COURSE #48762 — 5 CREDIT HOURS RELEASE DATE: 10/01/20 EXPIRATION DATE: 09/30/23

Diagnosis and Management of Chronic Kidney Disease in Primary Care

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Faculty

John J. Whyte, MD, MPH, is currently the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research. Previously, Dr. Whyte served as the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. In this role, Dr. Whyte developed, designed, and delivered educational programming that appeals to both a medical and lay audience.

Prior to this, Dr. Whyte was in the Immediate Office of the Director at the Agency for Healthcare Research Quality. He served as Medical Advisor/Director of the Council on Private Sector Initiatives to Improve the Safety, Security, and Quality of Healthcare. Prior to this assignment, Dr. Whyte was the Acting Director, Division of Medical Items and Devices in the Coverage and Analysis Group in the Centers for Medicare & Medicaid Services (CMS). CMS is the federal agency responsible for administering the Medicare and Medicaid programs. In his role at CMS, Dr.Whyte made recommendations as to whether or not the Medicare program should pay for certain procedures, equipment, or services. His division was responsible for durable medical equipment, orthotics/prosthetics, drugs/biologics/therapeutics, medical items, laboratory tests, and non-implantable devices. As Division Director as well as Medical Officer/Senior Advisor, Dr. Whyte was responsible for more national coverage decisions than any other CMS staff.

Dr. Whyte is a board-certified internist. He completed an internal medicine residency at Duke University Medical Center as well as earned a Master's of Public Health (MPH) in Health Policy and Management at Harvard University School of Public Health. Prior to arriving in Washington, Dr. Whyte was a health services research fellow at Stanford and attending physician in the Department of Medicine. He has written extensively in the medical and lay press on health policy issues.

Usker Naqvi, MD, is a resident in Physical Medicine and Rehabilitation at the University of Miami Leonard M. Miller School of Medicine/Jackson Memorial Hospital. A native of New Jersey, Dr. Naqvi spent time studying exercise physiology and nutrition prior to entering the medical profession and looks forward to integrating these into his practice. His clinical interests include sports medicine, pain management, and lifestyle interventions to improve health and physical functioning.

Faculty Disclosure

Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Usker Naqvi, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all primary care physicians and physician assistants involved in the care of patients with kidney disease.

A complete Works Cited list begins on page 19.

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Accreditations & Approvals

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Course Objective

The purpose of this course is to provide physicians and physician assistants with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with chronic kidney disease.

Learning Objectives

Upon completion of this course, you should be able to:

1. Review the epidemiology of chronic kidney disease (CKD) and its impact on different patient populations.
2. Explain diagnostic criteria and current screening guidelines for CKD.
3. Analyze the pathophysiology of CKD, including a discussion of morbidity and mortality.
4. Evaluate the various therapeutic options for CKD.
5. Outline the role of monitoring in the treatment of CKD.
6. Describe criteria for referring patients with CKD to a nephrology subspecialist.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Chronic kidney disease (CKD) is an increasingly common condition that has the potential to become a public health threat. CKD is defined as kidney damage or a decrease in kidney function for at least three months [1]. While it was once prevalent in 12.3% of the population, it is now seen in 14.8% [2]. In 2016, Medicare costs for the care of patients with CKD accounted for 23% of total expenditures [2]. Significant comorbidities include diabetes, hypertension, and cardiovascular disease (CVD). Caring for these patients and their comorbidities can be complex, especially with efforts concentrated toward preventing progression of CKD to end-stage renal disease (ESRD). Primary care physicians are often at the forefront of this care, whether as the physician initially diagnosing and managing the CKD or as the coordinator of specialist efforts. Guidelines for the management of patients with CKD are constantly evolving, and new data are frequently being published. The purpose of this course is to present current data on the diagnosis and management of CKD in the primary care setting.

EPIDEMIOLOGY AND HEALTHCARE DISPARITIES

The overall prevalence of CKD in the United States adult general population was 14.8% in 2013–2016, with CKD stage 3 (6.4%) being the most prevalent. Overall, CKD prevalence has remained relatively stable during the last two decades [2]. Point prevalence of CKD increases with age, from 10.1% at 65 to 74 years of age to 22.6% at 85 years of age and older. Men have a slightly higher prevalence than women [2]. Medicare data also show that more than 1.1 million patients with diabetes also have CKD; this is more than the number of CKD patients with congestive heart failure (CHF) or both diabetes and CHF [2]. The greatest number of patients with CKD overall have stage 3 disease, followed by unknown or unspecified staging [2].

The prevalence of CKD in African Americans (18.7%) was higher than that among white Americans (13.5%) [2]. Regarding comorbidities, 15% of NHANES participants with CKD also had diagnosed hypertension and 23% had diagnosed diabetes [2].

The average Medicare cost per patient with CKD per year exceeded $16,000 in 2016 [2]. Those who had diabetes and CHF concurrent with CKD reached a cost of $39,506 per patient [2]. Comparatively, the average cost to care for a Medicare patient without diabetes, CHF, or CKD is $8,620 per year [2]. The economic burden to society is significant.

There are socioeconomic differences in the prevalence of CKD. In the United States, whites in the lowest income quartile have an 86% increased odds of having CKD compared to the highest income quartile [3]. Additionally, odds are increased by two times among unemployed African Americans and six times among unemployed Mexican Americans compared to their employed counterparts [4]. When controlling for race, high socioeconomic status still shows an inverse association with CKD, as demonstrated by a 2010 study involving only African American participants [5].

Homeless adults with CKD tend to be younger, disproportionately male, and suffer from higher rates of depression and substance abuse than non-homeless patients [6]. Homeless adults also experience significantly higher risk of ESRD and death and are more likely to use acute care services than non-homeless patients [7].

Geographic differences may also present emerging risk factors for CKD. It is hypothesized that ambient temperature can increase the risk of CKD by predisposing patients to kidney stones [8]. Living in a poorly built environment, such as one with exposure to pollution and low walkability, may emerge as a risk factor for CKD given its association with other risk factors, like obesity, diabetes, and hypertension [9]. A greater number of moves to various residences in a patient's lifetime is also associated with lower prevalence of albuminuria and reduced kidney function, though the mechanisms for these differences are unknown [9].

Regarding racial differences, a large cohort study showed that Hispanic patients with CKD had twice the prevalence of low income and low educational attainment compared to white patients [10]. They also had significantly higher rates of self-reported diabetes and hypertension than black or white patients. Mean glomerular filtration rate (GFR) at the time of the study was lower in Hispanic patients than blacks or whites, while median proteinuria was higher [11]. This study found Hispanic patients to have disproportionately lower socioeconomic status, less angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACE-I/ARB) use, poorer blood pressure control, and more severe CKD complications than non-Hispanics [11].

Poor CKD outcomes in Hispanics may be attributable to a number of factors. Low levels of education and health literacy and limited access to health care are common culprits in ethnic disparities in care, and these can apply to other ethnic minorities as well [12]. Furthermore, Hispanic patients may have difficulty understanding physician instructions regarding lifestyle modifications, medications, and many other aspects of care depending on their fluency in English or access to a healthcare provider who is fluent in Spanish [13]. Additionally, unique cultural characteristics, such as adherence to a traditional Hispanic diet that is high in potassium and phosphorus, may not be targeted by physicians as areas for directed patient education or may not be things that patients are willing to change [13].

African American race also carries associations with CKD status. In particular, there is an association between African American race and faster disease progression; African Americans experience 3.2 greater odds of a significant decline in GFR per year compared to whites [14; 15; 16]. The prevalence of advanced CKD is also higher in African American patients [16; 17]. As mentioned, the odds of prevalent CKD are significantly lower in high-income African American patients compared to low-income patients [18]. Many of the typical precipitating factors are suspected to be the sources of these disparities, including unemployment, low level of education, limited access to healthy foods, and poor access to healthcare services [16].

All-cause hospitalization rates for Medicare patients with CKD are higher than for those without CKD [19]. This rate also increases with later stages of disease, as patients with stage 4 or 5 CKD have a 54% all-cause hospitalization rate compared to patients with stage 1 or 2 disease. Cardiovascular admissions are 64% higher in patients with stage 4 or 5 CKD compared to stage 1 or 2. In addition, 23.7% of patients with CKD were rehospitalized within 30 days of discharge in 2012; all-cause rehospitalization occurred at a slightly higher rate (25%) in stage 4 and 5 patients compared to stage 1 or 2 (23%) [19]. Rehospitalization in patients with CKD is also higher in African Americans than whites, though African Americans and whites have similar rates of mortality [19]. The unadjusted mortality rate for patients with CKD who are 66 years of age and older has declined 30% since 2004 [2]. Among Medicare patients, the adjusted mortality per 1,000 patient years at risk is 123 for all patients with CKD, greater in those with more advanced disease [2]. When adjusted for comorbid conditions, mortality was 47 per 1,000 patient years among all patients with CKD compared to 138 per 1,000 patient years in those with concurrent diabetes and cardiovascular disease. Mortality is higher in men than women. Among those with later stage CKD, mortality is 3% higher in African Americans than whites [2].

