Caring for Patients with Chronic Kidney Disease: A Joint Opinion of the Ambulatory Care and the Nephrology Practice and Research Networks of the American College of Clinical Pharmacy

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An increasing number of patients are developing chronic kidney disease (CKD). Appropriate care for patients with CKD must occur in the earliest stages, preferably before CKD progresses to more severe stages. Therefore, recognition and treatment of CKD and its associated complications must occur in primary care settings. Patients with CKD often have comorbid conditions such as diabetes mellitus, hypertension, and dyslipidemia, creating specific considerations when treating these diseases. Also, these patients have CKD-related conditions, including anemia and renal osteodystrophy, that are not traditionally evaluated and monitored by the primary care practitioner. Collectively, many opportunities exist for pharmacists who practice in the primary care setting to improve the care of patients with CKD.

Key Words: chronic kidney disease, patient care, primary care, pharmacists' role.

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Chronic kidney disease (CKD) is a health problem reaching epidemic proportions and encompasses a substantial segment of the adult ambulatory population. Although specific prevalence rates are difficult to calculate, an estimated 20 million people have CKD.[1] More specific data are available for the subset of patients with end-stage renal disease (ESRD), or renal failure, where the incidence reached almost 100,000 patients in 2000.[2] This number has doubled during the past 10 years and is expected to increase with the aging population. By 2010, the incidence of ESRD is projected to increase to more than 172,000 cases annually.[2] Similarly, the prevalence of ESRD was 372,000 cases in 2000 but is estimated to exceed 661,000 by 2010.[2] The cost of treating patients with ESRD consumes almost 6% of the total Medicare budget, accounting for approximately $19 billion annually. Although these are staggering numbers, they account for only the 2% of patients in the final stage of CKD. Millions of patients with less severe CKD represent a much broader portion of the adult ambulatory population. Therefore, the recognition and treatment of early CKD should be emphasized as a component of primary care.

The presence of CKD doubles the risk of mortality in affected individuals.[2] Meanwhile, progression to ESRD incurs a very poor prognosis, with patients having a 4 times greater rate of hospitalizations and a life expectancy that is one quarter to one fifth less than that of the general population. By far, the most common cause of death (48%) among patients with ESRD is cardiovascular disease.[3] Thus, an opportunity for improving care of patients with CKD exists through treatment of cardiovascular risk factors during earlier stages of the disease in primary

Table 1. Stages of Chronic Kidney Disease

Stage	Description	GFR Range (ml/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	< 15 or dialysis

GFR = glomerular filtration rate.

care. Current treatment recommendations stress the importance of therapies that improve the morbidity and mortality of these patients, as well as therapies that prevent or delay the progression of kidney disease.[4] Most of these therapeutic interventions target the adult, ambulatory patient population in primary care. Pharmacists in a wide variety of primary care practice settings are well suited to implement and monitor therapeutic interventions to improve the care of patients with CKD.

Detection and Staging of CKD

Chronic kidney disease is defined according to the presence of kidney damage and/or a reduction in the glomerular filtration rate (GFR) for a period of 3 months or more. Kidney damage refers to structural or functional abnormalities of the kidney, initially without decreased GFR.[5] Early detection of kidney damage is of paramount importance. Spot urine measurements by dipstick can detect the early presence of kidney damage and is recommended by the National Kidney Foundation (NKF) for all asymptomatic adult patients. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend the following procedures for identifying the presence of CKD: estimation of GFR by appropriate prediction equations, assessment of proteinuria in a spot urine sample, examination of the urinary sediment, and determination of the presence of red blood cells or white blood cells by dipstick.[5,6] A positive test for protein, albumin, red blood cells, or white blood cells may indicate kidney disease, with further evaluation recommended.

The NKF recently instituted the Kidney Early Evaluation Program (KEEP).[7] This program is a community-based screening program delivered through local NKF affiliates. Participants at risk for kidney disease undergo measurements of blood pressure, blood glucose, creatinine, hemoglobin, microalbuminuria, hematuria, pyuria, and GFR. Abnormal results are not considered diagnostic, but patients are referred to their physicians for follow-up. The program has screened more than 22,000 patients. Results from 11,246 patients who were screened revealed that more than 50% had evidence of CKD, whereas only 2–3% actually reported having CKD.[7] This and other results from KEEP emphasize the importance of strategies to detect this disease. Pharmacists can play an important role in the detection of this disease by promoting KEEP and/or ensuring that patients at risk for CKD receive similar screening measures.

Once CKD has been detected, it is classified based on GFR (Table 1). In the earlier stages, GFR is normal (stage 1) or mildly decreased (stage 2); however, there is evidence of kidney damage. Preventive treatment strategies including

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Table 2. Risk Factors for Development of Chronic Kidney Disease

Risk Factor	Definition	Examples
Susceptibility factors	Increased susceptibility to kidney damage	Older age, family history of chronic kidney disease, U.S. racial or ethnic minority status, low income or education
Initiation factors	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune diseases, systemic infections, drug toxicity

Adapted from reference 5.

blood pressure control, glycemic control, and smoking cessation may be effective in delaying progression during this time.[5] Symptoms are more clearly associated with stage 3 CKD, when there is a more appreciable decline in GFR and secondary complications such as anemia and secondary hyperparathyroidism may be present. As patients progress into stage 4, signs and symptoms including uremia, electrolyte abnormalities, and acid-base imbalances predominate. Stage 5 represents renal failure, or ESRD, for which dialysis, transplantation, or other renal replacement therapy is required for survival.

Etiology of CKD: The Link to Primary Care

There are many potential causes of CKD leading to gradual functional decline and the development of ESRD. Table 2 lists two categories of risk factors that may be responsible for CKD. Diabetes mellitus and vascular disease (including hypertension) account for almost 70% of cases.[2] Nondiabetic glomerular disease and tubulointerstitial disease are other causes of kidney disease, with drug-induced causes accounting for some of these cases. Research has also indicated that dyslipidemias may contribute to the development of kidney disease.[8] Similarly, tobacco use, owing to its propensity for promoting atherosclerosis, recently has been identified as a risk factor for glomerulosclerosis. Since disorders largely managed by primary care providers are responsible for many causes of CKD, there is a need for recognition of relationships between these disorders and CKD. Also, patients with CKD must be treated aggressively to achieve goals set forth by consensus guidelines.

Diabetes accounts for the largest percentage of patients (43%) with ESRD.[2] During early stages of nephropathy, there may be signs consistent with functional changes, such as increased kidney size, glomerular hyperfiltration, and albuminuria. Without intervention, approximately 80% of patients with type 1 diabetes and 20–40% of those with type 2 diabetes develop overt nephropathy in 10–15 years.[5] The mechanisms by which hyperglycemia may lead to CKD are complex. It is hypothesized that hyperglycemia increases capillary endothelial dysfunction, glomerular basement membrane thickening, and mesangial matrix production.[9] Research has shown that during periods of hyperglycemia, glucose forms chemical bonds with proteins. Some bonds form irreversible cross-links, known as advanced glycosylation end products, that accumulate in tissues, including the kidney. These end products impart abnormal structural protein function and vascular permeability, resulting in end-organ damage.[10] Evidence from the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrates that intensive glycemic control can significantly reduce the risk of developing microalbuminuria and overt nephropathy.[11, 12]

Hypertension is both a cause and a consequence of kidney damage. Hemodynamic abnormalities largely contribute to the development of CKD. Changes in blood pressure directly affect renal perfusion pressure. One of several theories of hypertensive glomerulosclerosis involves abnormal autoregulatory response to increased perfusion pressure.[13] The normal reflex afferent arteriolar (preglomerular) vasoconstriction, used to prevent full systemic pressure from being transmitted to the glomerulus, is impaired. This produces glomerular capillary hypertension and subsequent kidney damage. As damage to individual nephrons occurs, the remaining nephrons increase the workload by increasing individual glomerular capillary pressure in an attempt to maintain GFR. Over time, this hyperfiltration results in a progressive loss of individual nephron function and an overall decline in GFR.

