Management of Chronic Kidney Disease: What is the Evidence?

Godela Brosnahan, MD, and Mony Fraer, MD

Abstract: Chronic kidney disease (CKD) is a strong risk factor for cardiovascular events and death. Hypertension, dyslipidemia, anemia, vascular calcification, and secondary hyperparathyroidism have all been implicated in the pathogenesis of cardiovascular disease associated with CKD. Numerous trials have been performed assessing the effects of modifying these risk factors on cardiovascular events and on the progression to end-stage renal disease. Many guidelines have been issued. In this article we review the guidelines and the strength of evidence supporting them. Specifically, we discuss blood pressure goals for patients with CKD, the role of renin-angiotensin system blocking agents for blood pressure control and proteinuria reduction, and the evidence for treatment recommendations of dyslipidemia. We review the trials addressing risks and benefits of different hemoglobin targets for treatment of anemia with erythropoietin. The use of phosphate-binding drugs to prevent and treat secondary hyperparathyroidism is likely beneficial, but few data support the use of vitamin D compounds. Supplementation with sodium bicarbonate may be an inexpensive treatment to retard progression to end-stage renal disease. The article concludes with a discussion of the case vignette presented in the previous article.

Key Words: anemia, chronic kidney disease, dyslipidemia, hypertension, secondary hyperparathyroidism

Treatment of Hypertension in CKD

The majority (70–80%) of patients with CKD have hypertension which is usually systolic and more severe than in non-CKD patients.[1,2] In several studies the median number of antihypertensive classes required was 3 in nondiabetic and 3.5 in diabetic patients with CKD.[3,4] Hypertension is associated with more rapid progression of CKD.[5] Even small changes in blood pressure can significantly affect the rate of CKD progression: in 1513 patients with established nephropathy and hypertension associated with type 2 diabetes, every 10 mmHg-rise in baseline systolic blood pressure (SBP) increased the risk for end-stage renal disease (ESRD) or death by 6.7% ($P = 0.007$).[6] In the Modification of Diet in Renal Disease (MDRD) study, the mean decline in glomerular filtration rate (GFR) over 3 years was 11.8 mL/min slower in patients randomized to low blood pressure (mean arterial pressure [MAP] <92–98 mm Hg) compared with usual blood pressure (MAP 107–113 mmHg).[7] The greatest beneficial effect from blood pressure reduction on GFR decline was seen in patients with high urinary protein excretion (more than 1 g/day).[7] Lowering blood pressure markedly reduces proteinuria, even when agents other than renin-angiotensin-system (RAS) blockers are used.[7] Blood pressure control also prevents the development of cardio- and cerebrovascular events.[8]

Key Points

- Aggressive treatment of hypertension slows the progression of chronic kidney disease (CKD): Blood pressure goals are less than 130/80 mmHg for all patients and less than 125/75 mmHg for those with proteinuria of more than 1 g/day.
- Inhibitors of the renin-angiotensin system are particularly beneficial in CKD patients with proteinuria of more than 1 g/day. Increases in serum creatinine levels up to 30% should not lead to discontinuation; low-potassium diet and diuretics can be used to avoid hyperkalemia.
- Partial correction of anemia (hemoglobin level less than 9 g/dL) improves quality of life in patients with CKD.
- Aggressive treatment of dyslipidemia is likely beneficial in early stages of CKD (stages 1–3); benefit in stages 4 and 5 has not been shown.
- Hyperphosphatemia stimulates secretion of parathyroid hormone; phosphate binders should be used to keep serum phosphate levels in the normal range.
- Treatment of metabolic acidosis with sodium bicarbonate may slow the progression of CKD and improve nutritional status.

From the Department of Internal Medicine, Division of Nephrology, University of Arkansas for Medical Sciences, and Central Arkansas Veteran Healthcare System; and Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR.

