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CKD Series: Cardiovascular Risk Reduction in Patients with Chronic Kidney Disease

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Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) regardless of stage.¹ Forty percent to 50% of all deaths in the end-stage renal disease (ESRD) population are of cardiovascular origin.¹ Cardiovascular causes also account for the majority of deaths among patients with predialysis kidney disease.^{1,2} The burden of cardiovascular disease in this patient population is evident upon the initiation of renal replacement therapy. As shown in a Canadian cohort, 40% of patients starting dialysis already had evidence of coronary heart disease (CHD), and only 16% had normal echocardiographic studies.³

Early intervention is required to minimize the burden of cardiovascular disease in CKD. Risk reduction strategies are likely to be effective in reducing cardiovascular morbidity and mortality in CKD patients in the same way these interventions improve outcomes in the general population. However, the pathogenesis of cardiovascular damage in CKD patients is far more complex than in the general population and includes traditional risk factors as well as risk factors typical of chronic renal failure (**Table 1**).¹ Thus, risk reduction in these patients should target both traditional and CKD-specific risks for cardiovascular disease.

Traditional cardiovascular risk factors are highly prevalent in patients with chronic renal insufficiency. Diabetes is the most common cause of kidney disease in the United States and is the primary diagnosis in 45% of ESRD patients.⁴ The total burden of diabetes in patients surviving 1 year on dialysis was actually 60%.⁴ Similarly, hypertension and dyslipidemia are rampant in this population. In a cross-sectional analysis involving patients enrolled in the Modification of Diet in Renal Disease trial, 64% were hypertensive despite being on therapy, 64% had low-density lipoprotein (LDL) cholesterol levels greater than 130 mg/dL, and 38.3% had high-density lipoprotein (HDL) cholesterol levels less than 35 mg/dL.⁵

CKD-related risk factors for cardiovascular disease include the hemodynamic and metabolic abnormalities associated with renal insufficiency and the complications of decreased renal function. These risk factors are sometimes divided into those *altered* by the uremic state (eg, hypertension, dyslipidemia) and those *characteristic* of the uremic state (eg, anemia, oxidative stress) (**Table 1**).¹

Whether renal insufficiency itself is an independent risk factor for cardiovascular disease is unclear. The Heart Outcomes and Prevention Evaluation study demonstrated an increased incidence of cardiovascular death, myocardial infarction (MI), or stroke in patients with renal insufficiency, and this incidence increased with serum creatinine concentration.⁶ Other data from intervention studies in patients with hypertension, coronary disease, and congestive heart failure show a consistent role of renal dysfunction in predicting worse cardiovascular outcomes and death.⁷ Conversely, Garg et al⁸ found no independent association between moderate renal insufficiency and total as well as cardiovascular mortality after adjustment for coexisting risk factors in a large prospective cohort. Despite these conflicting data, we believe that a sufficient number of studies suggest an independent role of CKD in predicting cardiovascular risk, such that patients with CKD should be considered at highest risk for subsequent cardiovascular events.

This article outlines relevant cardiovascular risk factors in patients with CKD and summarizes the available evidence supporting the role of these factors

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Table 1. Cardiovascular Risk Factors in Chronic Kidney Disease

Traditional Risk Factors	Risk Factors Altered by Uremia	Uremia-Related Risk Factors
Hypertension	Dyslipidemia	Hemodynamic overload
Hyperlipidemia	High lipoprotein (a) levels	Anemia
Diabetes mellitus	Prothrombotic factors	Increased oxidative stress
Tobacco use	Hyperhomocysteinemia	Malnutrition
Physical inactivity	Hypertension	Hyperparathyroidism
	Sleep apnea	Elevated ADMA levels

Adapted with permission from Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 1999;10:1607.

ADMA = asymmetric dimethyl arginine.

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in development of cardiovascular disease. Data in support of strategies to reduce cardiovascular risks in renal patients also are highlighted. Although CKD and ESRD patients are somewhat different populations, the limited availability of data on cardiovascular outcomes in pre-ESRD demands that our discussion include both patient groups.