Many pharmacologic agents can also cause kidney damage. Common agents such as

analgesics, nonsteroidal antiinflammatory agents, contrast media, and antiinfectives are a few such examples. Although the mechanism of toxicity is distinct to each agent, renal ischemia, inflammation, and cellular disruption of nephrons are possible explanations.[14] Comprehensive drug histories, diligent prescribing of appropriate dosages, avoidance of nephrotoxins in patients with underlying renal problems, and monitoring of nephrotoxic drug therapies can help reduce drug-induced CKD in primary care.

Treatment of CKD in Primary Care

Glycemic Control

Nephropathy, in addition to retinopathy and neuropathy, is considered a microvascular complication of diabetes. Although the prevalence is lower than that of macrovascular complications (atherosclerotic vascular disease), microvascular complications in type 2 diabetes are considered a significant cause of overall morbidity and mortality. Evidence from prospective clinical trials shows reduced nephropathy with strict glycemic control.[11, 12, 15]

The DCCT was the first prospective, long-term study designed to examine whether intensive glycemic control reduces long-term microvascular complications in patients with type 1 diabetes.[11] In this study, 1441 patients, half with no baseline retinopathy and half with mild retinopathy, were randomly assigned to intensive therapy (using an external insulin pump) or conventional therapy (with three or more daily doses of insulin). Retinopathy was the primary microvascular complication evaluated, and nephropathy was a secondary outcome measure. After 6.5 years, mean hemoglobin A_{1c} (A1C) values throughout the study were significantly lower with intensive therapy than with conventional therapy (7.2% and 9.0%, respectively, $p<0.001$). Risks of microalbuminuria and albuminuria were reduced 39% ($p\leq0.002$) and 54% ($p<0.04$), respectively, with intensive therapy compared with conventional therapy. Hypoglycemia was 3-fold higher in the intensive therapy group, and practitioners may avoid this aggressive approach in certain patients with type 1 diabetes who are at high risk for serious hypoglycemia.

The UKPDS was a series of studies in patients with type 2 diabetes. The UKPDS 33 compared the effects of glycemic control on the risks of macrovascular and microvascular complications.[12] Microvascular complications (nephropathy and retinopathy) were primary study end points. A total of 3867 patients with newly diagnosed type 2 diabetes were randomly assigned to intensive control (fasting blood glucose levels < 110 mg/dl) or conventional control (fasting blood glucose levels < 270 mg/dl). A complex factorial design was employed to use diet, sulfonlyureas, metformin, and insulin as treatment options. During 10 years of follow-up, A1C values increased throughout the study in both groups and averaged 7.0% and 7.9% for intensive and conventional control, respectively ($p<0.0001$). Intensive control achieved a 25% relative risk reduction of microvascular complications ($p<0.01$). Other surrogate end points of nephropathy (microalbuminuria, albuminuria, and doubling of serum creatinine level) were all statistically significantly lower with intensive therapy after 9 years of treatment.

The UKPDS 34 compared intensive control with metformin-based therapy with conventional control therapy in 753 overweight patients with type 2 diabetes.[16] The A1C values were lower with metformin than with conventional therapy (7.4% vs 8.0%), all-cause mortality was reduced 36% ($p=0.011$), and hypoglycemic episodes were less frequent. Nephropathy (development of urine albumin > 50 mg/L) was not statistically significantly lower with intensive therapy, although this was considered a surrogate end point of study. These results are not as robust as those of UKPDS 33 for nephropathy but provide further information that shows reduced overall mortality with metformin therapy in patients with type 2 diabetes.

Collectively, the UKPDS data demonstrate reduced nephropathy with intensive glycemic control and reveal a continuous relationship between microvascular complications and glycemic control such that every point decrease in A1C (e.g., 9–8%) corresponds to a 35% reduction in risk.[17]

A study performed in Kumamoto, Japan, demonstrated that strict glycemic control with insulin prevents progression of nephropathy in Japanese patients with type 2 diabetes.[18] This study included 110 patients, 55 without baseline microvascular disease, who were randomly assigned to intensive control (with three or more daily doses of rapid-acting insulin and one daily dose of intermediate-acting bedtime insulin, with dosage titrated to a fasting and 2-hour postprandial glucose level of < 140 mg/dl and A1C values < 7%) or conventional control (one or two daily doses of intermediate-acting insulin, with dosage titrated to a fasting glucose level of < 140 mg/dl).

Table 3. Recommendations for Glycemic Control in Diabetes Mellitus[19, 23]

Glycemic Measure	Normal Values	Goal Values: American Diabetes Association	Goal Values: American College of Endocrinology
Hemoglobin A_{1c} (%)	< 6	< 7	< 6.5
Blood glucose (mg/dl)			
Preprandial	< 100	90–130[a]	≤ 110
Postprandial	< 140	< 180	≤ 140
Bedtime	< 110	100–140	NR

NR = no recommendation.
[a]Plasma glucose values.

Development of nephropathy (urinary albumin excretion > 30 mg/day) occurred in 7.7% and 28.0% (p=0.032) of the intensive and conventional treatment groups, respectively, in those with no baseline microvascular disease after 6 years. Progression of nephropathy occurred in 11.5% and 32.0% (p=0.044) of the intensive and conventional treatment groups, respectively, for those patients with baseline microvascular disease. Similar results were seen after 8 years in a follow-up analysis.[15] In contrast to DCCT and UKPDS, the magnitude of difference in A1C between the intensive and conventional treatment groups was large, 7.1% versus 9.4% (p<0.05), respectively.

Cardiovascular disease is the primary cause of mortality in patients with type 2 diabetes magnified with concomitant CKD.[19] Treatment and prevention of macrovascular complications must be included in the overall management of type 2 diabetes and may augment the nephropathy benefit seen with tight glycemic control. A multifactorial approach to managing hyperglycemia, hypertension, and dyslipidemia in patients with type 2 diabetes was evaluated in a study performed at the Steno Diabetes Centre (Copenhagen, Denmark).[20] Eighty patients were randomly assigned to standard care and 80 to intensive multifactorial intervention, with a primary end point being development of nephropathy. After 3.8 years, A1C values decreased 0.8% in the intensive intervention group compared with an increase of 0.2% in the standard care group (p<0.0001). Systolic blood pressure and low-density lipoprotein cholesterol (LDL) levels were also lower in the intensive intervention group (both p<0.05) compared with the standard care group. Eight patients in the intensive intervention group developed nephropathy compared with 19 in the standard care group (odds ratio 0.27, 95% confidence interval [CI] 0.10–0.75). When study patients were followed for a mean of 7.8 years, nephropathy was still lower in the intensive intervention group (hazard ratio [HR] 0.39, 95% CI 0.17–0.87), and cardiovascular disease risk was also reduced (HR 0.47, 95% CI 0.24–0.73).[21]

Optimizing glycemic control should be an evidence-based strategy to reduce the risk and/or slow the progression of nephropathy in patients with type 1 or type 2 diabetes.[22] The American Diabetes Association and the American College of Endocrinology are two organizations that advocate glycemic control as a primary target of therapy intended to prevent chronic complications (e.g., retinopathy, nephropathy, neuropathy). They recommended targeting several glycemic indexes to attain tight glycemic control (Table 3).[19, 23] The recommendations are slightly different, with the American College of Endocrinology recommendations being more aggressive. The compelling evidence described previously shows reduced nephropathy with A1C values ranging from 7.0–7.4%. Therefore, both definitions of tight glycemic control are reasonable.

