Managing advanced chronic kidney disease: A primary care guide

ABSTRACT
Chronic kidney disease (CKD) is a common disorder that requires close collaboration between the primary care physician and nephrologist. Most aspects of early CKD can be managed in the primary care setting with nephrology input. As the disease progresses, many aspects of care should be transitioned to the nephrologist, especially as the patient nears end-stage renal disease, when dialysis and transplantation must be addressed.

KEY POINTS
Steps to stabilize renal function include blood pressure and diabetes control.

Patients have a very high risk of cardiovascular disease, and one should try to reduce modifiable risk factors such as hypertension (which is also a risk factor for the progression of CKD) and hyperlipidemia.

In addition to controlling blood pressure, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduce proteinuria, a risk factor for progression of CKD.

Patients with CKD develop secondary hyperparathyroidism, hyperphosphatemia, and, in advanced CKD, hypocalcemia, all leading to disorders of bone mineral metabolism. Low vitamin D levels should be raised with supplements, and high phosphorus levels should be lowered with dietary restriction and phosphate binders.

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• Identify the cause of CKD, if possible; address potentially reversible causes such as obstruction or medication-related causes. If a primarily glomerular process (marked by heavy proteinuria and dysmorphic red blood cells and red blood cell casts in the urine sediment) or interstitial nephritis (manifested by white blood cells in the urine) is suspected, refer to a nephrologist early.

• Provide treatment to correct the specific cause (if one is present) or slow the deterioration of renal function.

• Address cardiovascular risk factors.

• Address metabolic abnormalities related to CKD.

• If the CKD is advanced, educate the patient about end-stage renal disease and its treatment options, and guide the patient through the transition to end-stage renal disease.

**WHEN SHOULD A NEPHROLOGIST BE CONSULTED?**

The ideal timing of referral to a nephrologist is not well defined and depends on the comfort level of the primary care provider.

Treatments to slow the progression of CKD and decrease cardiovascular risk should begin early in CKD (ie, in stage 3) and can be managed by the primary care provider with guidance from a nephrologist. Patients referred to a nephrologist while in stage 3 have been shown to go longer without CKD progression than those referred in later stages.4 Early referral to a nephrologist has also been associated with a decreased mortality rate.5 The studies that found these trends, however, were limited by the fact that patients with stage 3 CKD are less likely to progress to end-stage renal disease or to die of cardiovascular disease than patients with stage 4 or 5 CKD.

Once stage 4 CKD develops, the nephrologist should take a more active role in the care plan. In this stage, cardiovascular risk rises, and the risk of developing end-stage renal disease rises dramatically.6 With comprehensive care in a CKD clinic, even patients with advanced CKD are more likely to have a stabilization of renal function.7 Kinchen et al8 found that patients referred to a nephrologist within 4 months of starting dialysis had a lower survival rate than those referred earlier. Therefore, if a nephrologist was not involved in the patient’s care prior to stage 4, then a referral must be made.

**Recommendation.** Patients with stage 3 CKD can be referred for an initial evaluation and development of a treatment plan, but most of the responsibility for their care can remain with the primary care provider. Once stage 4 CKD develops, the nephrologist should assume an increasing role. However, if glomerular disease is suspected, we recommend referral to a nephrologist regardless of the estimated GFR.

**ELEVATED CARDIOVASCULAR RISK**

Patients with stage 3 CKD are 20 times more likely to die of a cardiovascular event than to reach end-stage renal disease.6 This increased risk does not quite reach the status of a cardiovascular disease risk equivalent, as does diabetes,9,10 but cardiovascular risk reduction should be a primary focus of care for the CKD patient.

