http://smokefree.gov/VET>, or texting the word VET to 47848.

## **Clinical Management Strategies**

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

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

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

Patient safety must also be considered and prudence applied when using medications to treat the complications of progressive kidney disease (e.g., iron, erythropoiesis-stimulating agents [ESAs] to treat

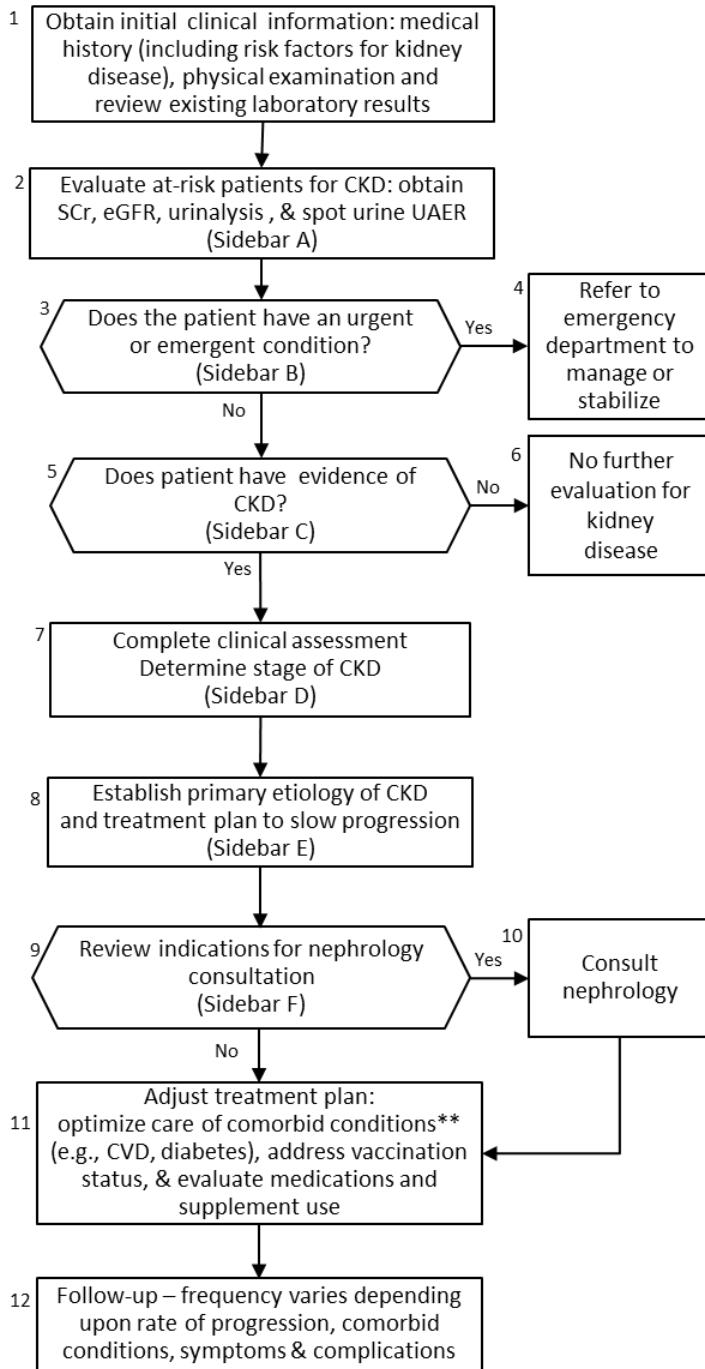
### **Additional Resources for Reduction of Cardiovascular Risk**

- Framingham (cohort age range 40-74):  
<http://cvdrisk.nhlbi.nih.gov/>
- ASCVD Pooled Risk Calculator from the 2013 ACC/AHA Lipid Guideline (cohort age range 40-79):  
<http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx>
- Cardiovascular Risk/Benefit Calculator (combines Framingham and ACC/AHA cohorts):  
<http://bestsciencemedicine.com/chd/calc2.html>
- Mayo Statin Decision Aid:  
<http://statindecisionaid.mayoclinic.org/index.php/site/index>

anemia, and oral phosphate binders, vitamin D analogs, and calcimimetics in the management of CKD bone and mineral disorders).