Achieving tight glycemic control should be included as an essential component of the comprehensive care of patients with diabetes and CKD. Evidence supports that tight glycemic control minimized development or progression of nephropathy in patients with diabetes. Patients with type 2 diabetes will often require multiple oral drugs (with or without insulin) to attain optimal control. Although no oral agent appears superior to another in their ability to reduce nephropathy, metformin should be used in overweight patients with type 2 diabetes because it has been shown to reduce macrovascular complications in this population.[16] Owing to an increased risk of life-threatening lactic acidosis, however, metformin has several contraindications that may preclude its use in patients with CKD. These contraindications include any patients

with elevated serum creatinine levels (≥ 1.4 mg/dl in women and ≥ 1.5 mg/dl in men) or an estimated GFR less than 60 ml/minute. Patients with type 1 diabetes will require multiple daily doses of insulin to attain strict glycemic control. Although this has been shown to reduce nephropathy, patients and providers should be cognizant of the increased risk of hypoglycemia, which may be a limiting factor for certain high-risk patients treated with insulin and must be considered on an individual basis.

Blood Pressure Control

High blood pressure is a well-recognized risk factor for the development of CKD. An estimated 90% of patients with renal failure have hypertension. However, it is rarely known which condition, elevated blood pressure or CKD, was the initiating event.[24] The frequency of hypertensive nephropathy, defined as a decreased GFR in which hypertension is the only causative factor, is difficult to isolate as many patients often experience multiple insults (i.e., dyslipidemia, hyperglycemia, cigarette smoking), which all contribute to the development of CKD.

The relationship between secondary hypertension and the development of renal failure has been well recognized for almost a century.[24] Several observational studies in the last 2 decades, both retrospective and prospective, describe the association between elevated blood pressure and decline in GFR.[25–35] One of these trials, the Multiple Risk Factor Intervention Trial (MRFIT), confirmed this relationship.[32] A total of 12,866 men aged 35–57 years were enrolled into the study, and 332,544 men participated as part of an observational cohort. During an average of 16 years of follow-up, 814 cases of all-cause ESRD developed in this cohort. Individuals in this cohort were then divided into groups based on their baseline blood pressure categories. The blood pressure categories were based on National Clinical Practice Guidelines and defined as follows: optimal, less than 120/80 mm Hg; stage 1, systolic blood pressure 140–159 mm Hg or diastolic blood pressure 90–99 mm Hg; stage 2, systolic blood pressure 160–179 mm Hg or diastolic blood pressure 100–109 mm Hg; stage 3, systolic blood pressure 180–209 mm Hg or diastolic blood pressure 110–119 mm Hg; stage 4, systolic blood pressure 210 mm Hg or greater or diastolic blood pressure 120 mm Hg or greater. A very apparent relationship between blood pressure stage and probability of developing ESRD was demonstrated. The relative risks of developing ESRD compared with those individuals with optimal blood pressure (< 120/80 mm Hg) at screening were as follows: stage 1, 3.1; stage 2, 6.0; stage 3, 11.2; stage 4, 22.1. An increased risk of developing ESRD occurred after 2 years for those with stage 4 hypertension ($p<0.01$), but took 7–9 years for those with stage 1–3 hypertension ($p<0.01$). It was estimated that for every 16-mm Hg increase in systolic blood pressure, there was a 1.8 relative risk of developing ESRD compared with those with optimal blood pressure.

Similarly, the Hypertension Detection and Follow-up Program (HDFP), an observational study with more than 10,000 patients, noted that a 5-year risk of elevated serum creatinine level (> 2.0 mg/dl) was strongly related to baseline diastolic blood pressure ($p<0.05$).[33] The incidence per 1000 patients was 13.2, 34.4, and 63.7 for patients with baseline diastolic blood pressures of 90–104, 105–115, or greater than 115 mm Hg, respectively.

The MRFIT and HDFP studies demonstrated a relationship between hypertension and CKD; however, neither study measured kidney outcomes as a primary end point. In two other trials, the primary outcome measured the effect of blood pressure lowering on the progression of renal disease. In the Modification of Diet in Renal Disease study, 840 patients with different levels of CKD were randomly assigned to usual blood pressure control (mean arterial pressure [MAP] < 107 mm Hg in those aged ≤ 60 yrs and < 113 mm Hg in those aged > 60 yrs) or aggressive blood pressure control (MAP < 92 mm Hg in those aged ≤ 60 yrs and < 98 mm Hg in those aged > 60 yrs).[34] Any antihypertensive agent could be used, but angiotensin-converting enzyme (ACE) inhibitors, diuretics, and calcium channel blockers were preferred. Declines in GFR were lower for patients assigned to the aggressive blood pressure control group, and this relationship was strongest in patients with greater degrees of proteinuria. A slower progression of proteinuria was also seen in the aggressive blood pressure control group. The rate of kidney function decline in patients with proteinuria (> 1 g/day) was slowest when an MAP of 92 mm Hg (blood pressure 125/75 mm Hg) was achieved. In patients with proteinuria of 0.25–1.0 g/day, the rate of decline in kidney function was slowest with an MAP of 98 mm Hg (blood pressure 130/80 mm Hg). The authors concluded that proteinuria is an independent risk factor for

progression of kidney disease and that those patients with greater than 1 g/day of proteinuria should have a target blood pressure of 125/75 mm Hg and those patients with 0.25–1.0 g/day of proteinuria should have a target blood pressure of 130/80 mm Hg.

More recently, the African American Study of Kidney Disease and Hypertension (AASK) trial addressed the question of whether more aggressive blood pressure goals are indicated in African-American patients with hypertensive kidney disease.[36] For inclusion, patients had a GFR of 20–65 ml/minute and could not have diabetes. Participants were randomly assigned in a 3 x 2 factorial design to either an aggressive blood pressure arm (MAP < 92 mm Hg, blood pressure < 130/80 mm Hg) or less aggressive blood pressure arm (MAP 102–107 mm Hg, blood pressure = 140/90 mm Hg). Then, patients were randomly assigned to receive metoprolol, ramipril, or amlodipine, and dosages were titrated to target blood pressure. If target blood pressure could not be achieved, additional agents could be added; however, these agents could not be in any of the classes represented by study drugs. The primary end point was the slope of the GFR change. A secondary outcome of combined clinical events (50% decrease in GFR, ESRD, or death) was prespecified. One thousand ninety-four participants were randomized in this study. The aggressive care group achieved an MAP of 95 mm Hg, and the usual care group achieved an MAP of 104 mm Hg. No difference was noted in the slope of GFR decrease between the aggressive care group and the usual care group (p=0.24). Also, no significant difference was noted in combined end points between these groups (p=0.85). No significant difference in the slope of GFR decline was found among patients with higher levels of proteinuria. The authors concluded that blood pressure reduction beyond those levels currently recommended in guidelines is unlikely to provide additional renal protection. Results from the AASK trial formed the basis for the recommendations from the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and from the NKF that patients with CKD should be treated to a blood pressure goal of less than 130/80 mm Hg and not a lower blood pressure as previously advocated.[37, 38]

Blood Pressure and Diabetic Nephropathy

Patients with diabetes constitute the largest group of patients to develop nephropathy. These patients have hyperglycemia as a risk factor for nephropathy; however, the effect of hypertension and its combined effect with hyperglycemia on progressive kidney disease are important.

In an observational trial, the authors determined various predictors for progression of diabetic nephropathy among 301 patients with type 1 diabetes.[39] Those patients with hypertension received a variety of antihypertensive agents to maintain blood pressure below 140/90 mm Hg. Patients were followed for a median of 7 years, and GFR was measured a median of 8 times. The average rate of GFR decline was 4.0 ml/minute/year. Patients who were normotensive at baseline (< 140/90 mm Hg) had a slower GFR decline of 1.9 ml/minute/year compared with 4.3 ml/minute/year for patients who were hypertensive at baseline (p<0.01). However, MAP was lower in these normotensive patients (95 mm Hg) than in the hypertensive patients (102 mm Hg). When normotensive patients were compared with hypertensive patients who were well controlled (i.e., had the same blood pressure level as that of normotensive patients), no difference was noted in decline of GFR (p>0.05). The independent variables predictive of progression of nephropathy were MAP, albuminuria, A1C, and serum cholesterol level. The interaction between hyperglycemia and hypertension was impressive; those with an MAP greater than 102 mm Hg and an A1C greater than 9.2% had a decline in GFR of 6.1 ml/minute/year. Those with an MAP less than 102 mm Hg and an A1C less than 9.2% had an annual decline in GFR of 1.5 ml/minute/year (p<0.01). These results were independent of the antihypertensive agent prescribed.