Reprint requests to Godela Brosnahan, MD, University of Arkansas for Medical Sciences, 4301 W Markham, Slot 501, Little Rock, AR 72205. Email: gbrosnahan@uams.edu

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Blood Pressure Goals in Patients With CKD

CKD patients are a high-risk group and a blood pressure goal of <130/80 mm Hg is recommended.[9,10] A meta-analysis of 11 randomized controlled trials evaluated the impact of SBP on renal outcome in 1860 patients with nondiabetic renal disease.[11] The lowest risk for CKD progression was demonstrated for a SBP of 110–129 mmHg. With regard to type 1 diabetes, a meta-analysis of nine longitudinal studies showed that a four-fold reduction in the decline of GFR was observed for MAP levels <99 mmHg, regardless of the type of treatment.[12] The Irbesartan in Diabetic Nephropathy Trial in type 2 diabetes demonstrated an optimal renoprotective effect for SBP of 120–130 mmHg, with no further benefits below 120 mmHg.[13] In the MDRD study, nondiabetic patients with proteinuria had better preservation of renal function at follow up when blood pressure was less than 125/75 mm Hg as compared to the target of <140/90 mmHg.[14,15]

Which Agents to Use in CKD

An angiotensin-converting enzyme inhibitor (ACEI) or angiotension receptor blocker (ARB) is considered the treatment of choice to delay progression of renal disease, particularly if proteinuria (>1 g/day) is present. The landmark trial by the Collaborative Study Group demonstrated the effectiveness of ACEI in slowing the progression of CKD in 409 patients with type 1 diabetes.[16] In another three-year trial involving 583 patients with CKD stage 3, the risk of the serum creatinine doubling or the need for dialysis was reduced by 53% in the benazepril group compared to the placebo group.[17] Similar results were shown in other studies where the decline in GFR per month was significantly lower in the ramipril group than in the conventional antihypertensive therapy group (0.53 vs 0.88 mL/min).[18,19] In patients with type 2 diabetes and overt nephropathy, several trials demonstrated that ARBs (irbesartan or losartan) were more effective than conventional therapy in slowing the progression of nephropathy, despite similar blood pressure control.[20,21] Use of RAS blocking agents can lead to deterioration of renal function; this is a hemodynamic effect and translates into long-term protection.[22] The increase in serum creatinine is usually less than 30% and temporary. If serum creatinine continues to rise, bilateral renal artery stenosis must be suspected and the RAS blocking agent should be stopped.

Numerous studies have examined the effect of combining ACEI with ARB in patients with cardiovascular disease and in those with proteinuric nephropathies (reviewed in 23); these studies showed additional reduction in proteinuria when combining ACEI with ARB compared to each agent alone, but all were small and short term and did not evaluate the effect on GFR. Most noted increased side effects such as hypotension or hyperkalemia with the combination.[23,24] The largest of the combination therapy trials, the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) trial in 25,620 patients with high cardiovascular risk, did not show a difference in cardiovascular outcomes, which was the primary endpoint, but a significantly higher rate of adverse renal outcomes (hyperkalemia, need for dialysis for acute renal failure) was found in the combination therapy group.[25] Therefore combination therapy is not recommended for routine clinical use.[23,26] Several trials comparing the combination with single use of ACEI or ARB, specifically in patients with proteinuric renal disease and with primary renal endpoints, are still ongoing.[23]

Most patients with CKD require more than one drug to control their blood pressure. The second agent is usually a diuretic because reduced GFR is associated with volume expansion and therefore blood pressure often cannot be controlled without a diuretic. Particularly with poor adherence to salt restriction (>2 g per day or urinary sodium excretion >100 mmol/day) or marked extracellular volume expansion, natriuretic agents become the cornerstone in the treatment of hypertension in CKD. Adding a diuretic restores and augments the antiproteinuric effect of ACEI therapy.[27] In mild renal dysfunction (GFR >40 mL/min, creatinine <2 mg/dL), hypertension can be managed by the administration of thiazide diuretics.[28,29] In stage 4–5 CKD a loop diuretic is the diuretic of choice. These patients often require a higher dose of loop diuretics because of the reduced number of functioning nephrons, lower renal blood flow, accumulation of organic acids, and presence of proteinuria.[28,29] For resistant patients, loop diuretics can be combined with thiazides or metolazone with close monitoring of serum potassium levels and creatinine.[30]