The cardiovascular risk in part is attributed to a high prevalence of traditional cardiovascular risk factors, including diabetes mellitus, hypertension, and hyperlipidemia.11,12 About two-thirds of CKD patients have metabolic syndrome, which is a risk factor for cardiovascular disease and is associated with more rapid progression of CKD.13

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**Studies discussed in this article**

- **AASK**—African American Study of Kidney Disease and Hypertension40
- **ACCORD**—Action to Control Cardiovascular Risk in Diabetes37
- **CHOIR**—Correction of Hemoglobin and Outcomes in Renal Insufficiency78
- **CREATE**—Cardiovascular Reduction Early Anemia Treatment Epoetin79
- **HOPE**—Heart Outcomes Prevention Evaluation16
- **IDEAL**—Initiating Dialysis Early and Late90
- **IDNT**—Irbesartan Diabetic Nephropathy Trial46
- **PREVEND**—Prevention of Renal and Vascular End-stage Disease17
- **SHARP**—Study of Heart and Renal Protection28
- **TREAT**—Trial to Reduce Cardiovascular Events With Aranesp Therapy80
In addition, renal dysfunction, proteinuria, and hyperphosphatemia are also risk factors for cardiovascular disease.\textsuperscript{14–19}

The risk of death from a cardiovascular event increases as kidney function declines, with reported 5-year death rates of 19.5% in stage 2, 24.3% in stage 3, and 45.7% in stage 4 CKD. However, imbalance between mortality risk and progression to end-stage renal disease may be age-dependent.\textsuperscript{20} Younger patients (age 45 and younger) are more likely to progress to end-stage renal disease, whereas in older patients (over age 65), the relative risk of dying of cardiovascular disease is higher.

Aggressive lipid management

Hyperlipidemia is a common risk factor for cardiovascular morbidity and mortality in CKD.\textsuperscript{21} However, until recently, all studies of outcomes of patients treated for hyperlipidemia excluded patients with CKD. Post hoc analyses of these studies \textsuperscript{22–27} showed statins to be beneficial in primary and secondary cardiovascular prevention in patients with “normal” serum creatinine values but estimated GFR levels of 50 to 59 mL/min/1.73 m\textsuperscript{2}.

The SHARP trial\textsuperscript{28} was the first prospective trial to study lipid-lowering therapy in patients with CKD. In this trial, patients with various stages of CKD, including advanced CKD, had fewer major vascular events if they received the combination of low-dose simvastatin (Zocor) and ezetimibe (Zetia). However, the evidence does not suggest that statin therapy slows the progression of CKD.\textsuperscript{28–31}

Recommendation. Manage hyperlipidemia aggressively using statin therapy with or without ezetimibe, with a target low-density lipoprotein cholesterol level below 100 mg/dL.\textsuperscript{32}

Manage other cardiovascular risk factors

Because hypertension and proteinuria are risk factors not only for cardiovascular disease but also for progression of CKD, they are discussed in the section below.

\header{ATTEMPT TO PREVENT WORSENING OF RENAL FUNCTION}

Medications to avoid

It is important to review a CKD patient’s medication list—prescription and over-the-counter drugs—to identify any that may contribute to a worsening of renal function. CKD patients need to be informed about avoiding medications such as nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and herbal supplements because they can cause

\begin{table}
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\caption{Stages of chronic kidney disease}
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Stage & Description & Glomerular filtration rate (GFR) \\
& & (mL/min/1.73 m\textsuperscript{2}) \\
\hline
1 & Kidney damage with normal or increased GFR & \geq 90 \\
2 & Kidney damage with mild decrease in GFR & 60–89 \\
3 & Moderately decreased GFR & 30–59 \\
4 & Severely decreased GFR & 15–29 \\
5 & Kidney failure & < 15 (or dialysis) \\
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\end{tabular}
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Chronic kidney disease is defined as either kidney damage or GFR < 60 mL/min/1.73 m\textsuperscript{2} for \geq 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

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further renal injury. In addition, other medications (eg, metformin) are contraindicated in CKD because of side effects that may occur in CKD.

Patients should be encouraged to discuss any changes in their medications, including over-the-counter products, with their primary care physicians.