As discussed, elevated blood pressure is a modifiable risk factor in the development and progression of CKD. It is also important to remember that many of the risk factors and comorbidities associated with CKD put the patient at increased risk for vascular events. The close relationship between the various organ systems damaged by longstanding hypertension make it difficult for researchers and clinicians to isolate a specific insult as the most important in a patient's overall health. As such, we must consider both renal protection and vascular risk reduction when choosing the blood pressure goal and agent of choice for managing hypertension.

Treatment of Hypertension

The largest trial comparing different agents for the initial management of hypertension has been

the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[40] In this study, more than 42,000 patients were randomly assigned to receive either a thiazide diuretic (chlorthalidone), an ACE inhibitor (lisinopril), a calcium channel blocker (amlodipine), or an α-blocker (doxazosin) as initial hypertension treatment. Patients were aged 55 years or older and had at least one additional risk factor for coronary heart disease (CHD). The study population included more than 15,000 patients with diabetes. In addition, study participants had an average baseline GFR of 78 ml/minute, indicating that most patients had at least mild CKD. The ALLHAT study outcomes included relevant end points such as the development of ESRD, combined CHD, and all-cause mortality. Final results indicated that there was no difference in the development of ESRD, combined CHD, or death among the groups (but the doxazosin arm was stopped early because of an increased frequency of heart failure compared with the diuretic arm). As such, there appears to be little difference in renal protection with use of these initial pharmacotherapeutic strategies. However, results of subgroup analyses of patients with diabetes and varying degrees of CKD have not yet been published. It is possible that these data, when available, may reveal benefits to using one agent over another in these hypertensive populations.

Many other studies have evaluated the effect of antihypertensive treatment on the progression of microalbuminuria. The ACE inhibitors have the greatest amount of data regarding protection against the progression of both diabetic and nondiabetic kidney disease. One of the earliest and longest trials of ACE inhibition for diabetic kidney disease was reported in 1993.[41] Ninety diabetic patients with microalbuminuria were randomly assigned to either placebo or enalapril 10 mg/day for a 5-year duration. Patients assigned to receive enalapril had a significantly lower degree of albuminuria progression ($p<0.05$). Only 12% of enalapril-treated patients developed macroalbuminuria versus 42% in the placebo group. Average kidney function (reciprocal creatinine) decreased by 13% in the placebo group, whereas there was no decrease in the enalapril group ($p<0.05$). In a meta-analysis among 698 patients with type 1 diabetes and microalbuminuria, investigators showed that ACE inhibition is beneficial for preventing progression of microalbuminuria or development of macroalbuminuria and for increasing the likelihood of achieving normoalbuminuria.[42]

More recently, trials have been conducted to investigate the role of angiotensin II receptor blockers (ARBs) in the progression of CKD. One group conducted a 2-year, double-blind, placebo-controlled trial to determine if irbesartan 150 or 300 mg/day would be effective for preventing the progression of microalbuminuria to nephropathy in hypertensive individuals with type 2 diabetes.[43] At the conclusion of the trial, the hazard ratio for developing nephropathy, adjusted for baseline albuminuria and achieved blood pressure during the study, was 0.56 in the 150-mg group and 0.32 in the 300-mg group compared with placebo ($p<0.05$).

Although these data clearly demonstrate that blockade of the renin-angiotensin system decreases the progression of microalbuminuria to macroalbuminuria, a more clinically relevant end point may be the development of fatal CHD, ESRD, or all-cause mortality. Several other trials have evaluated the effect of renin-angiotensin blockade on these end points.

In a pivotal trial, both renal and cardiovascular end points due to ACE inhibition were examined among patients with diabetes.[44] This randomized, double-blind, placebo-controlled trial compared captopril 25 mg 3 times/day with usual care (including blood pressure management) on the development of worsening kidney function in patients with macroalbuminuria. Worsening kidney function was defined as a doubling of the serum creatinine concentration. Four hundred nine patients were randomized and followed for 3 years. At the conclusion of the study, serum creatinine concentration doubled in 12.1% of captopril-treated patients and 21.3% of patients in the placebo group ($p=0.007$). The risk reduction for doubling serum creatinine concentration with captopril was greater as baseline kidney function decreased. Overall, captopril was associated with a 50% reduction in the risk of death, dialysis, or transplantation ($p=0.006$).

Another major study in which the benefits of ACE inhibition were studied was the Micro-Heart Outcomes Prevention Evaluation (HOPE) study.[45] The HOPE study was designed to determine the effect of ramipril on vascular events in a high-risk population. Micro-HOPE was a substudy of patients with diabetes and was designed to assess the effect of ACE inhibition on microalbuminuria and cardiovascular outcomes. Patients in the Micro-HOPE study had a history of diabetes and at least one additional cardiovascular risk factor. The results of HOPE were mirrored in Micro-

HOPE. A significant reduction (25%) was noted in the risk of experiencing a cardiovascular event in patients receiving ramipril ($p<0.05$). Furthermore, a 25% reduction in the development of overt nephropathy and ESRD was noted among patients receiving ramipril ($p=0.072$). The protective effects of ACE inhibition were apparent, despite a very small decrease in blood pressure among patients receiving ramipril, and remained robust when adjustments were made for this blood pressure reduction. This beneficial effect, despite very little antihypertensive effect, further supports the concept that renal protection with ACE inhibition may be a blood pressure–independent phenomenon. Additional studies confirmed the renoprotective effects of ACE inhibition in patients with CKD.[46–48]

The ARBs also have been evaluated for their composite end points of nephropathy, CHD, and death. One group conducted a randomized, double-blind, placebo-controlled trial to evaluate irbesartan, amlodipine, and placebo on the development of doubling of serum creatinine concentration, ESRD, or death from any cause.[49] A total of 1715 patients were randomized and followed for an average of 2.6 years. The goal blood pressure was 135/85 mm Hg in all three groups. Treatment with irbesartan was associated with a 20% decrease in the composite end point compared with placebo ($p=0.02$) and a 23% decrease compared with amlodipine ($p=0.006$). Most of this difference appeared to result from a 33% decrease in the doubling of serum creatinine concentration versus placebo ($p<0.05$) and, to a lesser degree, a 23% decrease in the development of ESRD. Neither irbesartan, amlodipine, nor placebo provided any mortality benefit.

Similarly, another group conducted a randomized, placebo-controlled trial to assess the effect of losartan on the primary composite end point of doubling of serum creatinine concentration, ESRD, or death from any cause.[50] Target blood pressure for the 3.4 years of this study was less than 140/90 mm Hg. Losartan was associated with a 16% risk reduction of the primary end point ($p=0.02$). Most of the beneficial effects for losartan versus placebo appeared secondary to reduced development for doubling serum creatinine concentration ($p=0.006$) and ESRD ($p=0.002$), rather than death ($p=0.88$).

Of importance, there are several limitations to the available data on antihypertensive drugs and renal protection. These include heterogeneity of populations studied (type 1 vs type 2 diabetes as well as nondiabetic nephropathy), differing definitions for micro- and macroalbuminuria, clinical trial end points, intensity of blood pressure control, sample size, and duration of follow-up. One of the most contentious issues surrounding the various trials is the degree of blood pressure lowering between control and treatment groups. In most studies, patients randomly assigned to receive an ACE inhibitor or ARB had a small but statistically significant reduction in blood pressure. Nonetheless, the beneficial effects due to disruption of the renin-angiostensin-aldosterone system (RAAS) appear robust, as decreased renal injury remains evident after adjustment for blood pressure values. Key areas for future investigation include dual inhibition of the RAAS by simultaneous ACE inhibitor and ARB administration and blockade of the aldosterone pathway.[51, 52]

Several different sets of evidence-based guidelines exist for the management of blood pressure, with or without renal injury. These are summarized in Table 4.[19, 37, 38, 53, 54] Lower blood pressure targets are uniformly recommended for patients with renal injury. The ACE inhibitors and ARBs are the most commonly recommended agents, as supported by the previously described clinical studies.