Other agents are considered acceptable as first-line therapy for those with nondiabetic CKD and with urine protein/creatinine ratios of less than 1. Although ACEI and ARB have been shown to reduce, proteinuria by 40–45%, with similar blood pressure reduction, proteinuria was also reduced by 15–20% in patients treated with other classes of drugs, showing that blood pressure control reduces proteinuria.[31,32] Therefore, if proteinuria is minimal, no additional benefit of RAS blocking agents over other antihypertensive drugs has been shown. Figure 1 shows a flowchart on hypertension management.

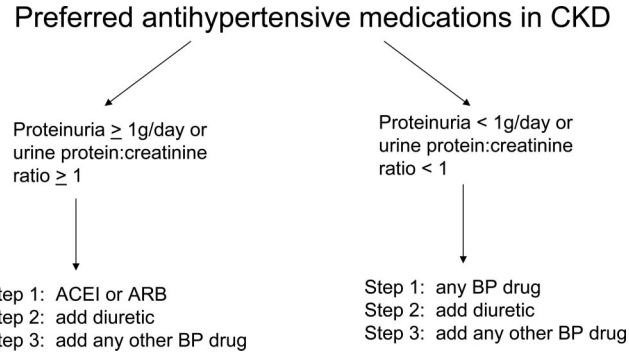

Fig. 1 Preferred antihypertensive medications in chronic kidney disease (CKD).

Treatment of Dyslipidemia in CKD

The rationale for treating dyslipidemia in patients with CKD is the high cardiovascular morbidity and mortality rate of these patients. However, the benefits of treatment have not been clearly established. In observational studies low cholesterol levels are associated with increased mortality, at least in patients on dialysis.[33,34] Moreover, two large randomized controlled trials in dialysis patients could not demonstrate a benefit of statins: one trial was conducted in 1255 dialysis patients with type 2 diabetes,[35] the other involved 2776 hemodialysis patients from 25 countries; patients were randomly assigned to rosuvastatin 10 mg daily or placebo. During a median follow up of 3.8 years there was no difference in any primary or secondary endpoint.[36]

However, there is evidence of benefit from statins in earlier stages of CKD (stages 1–3). Although no large randomized trials have studied cardiovascular endpoints specifically in patients with CKD, several post-hoc analyses of large population-based statin trials focusing on subgroups with mild CKD have been published. In general, these post hoc analyses show a moderate but significant reduction (25–32%) in cardiovascular endpoints for patients with stage 2 or 3 CKD.[37–42] None of these studies included people with more advanced (stage 4 or 5) CKD.

There is one randomized, controlled, and open study of endpoints in 143 patients with stage 4 and 5 CKD, including pre-dialysis, hemodialysis, and peritoneal dialysis patients with or without pre-existing cardiovascular disease.[43] Subjects were randomized to atorvastatin 10 mg/day or placebo and followed for a mean of 31 months. Although atorvastatin reduced total cholesterol and LDL cholesterol levels significantly, no difference in cardiovascular endpoints or survival was observed.[43] Primary endpoints occurred in 75% of study participants, indicating that these were very high-risk patients for whom modification of only one risk factor may not have been sufficient to alter the outcome.