Manage hypertension aggressively

Many patients with CKD also have hypertension,33,34 possibly because they have a higher frequency of underlying essential hypertension or because CKD often worsens preexisting hypertension. Moreover, uncontrolled hypertension is associated with a further decline in renal function.35,36

The ACCORD trial37 found no benefit in lowering systolic blood pressure to less than 120 mm Hg compared with less than 140 mm Hg in patients with diabetes mellitus. (The patients in this study did not necessarily have CKD.)

A meta-analysis38 of trials of antihypertensive treatment in patients with CKD found that the optimal target systolic blood pressure for decreasing the progression of CKD was 110 to 129 mm Hg. The relative risk of progression of renal dysfunction was:

- 1.83 (95% confidence interval [CI] 0.97–3.44) at 130 mm to 139 mm Hg, vs
- 3.14 (95% CI 1.64–5.99) at 160 mm Hg or higher.

There is also evidence that blood pressure control can be relaxed as patients age. While the exact age differs among published guidelines, the evidence supports a goal blood pressure of less than 150/90 mm Hg once a patient reaches the age of 70, regardless of CKD or proteinuria.

**Recommendation.** Current evidence suggests the following blood pressure goals in CKD patients:

- With diabetes mellitus or proteinuria: < 130/80 mm Hg
- Without proteinuria: < 140/90 mm Hg
- Age 70 and older: <150/90 mm Hg

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the preferred antihypertensive drugs in patients with diabetes or proteinuria (see below).

Manage proteinuria

Proteinuria is also associated with progression of CKD. AASK,40 a study that included nondiabetic African American patients whose estimated GFRs were between 20 and 60 mL/min/1.73 m², showed that higher levels of proteinuria were associated with a higher risk of decline in GFR and a higher risk of end-stage renal disease. Findings were similar to those in studies of other CKD populations.41-43 Proteinuria is also an independent risk factor for cardiovascular disease and death. Multiple large studies16,17,44,45 have found associations between higher levels of albumin excretion and risk of major cardiovascular events, cardiovascular death, and death from any cause in people with and without diabetes.

Reducing proteinuria has been shown to both slow progression of renal dysfunction and reduce the cardiovascular risk.44,45 In a sub-study of the IDNT46 in patients with diabetic nephropathy, each 50% reduction in urinary protein excretion was associated with a 56% reduction in risk of progression of CKD. Similar effects have been shown in nondiabetic CKD patients.47

**ACE inhibitors and ARBs** are the preferred treatments for proteinuria in patients with CKD.48-50 Combination therapy with an ACE inhibitor and an ARB has been used,51-53 with a better response in proteinuria reduction. However, combination therapy with these drugs cannot currently be recommended, as the only prospective study of this regimen to date suggested worse renal and overall outcomes in patients at high cardiovascular risk.54 These drugs may also have renoprotective effects independent of their effects on blood pressure and proteinuria.55 Dietary salt restriction and diuretic therapy can further increase the efficacy of proteinuria reduction by ACE inhibitors or ARBs.55,56

On the other hand, stopping ACE inhibitors or ARBs may be beneficial as the patient nears end-stage renal disease. Ahmed et al57 demonstrated that stopping ACE inhibitors or ARBs in advanced stage 4 CKD (mean estimated GFR 16 mL/min/1.73 m²) was associated with improved GFR and delayed onset of renal replacement therapy. This improvement may be due to regaining the slight decrease in GFR that occurred when these medications were started.
Nondihydropyridine calcium channel blockers such as diltiazem (Cardizem) and verapamil (Calan) have also been shown to be useful for reducing proteinuria, whereas dihydropyridine calcium channel blockers such as amlo- dipine (Norvasc) and nifedipine (Procardia), when used without ACE inhibitors or ARBs, can worsen proteinuria.