DIAGNOSIS AND STAGING

As noted, CKD is defined by the presence of renal damage or decreased function that persists longer than three months, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [20]. The diagnosis may be made by the use of blood or urine laboratory markers of kidney damage or abnormal renal function, by the demonstration of structural damage on imaging studies, or by pathologic change on renal biopsy. This includes:

- Abnormalities of urinary sediment: Red blood cell casts (glomerular injury), white cell casts (interstitial/tubular injury)
- Abnormal rate of albumin excretion (albuminuria) and/or reduced GFR
- Radiographic imaging abnormalities: Change in size or contour of the kidneys, hydronephrosis, polycystic disease, papillary necrosis
- Pathologic abnormalities on renal biopsy: Vascular disease, glomerulitis, tubulointerstitial damage

The simplest, most reliable, and recommended method to detect renal damage is by testing for albuminuria. Excessive albumin excretion is a reflection of primary kidney disease or renal involvement by a systemic vascular disorder such as follows long-standing hypertension, diabetes, and atherosclerosis. In select patients, screening could be initiated by urinalysis dipstick testing for proteinuria, which if positive would need to be confirmed by some measure of the albumin excretion rate. In adults at risk for CKD, urinary albumin dipstick testing and the measurement of the urinary albumin-to-creatinine ratio should be used [1]. The guidelines provided by the international Kidney Disease: Improving Global Outcomes (KDIGO) group recommend that an albumin-to-creatinine ratio >30 mg/g be used as the standard for establishing the diagnosis of CKD [20].

MODIFICATION OF DIET IN RENAL DISEASE (MDRD) EQUATION
GFR (mL/min/1.73 m^2) = 175 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)
Source: [20] *Table 1*

CKD-EPI EQUATION FOR ESTIMATING GFR
$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]
where: Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr /κ or 1, and max indicates the maximum of Scr /κ or 1.
Source: [20; 21] *Table 2*

Another way to diagnose CKD, and the preferred method for detecting and monitoring abnormal kidney function, is the measure or estimation of GFR [20]. A determination of GFR should be made in all patients with renal disease or signs of impaired renal function. The GFR indicates the degree of renal functional impairment, is a useful guide to dosage adjustment of drugs cleared by the kidney, and can be used to follow the course of kidney disease and to assess the response to therapy.

A GFR less than 60 mL/min/1.73 m^2 is diagnostic of CKD. Various prediction equations are available to determine GFR; however, the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) study equations are recommended by KDOQI, with the MDRD equation being preferred to Cockcroft-Gault (***Table 1***) [20]. More recently, the National Kidney Foundation has shown support for use of the CKD Epidemiology Collaboration (CKD-EPI) equation as the best and least expensive estimator of GFR and an improvement over the MDRD equation (***Table 2***) [21; 22]. Both the MDRD and CKD-EPI equations account for age and gender and provide corrective factors for African American race. How-

ever, the CKD-EPI equation has been shown to be more accurate and precise than the MDRD equation, especially at higher GFR levels, and results in fewer false-positive diagnoses [21; 23]. The KDIGO guidelines recommend the CKD-EPI equation as well, citing that it is less biased, more accurate, and more precise than the MDRD equation; this equation can use creatinine or cystatin C to estimate GFR [20].

Serum creatinine alone, while adequate for assessment of acute kidney injury, should not be used to assess kidney function in CKD [20]. An estimated 83% of laboratories report an estimated GFR along with reporting serum creatinine results [24].

As noted, threshold abnormalities of albumin excretion and GFR are diagnostic of CKD only when demonstrated to have been present for longer than three months, thereby excluding the patient who may be in the recovery phase of an acute, reversible kidney injury. The presence of chronicity can be confirmed by follow-up testing or inferred from known structural abnormalities on renal imaging or by review of past records that permit estimation of GFR at an earlier date.

Although the presence of CKD can be established on the basis of albuminuria and reduced GFR, proper diagnosis also includes identifying the underlying cause, as this may have important therapeutic and other management implications. A host of etiologies can be responsible for renal damage and diminished function, including hypertension, diabetes, autoimmune diseases, glomerulonephritis, drug-induced nephritis, and lower urinary tract obstructive disorders [20]. Consultation with a nephrologist is appropriate in most cases to determine the underlying cause of CKD [20].

KDOQI STAGING OF CHRONIC KIDNEY DISEASE

Stage	Description
1	Kidney damage with normal or elevated GFR (≥90 mL/min/1.73 m²)
2	Kidney damage with mild decrease in GFR (60–89 mL/min/1.73 m²)
3	Moderate decrease in GFR (30–59 mL/min/1.73 m²)
4	Severe decrease in GFR (15–29 mL/min/1.73 m²)
5	Kidney failure (<15 mL/min/1.73 m² or requires dialysis)

Source: [20] *Table 3*

STAGING

CKD is staged according to the severity of disease, as determined by the degree of reduced GFR and albuminuria, in combination with the specific cause of the kidney disease. In KDOQI staging, there are five stages of increasing severity as determined by GFR, with the fifth stage representing complete renal failure (***Table 3***) [1]. The KDIGO staging has separate classifications depending on whether the staging is by GFR or by degree of albuminuria, measured as either albumin-to-creatinine ratio or albumin excretion rate. If GFR is used to stage these patients, then the stages are annotated as G1–G5, corresponding to decreasing GFR and worsening severity [20]. If by albuminuria, the stages are A1–A3, corresponding to increasing albumin-to-creatinine ratio or albumin excretion rate (AER) and worsening severity [20]:

- Stage A1: Normal to mildly increased (AER <30 mg/day)
- Stage A2: Moderately increased (AER 30–300 mg/day)
- Stage A3: Severely increased (AER >300 mg/day)

Stage A3 may be further subdivided into nephrotic and non-nephrotic range, for purposes of differential diagnosis and management. The KDIGO guidelines also recommend taking the cause of CKD into account when staging patients [20].

The advantages of staging are many: to establish a baseline from which to monitor the rate of progression; to aid clinicians in patient management, for example guiding therapeutic decisions in relation to comorbidities such as hypertension and heart disease; and to assess risk for disease progression and complications, such as cardiovascular events and ESRD requiring hemodialysis. Later stages of disease are most closely associated with complications and risk of comorbidities [1; 20].

SYMPTOMS

In the early stages of CKD, patients are asymptomatic. With moderately severe loss of renal function (late stage 3 to early stage 4), symptoms and signs are variable and often attributable to comorbidities (e.g., poorly controlled hypertension) and to problems of volume overload, metabolic acidosis, and hyperkalemia. At advanced stage disease (late stage 4 approaching ESRD), the syndrome of uremia supervenes; patients develop gradual weakness, lethargy, anorexia, periodic vomiting, and in time show signs of pericarditis, peripheral neuropathy, or encephalopathy.

SCREENING

As of 2020, the U.S. Preventive Services Task Force (USPSTF) does not recommend regular screening for CKD in the general population [25]. Instead, the USPSTF concludes that the evidence is insufficient to assess the balance of benefits and harms of routine screening for chronic kidney disease in asymptomatic adults.

The KDOQI guidelines recommend considering risk factors for CKD at routine health examinations when deciding whether to evaluate patients for CKD; however, it does not have strict screening guidelines in place, such as at what age to initiate testing and how often [20]. The KDOQI recognizes the following as risk factors that may indicate a need to screen for kidney disease [20]:

- Diabetes
- Hypertension
- Autoimmune diseases
- Family history of CKD
- Age 60 years or older
- Daily nonsteroidal anti-inflammatory drug (NSAID) and nephrotoxic drug use
- African American or Hispanic race

In 2013, the American College of Physicians released practice guidelines for CKD that recommend against screening asymptomatic patients without risk factors, owing to insufficient evidence that there is a benefit in screening these patients [26]. This group recommends against testing for proteinuria in adults with or without diabetes who are currently taking an ACE-I or an ARB.

