



# Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary Care Clinician

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## ABSTRACT

A panel of internists and nephrologists developed this practical approach for the Kidney Disease Outcomes Quality Initiative to guide assessment and care of chronic kidney disease (CKD) by primary care clinicians. Chronic kidney disease is defined as a glomerular filtration rate (GFR)  $<60$  mL/min/1.73 m<sup>2</sup> and/or markers of kidney damage for at least 3 months. In clinical practice the most common tests for CKD include GFR estimated from the serum creatinine concentration (eGFR) and albuminuria from the urinary albumin-to-creatinine ratio. Assessment of eGFR and albuminuria should be performed for persons with diabetes and/or hypertension but is not recommended for the general population. Management of CKD includes reducing the patient's risk of CKD progression and risk of associated complications, such as acute kidney injury and cardiovascular disease, anemia, and metabolic acidosis, as well as mineral and bone disorder. Prevention of CKD progression requires blood pressure  $<140/90$  mm Hg, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for patients with albuminuria and hypertension, hemoglobin A<sub>1c</sub>  $\leq 7\%$  for patients with diabetes, and correction of CKD-associated metabolic acidosis. To reduce patient safety hazards from medications, the level of eGFR should be considered when prescribing, and nephrotoxins should be avoided, such as nonsteroidal anti-inflammatory drugs. The main reasons to refer to nephrology specialists are eGFR  $<30$  mL/min/1.73 m<sup>2</sup>, severe albuminuria, and acute kidney injury. The ultimate goal of CKD management is to prevent disease progression, minimize complications, and promote quality of life.

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Chronic kidney disease encompasses a broad range of disease severity and significant heterogeneity in the risks of progression to end-stage renal disease, morbidity, and mortality. In

2002, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative published the first guideline that defined chronic kidney disease, independent of the cause, as based on 3 or more months of either kidney damage (albuminuria, kidney biopsy findings, or imaging abnormalities) or an estimated glomerular filtration rate  $<60$  mL/min/1.73 m<sup>2</sup>.<sup>1</sup> Epidemiologic data have shown that low estimated glomerular filtration rate increases the risk of systemic complications (eg, cardiovascular disease, hypertension, mineral and bone disorders, and anemia), mortality, and progression to end-stage renal disease. Defining chronic kidney disease as based on abnormalities in kidney function or albuminuria that persist at least 3

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months distinguishes it from potentially preventable or reversible acute kidney injury of less than 3 months' duration. Since 2002, this chronic kidney disease classification has led to estimated glomerular filtration rate reporting added to serum creatinine outpatient testing panels, and its incorporation into diagnosis codes.<sup>2</sup>

New data from 50 cohorts totaling more than 2 million individuals has demonstrated a strong and linear increase in the risk of adverse outcomes for chronic kidney disease according to the 2002 definition of an estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> or albumin-to-creatinine ratio >30 mg/g (>3 mg/mmol).<sup>3</sup> In 2012 the Kidney Disease Improving Global Outcomes released a new guideline for chronic kidney disease that adds refinements based on cause, estimated glomerular filtration rate, and albuminuria categories (see [Appendix A](#) [available online] for guideline statements).<sup>4</sup> Consideration of the cause of chronic kidney disease fundamentally affects management by distinguishing a systemic condition from one that is localized to the kidney, such as a glomerular disease. The albuminuria is complementary to low estimated glomerular filtration rate because both independently influence prognosis, as demonstrated by a heat map of the new classification illustrating an increasing risk of chronic kidney disease progression, morbidity, and mortality ([Figure 1](#)).<sup>4</sup> This new grid offers a practical guide for primary care clinicians to inform monitoring and management of chronic kidney disease.

The estimated prevalence of chronic kidney disease in the general population exceeds 10%,<sup>3,5</sup> outstripping the availability of nephrology specialists and requiring primary care clinicians to care for the majority of these patients. A panel of internists and nephrologists developed this practical approach to guide assessment and care of chronic kidney disease by primary care clinicians, described in the following sections on detection, progression, patient safety, interaction with cardiovascular disease, and nephrology referral.

## TOPIC 1: DETECTION OF CHRONIC KIDNEY DISEASE

### Overview

Expert panels have identified insufficient evidence to support general population-based testing for chronic kidney disease.<sup>1,4,6-9</sup> Both the Kidney Disease Outcomes Quality Initiative and the Kidney Disease Improving Global Outcomes

chronic kidney disease guidelines have recommended targeted testing for chronic kidney disease among high-risk populations with diabetes and/or hypertension.<sup>1,4,9</sup> In practice, detection of chronic kidney disease often occurs during routine care because serum creatinine testing is included in ubiquitous basic and comprehensive metabolic panels. Early detection of chronic kidney disease offers a valuable opportunity to avert complications before symptoms occur and to slow loss of kidney function over time.<sup>10-16</sup>

Compared with persons whose chronic kidney disease remains undetected, those with chronic kidney disease diagnosed by a primary care clinician are more likely to avoid risky use of nonsteroidal anti-inflammatory drugs (NSAIDs)<sup>17</sup>; use angiotensin-converting-enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) when indicated<sup>17,18</sup>; and receive appropriate nephrology care.<sup>18</sup>

### Kidney Function: Estimated Glomerular Filtration Rate

Detection of chronic kidney disease based on estimated glomerular filtration rate is a more accurate assessment of kidney function than serum creatinine alone.<sup>1,4,9</sup> Two

equations are used in practice to estimate glomerular filtration rate, the Chronic Kidney Disease Epidemiology Collaboration equation and the older Modification of Diet in Renal Disease Study equation. Recent studies have found that the Chronic Kidney Disease Epidemiology Collaboration equation more accurately predicts prognosis and is less biased than the older Modification of Diet in Renal Disease Study equation.<sup>4,9,19</sup> One caveat is that any estimated glomerular filtration rate equation is inaccurate in the setting of acute kidney injury because kidney function is not in a steady state.

### Urine Studies to Evaluate for Albuminuria or Proteinuria

Although quantification of albuminuria has been less widely adopted in clinical practice than assessment of estimated glomerular filtration rate,<sup>5</sup> it is crucial to evaluating prognosis. A spot albumin-to-creatinine ratio is a more sensitive and specific marker of chronic kidney disease than a spot urine protein/creatinine ratio, although both are predictive of clinical outcomes.<sup>9</sup> Standardization of urine albumin measurement is ongoing but superior to urine protein that has much wider variability.<sup>9</sup> A random or spot urine specimen quantifies albumin as milligrams per gram of creatinine (mg/g) ([Figure 1](#)).<sup>4</sup>

### CLINICAL SIGNIFICANCE

- Chronic kidney disease (CKD) is defined by estimated glomerular filtration rate (eGFR) and urinary albumin/creatinine ratio.
- The 4 interventions that reduce CKD progression are blood pressure control <140/90 mm Hg, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for albuminuria and hypertension, diabetes control, and correction of metabolic acidosis.
- A patient safety approach to CKD considers the level of eGFR in prescription practice.
- Statin-based therapies reduce vascular events in CKD.
- Nephrology referral for advanced CKD is associated with improved outcomes.

<b>CKD is classified based on:</b> • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
<b>GFR categories (ml/min/1.73m<sup>2</sup>)</b> <b>Description and range</b>	G1	Normal or high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 1 Risk of chronic kidney disease progression, frequency of visits, and referral to nephrology according to estimated glomerular filtration rate (eGFR) and albuminuria. The GFR and albuminuria grid depict the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio (ACR) only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 and deep red 4 times per year. These are general parameters only, based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. "Refer" indicates nephrology services are recommended. \*Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. This figure is adapted with permission from reference 4.