TRADITIONAL RISK FACTORS

Hypertension

Hypertension is a common problem in CKD patients, and evidence strongly supports an association between hypertension and the occurrence of vascular events in this population.^{9,10} However, the data on hypertension and mortality in dialysis patients are potentially misleading. In this group, a U effect (ie, increased mortality at both ends of the spectrum of blood pressure) has been observed in multiple studies, implying that lower blood pressure levels are markers of worse outcomes.^{11,12} More recent studies with adjustment for comorbidities have suggested that a large portion of this effect is due to the presence of underlying cardiac disease.¹³ Patients with a large burden of pre-existing vascular disease are likely to die earlier in the course of ESRD, whereas those who survive longer than 5 years on dialysis experience a more substantial impact of hypertension on outcomes.¹⁴ Thus, the effects of hypertension on cardiovascular disease in CKD appear to be longer term and may be overshadowed by the impact of other serious coexisting conditions.

Identification and treatment of hypertension is important in CKD to slow the decline in renal function. Generally speaking, better blood pressure control will slow the progression of all types of kidney disease. In proteinuric diseases, tight blood pressure control (ie, to levels < 125/75 mm Hg) has been shown to significantly slow the decline of renal function.¹⁵ However, in the case of minimally proteinuric diseases (eg, hypertensive nephrosclerosis, polycystic kidney disease), no additional renal benefit has been achieved by lowering blood pressure below the usual 140/90 mm Hg target.^{16,17}

From a cardiovascular perspective, it is less clear that specific hypertension management approaches will improve cardiovascular outcomes in CKD patients. In stages 3 and 4 CKD (ie, pre-ESRD), antihypertensive therapy improves left ventricular hypertrophy (LVH),¹⁸ and a recent study of patients with polycystic kidney disease revealed greater reduction of LVH (35% versus 21%) in patients with aggressive blood pressure lowering (target of 120/80 mm Hg) compared with patients conventionally treated (target of 140/90 mm Hg).¹⁷ Available prospective data from the CKD population do not suggest improvement in cardiovascular morbidity or mortality with any particular type of drug therapy. In one study of patients with diabetic nephropathy, however, an angiotensin II type 1 receptor blocker (ie, losartan) decreased the rate of first hospitalization for a heart failure episode compared with conventional therapy.¹⁹ As for dialysis patients, interventional data are scarce. However, analyses of large cohort studies have revealed a protective effect with the use of (any) antihypertensive medication,^{11,20} and exposure to calcium channel blockers or β -blockers has been associated with decreased cardiovascular death in hemodialysis patients.^{13,21} Results with angiotensin-converting enzyme (ACE) inhibitors have been inconsistent across studies, and the 2 largest databases do not reveal any specific protective effect on mortality.^{13,21} In one of the rare prospective randomized trials in this population, carvedilol was shown to improve symptoms and left ventricular ejection fraction in hemodialysis patients with moderate-to-severe congestive heart failure.²² There was no effect on mortality in this 1-year study. In summary, from a strict cardiovascular perspective, it is not clear that drug choice affects outcomes in the CKD population. Interventional studies with longer follow-up and primary cardiovascular endpoints are needed to adequately address this question.

Diabetes Mellitus

A large proportion of patients with CKD has diabetes. Diabetes is a significant risk factor for cardiovascular disease, and this risk is even higher in diabetic

patients with renal complications. In patients without significant renal dysfunction, several studies have correlated markers of diabetic nephropathy with cardiovascular outcomes. For example, the World Health Organization Multinational Study of Vascular Disease in Diabetes demonstrated an almost 2-fold increase in the standardized mortality ratios in diabetic patients with microalbuminuria compared with the general population.²³ The mortality risk for patients with both microalbuminuria and hypertension increased to 2- to 3-fold, depending on sex. The risk for cardiovascular events extends to more advanced degrees of renal failure, so that diabetes is an independent risk factor for the development of de novo ischemic heart disease and de novo heart failure in dialysis patients.¹ Although these findings suggest only associations between diabetic nephropathy with cardiovascular outcomes and no intervention data are currently available in CKD, it is reasonable to attempt to achieve tight glycemic control (ie, glycosylated hemoglobin concentration of 7%) in CKD patients with diabetes.