PATHOPHYSIOLOGY

The pathophysiology of CKD is dependent on the underlying cause, the most common of which are the disease processes of diabetes and hypertension. Diabetic nephropathy has various proposed hypotheses for mechanisms of kidney damage, though it is most often and broadly attributed to hyperglycemic end-organ damage to the glomerulus, eventually to the point of proteinuria. Experts have suggested that there may be disadvantaged nephron development in those born to mothers with diabetes, predisposing the offspring to CKD during their lives. Some also posit that hyperglycemia sensitizes end-organs to hypertensive damage, and because diabetes and hypertension often occur together, this has an additive deleterious effect on the kidney [4]. The initial manifestation is often albuminuria and hyperfiltration (i.e., an elevation in GFR) [18]. Over time, albuminuria increases to the point of overt nephropathy, accompanied by a decline in GFR. Hyperglycemia-mediated overactivation of protein kinase C is also thought to be involved in progressive renal parenchymal damage, resulting in the loss of selective permeability in the glomerulus and an increase in local inflammation [27]. In addition to glomerular damage, thickening of the basement membrane and afferent and efferent arterioles may be noted [27].

Hypertensive nephropathy is another common cause of CKD and induces renal damage through a variety of mechanisms. One mechanism is sympathetic nervous overactivity resulting in constriction of efferent arterioles and decreased outflow from the glomerulus, allowing for increased oncotic pressure in the nephron. Activation of the renin-angiotensin-aldosterone system (RAAS) may also occur as a response to sympathetic nerve activity. Arterial stiffness, a central component of hypertension, is a contributing mechanism as well. Impaired salt and water excretion from sympathetic nervous overactivity or from RAAS activation serves to increase hypertension and thereby increase renal damage.

Other underlying causes of the renal damage leading to CKD are generally associated with unique mechanisms, including immune complex deposition and interstitial damage from prolonged use of nephrotoxic drugs. Acute kidney injury (AKI) may also lead to CKD if the initial insult has not been removed or if the initial injury has not been completely reversed. Even in cases of full recovery after AKI, the risk of developing CKD is increased [7]. Renal ischemia-reperfusion injury may also cause lasting damage [9].

Many of the complications and comorbidities associated with CKD stem from this initial damage and begin to manifest as renal damage progresses. Hypertension, a common comorbidity of CKD, can cause renal damage as well as be exacerbated by it, as discussed. Anemia is a common complication of CKD and is likely due to reduced renal production of erythropoietin, though other factors, such as uremia-induced inhibition of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis, also play a role [11]. A study of patients with stage 3 CKD determined that renal anemia is associated with rapid progression to stage 4 and a higher risk of CVD and hospitalization [13].

Alterations in bone and mineral metabolism are commonly seen in patients with CKD, starting in early-stage disease. Hypocalcemia is common in these patients, often leading to parathyroid hyperplasia and secondary hyperparathyroidism [16]. The hypocalcemia is likely attributable to phosphate retention, skeletal resistance to parathyroid hormone (PTH), altered vitamin D metabolism, or a combination of these factors [28]. In line with altered vitamin D metabolism, patients with CKD also have defective intestinal calcium absorption. Hyperphosphatemia is also common, and the resultant elevation in the plasma calcium-phosphate product often leads to precipitation of calcium phosphate in soft tissues and to calcific changes in the walls of arterioles and small arteries [28]. These electrolyte derangements are largely attributable to intrarenal damage and hormonal abnormalities, both of which affect electrolyte excretion and reabsorption. Activation of fibroblast growth factor 23 (FGF-23) and PTH is implicated in the regulation of phosphate reabsorption in the tubules. FGF-23 also inhibits vitamin D production and promotes catabolism of vitamin D stores [29].

MANAGEMENT

The management of CKD is multifaceted, involving a series of tactical measures (including the effective management of comorbidities) designed to reduce the risk of further damage and slow the progression of kidney disease. The clinician should first seek to identify and treat reversible causes, such as lower urinary tract obstruction, which should be considered in any patient with unexplained deterioration in renal function. Optimal glucose control in the patient with diabetes and blood pressure control in those with hypertension, as well as initiation of ACE-I or ARB therapy, are important to limit progression [1; 20]. Certain nephrotoxic agents should be avoided if at all possible, especially in the patient with diabetes or receiving loop diuretics. These include NSAIDs, aminoglycoside antibiotics, and radiographic contrast material. Additional measures to protect the kidney and slow progression include smoking cessation, statin therapy to control hyperlipidemia, dietary protein restriction, and satisfactory treatment of metabolic acidosis.

For cases of CKD that do progress to late-stage kidney disease, it is also important to anticipate and prepare patients for renal replacement therapy [20]. The KDOQI guidelines recommend timely referral for planning renal replacement therapy in people with progressive CKD in whom the risk of kidney failure within one year is 10% to 20% or higher [20]. Patients with a GFR less than 30 mL/min/1.73 m^2 should be referred to a nephrologist to make preparations for impending end-stage disease and renal replacement therapy [20]. It is well to keep in mind, however, that acute, intercurrent declines in GFR are often due to reversible factors such as volume depletion, radiographic contrast or nephrotoxic drug use, and urinary tract obstruction; efforts should be made to correct these in order to appropriately address declines in GFR and determine whether true progression of the disease has occurred [20].

An intensive and multifactorial management approach is required for patients with renal disease in order to address all risk determinants. The mainstays of treatment are management of complications and/or comorbidities, lifestyle modification, and dialysis for patients with severe or late-stage disease. Some patients may be candidates for kidney transplant, although the wait for a non-related donor can be long. Psychosocial issues and patient education (primarily to ensure compliance with the established treatment plan) are important as well.

MANAGEMENT OF COMORBIDITIES

Diabetes

As described, diabetes is a common comorbidity in patients with CKD and, in some cases, can be responsible for the renal damage leading to the diagnosis of CKD. Numerous studies have shown that intensive glycemic control reduces albuminuria in patients with diabetes [27; 30; 31]. Hemoglobin A1c (HbA1c) should be kept to a target of 7% to prevent or delay microvascular complications, including diabetic kidney disease, except in those who are at risk for hypoglycemia with intensive glucose control [20; 32].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The KDOQI Work Group recommends a target hemoglobin A1c of approximately 7% to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease.

(https://www.kidney.org/sites/default/files/docs/diabetes-ckd-update-2012.pdf. Last accessed September 14, 2020.)

Level of Evidence: 1A (Most patients should receive the recommended course of action based on high quality evidence.)

Though they are known for their renoprotective benefits in patients with diabetes, ACE-Is and ARBs should not be used for primary prevention of diabetic kidney disease in normotensive and normoalbuminuric patients, as there has been little evidence of benefits. However, these drugs should be used in normotensive diabetic patients with albuminuria ≥30 mg/g who are at high risk for progression to diabetic kidney disease [33]. Data from the NEPHRON-D study show that combination therapy of ACE-I and ARB together should be avoided in patients with diabetic nephropathy due to high risk of adverse outcomes [34]. The addition of aliskiren, a direct renin inhibitor, to either ACE-I or ARB therapy in patients with diabetes and CKD does not improve outcomes and may actually increase adverse events; thus, it should be avoided [35].

Due to decreased renal function, some antihyperglycemic medications are not adequately cleared and should be dosed appropriately to prevent hypoglycemia. First-generation sulfonylureas should be avoided altogether in the patient with CKD; glipizide, a second-generation sulfonylurea, is preferred and does not require dosage adjustment [33]. Adjustment of insulin dosage is not required for the usual patient, but may become necessary toward the advent of ESRD. Metformin, a commonly used antihyperglycemic that can reportedly cause lactic acidosis when levels accumulate, was previously contraindicated in patients with serum creatinine ≥1.4 mg/dL [33]. However, in 2016, the U.S. Food and Drug Administration (FDA) expanded its labeling for metformin products to include patients with an estimated GFR of 45 mL/min/1.73 m^2 [36].

In 2021, the FDA expanded approval of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin to reduce the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression [89]. Though this agent is typically used to treat type 2 diabetes, benefits were consistently demonstrated regardless of the presence diabetes.

Dyslipidemia

Because dyslipidemia is common in people with diabetes and CKD, reducing low-density lipoprotein cholesterol (LDL-C) with statins is essential for reducing the risk of major atherosclerotic events [20]. There is, however, no evidence that treatment of dyslipidemia improves kidney disease outcomes, progression to ESRD, or all-cause mortality [33]. Statins should not be started in patients on dialysis.

EVIDENCE-BASED PRACTICE RECOMMENDATION

In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), the KDOQI Work Group recommends evaluation with a lipid profile (i.e., total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides).