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

# Algorithm



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

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

†This list is not exhaustive, consult the discussion of Recommendation 16 for more information

\*\*As appropriate, refer to the following VA/DoD Clinical Practice Guidelines: Chronic Heart Failure, Diabetes, Hypertension, Dyslipidemia, Obesity & Tobacco Cessation

## Sidebar A: At-Risk Populations

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

## Sidebar B: Urgent/Emergent Conditions

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

## Sidebar C: Criteria for Confirmed CKD

**CKD is defined as sustained abnormality for >3 months of Either:**

- eGFR  $<60$  mL/min/1.73m<sup>2</sup>
- **Or any of the following:**
  - Albuminuria
  - Urine sediment abnormality
  - Abnormal renal histology
  - Structural renal abnormality by imaging
  - History of renal transplantation

## Sidebar D: Stage of CKD

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

### Albuminuria

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

## Sidebar E: Strategies to Slow Progression

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

## Sidebar F: Indications for Nephrology Consultation\*†

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

## Recommendations

**Table 2. Evidence-Based Clinical Practice Recommendations for the Management of CKD**

#	Recommendation	Strength
<b>Evaluation for Chronic Kidney Disease (CKD)</b>		
1.	While there is insufficient evidence to associate exposure to depleted uranium and solvents such as hydrocarbons with CKD, we suggest that clinicians take a detailed occupational and non-occupational history.	Weak For
2.	We suggest that periodic evaluation for CKD be considered in patients with the following: <ul style="list-style-type: none"> <li>a. Diabetes, hypertension, other end organ disease (e.g., chronic heart failure [CHF]), or a personal or family history of kidney disease</li> <li>b. Systemic illness (e.g., human immunodeficiency virus [HIV], systemic lupus erythematosus, multiple myeloma)</li> <li>c. History of acute kidney injury (AKI) (e.g., acute tubular necrosis, urinary tract obstruction, interstitial nephritis)</li> <li>d. Elderly patients</li> <li>e. Races and ethnicities associated with increased risk (e.g., African Americans, Hispanics, Native Americans)</li> </ul>	Weak For
<i>(Carryover modified from the 2008 CPG)**</i>		
<b>Acute Kidney Injury Avoidance</b>		
<b>Prevention of Contrast-induced Nephropathy (CIN) in Patients with CKD</b>		
3.	We suggest that patients at increased risk for CIN receive volume expansion with intravenous (IV) isotonic crystalloid solutions (saline or sodium bicarbonate) prior to and following iodinated contrast administration.	Weak For
4.	We suggest offering oral hydration to patients in which IV hydration is not feasible for CIN prophylaxis.	Weak For
5.	Given inconsistent evidence, we do not recommend for or against the routine administration of N-acetylcysteine (NAC) for CIN prophylaxis.	Weak For
6.	We recommend against the use of renal replacement therapy (RRT) for CIN prophylaxis.	Strong Against
7.	We suggest not initiating statin therapy for the purpose of CIN prophylaxis in patients undergoing elective angiography.	Weak Against
8.	We suggest not offering theophylline therapy for CIN prophylaxis for patients undergoing elective coronary angiography.	Weak Against
<b>Management of Chronic Kidney Disease</b>		
<b>Self-Management Strategies</b>		
9.	We suggest the use of dietary sodium restriction as a self-management strategy to reduce proteinuria and improve blood pressure control in patients with CKD.	Weak For
10.	In patients with stage 3 and 4 CKD, we suggest a protein diet of 0.6 to 0.8 g/kg/day as it may slow the decline in glomerular filtration rate (GFR) and progression to end-stage renal disease (ESRD). <i>(Carryover modified from the 2008 CPG)</i>	Weak For
11.	There is insufficient evidence to recommend for or against weight loss in obese patients as an intervention to reduce proteinuria or to slow progression of CKD. However, we suggest weight loss interventions in obese patients as part of an overall health improvement strategy.	Weak For
12.	There is insufficient evidence to recommend for or against exercise with or without lifestyle intervention to reduce ESRD, mortality, change in GFR, or change in urinary	Weak For