**Cause of Chronic Kidney Disease: Other Tests**

Evaluation with imaging or serologic testing to identify the cause of chronic kidney disease is not routinely required,<sup>20</sup> particularly in the presence of diabetes or hypertension. Kidney and bladder ultrasound should be performed when there is a history of urinary tract stones or obstruction, frequent urinary tract infections, or a family history of polycystic kidney disease.<sup>1</sup> Serologic workup is only required when a systemic or glomerular disease is suspected, such as myeloma or amyloidosis. Consider nephrology referral when the cause of kidney disease is not apparent, particularly for patients without diabetes and hypertension.

**TOPIC 2: CHRONIC KIDNEY DISEASE PROGRESSION AND COMPLICATIONS**

**Overview**

The treatment of chronic kidney disease aims to delay progressive loss of kidney function and prevent or manage

complications. Four interventions clearly delay chronic kidney disease progression, including management of hypertension; use of a renin angiotensin aldosterone system (RAAS) blocker, an ACE-I, or ARB for hypertension and albuminuria; control of diabetes; and correction of metabolic acidosis. Management to delay progression and treat chronic kidney disease complications is discussed in the following sections.

**Hypertension Management**

For the past 10 years, the Joint National Committee on hypertension (JNC) has recommended an office blood pressure target of 130/80 mm Hg or less for patients with chronic kidney disease.<sup>21</sup> Recently, JNC 8 has loosened this target to S140/90 mm Hg, the same as for the general population under 60 years of age.<sup>22</sup> This new recommendation reflects the lack of robust data supporting a lower blood pressure target. Accordingly, recent clinical practice guidelines for blood pressure management in chronic kidney disease have suggested that a target of S130/80 mm Hg should be sought

only in the context of severe albuminuria, but the evidence for this goal is of very low quality.<sup>23</sup> Sodium consumption is an important consideration for blood pressure control in chronic kidney disease. A diet high in sodium is a cause of resistance to hypertension medications, especially for patients with chronic kidney disease. The average American consumes more than 3500 mg sodium daily.<sup>24</sup> For patients with chronic kidney disease current guidelines recommend less than 2000 mg of sodium per day; however, there is low-quality evidence for this recommendation.<sup>4,9,23-25</sup>

### ACE-I or ARB

Treatment with ACE-I or ARB for hypertension in persons with chronic kidney disease with or without diabetes who have A2 and A3 levels of albuminuria is supported by low- to high-level evidence, respectively.<sup>23</sup> Although JNC 8 recommends a RAAS blocker for all patients with chronic kidney disease,<sup>22</sup> current evidence supports this treatment primarily for patients with albuminuria. Some chronic kidney disease patients can develop hyperkalemia or a decreased estimated glomerular filtration rate after starting an ACE-I or an ARB. Monitoring should include assessment of serum potassium and estimated glomerular filtration rate approximately within several weeks after initiation or dose escalation. When hyperkalemia develops, outpatient management strategies include identification and restriction of dietary potassium, treatment of metabolic acidosis if appropriate (see below), consideration of thiazide or loop diuretic use to increase potassium excretion, and treatment with a potassium-binding exchange resin. Discontinuation of the RAAS blocker should be considered only if these interventions fail. When the estimated glomerular filtration rate decreases more than 25% within 3 months of RAAS initiation, the patient deserves additional investigation for overdiuresis or renal artery stenosis.

### Dual RAAS Blockade

Combination therapy with an ACE-I plus an ARB should not be used for patients with chronic kidney disease and hypertension regardless of whether they have diabetes. Trials have shown greater complications, such as acute kidney injury and severe hyperkalemia, and no mortality or cardiovascular benefits with combination versus single-agent therapy.<sup>26,27</sup>

### Diuretic Therapy

Diuretics are generally necessary to manage extracellular fluid volume expansion and blood pressure control in chronic kidney disease. Thiazides are used especially for patients with stages G1-3b chronic kidney disease. A second-line option is a loop diuretic when the thiazide does not achieve volume control goals. Most patients with stage G4 chronic kidney disease will require a loop diuretic, and furosemide, the most common drug, should be dosed twice daily for effective diuresis.

### Glycemic Control

According to recent data regarding harms from overly intensive glycemic control, a target hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) of approximately 7% has been recommended, with a higher target for those with a limited life expectancy or an elevated risk of hypoglycemia.<sup>9,28</sup> In addition to cardiovascular risk reduction, the benefits of glycemic control in chronic kidney disease include reduced progression of albuminuria and reduced loss of kidney function over time.<sup>14,16,28</sup>

### Chronic Kidney Disease Anemia

Measurement of hemoglobin (Hb) at least annually is recommended beginning with stage G3a chronic kidney disease, because erythropoietin production decreases with low glomerular filtration rate.<sup>4,9</sup> Figure 2 shows a summary of chronic kidney disease anemia management.<sup>29</sup>

### Chronic Kidney Disease Mineral and Bone Disorder

Secondary hyperparathyroidism, hypocalcemia, hyperphosphatemia, decreased vitamin D, and vascular calcification typically begin in stage G3b, when serum calcium, phosphorus, intact parathyroid hormone, and total 25-hydroxy vitamin D should be measured at least once to document baseline levels. Figure 2 provides details on management.<sup>30,31</sup>

### Chronic Kidney Disease Metabolic Acidosis

Treatment of chronic kidney disease-associated metabolic acidosis with oral alkali to achieve a normal serum bicarbonate level has been shown in observational studies to slow chronic kidney disease progression.<sup>32-34</sup> When the bicarbonate level is less than 22 mmol/L, sodium bicarbonate (650 mg) should be prescribed 3 times daily. This dose corresponds to approximately 23 mEq daily of sodium and bicarbonate. Sodium citrate (30 mL daily) is an alternative, corresponding to 30 mEq of sodium and bicarbonate each day. If this does not result in a serum bicarbonate level of at least 22 mmol/L, a nephrology referral is indicated.

## TOPIC 3: PATIENT SAFETY IN CHRONIC KIDNEY DISEASE

### Overview

Many commonly prescribed medications and/or their metabolites are excreted by the kidneys. Dose adjustments based on estimated glomerular filtration rate need to be performed to avert or reduce complications (Table 1).<sup>4,9,35</sup> Several medications can cause acute kidney injury that, in turn, can initiate and/or accelerate chronic kidney disease progression. It may be prudent to discontinue or briefly withhold medications that may cause acute kidney injury (RAAS blockers, NSAIDs, diuretics) or those that can cause complications (eg, lactic acidosis due to metformin) when patients have an increased risk of volume depletion.