(https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2013-Lipids-Guideline-English.pdf. Last accessed September 14, 2020.)

Level of Evidence: IC (Most patients should receive the recommended course of action based on low quality evidence.)

Hypertension

Hypertension is both a cause and complication of CKD [37]. Approximately 50% to 75% of patients with CKD also have hypertension, and poorly controlled hypertension is associated with increased mortality, cardiovascular risk, and disease progression [1; 38]. Data show that blood pressure control is often suboptimal in patients with hypertension and stage 3 CKD, especially in those at the highest risk of adverse outcomes due to diabetes or albuminuria [39]. Furthermore, the prevalence of treatment-resistant hypertension is high in patients with CKD, ranging from 12.1% to 48.3% depending on stage [40]. Treatment-resistant hypertension in patients with CKD is associated with black race, male gender, larger waist circumference, diabetes, lower GFR, and higher albumin-to-creatinine ratio.

Regarding the evaluation of the patient with hypertension and CKD, guidelines recommend that blood pressure be checked at every health encounter [37]. Clinicians should take into account the patient's CKD stage, CVD risk factors, comorbid conditions, adherence and barriers to lifestyle modification and drug therapy, and complications of antihypertensive therapy. Appropriate steps should be taken to determine the cause of hypertension, and if there is suspicion for renal artery disease as the cause, noninvasive imaging and referral to a nephrologist are recommended [37]. The goals of antihypertensive therapy should be to lower blood pressure, reduce the risk of CVD, and slow the progression of kidney disease. An appropriate blood pressure goal is <130/80 mm Hg, though KDIGO recommends that those who have a urine albumin excretion <30 mg/day and whose office blood pressure is consistently >140/90 mm Hg should be treated to ≤140/90 mm Hg [20; 37].

Certain antihypertensive medications are preferred and should be used when appropriate. ACE-Is and ARBs are preferred in patients with proteinuria and otherwise can be used safely in patients with hypertension and CKD at moderate-to-high doses [37]. Most patients should also be treated with diuretics. Thiazide diuretics are recommended for patients with stage 1 through 3 disease, while loop diuretics are recommended for patients with stage 4 or 5 disease [37]. Potassium-sparing diuretics should be used cautiously in patients who are concurrently on ACE-I or ARB therapy due to the risk for hyperkalemia [37]. Dietary sodium should be reduced to less than 2.4 grams per day, or less than 2 grams according to KDIGO guidelines [20; 37].

All patients should be considered on an individual basis and have a treatment plan suited to their health status, disease severity, and comorbidities. Patient education is important in ensuring appropriate self-management and adherence [37].

Evidence shows that a low-sodium diet, well known as an intervention for hypertension, is beneficial for reducing proteinuria in patients with CKD. In one study, sodium restriction plus ACE-I was shown to be superior to ACE-I plus ARB for reduction of proteinuria and blood pressure [41].

Data from a large cohort study show that only 46.1% of patients with CKD and hypertension were controlled to a blood pressure <130/80 mm Hg [42]. In addition, 32% of these patients required four or more antihypertensive medications, thus highlighting the difficulty of controlling blood pressure in this patient population.

In its 2013 guidelines, the American College of Physicians (ACP) also recommends the use of either an ACE-I or ARB in patients with hypertension and CKD [26]. They state that these medications reduce the risk of progression to ESRD, the risk of doubling serum creatinine, and the progression from microalbuminuria to macroalbuminuria [26]. While these medications are effective, they should be avoided in combination with each other or with aliskiren when used in patients with diabetes [43; 44; 45]. The ACP guideline also cites evidence that reveals no difference in ESRD or mortality between strict blood pressure control (128–133/75–81 mm Hg) and standard control (134–141/81–87 mm Hg) [26].

In adult patients with stages 1 through 4 CKD, the Department of Veterans Affairs Guideline Panel recommends that blood pressure targets should be less than 140/90 mm Hg.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPG2014.pdf. Last Accessed: August 14, 2020)

Strength of Recommendation: Strong

Anemia

Anemia is a common finding in patients with CKD, associated with reduced quality of life and increased CVD, hospitalizations, and mortality [46]. Testing for hemoglobin should be carried out at least annually in all patients with CKD [46; 47]. Men with hemoglobin <13.0 g/dL and women with hemoglobin <12.0 g/dL are considered anemic and warrant further evaluation with a complete blood count including red blood cell indices, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count, differential, and platelet count [46; 47]. Absolute reticulocyte count, serum ferritin, and transferrin saturation should also be obtained [46; 47].

Anemic patients with CKD can be treated with erythropoiesis-stimulating agents (ESAs), which supplement the production of erythropoietin. Patients on ESA therapy should have their hemoglobin checked at least monthly [46; 47]. ESA therapy should be dosed individually according to the patient's hemoglobin concentration, body weight, and clinical circumstances [47]. The frequency of administration should be based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA [47]. Those who are not on dialysis can be administered ESA subcutaneously, while dialyzed patients may get ESA intravenously [46; 47]. Patients receiving dialysis should also receive intravenous iron, though non-dialysis patients may receive iron orally. Iron should be administered monthly during initial ESA therapy and at least every three months after ESA treatment is stable [46; 47].

Goals of treatment include a transferrin saturation >20% and serum ferritin >200 ng/mL in dialyzing patients and >100 ng/dL in non-dialyzing patients [47]. In those receiving ESA therapy, anemia should be corrected to a target hemoglobin of 11.0–12.0 g/dL [33]. The target hemoglobin should not exceed 13.0 g/dL, as no benefit has been demonstrated beyond this level [48].

Data show that ESA therapy may not be entirely safe in some patients. In one study, patients with CKD, anemia, and type 2 diabetes who received darbepoetin alfa did not experience reduced risk of death or CVD compared to placebo; however, they did experience a two-fold greater risk of stroke [49]. Additionally, high doses of ESA are associated with increased rates of hypertension and thrombotic events [50].

Vitamin and Mineral Imbalance

All patients with CKD should have serum calcium, phosphorus, and PTH levels measured. Frequency of measurement is dependent on staging; stage 3 patients should have serum calcium and phosphate levels checked every 6 to 12 months; the frequency for PTH measurement should be based on baseline level and CKD progression. In CKD stage 4, serum calcium and phosphate levels should be checked every 3 to 6 months, and PTH every 6 to 12 months. In CKD stage 5, serum calcium and phosphate levels should be checked every one to three months, and PTH should be checked every three to six months [16]. In patients who are not on hemodialysis, serum phosphorus should be kept between 2.7 mg/dL and 4.6 mg/dL [51; 52]. Dietary phosphorus should be restricted to 800–1,000 mg/day, and serum phosphorus should be monitored monthly after initiation of dietary phosphorus restriction [53].

In people with GFR <45 mL/min/1.73 m^2, the optimal PTH level is not known. If PTH levels cannot be controlled, it is appropriate to start phosphate binder therapy [16]. In patients with CKD stages 3–5, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. For patients receiving phosphate-lowering treatment, the KDIGO recommends restricting the dose of calcium-based phosphate binders [16]. Data from a 2013 review suggest that non-calcium-based phosphate binders are associated with lower all-cause mortality rates compared to calcium-based phosphate binders [43].

After kidney function has deteriorated to ESRD, maintaining normal serum phosphorus requires dietary restrictions, phosphate-binding medications, and dialysis. Even so, normal serum phosphorus remains elusive in many patients with stage 5 kidney disease. Researchers are testing novel targets that may inhibit intestinal transport of phosphorus to achieve better phosphate control [53].

Hypocalcemia is a classical feature of untreated CKD, in part secondary to diminished gastrointestinal uptake of calcium due to vitamin D deficiency. Because hypocalcemia contributes to the pathogenesis of secondary hyperparathyroidism and renal osteodystrophy, the KDIGO recommends maintaining serum calcium in the normal range, including the correction of hypocalcemia. While a retrospective analysis of a large dialysis cohort confirmed an association between hypocalcemia and mortality risk, two other observations raised doubts about the generalizability of the need to correct hypocalcemia [16]. The first observation is the potential harm for some adults with a positive calcium balance. (Note: serum calcium levels do not necessarily reflect calcium balance.) The second is that the prevalence of hypocalcemia may have increased after the introduction of calcimimetics in patients on dialysis. Retaining the original KDIGO recommendation (from 2009) on this issue supports the concept that patients developing hypocalcemia during calcimimetic treatment require aggressive calcium treatment. Given the unproven benefits of this treatment and the potential for harm, the 2017 KDIGO Work Group emphasizes an individualized approach to the treatment of hypocalcemia rather than recommending the correction of hypocalcemia for all patients, with the understanding that significant or symptomatic hypocalcemia should still be addressed [16].