The effect of statins on the progression of kidney disease has also been examined. In animal models, treatment with a statin reduced proteinuria and attenuated histological changes of inflammation and fibrosis.[44] Studies in humans were either very small or were post-hoc subset analyses from large population studies with mixed results.[45,46] The Cochrane Renal Group conducted a meta-analysis of 50 randomized and quasi-randomized controlled trials involving 30,144 patients with CKD stages 3–5, some of them undergoing dialysis.[47] The group concluded that statins significantly reduced total and LDL cholesterol levels and modestly reduced proteinuria but did not improve glomerular filtration rates in patients with CKD. Fatal and nonfatal cardiovascular events were significantly reduced, but there was no significant effect on all-cause mortality. The adverse effect profile of statins was similar to placebo.[47]

In the absence of definitive evidence, the KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines follow closely the National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines for the general population.[48,49] For patients with fasting triglycerides ≥500 mg/dL, treatment is recommended to prevent acute pancreatitis. This includes lifestyle changes such as diet, weight loss, treatment of hyperglycemia, avoidance of alcohol, and increased physical activity. If that is not sufficient, a fibrate or nicotinic acid should be considered. **The doses of fibrates need to be reduced in patients with reduced renal function.**

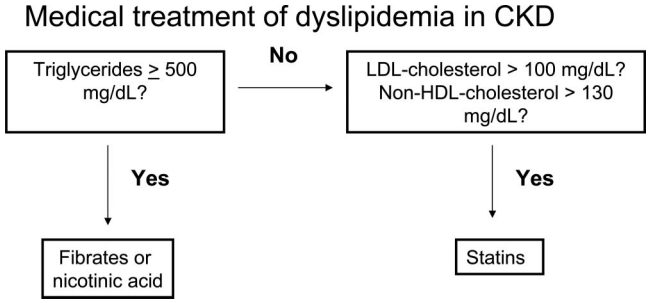

Fig. 2 Medical treatment of dyslipidemia in chronic kidney disease (CKD).

For CKD patients with fasting triglycerides below 500 mg/dL, treatment of elevated LDL cholesterol levels takes precedence as in the general population.[48] Because patients with CKD have a cardiovascular risk equal to that of patients with pre-existing heart disease, KDOQI recommends an LDL cholesterol goal below 100 mg/dL and non-HDL cholesterol below 130 mg/dL using a statin. Atorvastatin and fluvastatin are not renally excreted and are therefore preferred in patients with severe CKD (stages 4 and 5).[50] Fibrates, particularly fenofibrate, are predominantly renally excreted and dose reductions are necessary.[50]

Combinations of statins and fibrates are not recommended for patients with advanced CKD (stages 4 and 5) because of the increased risk of rhabdomyolysis.[48] Figure 2 summarizes the medical treatment of dyslipidemia in CKD.

Two randomized, controlled trials examining the effects of statins specifically in patients with CKD are still ongoing: The LORD (Lipid lowering and Onset of Renal Disease) trial with a goal of 200 patients is designed to assess the effect of atorvastatin on the progression of kidney disease.[51] The multinational SHARP (Study of Heart and Renal Protection) trial will randomize about 6000 patients with CKD stages 3–5 (plus an additional 3000 patients on dialysis) to treatment with simvastatin plus ezetimibe versus placebo; the primary outcome is time to a first major vascular event, a secondary outcome is progression to ESRD; treatment duration is at least 4 years.[52]

Treatment of Anemia in CKD

The KDOQI guidelines recommend evaluating patients for anemia if hemoglobin (Hb) levels are <13.5 g/dL in adult men or <12.0 g/dL in adult women.[53] The European guide-

lines recommend evaluation if the Hb level is 11 g/dL or less in adult men or women.[54] Both sets of guidelines recommend assessing iron stores and vitamin B12 and folate levels before considering therapy with erythropoiesis-stimulating agents (ESA). Iron stores are considered adequate if serum ferritin levels are >100 ng/mL and the transferrin saturation (TSAT) is >20% in pre-dialysis patients with CKD.