Correct metabolic acidosis

The kidneys play an important role in maintaining acid-base balance, keeping the blood from becoming too acidic both by reabsorbing bicarbonate filtered into the urine by the glomerulus and by excreting the daily acid load. Metabolic acidosis can develop when these functions break down at more advanced stages of CKD, most often when the estimated GFR declines to less than 20 mL/min.64

Bicarbonate levels of 22 mmol/L or less have been associated with a higher risk of worsening renal function. When such patients were treated with sodium bicarbonate to achieve a serum bicarbonate of at least 23 mmol/L, they had an 80% lower rate of progression to end-stage renal disease without any increase in edema, admission for congestive heart failure, or change in blood pressure.61

Susantitaphong et al reviewed six randomized trials of bicarbonate supplementation in CKD and found that it was associated with improved kidney function and a 79% lower rate of progression to end-stage renal disease.

The proposed mechanism behind this benefit lies in the increase in ammonia production that each surviving nephron must undertake to handle the daily acid load. The increased ammonia is thought to play a role in activating the alternative complement pathway, causing renal inflammation and injury.

Recommendation. Bicarbonate therapy should be used to maintain serum bicarbonate levels above 22 mmol/L in CKD.

OTHER ASPECTS OF CKD CARE

Bone mineral disorders

Patients with CKD develop secondary hyperparathyroidism, hyperphosphatemia, and (in advanced CKD) hypocalcemia, all leading to disorders of bone mineral metabolism.

Traditionally, it has been thought that decreased production of 1,25-dihydroxyvitamin D by dysfunctional kidneys leads to decreased suppression of the parathyroid gland and to secondary hyperparathyroidism. The major long-term adverse effect of this is a weakened bone matrix resulting from increased calcium and phosphorus efflux from bones (renal osteodystrophy).

The discovery of fibroblast growth factor 23 (FGF-23) has improved our understanding of the physiology behind disordered bone mineral metabolism in CKD. FGF-23, produced by osteoblasts and osteocytes, acts directly on the kidney to increase renal phosphate excretion. It also suppresses 1,25-dihydroxyvitamin D levels by inhibiting 1-alpha-hydroxylase, and it stimulates parathyroid hormone secretion. FGF-23 levels rise much earlier in CKD than do parathyroid hormone levels, suggesting that abnormalities in phosphorus balance and FGF-23 may be the earliest pathophysiologic changes.

The initial treatment of bone mineral disorders is to some extent guided by laboratory values. Phosphate levels higher than 3.5 or 4 mg/dL and elevated FGF-23 levels have been associated with increased mortality rates in CKD patients. All patients should also have their 1,25-dihydroxyvitamin D level checked and supplemented if deficient. In many patients with early stage 3 CKD, this may correct secondary hyperparathyroidism.

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<td>Target range of intact parathyroid hormone by stage of chronic kidney disease</td>
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CKD = chronic kidney disease; GFR = glomerular filtration rate; PTH = parathyroid hormone

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Serum phosphorus levels should be kept in the normal range in stage 3 and 4 CKD,\textsuperscript{71} either by restricting dietary phosphorus intake (< 800 or < 1,000 mg/day) or by using a phosphate binder, which is taken with meals to prevent phosphorus absorption from the gastrointestinal tract. Current US recommendations are to allow graded increases in parathyroid hormone based on the stage of CKD (\textbf{Table 2}).\textsuperscript{71} However, these targets are still an area of uncertainty, with some guidelines suggesting that wider variations in parathyroid hormone can be allowed, so there may be wider variation in clinical practice in this area.\textsuperscript{72} If the serum phosphorus level is in the goal range but parathyroid hormone levels are still high, an activated vitamin D analogue such as calcitriol is recommended, although with the emerging role of FGF-23, some experts also call for early use of a phosphate binder in this group.

The treatment of bone mineral disorders in CKD is fairly complex, and we recommend that it be done by or with the close direction of a nephrologist.