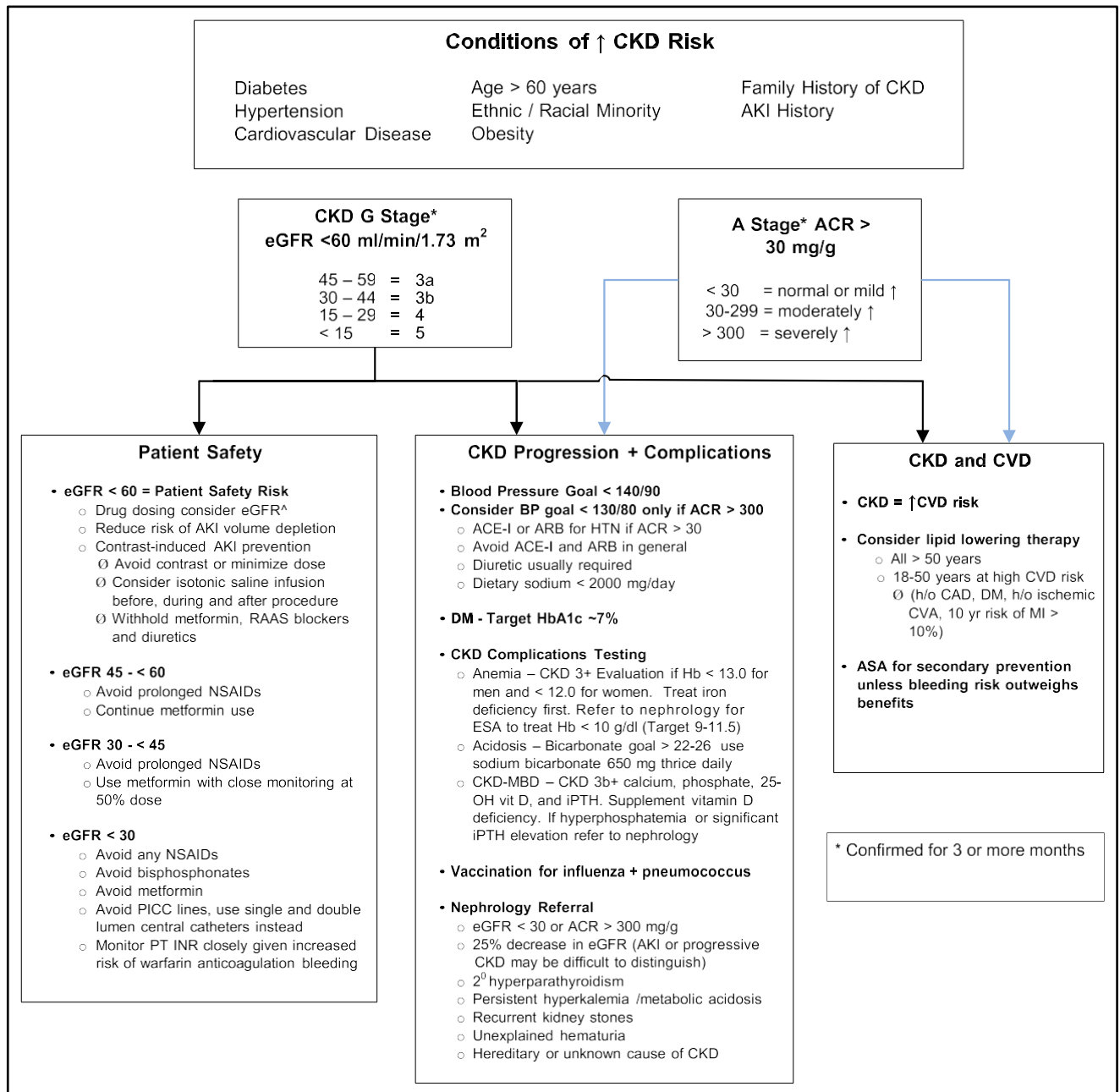


Figure 2 Summary of a practical approach to the detection and management of chronic kidney disease (CKD). ACE-I ¼ angiotensin-converting enzyme inhibitor; ACR ¼ albumin-to-creatinine ratio; AKI ¼ acute kidney injury; ARB ¼ angiotensin receptor blocker; ASA ¼ acetylsalicylic acid/ aspirin; A stage ¼ albuminuria category; CAD ¼ coronary artery disease; CKD ¼ chronic kidney disease; CKD-MBD ¼ chronic kidney disease mineral and bone disorder; CVA ¼ cerebrovascular accident; CVD ¼ cardiovascular disease; DM ¼ diabetes mellitus; eGFR ¼ estimated glomerular filtration rate; ESA ¼ erythropoietin-stimulating agent; G stage ¼ GFR category; Hb ¼ hemoglobin; HTN ¼ hypertension; iPTH ¼ intact parathyroid hormone; NSAIDs ¼ nonsteroidal anti-inflammatory drugs; 25-OH vit ¼ 25-hydroxy vitamin D; PICC ¼ peripherally inserted central catheter line; PT INR ¼ prothrombin time/ international normalized ratio; RAAS ¼ renin angiotensin aldosterone system.

## NSAIDs

Nonsteroidal anti-inflammatory inhibitors can cause acute kidney injury by inhibiting vasodilatory prostaglandins, especially in the context of other factors that impair renal perfusion, such as dehydration and congestive heart failure.<sup>36</sup> Long-term use of NSAIDs can also increase the rate of progression of chronic kidney disease.<sup>36,37</sup> These drugs are

available over the counter, so it is important that the clinician specifically inquire about their use and educate patients about potential harms. Other potential adverse effects of NSAIDs include allergic interstitial nephritis with or without minimal change disease, hyperkalemia, hypertension, and edema.<sup>36</sup> These medications should be avoided with an estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup> and limited

Table 1 Cautionary Notes for Prescribing in People with Chronic Kidney Disease

Agents	Cautionary Notes for Common Outpatient Medications
Antihypertensives/cardiac medications	
RAAS antagonists (ACE-I, ARB, aldosterone antagonist, direct renin inhibitor)	<ul style="list-style-type: none"> <li>• Use with caution in patients with renal artery stenosis</li> <li>• Start at lower dose in patients with GFR &lt;45 mL/min/1.73 m<sup>2</sup></li> <li>• Assess GFR and serum potassium 1-2 weeks after starting or escalating dose</li> <li>• Consider temporarily holding during IV contrast administration, or any potential cause of volume depletion (bowel preparation prior to colonoscopy, acute illness, and surgery)</li> <li>• Do not routinely discontinue when GFR &lt;30 mL/min/1.73 m<sup>2</sup> because they may remain nephroprotective</li> </ul>
b-Blockers	<ul style="list-style-type: none"> <li>• Reduce dose of hydrophilic b-blockers (acebutolol, atenolol, bisoprolol, and nadolol) by 50% when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> </ul>
Digoxin	<ul style="list-style-type: none"> <li>• Reduce dose according to plasma concentrations</li> </ul>
Analgesics	
NSAIDs	<ul style="list-style-type: none"> <li>• Avoid when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> <li>• Prolonged therapy is not recommended when GFR &lt;60 mL/min/1.73 m<sup>2</sup></li> <li>• Avoid when taking RAAS-blocking agents or lithium</li> </ul>
Opioids	<ul style="list-style-type: none"> <li>• Reduce dose of renally excreted agents (morphine, hydrocodone, codeine) when GFR &lt;60 mL/min/1.73 m<sup>2</sup></li> <li>• Use with caution in patients with GFR &lt;15 mL/min/1.73 m<sup>2</sup></li> </ul>
Antimicrobials	
Macrolides	
Fluoroquinolones	<ul style="list-style-type: none"> <li>• Reduce dose by 50% when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> </ul>
Tetracyclines	<ul style="list-style-type: none"> <li>• Reduce dose by 50% when GFR &lt;15 mL/min/1.73 m<sup>2</sup></li> </ul>
Antifungals	<ul style="list-style-type: none"> <li>• Reduce dose when GFR &lt;45 mL/min/1.73 m<sup>2</sup>; can exacerbate uremia</li> <li>• Reduce maintenance dose of fluconazole by 50% when GFR &lt;45 mL/min/1.73 m<sup>2</sup></li> <li>• Reduce dose of flucytosine when GFR &lt;60 mL/min/1.73 m<sup>2</sup></li> </ul>
Trimethoprim	<ul style="list-style-type: none"> <li>• Reduce dose by 50% when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> <li>• Risk factors for hyperkalemia include high doses, elderly, CKD, or with ACE-I and/or NSAIDs</li> </ul>
Hypoglycemics	
Sulfonylureas	<ul style="list-style-type: none"> <li>• Avoid mainly renally excreted agents (eg, glyburide/glibenclamide)</li> <li>• Agents mainly metabolized by the liver may need reduced dose when GFR &lt;30 mL/min/1.73 m<sup>2</sup> (eg, gliclazide, gliquidone)</li> </ul>
Insulin	<ul style="list-style-type: none"> <li>• Partly renally excreted and may need reduced dose when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> </ul>
Metformin	<ul style="list-style-type: none"> <li>• Avoid when GFR &lt;30 mL/min/1.73 m<sup>2</sup>, but consider risk-benefit if GFR is stable</li> <li>• Review use when GFR &lt;45 mL/min/1.73 m<sup>2</sup></li> <li>• Hold in patients during acute illness or before intravenous radiocontrast</li> </ul>
Lipid-lowering	
Statins	<ul style="list-style-type: none"> <li>• No increased toxicity for simvastatin 20 mg/d when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> <li>• Dose reduction/increased toxicity for GFR &lt;30 mL/min/1.73 m<sup>2</sup> for lovastatin, pravastatin, and rosuvastatin</li> </ul>
Fenofibrate	<ul style="list-style-type: none"> <li>• Associated with elevations in serum creatinine without a true change in GFR</li> </ul>