The use of ESA and the target level of Hb have been the subject of much research and debate. In the initial trials of recombinant erythropoietin, the drug was given to patients on dialysis who often had Hb levels of 7 g/dL or less, and their anemia was partially corrected to Hb levels between 10 and 12 g/dL.[55,56] These patients experienced a dramatic improvement in their quality of life. Subsequent trials expanded the use of ESA to patients with CKD not yet on dialysis, who also often had Hb levels <8 g/dL.[57–59] Partial correction of anemia was the aim.[59] Many studies confirmed the effectiveness of ESA in reaching that aim without causing deterioration in renal function.[57,60,61] Blood pressure usually increased during ESA therapy, requiring adjustments of antihypertensive medications. A meta-analysis published in 2004 examined the impact of ESA therapy on clinical endpoints and found that increasing Hb from <8 g/dL to >11 g/dL was associated with substantial improvements for all measures of quality of life, with reductions in hospitalization rate, hospital length of stay, transfusion rate, and number of units transfused.[62] There were no data on survival benefits.

Other clinical studies examined the effects of ESA therapy on left ventricular hypertrophy (LVH), which is present in 68% of patients with CKD stages 3 and 4.[63] Increasing Hb from 9.1 g/dL to 11.3 g/dL was associated with a significant decrease in left ventricular (LV) mass index; however, there was no control group in this study.[63] Because LVH is a predictor of mortality, the assumption was that correcting anemia would confer a survival benefit by reducing LVH, but no randomized controlled trial assessed survival directly until the CHOIR and CREATE trials (see below).

Instead of partial correction of anemia, observational and uncontrolled studies suggested that full correction to Hb over 13 g/dL led to further improvements in quality of life and cardiac outcomes.[64–66] However, a trial of 172 CKD patients did not find a significant difference in LV mass index between patients randomized to Hb of 12–13 g/dL versus 9–10.5 g/dL.[67] A Cochrane meta-analysis of randomized controlled trials published in 2004 found that Hb targets above 13 g/dL were associated with higher all-cause mortality compared to Hb targets <12 g/dL.[68] This analysis was criticized because it was dominated by one large trial in hemodialysis patients with preexisting cardiac disease.[69]

Subsequently two randomized controlled trials in CKD patients not yet on dialysis examined the effects of normalizing Hb on cardiovascular endpoints and death. The CHOIR trial randomized 1432 patients to Hb targets of 11.3 g/dL versus 13.5 g/dL but was terminated early by the data and safety monitoring board because the primary endpoint was significantly more common in the high-hemoglobin group than in the low-hemoglobin group (17.5% versus 13.5%).[70] The CREATE trial randomized 603 CKD patients to Hb targets of 13–15 g/dL versus 10.5–11.5 g/dL.[71] There was no significant difference in cardiovascular events and LV mass index after 3 years, but hypertensive episodes were significantly more frequent and dialysis was required in more patients in the high-hemoglobin group than in the low-hemoglobin group.

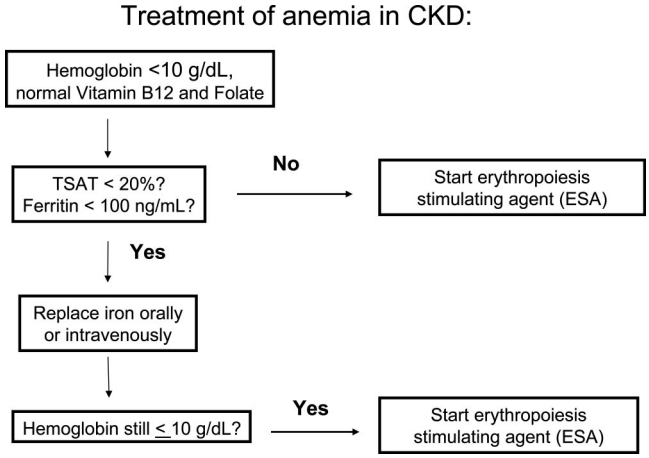

Fig. 3 **Treatment of anemia in chronic kidney disease (CKD).**

Based on these trials, the KDOQI guidelines were updated in 2007: The goal for Hb levels is between 11 and 12 g/dL.[72] The Food and Drug Administration recommends to maintain Hb between 10 and 12 g/dL and to start treatment with ESA only if Hb is less than 10 g/dL. Figure 3 shows a flow diagram for the evaluation and treatment of anemia in CKD.