\textbf{Recommendations on bone disorders}
- Check levels of calcium, phosphorus, 25-hydroxyvitamin D, and parathyroid hormone in all patients whose estimated GFR is less than 60 mL/min/1.73 m\textsuperscript{2}, with frequency of measurements based on the stage of CKD.\textsuperscript{71}
- Replace vitamin D if deficient.
- Treat elevated phosphorus levels with a protein-restricted diet (nutrition referral) and a phosphate binder.
- Treat elevated hyperparathyroid hormone levels with a vitamin D analogue once phosphorus levels have been controlled.
- Refer patients with an elevated phosphorus or parathyroid hormone level to a nephrology service for consultation before initiating medical therapy.

\textbf{Anemia is common, treatment controversial}

The treatment of anemia attributed to CKD has been a topic of controversy over the past decade, and we recommend that it be done with the guidance of a nephrologist.

Anemia is common in CKD, and declining kidney function is an independent predic-
Consider preemptive kidney transplantation

Any patient thought to be a suitable candidate for renal transplantation should be referred to a transplantation center for evaluation. Studies have shown that kidney transplantation offers a survival advantage compared with chronic dialysis and should preferably be done preemptively, ie, before dialysis is required. Therefore, patients with estimated GFRs in the low 20s should be referred for a transplantation evaluation.

If a living donor is available, the transplantation team usually waits to perform the procedure until the patient is closer to needing dialysis, often when the estimated GFR is around 15 to 16 mL/min/1.73 m². If no living donor is available, the patient can earn time on the deceased-donor waiting list once his or her estimated GFR falls to below 20 mL/min/1.7 m².

Plan for dialysis access

Patients starting hemodialysis first need to undergo a procedure to provide access to the blood. The three options are an arteriovenous fistula, an arteriovenous graft, and a central venous catheter (FIGURE 1).

An arteriovenous fistula is the best option, being the most durable, followed by a graft and then a catheter. Arteriovenous fistulas also have the lowest rates of infection, thrombosis, and intervention to maintain patency.

The fistula is created by ligating a vein draining an extremity, most often the non-dominant arm, and anastomosing the vein to an artery. The higher arterial pressure causes the vein to dilate and thicken (“arterialize”), thus making it able to withstand repeated cannulation necessary for hemodialysis.

An arteriovenous fistula typically takes 1 to 3 months to “mature” to the point where...
it can be used, and, depending on the patient and experience of the vascular surgeon, a significant number may never mature. Thus, it is important to discuss hemodialysis access before the patient reaches end-stage renal disease so that he or she can be referred to a vascular surgeon early, when the estimated GFR is about 20 mL/min/1.73 m².

**Reduce cardiovascular risk**
(often in concert with a nephrologist):
- Control blood pressure aggressively
  - Goal < 130/80 mm Hg if the patient has diabetes or proteinuria
  - Goal < 140/90 mm Hg for other patients
- Consider less-aggressive control in the very elderly
- Control lipids aggressively
  - Goal low-density lipoprotein level < 100 mg/dL
  - (< 70 mg/dL if at very high cardiovascular risk)
- Treat and control diabetes mellitus
- Reduce proteinuria
- Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, blood pressure control
- Encourage weight reduction

**Stabilize kidney function**
Avoid nephrotoxic medications such as nonsteroidal anti-inflammatory drugs, contrast agents, and sodium phosphasoda bowel preparations
- Adjust drug doses according to renal function
- Correct metabolic acidosis

**Treat bone mineral disorders**
Rule out and treat vitamin D deficiency

**Detect and manage anemia**
Rule out other causes of anemia, including iron deficiency anemia

**Prepare for end-stage renal disease**
Save the nondominant upper arm of patients with stage 4 and 5 disease for arteriovenous fistula creation (no blood pressure measurements, intravenous lines, venipuncture, peripherally inserted central catheter lines)

An arteriovenous graft. Not all patients have suitable vessels for creation of an arteriovenous fistula. In such patients, an arteriovenous graft, typically made of polytetrafluoroethylene, is the next best option. The graft is typically ready to use in 2 weeks and thus does not require as much advance planning. Grafts tend to narrow more often than fistulas and require more procedures to keep them patent.