#	Recommendation	Strength
	protein. However, we suggest regular exercise as part of an overall health improvement strategy.	
13.	There is insufficient evidence to recommend for or against health education to reduce time to dialysis initiation or to reduce mortality. However, we suggest CKD health education because it supports the aim of maximizing patient-centered care.	Weak For
14.	There is insufficient evidence to recommend smoking cessation to halt progression of CKD, however, we suggest tobacco cessation for cardiovascular risk reduction in patients with CKD.	Weak For
<b>Clinical Management Strategies</b>		
15.	We suggest offering multidisciplinary care, if available, for patients with CKD to reduce non-fatal stroke, slow progression from micro- to macroalbuminuria, and reduce all-cause mortality.	Weak For
16.	Although there is insufficient evidence to recommend for or against referral to a nephrology specialist for patients with stage 3 CKD for slowing CKD progression, we suggest consultation with a nephrologist to assist in the diagnosis and treatment of patients with any of the following conditions: <ul style="list-style-type: none"> <li>a. eGFR &lt;30 mL/min/1.73 m<sup>2</sup> to facilitate education and planning for renal replacement therapy (dialysis or kidney transplant)</li> <li>b. Kidney function that is rapidly worsening without obvious cause</li> <li>c. Metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism)</li> <li>d. CKD of unclear etiology after initial work-up, or has a known or suspected kidney condition requiring specialized care</li> <li>e. Nephrotic range proteinuria</li> <li>f. Nephrolithiasis</li> </ul>	Weak For
17.	We recommend that treatment with the following vaccinations be considered for patients with CKD as a measure to prevent infections: <ul style="list-style-type: none"> <li>a. Influenza vaccine*</li> <li>b. Tdap vaccine</li> <li>c. Pneumococcal polysaccharide vaccine (i.e., PCV 13 and PPSV23)</li> <li>d. Hepatitis B vaccine</li> <li>e. Zoster /shingles vaccine*</li> <li>f. Varicella vaccine*</li> <li>g. MMR vaccine*</li> </ul> (*Note: Live vaccines, including nasal influenza (LAIV), may be contraindicated in patients with CKD and severe immunodeficiency including treatment with immunosuppressive agents) <i>(Carryover modified from the 2008 CPG)</i>	Strong For
18.	We recommend that clinicians avoid or limit the use of nephrotoxic medications for patients with CKD. <i>(Carryover modified from the 2008 CPG)</i>	Strong For
19.	In patients with CKD, we suggest that medications should be reviewed and their dosing modified, where appropriate, according to the level of the patient's kidney function. <i>(Carryover modified from the 2008 CPG)</i>	Weak For
20.	We suggest the use of bicarbonate supplementation in CKD patients with metabolic acidosis to slow the progression of CKD.	Weak For
21.	In adult patients with stages 1-4 CKD, we recommend that blood pressure targets	Strong For

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

\*\*For additional information, please refer to the section Reconciling 2008 CPG Recommendations in the full CPG.

## Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [5]

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

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains. [5]

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

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

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

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

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

- Strong For (or “We recommend offering this option ...”)
- Weak For (or “We suggest offering this option ...”)
- Weak Against (or “We suggest not offering this option ...”)
- Strong Against (or “We recommend against offering this option ...”)

**Table 3. Evidence to Recommendation Framework**

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

## References

1. U.S. Department of Health and Human Services Centers for Disease Control and Prevention. *National chronic kidney disease fact sheet*. Atlanta, GA: 2014. [http://www.cdc.gov/diabetes/pubs/pdf/kidney\\_factsheet.pdf](http://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf). Accessed February 24, 2014.
2. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney inter., Suppl.* 01//print 2013;3(1):1-150.
3. International Society of Nephrology. KDIGO guidelines. Chapter 2: Definition, identification, and prediction of CKD progression. *Kidney inter., Suppl.* 01//print 2013;3(1):63-72.
4. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis.* Feb 2002;39(2 Suppl 1):S1-266.
5. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. *J Clin Epidemiol.* Jul 2013;66(7):719-725.