Treatment of Mineral and Bone Disorder in CKD

Reduced GFR leads to reduced renal excretion of phosphorus, which directly stimulates the release of parathyroid hormone (PTH) from the parathyroid glands. Rising phosphorus levels also inhibit 1,25-dihydroxyvitamin D synthesis. Therefore the consequences of hyperphosphatemia are secondary hyperparathyroidism and deficiency of active vitamin D. Serum calcium levels are often low but can be normal or even high. These disturbances in mineral metabolism are associated with abnormalities in bone homeostasis and with increased bone fragility and fractures, known as renal osteodystrophy.[73,74] They have also been linked to vascular and soft-tissue calcification, increased cardiovascular events, and death.[75–77] There are several observational cohort studies showing a positive association between higher serum phosphorus levels and vascular calcification, cardiovascular events, and mortality in patients with CKD and even in people with normal kidney function.[75,78,79] Therefore a low phos-

phorus diet and phosphate-binding drugs are recommended when GFR falls below 60 mL/min/1.73 m^2, to maintain serum phosphorus levels between 2.5 and 4.5 mg/dL and to suppress PTH. Calcium carbonate and calcium acetate are being used as first-line therapy because they effectively bind phosphorus, can correct hypocalcemia, and are inexpensive.[80]

Newer phosphate binders include sevelamer and lanthanum carbonate. No phosphate-binding agent has been proved to be superior over another, and no randomized trial has been performed to confirm that phosphate-binding drugs improve mortality.

Vitamin D compounds are also frequently used in patients with CKD, although the evidence for any beneficial effects is very weak. This was the conclusion of a meta-analysis of 76 randomized trials involving 3667 patients.[81] Administration of vitamin D compounds has been advocated widely to lower serum PTH levels, however this is often accomplished at the expense of higher serum calcium and phosphorus levels, thus potentially doing more harm than good.[82] Any beneficial effects on patient outcomes are still unproven, and further trials with sufficient patient numbers are necessary.[81,82]

Because of the paucity of evidence-based data, most of the KDOQI recommendations are based on expert opinion. The current guidelines recommend measuring calcium, phosphorus, and PTH levels annually in patients with CKD stage 3 and every 3 months in those with CKD stage 4.[48] In patients with elevated PTH concentrations, measurement of 25-hydroxycholecalciferol (calcidiol) levels is recommended. If calcidiol levels are low, KDOQI recommends therapy with ergocalciferol, the dose being dependent on the severity of calcidiol deficiency. If calcidiol levels are above 30 ng/mL, KDOQI recommends treatment with active vitamin D, ie with 1,25-dihydroxycholecalciferol (calcitriol) or a synthetic analog with the goal of decreasing PTH to a target range specific for stage 3 or 4 CKD.[83] These targets are also opinion-based. Tables 1–3 show the KDOQI guidelines.

Treatment of Metabolic Acidosis

Renal function decline is associated with reduced ability to excrete the daily acid load, which is derived from protein intake and catabolism. The resultant metabolic acidosis increases protein catabolism, leading to bone and muscle loss and malnutrition. Metabolic acidosis also stimulates ammonia production in the remnant nephrons, which in turn increases interstitial inflammation and fibrosis, accelerating the decline in renal function. A recent single-center randomized trial in 134 adult patients with CKD stage 4 and serum bicarbonate levels of 16–20 mmol/L has tested the hypothesis that treatment of metabolic acidosis with bicarbonate supplementation (to achieve serum bicarbonate levels of ≥23 mmol/L) can slow the progression of CKD and improve nutritional status[84]: after 2 years of treatment, 6.5% of patients in the sodium bicarbonate group required dialysis compared to 33% in the control group, which was highly significant with $P < 0.001$. Nutritional parameters such as dietary protein intake, lean body mass, and serum albumin level also improved significantly. No increase in blood pressure or need for additional antihypertensive medications was observed.[84] If these findings can be replicated in a larger, multicenter trial, it will change clinical practice and produce significant benefits for patients at low cost.