A central venous catheter is most often inserted into the internal jugular vein and tunneled under the skin to exit in an area covered by the patient’s shirt.

Tunneled dialysis catheters are associated with higher rates of infection, thrombosis, and overall mortality and are therefore the least preferred choice. They are reserved for patients who have not had advance planning for end-stage renal disease, who do not have acceptable vessels for an arteriovenous fistula or graft, or who have refused surgical access.

Protect the fistula arm. It is recommended that venipuncture, intravenous lines, and blood pressure measurements be avoided in the nondominant upper arm of patients with stage 4 and 5 CKD to protect those veins for the potential creation of an arteriovenous fistula. For the same reason, peripherally inserted central catheter lines and subclavian catheters should be avoided in these patients. If an arteriovenous fistula has already been placed, this arm must be protected from such procedures at all times.

Studies have shown that late referral to a nephrologist is associated with a lower incidence of starting dialysis with a permanent vascular access.

If the patient wishes to start peritoneal dialysis, the peritoneal dialysis catheter can usually be used 2 weeks after being inserted.

**Starting dialysis**
The appropriate time for starting dialysis remains controversial, especially in elderly patients with multiple comorbid conditions.

The IDEAL study found no benefit in starting dialysis at a GFR of 10 to 14 mL/min compared with 5 to 7 mL/min. Thus, there is no single estimated GFR at which dialysis should be started. Rather, the development of early uremic symptoms and the patient’s quality of life should guide this decision.

Hemodialysis involves three sessions per week, each taking about 4 hours. Evidence sug-
gests that longer sessions or more sessions per week may offer benefits, especially in terms of blood pressure, volume, and dietary management. This has led to an increase in the popularity of home and in-center nocturnal hemodialysis programs across the United States.

Peritoneal dialysis?
Peritoneal dialysis is an excellent choice for patients who are motivated, can care for themselves at home, and have a support system available to assist them if needed. It allows for daily dialysis, less fluid restriction, and less dietary restriction, and it gives the patient an opportunity to stay independent. It also spares the veins in the arms, which may be needed for vascular access later in life if hemodialysis is needed.

Recommendation. We recommend that peritoneal dialysis be offered to any suitable patient who is approaching end-stage renal disease.

A COMPREHENSIVE, COLLABORATIVE APPROACH
Chronic kidney disease is a multisystem disorder, and its management requires a comprehensive approach (Table 3). Early detection and interventions are key to reducing cardiovascular events and progression to kidney failure.

Early referral to a nephrologist and team collaboration between the primary care provider, the nephrologist, and other health care providers are essential. Early in the course of CKD, it may be appropriate for a nephrologist to evaluate the patient and recommend a set of treatment goals. Follow-up may be infrequent or unnecessary.

As CKD progresses, especially as the patient reaches an estimated GFR of 30 mL/min/1.73 m², the nephrologist will take a more active role in the patient’s care and medical decision-making. In some circumstances, it may even be appropriate for the nephrologist to be the patient’s source of primary care, with the primary care provider as a consultant.

Caring for patients with CKD includes not only strategies to preserve renal function and prolong survival, but also making critical decisions about starting dialysis and about the need for transplantation. Early involvement of a nephrologist and early preparation for end-stage renal disease with preemptive transplantation and arteriovenous fistula placement are associated with better patient outcomes. Key to this is collaboration between the primary care provider and the nephrologist, with levels of responsibility for patient care that adapt to the patient’s degree of renal dysfunction and other comorbidities. Such strategies to select patients for timely nephrology referral may help improve outcomes in this vulnerable population.

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