Lipid Management

The appropriate management of dyslipidemia plays an important role in the overall care of the patient with CKD. Unfortunately, many patients with CKD who are candidates for lipid-lowering therapy do not receive this drug therapy.[55] This may be due to a combination of lack of perceived benefit and concerns regarding toxicity in this patient population. In addition, the data associating dyslipidemia with the progression of renal disease is unclear. Therefore, lipid-lowering therapy is not traditionally considered as part of the available drug therapies for these patients. However, recognition of the cardiovascular risk among patients with CKD should prompt clinicians to consider evaluation and treatment of dyslipidemia.

Many large clinical trials have demonstrated the benefits of lowering lipid levels in both medium- and high-risk patient populations. Subgroup analyses of these studies show that patients with mild CKD benefit to a similar degree as those with intact kidney function.[56, 57] Unfortunately, patients with more advanced stages of CKD have been excluded from large lipid-intervention trials; therefore, benefits and

Table 4. Summary of Recommendations from Treatment Guidelines

			Goal Blood Pressure (mm Hg)		
Guideline	Year	Country	No Kidney Disease	Chronic Kidney Disease	Preferred Agent(s)
NKF[38]	2004	United States	NR	< 130/80	ACEI, ARB, diuretic[a]
JNC 7[37]	2003	United States	< 140/90	Albuminuria or GFR < 60 ml/min: < 130/80	ACEI, ARB
ADA[19]	2003	United States	NR	All diabetics: < 130/80	ACEI, ARB
CHWG[53]	2002	Canada	< 140/90	Proteinuria < 1 g/day: < 130/80 Proteinuria ≥ 1 g/day: < 125/75	ACEI, ARB Thiazide
BHS[54]	1999	United Kingdom	< 140/85	Proteinuria < 1 g/day: < 130/80 Proteinuria ≥ 1 g/day: < 125/75	ACEI, ARB

NKF = National Kidney Foundation; NR = no recommendation; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; JNC = Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; GFR = glomerular filtration rate; ADA = American Diabetes Association; CHWG = Canadian Hypertension Working Group; BHS = British Hypertension Society.
[a]ACEI or ARB preferred for all patients with diabetic kidney disease and patients with nondiabetic kidney disease in whom the spot urine total protein:creatinine ratio is ≥ 200 mg/g. Diuretics are preferred for patients with nondiabetic kidney disease in whom the spot urine total protein:creatinine ratio is < 200 mg/g.

Table 5. Features of the National Kidney Foundation K/DOQI Guidelines that Differ from Those of the National Cholesterol Education Program Adult Treatment Panel III

NKF K/DOQI Guidelines	Adult Treatment Panel III Guidelines
Patients with CKD should be considered to be in the highest risk category.	Patients with CKD should not be managed differently from other patients.
Evaluation of dyslipidemias should occur at presentation with CKD, following a change in kidney therapy modality, and annually.	Evaluation of dyslipidemias should occur every 5 years.
Drug therapy should be used for LDL level of 100–129 mg/dl after 3 months of therapeutic lifestyle change.	Drug therapy is considered optional for LDL level of 100–129 mg/dl.
Initial drug therapy for high LDL level should be with a statin.	Initial drug therapy for high LDL level should be with a statin, bile acid sequestrant, or nicotinic acid.
Recommendations are made for patients < 20 years old.	No recommendations are made for patients < 20 years old.
Fibrates may be used in stage 5 CKD for patients with triglyceride levels ≥ 500 mg/dl, and for patients with both triglyceride levels ≥ 200 mg/dl and non-HDL cholesterol levels ≥ 130 mg/dl who do not tolerate statins.	Fibrates are contraindicated in stage 5 CKD.
Gemfibrozil may be the fibrate of choice for treatment of high triglycerides in patients with CKD.	No preferences are indicated for which fibrate should be used to treat hypertriglyceridemia.

NKF = National Kidney Foundation; K/DOQI = Kidney Disease Outcomes Quality Initiative; CKD = chronic kidney disease; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol.
To convert mg/dl to mmol/L, multiply triglycerides by 0.01129 and cholesterol by 0.02586.
Reprinted with permission from reference 58.

risks are difficult to predict accurately.

Dyslipidemia in the patient with CKD may require a different screening and management approach than in the other populations.[58] Dyslipidemia may be secondary to proteinuria, hyperglycemia, or immunosuppressive drugs, all requiring a slightly tailored approach for optimal management.[58] Furthermore, patients with advanced stages of CKD may have altered metabolism and elimination of lipid-lowering drugs, possibly changing the safety profiles of commonly used agents. It is interesting to recognize that the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, may have beneficial effects on maintenance of kidney function in patients with CKD. Many small studies of short duration have been conducted to evaluate lipid-lowering agents, especially statins, and their effect on preserving kidney function.[59–72] A meta-analysis of these trials confirmed the

beneficial effect of lipid-lowering agents on preservation of kidney function.[73] Unfortunately, a clear role for lowering lipid levels and renoprotection cannot be discerned until large, randomized controlled trials are conducted. As such, prevention of CHD remains the primary goal of lipid management in patients with CKD.

In general, screening recommendations for patients with CKD should follow the recommendation from the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines. Although all individuals older than 20 years should be screened every 5 years, patients with CKD require more frequent assessment of fasting lipid concentrations because of proteinuria, dialysis-induced alterations in lipoprotein concentrations, nutritional supplementation, dietary modification, and immunosuppressive drugs.[58] Patients in later stages of CKD may require a lipid reevaluation 3 months after a change in any of the variables listed above. Additional differences between the ATP III guidelines and the NKF K/DOQI guidelines are listed in Table 5.

Treatment Goals

The ATP III guidelines recognize CKD as a cause of secondary dyslipidemia but do not specifically identify CKD as a risk factor for CHD. However, the K/DOQI guidelines consider CKD to be a CHD equivalent.[58] The K/DOQI guidelines also recommend an LDL target of less than 100 mg/dl, with statins recommended as first-line therapy and more frequent assessment of lipid status. To our knowledge, there are no large, randomized, well-conducted trials of lowering of lipid levels in patients with CKD to determine the optimal degree to which levels should be lowered and which lipid-lowering agent(s) is superior.

If one considers the likely comorbidities present in patients with CKD, virtually all patients will have an ATP III LDL goal of less than 130 mg/dl and many will have a goal of less than 100 mg/dl. Although it is not unreasonable to establish an LDL target of less than 100 mg/dl in patients with CKD, specific data showing the benefits with this degree of lowering the lipid level are lacking. Of interest, more recent data from the Heart Protection Study indicate that the LDL level may not be as important in vascular risk reduction as previously thought.[57] Patients considered to be at high risk for CHD were included in this study, including diabetic patients with at least one other cardiac risk factor. Patients received either simvastatin 40 mg or placebo and were followed for an average of 5 years. Patients randomly assigned to receive statin therapy experienced 25% fewer vascular events than those randomly assigned to receive placebo, irrespective of baseline or on-treatment LDL concentrations. These findings were particularly robust in the subset of patients with mild CKD.

The priority when managing dyslipidemia is LDL level. The LDL level should be at least less than 130 mg/dl. Patients considered to be at very high risk (10-yr risk of CHD > 20%) should have an LDL target of less than 100 mg/dl. If LDL goals are not achieved after 3 months of lifestyle modification, statin therapy should be started. Fibrate therapy should be started in patients with triglyceride levels greater than 500 mg/dl who have failed after 3 months of lifestyle modification. The fibrate of choice, particularly in patients with more advanced CKD, is gemfibrozil. Other fibrates may require dosage reduction in more advanced stages of CKD. The combination of statins and fibrates should be avoided. Statins may be combined with bile acid sequestrants if triglyceride levels are less than 400 mg/dl. Alternatively, nicotinic acid may be used in situations where bile acid sequestrants are inappropriate or ineffective. The potential benefit of combination therapy must be closely weighed against the increased risk of adverse effects, adherence issues, and cost.