with an estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>. Furthermore, they should be used with extreme caution in patients with chronic kidney disease and concomitant RAAS blocking agents and/or diuretic therapy.<sup>4,9</sup>

### Metformin

Although the US Food and Drug Administration has a black-box warning for metformin use in patients with serum creatinine 2"1.5 mg/dL in men and 2"1.4 mg/dL in women owing to an increased risk for lactic acidosis, it is now recognized that

this risk is extremely low.<sup>38,39</sup> Many practice guidelines recommend discontinuing metformin use only when the estimated glomerular filtration rate is <30 mL/min/1.73 m<sup>2</sup>, and use with caution for patients with an estimated glomerular filtration rate of 30-45 mL/min/1.73 m<sup>2</sup>.<sup>4,9,28</sup>

### Iodinated Contrast

The major risk factor for contrast-induced nephropathy is chronic kidney disease. Use of N-acetylcysteine to prevent contrast-induced acute kidney injury is not consistently

Table 1 Continued

Agents	Cautionary Notes for Common Outpatient Medications
Anticoagulants	
Low-molecular-weight heparins	<ul style="list-style-type: none"> <li>• Reduce dose by 50% when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> <li>• Consider switch to conventional heparin or monitor plasma anti-factor Xa in those at high risk for bleeding</li> </ul>
Warfarin	<ul style="list-style-type: none"> <li>• Increased risk of bleeding when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> </ul>
Direct oral anticoagulants	<ul style="list-style-type: none"> <li>• If GFR is &lt;60 mL/min/1.73 m<sup>2</sup>, confirm correct dosing because recommended dose varies by indication and level of kidney function. Additionally, assess for potential drug interactions for inhibitors or inducers of CYP3A4 and P-gp metabolism. Note that if there are bleeding complications, the anticoagulant effects of these agents are more difficult to reverse compared with warfarin.</li> <li>• Suggested doses for nonvalvular atrial fibrillation follow: Apixiban 5 mg twice daily: eGFR 15-60 mL/min/1.73 m<sup>2</sup> reduce dose 2.5 mg twice daily eGFR &lt;15 mL/min/1.73 m<sup>2</sup> avoid use, limited data Dabigatran 150 mg twice daily: eGFR 30-60 mL/min/1.73 m<sup>2</sup> reduce dose 75 mg twice daily eGFR &lt;30 mL/min/1.73 m<sup>2</sup> avoid use Rivaroxiban 20 mg daily: eGFR 15-60 mL/min/1.73 m<sup>2</sup> reduce dose 15 mg daily eGFR &lt;15 mL/min/1.73 m<sup>2</sup> avoid use</li> </ul>
Miscellaneous	
Lithium	<ul style="list-style-type: none"> <li>• Nephrotoxic and may cause diabetes insipidus with prolonged use</li> <li>• Monitor GFR, electrolytes, and lithium levels every 6 mo or more frequently if the dose increases or the patient is acutely ill</li> <li>• Avoid using NSAIDs</li> <li>• Maintain hydration during acute illness</li> </ul>
Bisphosphonates	<ul style="list-style-type: none"> <li>• Most are not recommended when GFR &lt;30 mL/min/1.73 m<sup>2</sup></li> <li>• Refer to bone specialist if GFR &lt;30 mL/min/1.73 m<sup>2</sup> and no evidence of CKD-MBD (calcium, phosphate, alkaline phosphatase, and intact PTH normal)</li> </ul>
Oral sodium phosphate containing bowel preparations	<ul style="list-style-type: none"> <li>• Can cause AKI</li> <li>• Risk factors are CKD, &gt;60 y of age, female gender, HTN, diabetes, CHF, volume depletion, active colitis, and medications that may predispose to AKI (RAAS blockers, diuretics, lithium and NSAIDs)</li> </ul>
Gabapentin	<ul style="list-style-type: none"> <li>• Altered mental status, myoclonus, and asterixis with severe CKD</li> <li>• GFR 30-59 mL/min/1.73 m<sup>2</sup>: 200-700 mg twice daily</li> <li>• GFR 15-29 mL/min/1.73 m<sup>2</sup>: 200-700 mg daily</li> <li>• GFR &lt;15 mL/min/1.73 m<sup>2</sup>: 300 mg every 2 days</li> <li>• Extended release: GFR 30-59 mL/min/1.73 m<sup>2</sup>: 600-1800 mg daily; GFR &lt;30 mL/min/1.73 m<sup>2</sup>: not recommended</li> </ul>

See reference 35 for details on direct oral anticoagulant comments. This is a partial list. Many other medications require dose adjustment for eGFR. ACE-I ¼ angiotensin-converting enzyme inhibitor; AKI ¼ acute kidney injury; ARB ¼ angiotensin receptor blocker; CHF ¼ congestive heart failure; CKD ¼ chronic kidney disease; CKD-MBD ¼ CKD mineral and bone disorder; eGFR ¼ estimated glomerular filtration rate; HTN ¼ hypertension; NSAIDs ¼ nonsteroidal anti-inflammatory drugs; PTH ¼ parathyroid hormone; RAAS ¼ renin angiotensin aldosterone system. Modified with permission from reference 4

supported by clinical trial results, although the oral formulation has little risk.<sup>40</sup> Other preventive strategies include minimizing the dose of contrast, volume expansion with intravenous isotonic saline or bicarbonate, and consideration of holding medications that increase risk of acute kidney injury or complications (eg, NSAIDs, diuretics, RAAS blockers, metformin).<sup>4,9,40</sup> Most studies suggest hydration with isotonic fluids at a rate of 1 mL/kg/h, ideally started at least 1 hour before the procedure and continued for 3-6 hours afterwards.<sup>40</sup> The kidney function should be measured 48-96 hours after exposure during the peak in the incidence of contrast-induced acute kidney injury.