Table 1. Recommended frequency of measurement of calcium, phosphorus, and PTH

CKD stage	GFR range (mL/min/1.73 m^2)	Measurement of calcium and phosphorus	Measurement of PTH
3	30–59	Every 12 mo	Every 12 mo
4	15–29	Every 3 mo	Every 3 mo
5	<15 or dialysis	Every month	Every 3 mo

CKD, chronic kidney disease; GFR, glomerular filtration rate; PTH, parathyroid hormone.

Table 2. Target range of intact plasma PTH by stage of CKD

CKD stage	GFR range (mL/min/1.73 m^2)	Target intact PTH (pg/mL)
3	30–59	35–70 (opinion)
4	15–29	70–110 (opinion)
5	<15 or dialysis	150–300 (evidence)

PTH, parathyroid hormone; CKD, chronic kidney disease; GFR, glomerular filtration rate.

Summary

CKD is common and can be diagnosed by simple blood and urine tests. Patients with diabetes, hypertension, cardiovascular disease, obesity, family history, and age greater than

Table 3. Recommended supplementation for vitamin D deficiency in patients with CKD stages 3 and 4

Serum 25(OH)D-level (ng/mL)	Definition	Ergocalciferol dose (vitamin D2)
<5	Severe vitamin D deficiency	50,000 IU weekly orally for 12 wk, then monthly for total of 6 mo
5–15	Mild vitamin D deficiency	50,000 IU weekly orally for 4 wk, then monthly for total of 6 mo
16–30	Vitamin D insufficiency	50,000 IU orally monthly for 6 mo

CKD, chronic kidney disease; IU, international units.

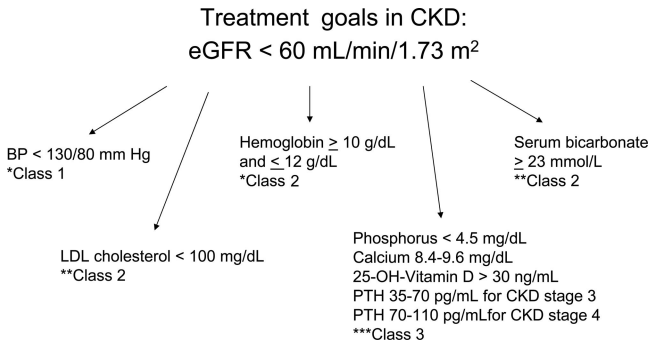

Fig. 4 Treatment goals in chronic kidney disease (CKD): estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. *Class 1 recommendations are supported by high-quality prospective trials with consistently positive results. Recommendations are definitely useful and safe. **Class 2 recommendations are supported by less robust trials; they are probably useful and safe. ***Class 3 recommendations are based on case series and consensus statements; they are possibly useful; safety has not always been established.

55 years should be screened for CKD during their primary care visits. CKD is associated with high cardiovascular morbidity and mortality; therefore risk factors for cardiovascular disease such as hypertension and dyslipidemia should be treated aggressively. Many trials support a blood pressure goal of less than 130/80 mm Hg in patients with proteinuria less than 1 g per day and less than 125/75 mmHg in patients with proteinuria of more than 1 g per day. Blockers of the RAS are renoprotective, particularly in patients with proteinuria of more than 1 g a day. There is some evidence that treatment of hypercholesterolemia in patients with CKD stages 1–3 may decrease their heightened cardiovascular risk; in patients with advanced CKD (stages 4 and 5), a benefit of statins has not been shown. Partial correction of anemia of CKD leads to significant improvements in quality of life, but full correction is associated with higher cardiovascular risk and should be avoided. Blood levels of calcium and phosphate should be kept in the normal range using phosphate binders. Treatment with calcidiol or calcitriol may be beneficial, but definitive evidence for their usefulness or their risks is lacking. Finally, patients with CKD stage 4 and metabolic acidosis have benefitted from sodium bicarbonate supplementation in a very recent study, diminishing the need for dialysis and improving nutritional status. Figure 4 summarizes treatment goals for patients with CKD.