Smoking

Previous studies have demonstrated that smoking further aggravates the excessive cardiovascular risk in patients with impaired renal function.²⁴ Stack and Bloembergen²⁵ noted in a random sample of new ESRD patients in the United States that smokers had a 22% greater risk of developing coronary artery disease. Kawagishi et al²⁶ found a correlation between carotid artery intima media thickness and smoking in patients on maintenance hemodialysis. In another study, the predictive ability of smoking for carotid atherosclerosis in dialysis patients was similar to that of hypercholesterolemia and age.²⁷ Thus, smoking has a clear association with cardiovascular disease in CKD, and attempts to modify this behavior seem warranted. To our knowledge, no published studies have reported on the efficacy of specific smoking cessation strategies in patients with CKD or ESRD. However, we believe that smoking cessation is an important preventive intervention, and we anecdotally have used nicotine replacement as a patch or gum in such patients, with results similar to those in the general population (ie, response rates of 9% to 35%).²⁸ There are no studies of bupropion for smoking cessation in patients with CKD.

Physical Inactivity

The benefits of exercise in the general population are well established, but studies of exercise in CKD patients are few. Exercise has been shown to improve blood pressure control in patients with CKD.²⁹ In ESRD

patients on hemodialysis, exercise has been associated with improvements in blood pressure control as well as insulin sensitivity.³⁰ Patients who commence an exercise program also report small but significant changes in physical functioning.³¹ Exercise programs, however, have not been shown to improve lipid profiles in patients with CKD²⁹ or ESRD.³² Furthermore, adherence to an exercise prescription is limited due to the CKD patients' significant chronic ailment.²⁹ Nevertheless, the potential physical and emotional benefits of exercise justify an attempt at this intervention in all patients with CKD, provided the chosen physical activities are deemed safe from cardiovascular and musculoskeletal standpoints.

RISK FACTORS ALTERED BY UREMIA

Dyslipidemia

The prevalence of hyperlipidemia is higher in CKD patients than in the general population but varies depending on the specific lipid measured, target population, course of renal disease, and level of renal function. Total and LDL cholesterol levels are increased most often in patients with chronic renal insufficiency and nephrotic syndrome, in patients treated by peritoneal dialysis, and in renal transplant recipients.³³

Uremic dyslipidemia is common in ESRD patients and is characterized by increased plasma triglyceride levels (due to elevated very-low-density lipoproteins and intermediate-density lipoproteins), decreased HDL levels, and normal LDL levels. Triglyceride and HDL levels have been found to be more markedly abnormal in individuals with more severe renal insufficiency. Other plasma lipoprotein changes found in ESRD patients include triglyceride-enrichment of LDL and HDL and increased levels of lipoprotein (a).³⁴

Few studies have examined the relationship between lipid abnormalities and cardiovascular disease in chronic renal insufficiency. Jungers et al⁹ prospectively examined the relationship between serum lipids and the incidence of MI in 147 patients with creatinine clearance of 20 to 50 mL/min/1.73 m². The incidence of MI was approximately 2.5 times higher than in the general population. The 41 patients who developed MI had lower HDL cholesterol levels and higher levels of triglycerides, LDL cholesterol, apolipoprotein B, and lipoprotein (a).⁹

In April 2003, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Group published clinical practice guidelines for managing dyslipidemia in CKD.³⁵ According to these guidelines, the most recent recommendations of the National Cholesterol Education Program Expert Panel³⁶ can be used to guide treatment for hyperlipidemia in

patients with CKD stages 1 through 4 (pre-ESRD). Patients with CKD should be considered in the highest risk group. Dietary or pharmacologic therapy should be initiated at LDL cholesterol levels greater than 100 or 130 mg/dL, respectively, with a therapeutic goal of less than 100 mg/dL.³⁶ Dietary therapy is effective in reducing total and LDL cholesterol levels as well as triglyceride levels, but the effects are limited.³⁶ 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (also called *statins*) are the most effective of all currently available medications for reducing total and LDL cholesterol and have been associated with decreased mortality in a cohort of hemodialysis patients.³⁷ Patients with elevated triglyceride levels or low HDL levels should initially be treated with therapeutic lifestyle changes unless LDL levels are also increased.³⁶ If therapeutic lifestyle changes are insufficient, fibric acid analogs are the most effective agents for reducing triglyceride levels in patients with CKD.³⁵ Caution should be exercised when using these agents in higher doses or in combination due to increased risk of myopathy in patients with renal disease.