## TOPIC 4: CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE

### Overview

All people with chronic kidney disease should be considered at increased risk for cardiovascular disease.<sup>1,4,9</sup> In addition to well-known Framingham risk factors for cardiovascular disease, low estimated glomerular filtration rate and albuminuria have been reported to be independently predictive of cardiovascular disease and cardiovascular disease mortality in prospective cohort studies (Figure 1).<sup>4</sup> Other chronic kidney disease-specific risk factors (anemia, mineral and bone

Table 2 Recommendations for Referral to Nephrology Services

- GFR <30 mL/min/1.73 m<sup>2</sup> (GFR categories G4-G5)\*
- A 25% drop in eGFR
- Progression of CKD with a sustained decline in eGFR of more than 5 per year†
- A consistent finding of significant albuminuria‡
- Persistent unexplained hematuria
- Secondary hyperparathyroidism, persistent anion gap acidosis, noneiron deficiency anemia
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
- Persistent abnormalities of serum potassium
- Recurrent or extensive nephrolithiasis
- Hereditary kidney disease or unknown cause of CKD

CKD % chronic kidney disease; eGFR % estimated glomerular filtration rate.

\*If this is a stable isolated finding, formal referral (ie, formal consultation and ongoing care management) may not be necessary, and advice from specialist services may be all that is required to facilitate best care for the patients. This will be healthcare system dependent.

†Progression of CKD is defined as 1 or more of the following: (1) a decline in GFR category accompanied by a 25% drop in eGFR from baseline; and/or (2) rapid progression of CKD, defined as a sustained decline in eGFR of more than 5 mL/min/1.73 m<sup>2</sup>/y.

‡Significant albuminuria is defined as albumin-to-creatinine ratio 2300 mg/g (230 mg/mmol) or albumin excretion rate 2300 mg/24 h, approximately equivalent to protein-to-creatinine ratio 2500 mg/g (250 mg/mmol) or protein excretion rate 2500 mg/24 h.

This table is adapted from reference 4.

disease, and vascular calcification) seem to also play a role in cardiovascular disease in patients with chronic kidney disease.

## Lipid Management: Fire and Forget Strategy in Chronic Kidney Disease

Guidelines for lipid management in adults no longer mandate treating to a low-density lipoprotein cholesterol (LDL-C) target of 70 or 100 mg/dL, because it has not been shown to be beneficial in clinical trials.<sup>41</sup> Randomized controlled trials of fixed-dose statin-based therapies in chronic kidney disease have shown a reduced risk of primary and secondary atherosclerotic events, but no benefit has been demonstrated for all-cause mortality or slower progression of chronic kidney disease.<sup>41,42</sup> Lipid-lowering therapy in persons with chronic kidney disease who are aged 25 years should be based on assessing cardiovascular disease risk instead of an elevated LDL-C level.<sup>41</sup> Among adults with chronic kidney disease aged 18-49 years, treatment with lipid-lowering therapy is indicated for those with known coronary disease (myocardial infarction or coronary revascularization); diabetes mellitus; prior ischemic stroke; or an estimated 10-year risk of coronary death or nonfatal myocardial infarction greater than 10%.<sup>41,43</sup> The currently recommended “fire and forget” strategy involves the following steps: (1) exclude remediable causes of secondary dyslipidemia (eg, nephrotic syndrome, hypothyroidism, and certain drugs); (2) assess for risk factors that

warrant lipid-lowering therapy and initiate when indicated; and (3) do not remeasure LDL-C unless results would alter management.<sup>41</sup> This last step has been particularly controversial. Measuring a lipid profile 6-12 weeks after initiating statins might be useful to ensure that an adequate (230%) decline in LDL-C is observed, and poor adherence or inadequate response should be considered if this goal is not achieved.<sup>41</sup> Many believe that continued periodic monitoring is necessary to assess ongoing adherence and for lipid alterations associated with chronic kidney disease progression.<sup>41</sup>

## Antiplatelet Agents in Chronic Kidney Disease

Adults with chronic kidney disease should be advised to take low-dose aspirin for secondary prevention of cardiovascular disease unless the risk of bleeding outweighs the benefits.<sup>49</sup> Unlike NSAIDs, low-dose aspirin is not associated with acute kidney injury or rapid chronic kidney disease progression.<sup>44</sup>

## TOPIC 5: REFERRAL TO NEPHROLOGISTS

### Overview

Primary care clinicians play a central role in referral to specialists and care coordination for patients with chronic kidney disease. Timely referral to subspecialty care affords sufficient time to plan and prepare patients for kidney replacement therapy, as well as allowing for coordination of interventions to prevent chronic kidney disease progression and management of chronic kidney disease complications. Timely referral has been consistently shown to improve preparation for kidney replacement therapy, lower use of hemodialysis catheters and emergent hemodialysis, and increase use of transplantation and self-care dialysis (peritoneal dialysis and home hemodialysis).<sup>45-48</sup> Studies also suggest that timely referral improves outcomes, including clinical status at kidney replacement initiation; improved management of chronic kidney disease-related comorbidities; and improved survival.<sup>45</sup> In most cases the primary care practitioner should continue to share care with the specialist because they provide complementary services.

### Nephrology Referral Recommendations

Indications for nephrology referral are shown in Table 2.<sup>4</sup> The primary care clinician may choose not to refer many patients with severe albuminuria, especially those who have a clear etiology, such as diabetes. For those categories marked with an asterisk in Figure 1, clinicians may wish to review the need to refer with a nephrology consultant on the basis of availability and the clinical context.

Conservative management without kidney replacement therapy may be appropriate for patients with stage G4 and G5 chronic kidney disease and limited life expectancy or conditions such as advanced dementia, where the burden of dialysis may outweigh its benefits. Conservative management involves medical therapy as well as treating patient symptoms (eg, pruritis, pain) and psychosocial needs



including hospice care and other end-of-life concerns. The nephrologist may be able to assist primary care clinicians to help the patient and their family make individualized decisions that reflect best evidence in addition to their personal values and preferences.

A common challenge for primary care clinicians is exemplified by a patient aged 2<sup>nd</sup> 65 years who has an estimated glomerular filtration rate of 45–60 mL/min/1.73 m<sup>2</sup> but no albuminuria or urinalysis abnormalities. It is controversial whether this patient's kidney function reflects normal aging or chronic kidney disease.<sup>49</sup> These patients should be managed conservatively by avoiding use of RAAS blockers<sup>50</sup> and limiting NSAID and contrast exposures. Last, elderly with laboratory evidence of stage G3a chronic kidney disease should be monitored closely for acute kidney injury after major surgical procedures, particularly cardiac surgery.<sup>51</sup>

## CONCLUSION

Diabetes and hypertension present the dominant risk factors for chronic kidney disease. Testing, risk stratification, and treatment plans differ according to estimated glomerular filtration rate and urinary albumin/creatinine ratio. The major approaches to chronic kidney disease therapy include avoidance of exacerbating drugs, tests and interventions, and expectant treatment of chronic kidney disease to slow progression and reduce complications, including cardiovascular disease. A practical approach to detection and management of chronic kidney disease is provided in [Figure 2](#).

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#### SUPPLEMENTAL DATA

Supplemental appendix accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.amjmed.2015.08.025>.