The KDIGO recommends that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population [16; 20]. Routine prescribing of vitamin D supplements or analogs is not recommended in the absence of suspected or documented deficiency to suppress elevated PTH concentrations in people with CKD

not on dialysis [20]. In patients with stage 5 CKD who require PTH-lowering therapy, calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs, is recommended [16].

Vitamin D insufficiency is independently related to impaired GFR and correlated with mortality risk in patients with CKD [44; 54]. A meta-analysis of 10 prospective studies showed that higher vitamin D levels are associated with significantly improved survival in patients with CKD [39]. A 2013 meta-analysis of 20 observational studies shows that vitamin D treatment is associated with decreased risk of all-cause and CV mortality in patients with CKD who are not undergoing dialysis [55]. Vitamin D supplementation in patients with CKD can also reduce left atrial volume index, which is associated with decreased cardiovascular morbidity and mortality [56]. However, the ability to improve other markers of cardiac function with vitamin D supplementation is lacking evidence. Randomized controlled trials show that although paricalcitol supplementation can reduce PTH levels, it does not appear to improve left ventricular structure or function or diastolic dysfunction [57; 58]. Additionally, data from a prospective study indicate that bisphosphonate treatment in female patients with CKD is associated with lower risk of death, although not with lower risk of cardiovascular events [59].

LIFESTYLE MODIFICATION

Dietary Management

Patients with CKD derive significant benefit from careful diet and regular physical activity. Nutrition is especially important in these patients, and they should receive expert dietary consultation to guide their transitions to an appropriate diet [20]. The KDIGO recommends reducing protein intake in order to limit the accumulation of harmful toxins, (e.g., uremic toxins) in the body [20]. Of note, the first large-scale study of dietary protein intake in patients with CKD—the MDRD study—did not show conclusive evidence regarding the efficacy of a protein-restricted diet in slowing the progression of CKD [60]. However, secondary analyses that have emerged since the publication of the initial results show potential benefit from a protein-restricted diet [61]. Guidelines recommend dietary protein restriction to 0.8 g/kg/day in adults with GFR <30 mL/min/1.73 m^2; further protein restriction beyond this level offers no advantage [20]. High protein intake, defined as more than 1.3 g/kg/day, should be avoided in adults with CKD at risk for progression [20]. High total protein intake, especially high intake of non-dairy animal protein, may speed the decline in renal function in patients with CKD [20]. Protein should come from various alternative sources, including vegetable sources, as these are associated with decreased production of uremic toxins, are low in phosphorus, and may lead to lower production of endogenous acid compared to animal protein [62]. The efficacy of protein restriction, however, remains a topic of debate.

The KDIGO also recommends reducing sodium intake to <2 g per day in adults, citing that sodium excretion is already impaired in patients with CKD and that high intakes can worsen hypertension and proteinuria and blunt the response to the RAAS blockade [20]. A 2013 randomized controlled trial of 20 patients found that sodium restriction resulted in statistically significant reductions in blood pressure, extracellular fluid volume, albuminuria, and proteinuria in patients with stage 3 or 4 CKD [48]. A 2015 Cochrane Review found that sodium reduction in people with CKD reduced blood pressure and consistently reduced proteinuria, but whether such reductions could be maintained long term was not determined [63]. Further studies with larger sample sizes will be needed to expand on these findings in the future.

Dietary phosphorus is commonly restricted in patients with CKD. As discussed, impaired phosphorus metabolism can have serious implications, particularly in regards to mineral and bone disease. Higher serum phosphorus levels have been shown to be associated with increased mortality in patients with CKD [64]. Additionally, studies in rats demonstrate that uremic rats fed a low-phosphorus diet had slower progression of kidney disease than those on a non-restricted diet [65].

Restriction of dietary potassium is based on concern for hyperkalemia in patients with CKD not only because of reduced renal function but also because of concurrent diabetes or use of medications that can raise potassium levels, such as ACE-Is or ARBs [28]. Severely elevated potassium levels can put these patients at significant risk for ventricular arrhythmias. The prevalence of hyperkalemia is high in patients with CKD before they start dialysis, with one study reporting serum potassium ≥5.0 mEq/L in 54.2% of patients and ≥5.5 mEq/L in 31.5% of patients [66]. While a low-potassium diet may be encouraged, hypokalemia is also associated with increased risk of ESRD [67]. One possible risk of a low-potassium diet is that many potassium-containing foods, often fruits and vegetables, are also rich in fiber, and thus patients may risk missing out on important sources of fiber by excluding these foods. Fiber supplementation may be useful in these patients [68].

Metabolic acidosis is a common complication of CKD, increasing in prevalence with declining GFR [20; 69]. It can contribute to protein and muscle wasting, renal osteodystrophy, and increased morbidity and mortality in patients with CKD [55]. Some evidence shows that treating metabolic acidosis can be renoprotective and slow the decline in GFR [70]. This can be done either with sodium alkali supplementation or consumption of fruits and vegetables [70]. However, fruits and vegetables should be recommended with caution due to the concern for hyperkalemia [70].

Physical Activity

Patients with CKD should partake in physical activity to benefit their cardiovascular health and maintain a healthy weight [20]. Obesity is associated with glomerular hyperfiltration, increased kidney venous pressure, and glomerular hypertrophy, suggesting that obesity may be a risk factor for CKD [68]. Weight loss leads to improved blood pressure control, glycemic control, reduction of hyperfiltration, and proteinuria, suggesting that it can be an effective strategy in slowing the progression of kidney disease [68].

In the CKD population, exercise training has been shown to improve physical performance and functioning [71]. Many studies also support the role of exercise in improving hypertension, inflammation, oxidative stress, and other cardiovascular risk factors in patients with CKD, with no evidence of a harmful effect on renal function [72]. Referral to physical therapy or cardiac rehabilitation may be appropriate to safely increase physical activity in these patients [72]. A Cochrane Review found evidence for significant benefit of regular exercise on physical fitness, walking capacity, cardiovascular dimensions, health-related quality of life, and some nutritional parameters in adults with CKD [73]. A study of rats that had CKD induced by doxorubicin administration demonstrated that exercise ameliorated CKD by regulating renal cell apoptotic pathways; a greater beneficial effect was shown in rats that exercised for 60 minutes compared to 30 minutes, suggesting a duration-dependent benefit [74]. A randomized controlled trial of 90 patients with CKD undergoing either standard care or exercise intervention demonstrated significant improvements in the exercise patients [75]. These patients took part in a combined aerobic and resistance training program for 12 months. Cardiorespiratory fitness (measured as peak oxygen consumption [VO2 max]), body composition, and diastolic function all improved significantly in this time period [75]), body composition, and diastolic function all improved significantly in this time period [75]. An extended program may produce further benefits.

MONITORING

Primary care physicians often have questions about monitoring patients with CKD. The KDIGO guidelines recommend at least annual testing for reassessment of GFR and albuminuria in patients with CKD to monitor for progression of disease; those at higher risk for progression should be assessed more frequently [20]. Though small fluctuations in GFR may occur, a decline in an entire GFR category or a ≥25% decrease in GFR from baseline is cause for concern and signifies disease progression [20]. A 5

mL/min/1.73 m^2 or greater decline in GFR per year is considered rapid progression [20]. As mentioned, prognosis is generally informed by factors associated with CKD progression, including cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated blood pressure, hyperglycemia, dyslipidemia, smoking, obesity, CVD, and exposure to nephrotoxic agents [20]. The American College of Physicians recommends against testing for proteinuria in adults with or without diabetes who are taking an ACE-I or ARB, citing no additional benefit with testing [26]. Patients who have significant complications of CKD, such as anemia and mineral and bone disease, should have these monitored, as discussed.

ADHERENCE

Adequate treatment of CKD is multidimensional and involves lifestyle modification as well as pharmacologic interventions, making adherence to treatment of particular concern. Patients with CKD have been shown to have similarly poor medication adherence as patients without CKD in a large study of antihypertensive adherence [76]. Compliance may be complicated by high rates of resistant hypertension requiring multiple medications for adequate blood pressure control [58].

An analysis of 2,288 NHANES III participants with CKD assessed adherence to lifestyle modifications by assigning healthy lifestyle scores to each participant based on factors like smoking, BMI, physical activity, and diet [61]. Those who were non-smokers experienced the greatest reduction in all-cause mortality. Regular exercisers also experienced a 20% reduction mortality compared to non-exercisers. Those with a healthy BMI (18.5–22 kg/m^2) had a 30% decrease in mortality [61].