The clinician must carefully consider the effect of altered metabolism and elimination of lipid-lowering agents, irrespective of class, in patients with CKD. Particular consideration must be given to the possibility of drug interactions, especially after transplantation. Clinicians must closely follow patients and assess for signs, symptoms, or laboratory abnormalities associated with drug toxicity.

Tobacco Cessation

Tobacco use is a well-documented cause or risk factor for many diseases including heart disease, peripheral vascular disease, lung cancer, oral cancer, and chronic obstructive pulmonary disease. Often unrecognized is the fact that smoking exerts damaging effects on the kidney and has recently been identified as a risk factor for the progression of CKD. In otherwise healthy adults, research has shown that smoking, in a dose-dependent manner, increases urinary

Table 6. The Five A's for Brief Smoking Cessation Intervention[78]

The Five A's	Intervention
Ask about tobacco use.	Identify and document tobacco use status for every patient at every visit.
Advise to quit.	In a clear, strong, and personalized manner, urge every tobacco user to quit.
Assess willingness to make a quit attempt.	Is the tobacco user willing to make a quit attempt at this time?
Assist in quit attempt.	For patients willing to make a quit attempt, use counseling and pharmacotherapy to help them quit.
Arrange follow-up.	Schedule follow-up contact, preferably within the first week after the quit date.

excretion of albumin.[74, 75] There is also evidence that smoking may accelerate a decline in GFR, especially among men.[32, 74] The harmful effects of smoking on kidney function are much more pronounced among patients with concomitant hypertension and/or diabetes.[76] Smoking is a predictor of albuminuria among patients with essential hypertension. Likewise, smoking has been found to be an independent predictor of microalbuminuria in both diabetic and non-diabetic subjects.[77] Collectively, this evidence highlights the importance of promoting the cessation of smoking or tobacco use to reduce health risk among all adults, including patients at risk for or with a diagnosis of CKD.

Recent clinical practice guidelines on tobacco cessation have been published to assist health care practitioners in delivering cessation support.[78] The guidelines clearly recommend that every tobacco user should be offered at least a brief smoking cessation intervention. Evidence demonstrates that the success rate for smoking abstinence can be increased when interventions are provided by many clinician types.[79–84] Therefore, the guidelines recommend that all clinicians, including pharmacists, provide smoking cessation interventions.

An acronym, known as the Five A's, is suggested to provide smoking cessation counseling (Table 6). To assist those smokers willing to make a quit attempt, behavioral modification counseling is first-line therapy. Pharmacotherapeutic agents are recommended as an adjunct therapy. Although, to our knowledge, no specific clinical trials have evaluated smoking cessation agents in patients with CKD, all therapies approved by the United States Food and Drug Administration would be expected to be effective. In general, no single cessation product has been proved superior to another. Patient preference and proper use of the drugs are most important for selecting and implementing therapy.

Despite the paucity of data, there are several therapeutic considerations when using smoking cessation therapies among patients with CKD. Some evidence indicates that renal elimination of nicotine is slowed as CKD progresses.[85] Therefore, smokers with CKD may have higher nicotine concentrations and may also have a higher tolerance for nicotine than those without CKD. Consequently, higher initial dosages of nicotine replacement therapy may be required to curb withdrawal symptoms in these patients. However, during a cessation attempt and tapering of nicotine replacement therapy, lower dosages of nicotine replacement therapy may be used to achieve a relatively higher steady-state nicotine concentration. Also, little data exist on the elimination of bupropion in patients with CKD.[86] Elimination of the major active metabolites of bupropion may be impaired in patients with reduced kidney function, but studies have not been performed. Therefore, bupropion for smoking cessation should be used with caution in patients with severe CKD.

Anemia

The primary pathophysiologic mechanism for anemia in patients with CKD is a progressive, relative erythropoietin deficiency as the kidney's functional capacity to produce erythropoietin diminishes. Therefore, a normochromic, normocytic anemia is common in patients with CKD. Additional factors such as iron deficiency also contribute to the development of anemia in this population. According to recent data from the Third National Health and Nutrition Examination Survey, approximately 830,000 adults have CKD-associated anemia, defined as a hemoglobin level below 11 g/dl.[87] If defined as a hemoglobin level below 12 g/dl, the number of adults increases to 1.6 million. Despite the prevalence of anemia in CKD, it is underrecognized and undertreated. Data confirm that less than

30% of patients report receiving anemia treatment before dialysis.[88] Benefits of early treatment of anemia in patients with CKD include decreased hospitalizations for cardiovascular complications and improved survival, exercise capacity, cognitive function, and quality of life.

In a study of 176 patients, the relationship between declining GFR and the development of anemia was established.[89] Anemia manifested and was positively correlated with a GFR of less than 40 ml/minute. In a more recent study, 403 patients with a baseline serum creatinine level above 2.3 mg/dl were followed prospectively to analyze the influence of various factors on the development of anemia and the use of erythropoietin.[90] Most patients developed anemia when GFR was less than 20 ml/minute.

Complications of anemia in CKD contribute to the high rates of cardiovascular morbidity and mortality.[91] Chronic kidney disease contributes to the development of left ventricular hypertrophy. In a study of 175 patients with a mean GFR of 25.5 ml/minute, 39% had evidence of left ventricular hypertrophy by echocardiography.[92] In another study of more than 400 patients receiving dialysis, left ventricular hypertrophy was present in 74%.[93] Anemia appears to be associated with these changes in left ventricular mass. In a prospective trial, 432 patients receiving dialysis were followed for approximately 3.4 years.[94] Through multiple logistic regression modeling, left ventricular mass index was shown to increase by 5.8 g/m^2 for every 1-g/dl decrease in hemoglobin level. In addition, the same investigators showed that for every 1-g/dl decrease in hemoglobin level, there was a 42% increased risk of left ventricular dilatation. These data support the association between cardiovascular disease and anemia.

Anemia also contributes to a poor quality of life among patients with CKD. Markers of quality of life correlate with the degree of anemia and improve with treatment.[95] As anemia worsens, cognitive function deteriorates. Several studies have documented improvements in both neuropsychologic and neurophysiologic tests with treatment of anemia.[96] Patients have reported improvements in energy, activity levels, sleep quality, eating behavior, satisfaction with health, and sexual function.[97] The ramifications from anemia complications are clear and support the need for aggressive screening, treatment, and monitoring before patients develop ESRD.

The K/DOQI working group for anemia has developed clinical practice guidelines for anemia of CKD.[98] These guidelines outline the proper workup, management, and monitoring of this complication. Screening for anemia should be conducted routinely for all patients with reduced GFR. For those patients with CKD, a workup for anemia should begin once the hemoglobin level is less than 12 g/dl in adult men and postmenopausal women and less than 11 g/dl in premenopausal women and prepubertal patients. Iron stores should also be evaluated to ensure efficient red blood cell production. The goal of anemia therapy should be an achieved target hemoglobin level of 11–12 g/dl, possibly up to 13 g/dl. Hemoglobin levels below 11 g/dl are considered unacceptable.

Contemporary management of CKD-associated anemia involves the use of both erythropoietin or darbepoetin alfa, as well as supplemental oral and/or intravenous iron. Although guidelines for the dosing of erythropoietin are well established, dosing of this agent in clinical practice does not adhere to these recommendations. Common mistakes for erythropoietin therapy include premature dosage increases, a starting dosage that is too high, and changing dosages by too large a margin.[99] Pharmacists can play a key role in this environment by developing administration protocols, monitoring patient responses to therapy, and educating prescribers on appropriate dosing strategies.