## APPENDIX A

Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease (CKD) Guideline Statements<sup>1</sup>

## Definition of CKD.

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implication for health. (Not Graded)

## Staging of CKD.

1.2.1: We recommend that CKD is classified based on cause, glomerular filtration rate (GFR) category, and albuminuria category (CGA). (1B)

1.2.2: Assign cause of CKD based on presence or absence of systemic disease and the location within the kidney of observed or presumed pathologic/anatomic findings. (Not Graded)

1.2.3: Assign GFR categories (Figure 1). (Not Graded)

1.2.4: Assign albuminuria\* categories (Figure 1). (Not Graded)

## Predicting Prognosis of CKD.

1.3.1: In predicting risk for outcome of CKD, identify the following variables: 1) cause of CKD; 2) GFR category; 3) albuminuria category; 4) other risk factors and comorbid conditions. (Not Graded)

1.3.2: In people with CKD, use estimated risk of concurrent complications and future outcomes to guide decisions for testing and treatment for CKD complications (Figure 1). (Not Graded)

1.3.3: In populations with CKD, group GFR and albuminuria categories with similar relative risk for CKD outcomes into risk categories (Figure 1). (Not Graded)

## Evaluation of CKD.

## 1.4.1: Evaluation of chronicity

1.4.1.1: In people with GFR <60 mL/min/1.73 m<sup>2</sup> (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (Not Graded)

- If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.
- If duration is not >3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including acute kidney injury [AKI]) or both, and tests should be repeated accordingly.

## 1.4.2: Evaluation of cause

1.4.2.1: Evaluate the clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis to determine the causes of kidney disease. (Not Graded)

## 1.4.3: Evaluation of GFR

1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (1A)

1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (2B)

1.4.3.3: We recommend that clinicians (1B):

- use a GFR estimating equation to derive GFR from serum creatinine (eGFR<sub>creat</sub>) rather than relying on the serum creatinine concentration alone.
- understand clinical settings in which eGFR<sub>creat</sub> is less accurate.

1.4.3.4 : We recommend that clinical laboratories should (1B):

- measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared with isotope-dilution mass spectrometry reference methodology.
- report eGFR<sub>creat</sub> in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFR<sub>creat</sub>.
- report eGFR<sub>creat</sub> in adults using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared with the 2009 CKD-EPI creatinine equation.

When reporting serum creatinine:

- We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (mmol/L) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL).

When reporting eGFR<sub>creat</sub>:

- We recommend that eGFR<sub>creat</sub> should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m<sup>2</sup> in adults using the units mL/min/1.73 m<sup>2</sup>.
- We recommend eGFR<sub>creat</sub> levels less than 60 mL/min/1.73 m<sup>2</sup> should be reported as "decreased."

1.4.3.5: We suggest measuring cystatin C in adults with eGFR<sub>creat</sub> 45-59 mL/min/1.73 m<sup>2</sup> who do not have markers of kidney damage if confirmation of CKD is required. (2C)

- If eGFR<sub>cys</sub>/eGFR<sub>creat-cys</sub> is also <60 mL/min/1.73 m<sup>2</sup>, the diagnosis of CKD is confirmed.
- If eGFR<sub>cys</sub>/eGFR<sub>creat-cys</sub> is ≥60 mL/min/1.73 m<sup>2</sup>, the diagnosis of CKD is not confirmed.

1.4.3.6: If cystatin C is measured, we suggest that health professionals (2C):

- use a GFR estimating equation to derive GFR from serum cystatin C rather than relying on the serum cystatin C concentration alone.

\*Note that where albuminuria measurement is not available, urine reagent strip results can be substituted.

- understand clinical settings in which  $eGFR_{cys}$  and  $eGFR_{creat-cys}$  are less accurate.

1.4.3.7: We recommend that clinical laboratories that measure cystatin C should (*1B*):

- measure serum cystatin C using an assay with calibration traceable to the international standard reference material.
- report  $eGFR$  from serum cystatin C in addition to the serum cystatin C concentration in adults and specify the equation used whenever reporting  $eGFR_{cys}$  and  $eGFR_{creat-cys}$ .
- report  $eGFR_{cys}$  and  $eGFR_{creat-cys}$  in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations, respectively, or alternative cystatin C-based GFR estimating equations if they have been shown to improve accuracy of GFR estimates compared with the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations.

When reporting serum cystatin C:

- We recommend reporting serum cystatin C concentration rounded to the nearest 100th of a whole number when expressed as conventional units (mg/L).

When reporting  $eGFR_{cys}$  and  $eGFR_{creat-cys}$ :

- We recommend that  $eGFR_{cys}$  and  $eGFR_{creat-cys}$  be reported and rounded to the nearest whole number and relative to a body surface area of  $1.73 \text{ m}^2$  in adults using the units  $\text{mL}/\text{min}/1.73 \text{ m}^2$ .
- We recommend  $eGFR_{cys}$  and  $eGFR_{creat-cys}$  levels less than  $60 \text{ mL}/\text{min}/1.73 \text{ m}^2$  should be reported as “decreased.”

1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions. (*2B*)

#### Evaluation of Albuminuria.

1.4.4.1: We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred (*2B*);

- 1) urine albumin-to-creatinine ratio (ACR);
- 2) urine protein-to-creatinine ratio (PCR);
- 3) reagent strip urinalysis for total protein with automated reading;
- 4) reagent strip urinalysis for total protein with manual reading;

1.4.4.2: We recommend that clinical laboratories report ACR and PCR in untimed urine sample in addition to albumin concentration or proteinuria concentrations rather than concentrations alone. (*1B*)

1.4.4.2.1: The term microalbuminuria should no longer be used by laboratories. (*Not Graded*)

1.4.4.3 : Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated (*Not Graded*):

- Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.
- Confirm ACR  $>30 \text{ mg}/\text{g}$  ( $>3 \text{ mg}/\text{mmol}$ ) on a random untimed urine with a subsequent early morning urine sample.
- If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.

1.4.4.4 : If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g.,  $\alpha_1$ -microglobulin, monoclonal heavy or light chains [known in some countries as “Bence Jones” proteins]). (*Not Graded*)

#### Definition and Identification of CKD Progression.

2.1.1: Assess GFR and albuminuria at least annually in people with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/or where measurement will impact therapeutic decisions. (*Not Graded*)

2.1.2: Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression. (*Not Graded*)

2.1.3: Define CKD progression on the basis of one of more of the following (*Not Graded*):

- Decline in GFR category (2<sup>nd</sup>90 [G1], 60-89 [G2], 45-59 [G3a], 30-44 [G3b], 15-29 [G4],  $<15$  [G5]  $\text{mL}/\text{min}/1.73 \text{ m}^2$ ). A certain drop in  $eGFR$  is defined as a drop in GFR category accompanied by a 25% or greater drop in  $eGFR$  from baseline.
- Rapid progression is defined as a sustained decline in  $eGFR$  of more than  $5 \text{ mL}/\text{min}/1.73 \text{ m}^2/\text{y}$ .
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.