A study of older adults with CKD revealed that they typically take more than five medications, often prescribed by multiple physicians [68]. Interviews with these subjects also revealed that patients have assigned priorities to their medications that may not be in agreement with physicians' priorities. While most subjects expressed a desire to be adherent to medication, many admitted to regularly skipping medications that they perceived as less important, even if that view was not consistent with physicians' recommendations. Many patients also reported reluctance in addressing their concerns with physicians and finding these discussions unsatisfying. Improved communication between patients and physicians can improve understanding of medication importance and thus adherence.

CONSIDERATIONS FOR HEALTH LITERACY AND NON-ENGLISH-PROFICIENT PATIENTS

In order to comply with the established treatment plan for CKD, patients require a clear understanding of the processes as well as the expected effects of various interventions. The ability to understand health information and make informed health decisions, known as health literacy, is integral to good health outcomes [77]. Yet, the National Assessment of Adult Literacy estimated that only 12% of adults have "proficient" health literacy and 14% have "below basic" health literacy [78]. Rates of health literacy are especially low among ethnic minority populations and individuals older than 60 years of age [77]. Compounding the issue of health literacy is the high rate of individuals with limited English proficiency. According to U.S. Census Bureau data from 2018, more than 44.7 million Americans are foreign-born, and more than 25.6 million (8.3% of the population) speak English less than "very well" [79].

Clinicians should assess their patients' literacy level and understanding and implement interventions as appropriate. Healthcare professionals should use plain language in their discussions with patients who have low literacy or limited English proficiency. They should ask them to repeat pertinent information in their own words to confirm understanding, and reinforcement with the use of low-literacy or translated educational materials may be helpful.

Translation services should be provided for patients who do not understand the clinician's language. "Ad hoc" interpreters (family members, friends, bilingual staff members) are often used instead of professional interpreters for a variety of reasons, including convenience and cost. However, this should be avoided, as it impedes communication and compliance. Clinicians should also check with their state's health officials about the use of ad hoc interpreters, as several states have laws about who can interpret medical information for a patient [80]. Children should especially be avoided as interpreters, as their understanding of medical language is limited and they may filter information to protect their parents or other adult family members [80].

REFERRAL TO A NEPHROLOGY SUBSPECIALIST

Referral of the patient with CKD to a nephrologist is dependent on a number of considerations, including the stage of kidney disease and severity of illness, the primary care physician's experience managing CKD, and practice patterns and access to subspecialty service in the given geographic locale. In general, all patients with severe disease—late stage 3 or early stage 4 (GFR in the range of 30–35 mL/min)—should be referred, as most patients with this degree of renal dysfunction are known to have progressive kidney disease and are at risk for progressing soon to ESRD. Indications for earlier referral include the presence of high-grade albuminuria (AER >300 mg/day), difficulty determining the cause of kidney disease, unexplained hematuria, and the presence of resistant comorbidities or complications such as hypertension, anemia, hyperkalemia, and problems of calcium-phosphate metabolism.

Timely referral of the patient with severe, progressive CKD is important for patient and physician alike, in order to ensure sufficient time to prepare for the eventually of dialysis or organ transplantation. The best preparation, in terms of choice, efficiency, safety, and cost, requires weeks to months. For the patient, it involves discussions of the rationale, requirements, needed lifestyle alterations, and technical aspects of dialysis and transplantation. For physicians, in anticipation that the patient will likely need to undergo dialysis, timely preparation requires planning for the optimal time to establish peritoneal or vascular access [81].

PREPARATION FOR HEMODIALYSIS

Long-term hemodialysis requires stable vascular access that is enduring and subject to minimum complications. There are three types of access commonly used and surgically placed: the autologous (native) arteriovenous (AV) fistula, a synthetic arteriovenous fistula (AV graft), or a double lumen, cuffed tunneled catheter. The optimal choice is the autologous AV fistula, preferred because of its high rate of long-term patency and low rate of complications [81]. In order to ensure sufficient time for maturity of the fistula into a functioning hemodialysis access site, the surgeon must create the fistula months in advance. Guidelines recommend that the patient be referred for vascular access surgery at least six months prior to the anticipated need to initiate hemodialysis [82].

CASE STUDIES

CASE STUDY 1

Patient A is a white man, 55 years of age, with diabetes. His hemoglobin A1c is 11%, and he suffers from diabetic retinopathy. Upon presentation, his blood pressure is 147/88 mm Hg, cholesterol is 213 mg/dL, and LDL is 136 mg/dL. His serum creatinine is 1.3 mg/dL. He is 5 foot 10 inches tall, his weight is 223 pounds, and he suffers from peripheral neuropathy. Patient A reports not having seen a primary care provider in years and is not on medication. He works at a factory and does not have health insurance.

Discussion: *A few points come to mind when reviewing Patient A's history. Patients with poorly controlled diabetes are at an increased risk of renal disease. For every point the hemoglobin A1c is above normal, the incidence of end organ damage rises 10%. In this patient, the presence of end organ damage (i.e., retinopathy and neuropathy) indicates a high probability of renal disease. It is important to remember serum creatinine does not rise substantially until late in the renal disease process.*

Patient A is found to have proteinuria on dipstick testing. A 24-hour urine collection reveals a GFR of 57 mL/min/1.73 m^2. This categorizes the patient as having stage 3 CKD with hypertension and diabetes.

Patient A's primary care physician discusses this diagnosis with him and they develop a management plan, including medication and diet to better control his diabetes, with an hemoglobin A1c goal of less than 7%. He is also placed on an ACE-I and a statin to achieve a blood pressure less than 130/85 mm Hg and an LDL less than 70 mg/dL. Because the patient has no health insurance, generic formulations of simvastatin and lisinopril are prescribed. The patient also starts generic metformin 1 g twice daily.

Discussion: *According to the National Kidney Foundation guideline, the goals of treatment should be to diagnose and treat the specific causes of CKD, reduce the risks of cardiovascular disease, slow progression, and evaluate and treat complications and comorbidities.*

When given to patients with advanced renal disease, metformin can lead to lactic acidosis, which can be fatal. Therefore, it should not be prescribed to patients with an estimated GFR of 30 mL/min/1.73 m^2 or less (if the metformin is initiated when the patient's GFR is at or above 45 mL/min/1.73 m^2. Patient A's GFR will be regularly monitored; if the level falls to less than 30 mL/min/1.73 m^2, the metformin must be halted due to the risk of lactic acidosis.

Goals for hemoglobin A1c, LDL, and blood pressure should be secondary prevention goals for patients with diabetes and CKD. The target LDL is <70 mg/dL, and blood pressure should be less than 130/85 mm Hg. The hemoglobin A1c goal for patients with diabetes should be within 10% of normal, taking into account that studies have shown that older patients with cardiovascular disease actually have worse outcomes with hemoglobin A1c levels less than 6%.

Use of less expensive generic medications can greatly increase compliance, especially for uninsured patients. So, this was a good choice for Patient A. The costs associated with tests should also be considered. Although Medicare prefers reimbursing for "bundled" labs (e.g., chem-7 or chem-20), very often a single test, such as a serum creatinine, may be less expensive than a bundled panel of tests. The hemoglobin A1c is a test that changes slowly over the course of 90 days and does not require more frequent monitoring. After the LDL goal has been reached, monitoring cholesterol less frequently may be considered as well.

CASE STUDY 2

Patient C is a black woman, 53 years of age, who is currently employed as an administrative assistant at a Veterans Hospital. She has a long history of bipolar disorder and has been stable for many years on a combination of lithium and olanzapine. She states that in the last several years her weight has increased from 155 pounds to 217 pounds; her height is 5 feet 4 inches. She complains of frequent thirst and urination, lethargy, weakness, and blurred vision. A medical work-up reveals the following:

- Fasting blood glucose: 210 mg/dL
- Hemoglobin A1c: 9.4%
- Blood urea nitrogen (BUN): 83 mg/dL
- Serum creatinine: 3.4 mg/dL
- PTH: 83 pg/mL
- Serum cholesterol: 230 mg/dL
- LDL: 163 mg/dL
- Blood pressure: 164/93 mm Hg

Discussion: *Many widely prescribed medications for bipolar disorder have a variety of serious long-term side effects. Olanzapine has a documented risk of weight gain, hyperglycemia, type 2 diabetes, and in rare cases, diabetic ketoacidosis. While widely used for many years, lithium also has both endocrine and renal side effects.*

Patient C is directed to report to her local emergency room, where she receives intravenous fluids for dehydration, insulin, amlodipine for hypertension, and glyburide for diabetes. Her primary care practitioner starts her on levothyroxine for hypothyroidism and simvastatin for high cholesterol. She is also referred to endocrinology and nephrology. Her psychiatrist will conduct an evaluation of her psychiatric medications.