Case (Vignette) Conclusions

The vignette asked the following questions: Does this patient have chronic kidney disease? What is the etiology? Is her blood pressure adequately controlled? Is she on the best medications to control her blood pressure? Is her cholesterol level optimal? Does she need evaluation and treatment for anemia? What else needs to be done?

This 65-year-old woman with a serum creatinine of 1.3 mg/dL has an estimated GFR of 41 mL/min/1.73 m^2 if she is Caucasian and 50 mL/min/1.73 m^2 if she is African-American. She also has 1+ proteinuria, and, if confirmed on a second visit, she can be diagnosed as having chronic kidney disease. Also, she gives no history of any acute event that could cause acute kidney injury, and she is not taking medications that decrease renal function such as nonsteroidal anti-inflammatory agents.

She has two of the most common risk factors for CKD and was appropriately screened for CKD using serum creatinine and urinalysis by her new provider. The next test to be performed should be quantification of the proteinuria. Since the dipstick is positive for protein, she has overt proteinuria and a urine protein: creatinine ratio should be obtained. If the dipstick were negative, a urine albumin: creatinine ratio should be measured to look for microalbuminuria.

Her blood pressure should be below 130/80 mmHg; therefore, it is not adequately controlled (assuming that her blood pressure is above 130/80 mmHg most of the time, not only once in the clinic). ACEI or ARB should be added to her medication regimen, and the dose should be titrated up to minimize her proteinuria. Atenolol can be discontinued if her blood pressure drops on maximal doses of ACEI or ARB. Her serum potassium needs to be monitored and, if it rises, she should be educated about low potassium diet; in addition, furosemide may be given instead of HCTZ with triamterene. Her serum creatinine may rise up to 30% after adding ACEI or ARB due to a hemodynamic effect. This should not prompt discontinuation of the drugs. The combination of ACEI and ARB is not routinely recommended. Her serum LDL cholesterol level is above the recommended goal of less than 100 mg/dL for patients with CKD. Therefore the dose of simvastatin may be increased to 40 mg daily.

The patient has mild anemia, with a hemoglobin level of 11.0 g/dL. According to the KDOQI guidelines, she should have her iron stores and vitamin B12 and folate levels assessed and optimized. Her transferrin saturation should be >20%, and her serum ferritin level should be >100 ng/mL. If no iron or vitamin deficiency is found, her anemia is likely due to CKD, and further tests are not necessary (unless there are strong reasons to suspect another diagnosis). Her hemoglobin level is in the target range (10–12 g/dL), therefore treatment with ESA is not indicated at this time.

Other possible complications of GFR levels below 60 mL/min/1.73 m^2 are disorders of calcium, phosphorus and vitamin D metabolism, and secondary hyperparathyroidism. Therefore she should have her serum calcium and phosphorus levels monitored and kept in the normal range. If her 25-hydroxyvitamin D level is below 30 ng/mL, vitamin D_2 (ergocalciferol) may be replaced. Her PTH level should also be measured. If she develops metabolic acidosis, sodium bicarbonate should be supplemented.

Note Added in Proof:

Another randomized double-blind trial of erythropoietin treatment in 4038 patients with type 2 diabetes and chronic kidney disease was published in November 2009[85] and confirmed that a hemoglobin target of 13 g/dL is associated with increased thromboembolic events including strokes; patients in the control group received erythropoietin only if their hemoglobin level fell below 9 g/dL. The primary endpoint and total mortality were not different between the groups. Recommendations for hemoglobin targets may be lower (9–11 g/dL) in future guidelines.

Acknowledgments

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