2.1.4: In people with CKD progression, as Recommendation 2.1.3, review current management, examine for reversible causes of progression, and consider referral to a specialist. (*Not Graded*)

#### Predictors of Progression.

2.2.1: Identify factors associated with CKD progression to inform prognosis. These include cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated BP, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, ongoing exposure to nephrotoxic agents, and others. (*Not Graded*)

#### Prevention of CKD Progression. *Blood pressure (BP) and renin angiotensin aldosterone system (RAAS) interruption*

3.1.1: Individualize BP targets and agents according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment as described in the KDIGO 2012 Blood Pressure Guideline. (*Not Graded*)

3.1.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. (*Not Graded*)

3.1.3: Tailor BP treatment regimens in elderly patients with CKD by carefully considering age, comorbidities, and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension, and drug side effects. (*Not Graded*)

3.1.4: We recommend that in both diabetic and nondiabetic adults with CKD and urine albumin excretion <30 mg/24 hours (or equivalent) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently S140 mm Hg systolic and S90 mm Hg diastolic. (*1B*)

3.1.5: We suggest that in both diabetic and nondiabetic adults with CKD and with urine albumin excretion of 2"30 mg/24 hours (or equivalent) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently S130 mm Hg systolic and S80 mm Hg diastolic. (*2D*)

3.1.6: We suggest that an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACE-I) be used in diabetic adults with CKD and urine albumin excretion 30-300 mg/24 hours (or equivalent). (*2D*)

3.1.7: We recommend that an ARB or ACE-I be used in both diabetic and nondiabetic adults with CKD and urine albumin excretion >300 mg/24 hours (or equivalent). (*1B*)

3.1.8: There is insufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD. (*Not Graded*)

3.1.9: We recommend that in children with CKD, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. (*1C*)

3.1.10 : We suggest that in children with CKD (particularly those with proteinuria), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. (*2D*)

3.1.11 : We suggest that an ARB or ACE-I be used in children with CKD in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. (*2D*)

#### *CKD and risk of AKI*

3.1.12 : We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

3.1.12.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

#### *Protein intake*

3.1.13 : We suggest lowering protein intake to 0.8 g/kg/d in adults with diabetes (*2C*) or without diabetes (*2B*) and

<30 mL/min/1.73 m<sup>2</sup> (GFR categories G4-G5), with appropriate education.

3.1.14 : We suggest avoiding high protein intake (>1.3 g/ kg/d) in adults with CKD at risk of progression. (*2C*) *Glycemic control*

3.1.15 : We recommend a target hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) of w7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including dia- betic kidney disease. (*1A*)

3.1.16 : We recommend not treating to an HbA<sub>1c</sub> target of <7.0% (<53 mmol/mol) in patients at risk of hypoglycemia. (*1B*)

3.1.17: We suggest that target HbA<sub>1c</sub> be extended above 7.0% (53 mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (*2C*)

3.1.18: In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (*Not Graded*)

#### *Salt intake*

3.1.19: We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated (see rationale). (*1C*)

3.1.19.1: We recommend restriction of sodium intake for children with CKD who have hypertension (systolic and/or diastolic blood pressure >95th percentile) or pre-hypertension (systolic and/or diastolic blood pressure >90th percentile and >95th percentile), following the age-based Recommended Daily Intake. (*1C*)

3.1.19.2: We recommend supplemental free water and sodium supplements for children with CKD and polyuria to avoid chronic intravascular depletion and to promote optimal growth. (*1C*)

#### *Hyperuricemia*

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (*Not Graded*)

#### *Lifestyle*

3.1.21: We recommend that people with CKD be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (body mass index 20-25 kg/m<sup>2</sup>, according to country-specific demographics), and stop smoking. (*1D*)

#### *Additional dietary advice*

3.1.22: We recommend that individuals with CKD receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated. (*1B*)

Complications Associated with Loss of Kidney Function.

#### *Definition and identification of anemia in CKD*

3.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dL (<130 g/L) in males and <12.0 g/dL (<120 g/L) in females. (*Not Graded*)

3.2.2: Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dL (<110 g/L) in children 0.5-5 years, <11.5 g/dL (115 g/L) in children 5-12 years, and <12.0 g/dL (120 g/L) in children 12-15 years. (*Not Graded*)  
*Evaluation of anemia in people with CKD*

3.2.3: To identify anemia in people with CKD measure Hb concentration (*Not Graded*):

- when clinically indicated in people with GFR  $2^{\circ}60$  mL/min/1.73 m<sup>2</sup> (GFR categories G1-G2);
- at least annually in people with GFR  $30^{\circ}59$  mL/min/1.73 m<sup>2</sup> (GFR categories G3a-G3b);
- at least twice per year in people with GFR <30 mL/min/1.73 m<sup>2</sup> (GFR categories G4-G5).

### CKD Metabolic Bone Disease Including Laboratory Abnormalities.

3.3.1: We recommend measuring serum levels of calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase activity at least once in adults with GFR <45 mL/min/1.73 m<sup>2</sup> (GFR categories G3b-G5), to determine baseline values and inform prediction equations if used. (*1C*)

3.3.2: We suggest not to perform bone mineral density testing routinely in those with eGFR <45 mL/min/1.73 m<sup>2</sup> (GFR categories G3b-G5), because information may be misleading or unhelpful. (*2B*)

3.3.3: In people with GFR <45 mL/min/1.73 m<sup>2</sup> (GFR categories G3b-G5), we suggest maintaining serum phosphate concentrations in the normal range according to local laboratory reference values. (*2C*)

3.3.4 : In people with GFR <45 mL/min/1.73 m<sup>2</sup> (GFR categories G3b-G5) the optimal PTH level is not known. We

suggest that people with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. (*2C*)

*Vitamin D supplementation and bisphosphonates in people with CKD*  
3.3.5: We suggest not to routinely prescribe vitamin D supplements or vitamin D analogs, in the absence of suspected or documented deficiency, to suppress elevated PTH concentrations in people with CKD not on dialysis. (*2B*)

3.3.6: We suggest not to prescribe bisphosphonate treatment in people with GFR <30 mL/min/1.73 m<sup>2</sup> (GFR categories G4-G5) without a strong clinical rationale. (*2B*)

### Acidosis.

3.4.1: We suggest that in people with CKD and serum bicarbonate concentrations <22 mmol/L treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (*2B*)

### CKD and Cardiovascular Disease (CVD).

4.1.1: We recommend that all people with CKD be considered at increased risk for CVD. (*1A*)

4.1.2: We recommend that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. (*1A*)

4.1.3: We suggest that adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits. (*2B*)

4.1.4: We suggest that the level of care for heart failure offered to people with CKD should be the same as is offered to those without CKD. (*2A*)

4.1.5: In people with CKD and heart failure, any escalation in therapy and/or clinical deterioration should prompt monitoring of eGFR and serum potassium concentration. (*Not Graded*)

### Caveats When Interpreting Tests for CVD in People with CKD.

#### *Brain natriuretic peptide (BNP)/N-terminal-proBNP (NT-proBNP)*

4.2.1: In people with GFR <60 mL/min/1.73 m<sup>2</sup> (GFR categories G3a-G5), we recommend that serum concentrations of BNP/NT-proBNP be interpreted with caution and in relation to GFR with respect to diagnosis of heart failure and assessment of volume status. (*1B*)

#### *Troponins*

4.2.2: In people with GFR <60 mL/min/1.73 m<sup>2</sup> (GFR categories G3a-G5), we recommend that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome. (*1B*)

#### *Noninvasive testing*

4.2.3: We recommend that people with CKD presenting with chest pain should be investigated for underlying cardiac disease and other disorders according to the same local practice for people without CKD (and subsequent treatment should be initiated similarly). (*1B*)

4.2.4: We suggest that clinicians are familiar with the limitations of noninvasive cardiac tests (eg, exercise electrocardiography [ECG], nuclear imaging, echocardiography, etc) in adults with CKD and interpret the results accordingly. (*2B*)

### CKD and Peripheral Arterial Disease.

4.3.1: We recommend that adults with CKD be regularly examined for signs of peripheral arterial disease and be considered for usual approaches to therapy. (*1B*)