Discussion: *Collaboration between specialists and primary care providers is a necessary component in the care of patients with renal disease. Many psychiatric medications can impact the care of patients with CKD, worsen preexisting diabetes and hypertension, or cause weight gain. Often, these side effects may be lessened by a change in medications. While psychiatric providers may be reluctant to change medications when a patient has been stabilized on his or her current regimen, patient safety may necessitate it. It is important that all team members be alert for signs and symptoms of psychiatric decompensation, especially if a patient is undergoing medication changes while simultaneously dealing with a new medical diagnosis.*

CONCLUSION

Due to the high prevalence of CKD in relation to the number of nephrologists, much of CKD care is dispensed by primary care physicians. However, this care tends to be suboptimal, characterized by underuse of important medications, failure to reach therapeutic blood pressure goals, and late referral to nephrologists [83]. A national study of primary care providers and nephrologists revealed that primary care clinicians were less likely to recognize CKD, differed from nephrologists in recommendations for diagnostic testing, and recommended referral less [84]. A study of patients with CKD treated by primary care physicians showed that only 54% achieved KDOQI blood pressure goals, 70% did not have annual urine testing, and 26% were prescribed nephrotoxic drugs [85]. Lack of awareness of published clinical practice guidelines and lack of available clinical and administrative resources were cited as barriers to care [85]. Patients who are referred late to nephrologists have significantly higher mortality compared to those who are referred early, and late referrals also result in increased early hospitalization for CKD [66].

There is a need for primary care in the identification and treatment of CKD. Evaluation of risk factors and diagnostic testing can easily be done in this setting. Primary care physicians can also provide valuable counseling on lifestyle modifications and are often adept in the treatment of diabetes and hypertension, both of which are cornerstones of treatment in CKD [86]. Early recognition of CKD and early initiation of ACE-I or ARB therapy can provide significant benefit in slowing the progression of CKD [86].

Overcoming barriers to treatment by primary care providers involves many possible strategies. Widespread education on clinical practice guidelines would provide marked benefit, though there may still be difficulty translating these into practice [87]. Routine reporting of GFR when reporting serum creatinine has also shown promise as an effective strategy for early recognition of CKD [70]. Clinical decision support tools may provide benefit and comfort in caring for patients with CKD in the primary care setting [72]. Technologic advances such as telemedicine also improve primary care access to the latest information and guidelines on CKD [88]. Finally, overall reorganization of healthcare delivery that emphasizes multidisciplinary care and the role of primary care, such as the patient-centered medical home model, may produce rewarding results in CKD care [86].

Works Cited

1. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis*. 2002;39(Suppl 1):S1-S266.
2. U.S. Renal Data System. *2018 USRDS Annual Data Report: Volume 1: CKD in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
3. White SL, McGeechan K, Jones M, et al. Socioeconomic disadvantage and kidney disease in the United States, Australia, and Thailand. *Am J Public Health*. 2008;98(7):1306-1313.
4. Gross ML, Dikow R, Ritz E. Diabetic nephropathy: recent insights into the pathophysiology and the progression of diabetic nephropathy. *Kidney Int*. 2005;(94):S50-S53.
5. Bruce MA, Beech BM, Crook ED, et al. Association of socioeconomic status and CKD among African Americans: the Jackson Heart Study. *Am J Kidney Dis*. 2010;55(6):1001-1008.
6. Hall YN, Choi AT, Himmelfarb J, Chertow GM, Bindman AB. Homelessness and CKD: a cohort study. *Clin J Am Soc Nephrol*. 2012;7(7):1094-1102.
7. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis*. 2012;60(3):402-408.
8. McClellan AC, Plantinga L, McClellan WM. Epidemiology, geography and chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2012;21(3):323-328.
9. Hart PD, Bakris GL. Hypertensive nephropathy: prevention and treatment recommendations. *Expert Opin Pharmacother*. 2010;11(16):2675-2686.
10. Fischer MJ, Go AS, Lora CM, et al. CKD in Hispanics: baseline characteristics from the CRIC and Hispanic-CRIC studies. *Am J Kidney Dis*. 2011;58(2):214-227.
11. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol*. 2012;23(10):1631-1634.
12. Lora CM, Gordon EJ, Sharp LK, Fischer MJ, Gerber BS, Lash JP. Progression of CKD in Hispanics: potential roles of health literacy, acculturation, and social support. *Am J Kidney Dis*. 2011;58(2):282-290.
13. Portolés J1, Gorriz JL, Rubio E, et al. The development of anemia is associated to poor prognosis in NKF/KDOQI stage 3 chronic kidney disease. *BMC Nephrol*. 2013;14:2.
14. Crews DC, Pfaff T, Powe NR. Socioeconomic factors and racial disparities in kidney disease outcomes. *Semin Nephrol*. 2013;33(5):468-475.
15. Peralta CA, Ziv E, Katz R, et al. African ancestry, socioeconomic status, and kidney function in elderly African Americans: a genetic admixture analysis. *J Am Soc Nephrol*. 2006;17:3491-3496.
16. National Kidney Foundation. KDOQI 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *J Int Soc Nephrol*. 2017;7(1):1-60.
17. McClellan WM, Newsome BB, McClure LA, et al. Poverty and racial disparities in kidney disease: the REGARDS study. *Am J Nephrol*. 2010;32:38-46.
18. Shumway JT, Gambert SR. Diabetic nephropathy: pathophysiology and management. *Int Urol Nephrol*. 2002;34(2):257-264.
19. U.S. Renal Data System. USRDS *2014 Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.
20. 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*. 2013;3:1-150.
21. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9): 604-612.
22. Becker BN, Vassalotti JA. A software upgrade: CKD testing in 2010. *Am J Kidney Dis*. 2010;55(1):8-10.
23. Stevens LA, Li S, Kurella Tamura M, et al. Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations: risk factors for and complications of CKD and mortality in the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*. 2011;57(3 Suppl 2):S9-S16.
24. College of American Pathologists. Current Status of Reporting Estimated Glomerular Filtration Rate. Available at https://webapps.cap.org/apps/docs/committees/chemistry/current_status_reporting_egfr2012.pdf. Last accessed August 24, 2020.
25. Moyer VA, U.S. Preventative Service Task Force. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157(8):567-570.
26. Qaseem A, Hopkins RH, Sweet DE, Starkey M, Shekelle P. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: a clinical practical guideline from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2013;159(12):835-847.
27. UK Prospective Diabetes Study Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854-865.
28. Sarafidis PA, Blacklock R, Wood E, et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin Am J Soc Nephrol*. 2012;7(8):1234-1241.