The longer half-life of darbepoetin alfa has improved management for the ambulatory CKD population. Benefits of this drug may include less frequent dosing, lower use of supplies, fewer office visits, and improved adherence.[100] Patients receiving therapy with erythropoietic agents require consistent monitoring of hemoglobin and hematocrit for dose and frequency changes. Finally, erythropoietic proteins have been associated with various adverse events including hypertension or worsening blood pressure, seizures, hyperkalemia, and increased risk of blood clots.[101] Pharmacists should be aware of these complications and routinely screen for adverse effects in this patient population. Pharmacists may be the first clinicians to recognize worsening blood pressure and facilitate treatment for this adverse event.

Pharmacist can also facilitate appropriate iron therapy to complement anemia management. With iron necessary for efficient red blood cell production, it is imperative that patients achieve and maintain normal iron stores. The K/DOQI guidelines suggest that sufficient iron should be

Table 7. Recommended Goal Concentrations for Bone Disease in Chronic Kidney Disease[107]

Laboratory Parameter	CKD Stage 3	CKD Stage 4	CKD Stage 5
PTH (pmol/L)	35–70	70–110	150–300
PO_4 (mg/dl)	2.7–4.6	2.7–4.6	3.5–5.5
Ca (mg/dl)	8.4–10.2	8.4–10.2	8.4–9.5
Ca-PO_4 product (mg^2/dl^2)	< 55	< 55	< 55

CKD = chronic kidney disease; PTH = parathyroid hormone, PO_4 = serum phosphorous, Ca = serum-corrected calcium.

administered to maintain a transferrin saturation of 20% or greater and a serum ferritin level of 100 ng/ml or greater.[98] At least 200 mg/day of oral elemental iron supplementation should be administered for adults. However, many patients with CKD may require intravenous iron therapy to achieve target iron stores. Therefore, several dosing strategies for intravenous iron therapy are outlined in the K/DOQI guidelines. When starting therapy with erythropoietic agents, the transferrin saturation and serum ferritin level should be monitored every month in patients not receiving intravenous iron and once every 3 months in patients receiving intravenous iron. Once the goal hemoglobin level is achieved, iron status should be monitored every 3 months.

Hyperparathyroidism and Renal Osteodystrophy

Evidence indicates that the derangements in mineral and bone metabolism in CKD are associated with increased morbidity and mortality.[102–104] Progressive CKD leads to hypocalcemia, subsequent secondary increases in parathyroid hormone levels, and bone metabolism abnormality, known collectively as renal osteodystrophy. These laboratory alterations can occur in the early stages of CKD and continue as kidney function deteriorates. Several pathogenetic mechanisms create the environment for hypocalcemia to develop. These include phosphate retention due to inability of the kidney to eliminate the mineral, skeletal parathyroid hormone resistance, and inability of the kidney to activate vitamin D needed for calcium absorption from the gut. The complications of renal osteodystrophy can affect tissues outside bone, including soft-tissue calcification, pruritus, proximal myopathy, skin ulceration, and soft-tissue necrosis. The long-term effects of soft-tissue calcifications can lead to impaired pulmonary function, pulmonary fibrosis, chronic heart failure, cardiac arrhythmias, and ischemic heart disease.[104–106] Therefore, strategies for early prevention and management of renal osteodystrophy are extremely important in improving patients' quality of life and longevity. Recently, the NKF K/DOQI published guidelines for bone metabolism and disease in patients with CKD.[107]

Secondary hyperparathyroidism develops in patients with CKD once there is a loss of approximately 50% of kidney function, corresponding to stage 3 CKD. Monitoring of serum chemistries for calcium, phosphorus, and parathyroid hormone should begin once patients enter stage 3 CKD (GFR < 60 ml/min). The frequency of monitoring varies from yearly to monthly according to the progressive stage of CKD.[107] Proper management of metabolic disturbances and bone disease in patients with CKD is multifactorial. This includes maintenance of goal concentrations for serum phosphorous, calcium, and parathyroid hormone. The K/DOQI guidelines provide practitioners with goals for each laboratory value (Table 7). The goals differ depending on the stage of CKD. In general, the guidelines group recommendations for patients with stage 3 or 4 CKD and patients with stage 5 CKD.

When phosphorus retention and elevated phosphorus concentrations are observed, restriction of dietary phosphorus (< 1 g/day) and use of phosphate binders become crucial. Dietary phosphorus restriction in early CKD is warranted as long as dietary protein requirements are met. Calcium-based phosphate binders and the nonelemental binder, sevelamer hydrochloride, can be used if dietary phosphorus restriction is unsuccessful. Although, to our knowledge, no prospective, controlled trials have evaluated the efficacy of phosphate binders in stages 3–4 CKD, the K/DOQI guidelines suggest that initial therapy should use calcium-based binders. Most phosphate binders have clear evidence supporting their efficacy in stage 5 CKD, but caution is warranted with liberal use of calcium-based

binders for these patients. Excessive calcium ingestion has been linked with an increased risk of vascular and tissue calcification. For all patients with CKD in stages 3–5, total daily dietary elemental calcium should not exceed 2000 mg, including calcium intake from phosphate binder therapy. Corrected total calcium levels should be maintained within the normal therapeutic range by using both dietary and pharmacologic interventions. To maintain both corrected total calcium and serum phosphorus in their proper therapeutic ranges, attention should also be directed to maintaining a calcium-phosphorus product of less than 55 mg^2/dl^2.

In addition to both calcium and phosphorus derangements, patients with CKD are at risk for developing vitamin D (25-hydroxyvitamin D) insufficiency. These individuals need to be treated with vitamin D therapy. Treatment with vitamin D should be integrated with serum calcium, phosphorous, and parathyroid hormone measurements. Several algorithms have been developed in the K/DOQI guidelines to assist practitioners in the dosing of vitamin D therapies.[107] After starting vitamin D therapy, monitoring of parathyroid hormone, vitamin D, and calcium levels is warranted.

Although less common today, aluminum accumulation can occur in patients with CKD. This is particularly evident in patients undergoing dialysis but is of concern once GFR decreases below 30 ml/minute. Aluminum toxicity is associated with devastating neurologic adverse effects. Therefore, it is prudent to monitor aluminum concentrations in these patients and, if necessary, treat accordingly with deferoxamine. Aluminum-containing compounds (e.g., antacids, sucralfate) and citrate salts (e.g., calcium citrate) should be avoided since they enhance absorption of aluminum. Certain additional risk factors may contribute to bone disease and include drug exposure (e.g., glucocorticoids), comorbid disease states (diabetes), and metabolic abnormalities associated with progressive kidney damage (metabolic acidosis). Awareness of these additional risk factors can minimize their effect on bone disease associated with CKD.

Additional Considerations

Other interventions to prevent complications in patients with CKD are recommended. Low-dose daily aspirin is a primary prevention strategy recommended by the United States Preventive Services Task Force to reduce cardiovascular risk in patients at an increased risk for CHD.[108] Patients with CKD are independently at high risk for CHD, and the presence of additional risk factors (advanced age, elevated blood pressure, diabetes, dyslipidemia, family history of CHD, and smoking) warrants aspirin preventive therapy. Influenza, pneumococcal, and hepatitis B vaccinations should be strongly considered, as patients with kidney disease are a target population who are at high risk for infection-related complications.[109, 110] In addition, it is important to estimate and document GFR (using an appropriate prediction equation like Cockcroft-Gault or Modification of Diet in Renal Disease) at least annually in all patients.[111, 112] Patients with stage 3 or higher CKD should have GFR documented at least biannually. Table 8 contains a summary of recommendations to improve the care of patients with CKD.

Implicit in this population is the avoidance of pharmacologic agents or situations that may cause acute decline in GFR. Volume depletion, obstruction of the urinary tract, intravenous radiographic contrast agents, selected antimicrobials (e.g., aminoglycosides, amphotericin B), nonsteroidal antiinflammatory agents (including cyclooxygenase 2–selective inhibitors), cyclosporine, and tacrolimus are all identified as drug-induced causes of acute renal function decline in patients with CKD.[5] These pharmacologic agents should be avoided or used with caution in patients with CKD.