4.3.2: We suggest that adults with CKD and diabetes are offered regular podiatric assessment. (*2A*)

### Medication Management and Patient Safety in CKD.

4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (*1A*)

4.4.2: Where precision is required for dosing (due to narrow therapeutic or toxic range) and/or estimates may be unreliable (eg, owing to low muscle mass), we recommend methods based upon cystatin C or direct measurement of GFR. (*1C*)

4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 mL/min/1.73 m<sup>2</sup> (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk

of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, nonsteroidal anti-inflammatory drugs, metformin, lithium, and digoxin. (IC)

4.4.4: We recommend that adults with CKD seek medical or pharmacist advice before using over-the-counter medicines or nutritional protein supplements. (IB)

4.4.5: We recommend not using herbal remedies in people with CKD. (IB)

4.4.6: We recommend that metformin be continued in people with GFR  $2^{\circ}45$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G1-G3a); its use should be reviewed in those with GFR 30-44 mL/min/ $1.73$  m<sup>2</sup> (GFR category G3b); and it should be discontinued in people with GFR  $<30$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G4-G5). (IC)

4.4.7: We recommend that all people taking potentially nephrotoxic agents such as lithium and calcineurin inhibitors should have their GFR, electrolytes, and drug levels regularly monitored. (IA)

4.4.8: People with CKD should not be denied therapies for other conditions such as cancer, but there should be appropriate dose adjustment of cytotoxic drugs according to knowledge of GFR. (Not Graded)

#### Imaging Studies.

4.5.1: Balance the risk of acute impairment in kidney function due to contrast agent use against the diagnostic value and therapeutic implications of the investigation. (Not Graded)

##### Radiocontrast

4.5.2: We recommend that all people with GFR  $<60$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G3a-G5) undergoing elective investigation involving the intravascular administration of iodinated radio contrast media should be managed according to the KDIGO Clinical Practice Guideline for AKI, including:

- avoidance of high osmolar agents (IB);
- use of lowest possible radio contrast dose (Not Graded);
- withdrawal of potentially nephrotoxic agents before and after the procedure (IC);
- adequate hydration with saline before, during, and after the procedure (IA);
- measurement of GFR 48-96 hours after the procedure (IC).

##### Gadolinium-based contrast media

4.5.3 : We recommend not using gadolinium-containing contrast media in people with GFR  $<15$  mL/min/ $1.73$  m<sup>2</sup> (GFR category G5) unless there is no alternative appropriate test. (IB)

4.5.4: We suggest that people with a GFR  $<30$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G4-G5) who require gadolinium containing contrast media are preferentially offered a macrocyclic chelate preparation. (2B)

##### Bowel preparation

4.5.5: We recommend not to use oral phosphate-containing bowel preparations in people with a GFR  $<60$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G3a-G5) or in those known to be at risk of phosphate nephropathy. (IA)

CKD and Risks for Infections, AKI, Hospitalizations, and Mortality.

##### CKD and risk of infections

4.6.1: We recommend that all adults with CKD are offered annual vaccination with influenza vaccine, unless contraindicated. (IB)

4.6.2: We recommend that all adults with eGFR  $<30$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G4-G5) and those at high risk of pneumococcal infection (eg, nephrotic syndrome, diabetes, or those receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated. (IB)

4.6.3: We recommend that all adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years. (IB)

4.6.4: We recommend that all adults who are at high risk of progression of CKD and have GFR  $<30$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G4-G5) be immunized against hepatitis B and the response confirmed by appropriate serological testing. (IB)

4.6.5: Consideration of live vaccine should include an appreciation of the patient's immune status and should be in line with recommendations from official or governmental bodies. (Not Graded)

4.6.6: Pediatric immunization schedules should be followed according to official international and regional recommendations for children with CKD. (Not Graded)

##### CKD and risk of AKI

4.6.7: We recommend that all people with CKD are considered to be at increased risk of AKI. (IA)

4.6.7.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (Not Graded)

##### CKD and risk of hospitalization and mortality

4.6.8: CKD disease management programs should be developed to optimize the community management of people with CKD and reduce the risk of hospital admission. (Not Graded)

4.6.9: Interventions to reduce hospitalization and mortality for people with CKD should pay close attention to the management of associated comorbid conditions and cardiovascular disease in particular. (Not Graded)

#### Referral to Specialist Services.

5.1.1: We recommend referral to specialist kidney care services for people with CKD in the following circumstances (IB):

- AKI or abrupt sustained fall in GFR;
- GFR  $<30$  mL/min/ $1.73$  m<sup>2</sup> (GFR categories G4-G5)\*;

\*If this is a stable isolated finding, formal referral (ie, formal consultation and ongoing care management) may not be necessary, and advice from specialist services may be all that is required to facilitate best care for the patients. This will be health-care system dependent.

- a consistent finding of significant albuminuria (ACR  $\geq 300$  mg/g [ $\geq 30$  mg/mmol] or albumin excretion rate  $\geq 300$  mg/24 hours, approximately equivalent to protein/creatinine ratio  $\geq 500$  mg/g [ $\geq 50$  mg/mmol] or protein excretion rate  $\geq 500$  mg/24 hours);
- progression of CKD (see Recommendation 2.1.3 for definition);
- urinary red cell casts, red blood cells  $> 20$  per high-power field sustained and not readily explained;
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents;
- persistent abnormalities of serum potassium;
- recurrent or extensive nephrolithiasis;
- hereditary kidney disease.

5.1.2 : We recommend timely referral for planning renal replacement therapy (RRT) in people with progressive CKD in whom the risk of kidney failure within 1 year is 10-20% or higher,<sup>†</sup> as determined by validated risk prediction tools. (*1B*)

#### Care of the Patient with Progressive CKD.

5.2.1: We suggest that people with progressive CKD should be managed in a multidisciplinary care setting. (*2B*)

5.2.2: The multidisciplinary team should include or have access to dietary counseling, education and counseling about different RRT modalities, transplant options, vascular access surgery, and ethical, psychological, and social care. (*Not Graded*)

#### Timing the Initiation of RRT.

5.3.1 : We suggest that dialysis be initiated when 1 or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to

dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 mL/min/1.73 m<sup>2</sup>. (*2B*)

5.3.2: Living donor pre-emptive renal transplantation in adults should be considered when the GFR is  $< 20$  mL/min/1.73 m<sup>2</sup> and there is evidence of progressive and irreversible CKD over the preceding 6-12 months. (*Not Graded*)

#### Structure and Process of Comprehensive Conservative Management.

5.4.1: Conservative management should be an option in people who choose not to pursue RRT and this should be supported by a comprehensive management program. (*Not Graded*)

5.4.2: All CKD programs and care providers should be able to deliver advance care planning for people with a recognized need for end-of-life care, including those people undergoing conservative kidney care. (*Not Graded*)

5.4.3: Coordinated end-of-life care should be available to people and families through either primary care or specialist care as local circumstances dictate. (*Not Graded*)

5.4.4: The comprehensive conservative management program should include protocols for symptom and pain management, psychological care, spiritual care, and culturally sensitive care for the dying patient and their family (whether at home, in a hospice or a hospital setting), followed by the provision of culturally appropriate bereavement support. (*Not Graded*)

#### Reference

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3: 1-150.

<sup>†</sup>The aim is to avoid late referral, defined here as referral to specialist services less than 1 year before start of RRT.



## APPENDIX B

### Acknowledgment

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