29. Block GA, Ix JH, Ketteler M, et al. Phosphate homeostasis in CKD: report of a scientific symposium sponsored by the National Kidney Foundation. *Am J Kidney Dis*. 2013;62(3):457-473.
30. The DCCT Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int*. 1995;47(6):1703-1720.
31. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000;23(Suppl 2):B21-B29.
32. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.
33. National Kidney Foundation. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis*. 2007;50(3):471-530.
34. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892-1903.
35. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204-2213.
36. U.S. Food and Drug Administration. FDA Revises Warnings Regarding Use of the Diabetes Medicine Metformin in Certain Patients with Reduced Kidney Function. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain. Last accessed August 24, 2020.
37. National Kidney Foundation. KDOQI clinical practice guideline for the management of blood pressure in chronic kidney disease. *J Int Soc Nephrol*. 2012;2(5):1-85.
38. Fraser SD, Roderick PJ, McIntyre NJ, et al. Suboptimal blood pressure control in chronic kidney disease stage 3: baseline data from a cohort study in primary care. *BMC Fam Pract*. 2013;14:88.
39. Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S. Vitamin D status and mortality risk in CKD: a meta-analysis of prospective studies. *Am J Kidney Dis*. 2011;58(3):374-382.
40. Tanner RM, Calhoun DA, Bell EK, et al. Prevalence of apparent treatment-resistant hypertension among individuals with CKD. *Clin J Am Soc Nephrol*. 2013;8(9):1583-1590.
41. Slagman MCJ, Waanders F, Hemmelder MH, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomized controlled trial. *BMJ*. 2011;343:d4366.
42. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2010;55(3):441-451.
43. Jamal SA, Vandermeer B, Raggi P, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet*. 2013;382(9900):1268-1277.
44. Ureña-Torres P, Metzger M, Haymann JP, et al. Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD. *Am J Kidney Dis*. 2011;58(4):544-553.
45. U.S. Food and Drug Administration. FDA Drug Safety Communication: New Warning and Contraindication for Blood Pressure Medicines Containing Aliskiren (Tekturna). Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warning-and-contraindication-blood-pressure-medicines-containing. Last accessed August 24, 2020.
46. National Kidney Foundation. KDOQI clinical practice guideline for anemia in chronic kidney disease. *J Int Soc Nephrol*. 2012;2(4):1-64.
47. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int*. 2012;2(S2):S279-S335.
48. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol*. 2013;24(12):2096-2103.
49. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361(21):2019-2032.
50. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a meta-regression analysis. *Am J Kidney Dis*. 2013;61(1):44-56.
51. Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of chronic kidney disease. *Kidney Int*. 2008;74(2):148-157.
52. Spasovski G, Massy Z, Vanholder R. Phosphate metabolism in chronic kidney disease: from pathophysiology to clinical management. *Semin Dial*. 2009;22(4):357-362.
53. Suki WN, Moore LW. Phosphorus regulation in chronic kidney disease. *Methodist Debakey Cardiovasc J*. 2016;12(4 Suppl):6-9.
54. Zheng Z, Shi H, Jia J, Li D, Lin S. Vitamin D supplementation and mortality risk in chronic kidney disease: a meta-analysis of 20 observational studies. *BMC Nephrol*. 2013;14(1):199.
55. Goraya N, Wesson DE. Does correction of metabolic acidosis slow chronic kidney disease progression? *Curr Opin Nephrol Hypertens*. 2013;22(2):193-197.

56. Tamez H, Zoccali C, Packham D, et al. Vitamin D reduces left atrial volume in patients with left ventricular hypertrophy and chronic kidney disease. *Am Heart J*. 2012;164(6):902-909.
57. Wang AY, Fang F, Chan J, et al. Effect of paricalcitol on left ventricular mass and function in CKD—the OPERA trial. *J Am Soc Nephrol*. 2013;25(1):175-186.
58. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA*. 2012;307(7):674-684.
59. Hartle JE, Tang X, Kirchner HL, et al. Bisphosphonate therapy, death, and cardiovascular events among female patients with CKD: a retrospective cohort study. *Am J Kidney Dis*. 2012;59(5):636-644.
60. Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. *J Am Soc Nephrol*. 1999;10(11):2426-2439.
61. Ricardo AC, Madero M, Yang W, et al. Adherence to a healthy lifestyle and all-cause mortality in CKD. *Clin J Am Soc Nephrol*. 2013;8(4):602-609.
62. Filipowicz R, Beddhu S. Optimal nutrition for predialysis chronic kidney disease. *Adv Chronic Kidney Dis*. 2013;20(2):175-180.
63. McMahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database Syst Rev*. 2015;(2):CD010070.
64. Eddington H, Hoefield R, Sinha S, et al. Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(12):2251-2257.
65. Kusano K, Segawa H, Ohnishi R, Fukushima N, Miyamoto K. Role of low protein and low phosphorus diet in the progression of chronic kidney disease in uremic rats. *J Nutr Sci Vitaminol*. 2008;54(3):237-243.
66. Chan MR, Dall AT, Fletcher KE, Lu N, Trivedi H. Outcomes in patients with chronic kidney disease referred late to nephrologists: a meta-analysis. *Am J Med*. 2007;120(12):1063-1070.
67. Wang HH, Hung CC, Hwang DY, et al. Hypokalemia, its contributing factors, and renal outcomes in patients with chronic kidney disease. *PLoS One*. 2013;8(7):e67140.
68. Rifkin DE, Laws MB, Rao M, Balakrishnan VS, Sarnak MJ, Wilson IB. Medication adherence behavior and priorities among older adults with CKD: a semi-structured interview study. *Am J Kidney Dis*. 2010;56(3):439-446.
69. Hsu CY, Chertow GM. Elevations of serum phosphorus and potassium due to mild to moderate chronic renal insufficiency. *Nephrol Dial Transplant*. 2002;17(8):1419-1425.
70. Jain AK, McLeod I, Huo C, et al. When laboratories report estimated glomerular filtration rates in addition to serum creatinines, nephrology consults increase. *Kidney Int*. 2009;76(3):318-323.
71. Johansen KL, Painter P. Exercise in individuals with CKD. *Am J Kidney Dis*. 2012;59(1):126-134.
72. Patwardhan MB, Kawamoto K, Lobach D, Patel UD, Matchar DB. Recommendations for a clinical decision support for the management of individuals with chronic kidney disease. *Clin Am J Soc Nephrol*. 2009;4(2):273-283.
73. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev*. 2011;5(10):CD003236.
74. Chen KC, Peng CC, Hsieh CL, Peng RY. Exercise ameliorates renal cell apoptosis in chronic kidney disease by intervening in the intrinsic and extrinsic apoptotic pathways in a rat model. *Evid Based Complement Alternat Med*. 2013;2013:368450.
75. Howden EJ, Leano R, Petchey W, Coombes JS, Isbel NM, Marwick TH. Effects of exercise and lifestyle intervention on cardiovascular function in CKD. *Clin J Am Soc Nephrol*. 2013;8(9):1494-1501.
76. Muntner P, Judd SE, Krousel-Wood M, McClellan WM, Safford MM. Low medication adherence and hypertension control among adults with CKD: data from the REGARDS study. *Am J Kidney Dis*. 2010;56(3):447-457.
77. Committee on Health Literacy Board on Neuroscience and Behavioral Health. *Health Literacy: A Prescription to End Confusion*. Washington, DC: The National Academies Press; 2004.
78. Kirsch I, Jungeblut A, Jenkins L, Kolstad A. *Adult Literacy in America: A First Look at the Results of the National Adult Literacy Survey (NALS)*. Washington, DC: National Center for Education Statistics, U.S. Department of Education; 1993.
79. U.S. Census Bureau. Selected Social Characteristics in the United States: 2018. Available at https://data.census.gov/cedsci/table?q=selected%20social%20characteristics&tid=ACSDP1Y2018.DP02&hidePreview=false. Last accessed August 24, 2020.
80. Sevilla Matir J, Willis DR. Using bilingual staff members as interpreters. *Fam Pract Manage*. 2004;11(7):34-36.
81. Avon J, Winkelmeyer WC, Bohn RL, et al. Delayed nephrologist referral and inadequate vascular access in patients with chronic kidney failure. *J Clin Epidemiol*. 2002;55(7):711-716.
82. National Kidney Foundation. Clinical practice guidelines for hemodialysis adequacy: 2015 update. *Am J Kidney Dis*. 2015;66(5):884-930.
83. Abdel-Kader K, Fischer GS, Li J, Moore CG, Hess R, Unruh ML. Automated clinical reminders for primary care providers in the care of CKD. *Am J Kidney Dis*. 2011;58(6):894-902.
84. Boulware LE, Troll MU, Jaar BG, Myers DI, Powe NR. Identification and referral of patients with progressive CKD: a national study. *Am J Kidney Dis*. 2006;48(2):192-204.

85. Allen AS, Forman JP, Orav EJ, Bates DW, Denker BM, Sequist TD. Primary care management of chronic kidney disease. *J Gen Intern Med*. 2011;26(4):386-392.

86. Shahinian VB, Saran R. The role of primary care in the management of the chronic kidney disease population. *Adv Chron Kidney Dis*. 2010;17(3):246-253.

87. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA*. 1999;282(15):1458-1465.

88. Taal MW. Chronic kidney disease in general populations and primary care: diagnostic and therapeutic considerations. *Curr Opin Nephrol Hypertension*. 2013;22(6):593-598.

89. U.S. Food and Drug Administration. FDA Approves Treatment for Chronic Kidney Disease. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-chronic-kidney-disease. Last accessed October 11, 2021.

Evidence-Based Practice Recommendations Citations

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis*. 2012;60(5):850-886. Available at https://www.kidney.org/sites/default/files/docs/diabetes-ckd-update-2012.pdf. Last accessed September 14, 2020.

National Kidney Foundation. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl*. 2013;3(3):259-305. Available at https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2013-Lipids-Guideline-English.pdf. Last accessed September 14, 2020.

Management of Chronic Kidney Disease Working Group. *VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care*. Washington, DC: Department of Veterans Affairs, Department of Defense; 2014. Available at https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPG2014.pdf. Last accessed September 14, 2020.