The ACE inhibitors and ARBs are also known to cause acute decline in GFR and a corresponding rise in serum creatinine level. The decline in GFR is a hemodynamic response and does not signal renal damage. Rarely do these agents cause frank renal injury. The benefits of continued therapy with an ACE inhibitor or ARB outweigh the risks. If the serum creatinine level increases several tenths (e.g., from 1.5 to 1.9), decreasing the dosage and slowly titrating the dosage will minimize the risk of kidney damage.

Documentation of Pharmaceutical Care in Patients with CKD

The effect of pharmacists' involvement in the multidisciplinary treatment of common causes of ESRD, such as hypertension and diabetes mellitus, is well documented. In one study, physician-pharmacist comanagement of hypertension led to significantly more (60% vs 43%)

Table 8. Summary of Recommendations for Clinicians Treating Patients with Chronic Kidney Disease

Stage	Actions[a]
At risk[b]	Do annual spot urine test for albumin. Perform annual estimation and documentation of GFR. Control blood pressure to < 140/90 mm Hg (< 130/80 mm Hg for patients with diabetes). Screen for diabetes and/or treat to recommended goals. Screen for dyslipidemia and/or treat to recommended goals. Promote smoking cessation, if indicated.
1–2	Control blood pressure to < 130/80 mm Hg. Encourage daily aspirin therapy. Recommend annual flu vaccine. Administer pneumococcal and/or hepatitis B vaccine, if needed. Limit exposure of nephrotoxic drugs.
3–5	Perform biannual estimation and documentation of GFR. Screen for and/or treat anemia. Screen for and/or treat hyperparathyroidism. Avoid use of nephrotoxic drugs.

GFR = glomerular filtration rate.
[a]Each stage includes actions from preceding stages.
[b]Any patients with risk factors for developing chronic kidney disease.

patients achieving blood pressure control (p=0.02) compared with those receiving usual care.[113] The comanaged patients experienced average systolic blood pressure reductions of 22 mm Hg, compared with 11 mm Hg in the usual care group. Likewise, when Veterans Affairs patients with hypertension were provided patient-centered pharmaceutical care for 6 months, greater reductions in systolic blood pressure (8.2 vs 1.3 mm Hg, p=0.044), improved drug therapy compliance, and decreased hospitalizations (p=0.043) were noted compared with a usual care control group.[114]

A similar effect was seen when pharmacists were involved in interdisciplinary efforts to treat diabetes. One group reported a mean A1C reduction of 1.3% at 6 months (compared with 0.2% reduction for control patients) when patients were provided multidisciplinary care management, including a pharmacist (p<0.0001).[115] Both outpatient and inpatient service utilization were significantly lower in the patient group receiving team care (p<0.01). A multidisciplinary diabetic management group at the University of Mississippi likewise compared usual care by internal medicine physicians with multidisciplinary care.[116] Team care resulted in an average decrease in A1C of 2.06% vs 0.28% in the internal medicine clinic (p<0.001). Of importance, screening for microalbuminuria was performed more frequently in patients receiving team care than in those receiving usual care (86% vs 34%, p<0.01).[116] Another study of primary care physicians revealed that only 37% monitor for microalbuminuria appropriately in patients with diabetes and that referral rates to nephrologists were extremely low (3–11%) during early stages of CKD.[117] An opportunity for pharmacists exists by ensuring that monitoring for microalbuminuria is performed routinely along with appropriate communication to patients and primary care providers about the need to consult a nephrologist.

Involvement of the pharmacist in multidisciplinary care for patients at risk for CKD not only increases the likelihood of achieving treatment goals, but also results in lower health care utilization and presumably lower associated costs. Treatment of anemia has been shown to improve cardiac function and is associated with a decrease in the rate of GFR decline in patients with CKD.[118, 119] However, mean hematocrit values of patients beginning chronic dialysis averaged 27.7% in one study, with less than 30% of patients receiving erythropoietin therapy.[88] One study of 1936 patients undergoing dialysis revealed that despite a high overall utilization of services, only 10.5% received erythropoietin and only 38% received an ACE inhibitor in the 12 months before starting dialysis.[120]

Pharmacist-implemented anemia management protocols have proved successful in outpatient hemodialysis units.[121] Such management has been shown to reduce erythropoietin dosage requirements from 19,612 to 13,481 U/week, while maintaining stable hematocrit concentrations

in the 32–36% range.[122] Cost-benefit analyses of another pharmacist-managed anemia protocol in patients undergoing dialysis projected a cost savings of $1086/patient/year versus physician management.[123] Dosage reductions have justified the salaries for full-time pharmacist involvement in this arena.[124]

Although early recognition of secondary hyperparathyroidism is important for preventing long-term consequences, the activities of pharmacists in the care of patients with CKD who have secondary hyperparathyroidism not yet receiving dialysis therapy are not well described. Overall, phosphate binder therapy is underused in the CKD population.[120] When pharmacists collaboratively managed secondary hyperparathyroidism in patients already receiving hemodialysis, a reduction in moderate-to-severe hyperparathyroidism was seen with an associated decreased cost.[125] It was recommended that patient evaluation for secondary hyperparathyroidism (serum calcium, serum phosphorus, intact parathyroid hormone concentrations) begin when GFR is less than 60 ml/minute.[5] Perhaps if more pharmacists became involved in advocating or initiating these evaluations, a greater percentage of patients with CKD who have secondary hyperparathyroidism would receive appropriate therapy.

Drug counseling that emphasizes adherence is another area where pharmacists have an opportunity for involvement with patient care. Pharmacists' education for patients with ESRD after transplantation improves immunosuppressant adherence.[126] The same holds true for older patients receiving more than three drugs in a general practice environment[127] and for patients during hospital discharge.[128] This underscores the importance of drug counseling by pharmacists in all practice environments; however, room for improvement exists. One study of patients already undergoing dialysis demonstrated only 39% of patients undergoing hemodialysis recall all of their drugs and missed an average of 13 doses/month of phosphate binder therapy. Less than 15% identified pharmacists as their main source of drug information.[129] Data specific to patients with pre-ESRD are somewhat lacking, but the lack of reliance on pharmacy services is likely an issue in this population as well. Pharmacists are easily accessible to the public. This is an opportunity to improve drug adherence through education and should not be overlooked.

Drug noncompliance is more likely in patients without prescription coverage. The cost of antihypertensives, antidiabetic agents, and other drugs received by patients with CKD can be prohibitive for many patients. Again, pharmacists are distinctly prepared to assist patients with this barrier. For example, one large university medical center drug assistance program netted a 6-month savings of $127,447.[130] Referrals for Medicaid assessment and contact with individual state and industry-sponsored programs should be made for eligible patients. Several useful Internet tools are available to assist pharmacists: http://www.rxassist.org, http://www.needymeds.com, http://www.phrma.org.

The following is a summary of potential roles and responsibilities for pharmacists in the care of patients with CKD:

- Attainment of blood pressure goal
- Attainment of glycemic goals in those with diabetes
- Early evaluation and treatment for proteinuria
- Early evaluation and therapy for anemia
- Early evaluation and therapy for secondary hyperparathyroidism
- Attainment of lipid goals, where appropriate.
- Appropriate drug dosing adjustments
- Minimization of drug-related nephrotoxin exposure
- Provision of drug therapy instruction
- Screening for ability to afford drugs
- Education regarding smoking cessation, where appropriate

Summary

An increasing number of patients are expected to develop CKD in the future, especially due to the aging population. Recognizing and treating this disease during the initial stages are important, especially in primary care settings. Patients with CKD require evaluation, treatment, and control of primary care conditions, such as diabetes, hypertension, dyslipidemia, and smoking, to reduce progression of kidney damage. Of importance, comorbidity of CKD and these conditions confer additional treatment considerations. These patients may have distinct conditions such as anemia and secondary hyperparathyroidism that are not traditionally evaluated and monitored by primary care practitioners. Thus, many opportunities exist for pharmacists who practice in the primary care setting to improve the care of patients with CKD.

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