Hyperhomocysteinemia

Emerging evidence suggests a dose-dependent relationship between plasma homocysteine levels and the risk for atherosclerosis in the general population, and this link appears to be independent of other risk factors.³⁸ Hyperhomocysteinemia is highly prevalent in CKD patients, with a possible relationship to increased atherosclerosis in this population as well.³⁹ It is estimated that approximately 90% of patients with ESRD have elevated plasma homocysteine levels, likely as a result of impaired homocysteine metabolism.⁴⁰ The clinical impact of lowering homocysteine levels via high-dose folate, vitamin B₆, and vitamin B₁₂ supplementation still must be assessed; conventional doses seldom correct the abnormal levels observed in advanced kidney disease.^{39,40} Although previous, primarily prospective studies have looked at absolute reduction of homocysteine levels with high-dose supplementation, there have been no randomized studies measuring clinical outcomes. A large Veterans Affairs–based multicenter trial (the Homocysteine Study) is underway to address the question of whether high-dose folate supplementation decreases cardiovascular endpoints in CKD and ESRD. Another multicenter trial that is in progress involves renal transplant recipients with hyperhomocysteinemia who are being treated with high-dose folic acid and vitamin B–based therapy. These 2 studies should provide answers on the value of homocysteine-lowering interventions within the next few years.

UREMIA-RELATED RISK FACTORS

Anemia

Under normal conditions, anemia leads to reversible increased cardiac output and blood flow. In effect, there is an increase in left ventricular diastolic diameter and volume and a subsequent increase in left ventricular wall tension, leading to adaptive hypertrophy and remodeling. Under uremic conditions, these changes become maladaptive, resulting in irreversible hypertrophy and arteriosclerosis.⁴¹ Early intervention to address anemia, therefore, is important to mitigate cardiovascular damage in the CKD patient.

A growing body of evidence supports the role of anemia as a correlate of left ventricular growth and, therefore, a cardiac risk factor in CKD patients, beginning at the early stages of renal disease.^{42,43} In predialysis patients, anemia has been shown to correlate with left ventricular growth.⁴³ In a Canadian cohort of predialysis patients with renal insufficiency, a 0.5 g/dL decrease in hemoglobin level was associated with a 32% increase in the risk of left ventricular growth.⁴³ Studies in dialysis patients indicate that anemia is associated with increased cardiovascular morbidity and higher mortality. For example, in ESRD dialysis patients, each 1 g/dL decrease in hemoglobin was independently associated with increases in the presence of LVH on echocardiography (50%), the development of new or recurrent heart failure (relative risk of 1.28 or 1.2, respectively), and mortality (18% to 25%).⁴⁴ A retrospective study of nearly 100,000 dialysis patients showed that improved survival was associated with sustained increases in hematocrit levels.⁴⁵

In one study, regression of LVH was demonstrated in predialysis patients after 12 months of erythropoietin treatment aimed at normalizing hematocrit, without negative effects on renal function or blood pressure control.⁴⁶ However, in another study performed in hemodialysis patients this was not the case; normalization of hemoglobin levels was found to have little effect on left ventricular morphology once dilatation had occurred.⁴⁷

While the hemoglobin/hematocrit safety ceiling and target levels of erythropoietin therapy are under debate, a target hemoglobin level of 12 g/dL seems to be appropriate and safe for most patients at any stage of CKD, provided that a rapid increase is avoided and blood pressure is carefully controlled.^{48,49} Because erythropoietin therapy has been shown to raise blood pressure in up to 30% of dialysis patients, there is concern that an untreated rise in blood pressure will increase cardiac workload and exacerbate cardiovascular disease. Moreover, the correction of anemia

improves uremic coagulopathy, increases blood viscosity, and reduces erythrocyte deformability, thereby enhancing the potential for thrombus formation.⁴⁹ Thus, a conservative approach that can be employed safely and easily in most patients would be to increase hemoglobin levels by no more than 1 g/dL per month.

Another unresolved issue in the management of anemia in CKD is whether iron supplementation may create cardiovascular problems in the long term. This issue is particularly relevant to dialysis patients receiving large doses of parenteral iron. While awaiting illuminating data on the risk/benefit ratio of aggressive iron support of erythropoiesis, it is reasonable not to exceed ferritin levels of 500 ng/mL.⁴⁹

Hyperparathyroidism

Disturbances of calcium and phosphate metabolism may play a role in cardiovascular disease in patients with CKD. Elevated serum calcium and phosphate, secondary hyperparathyroidism, administration of phosphate-chelating agents, and vitamin D supplementation have been implicated, but the effect of these different factors on the cardiovascular system is incompletely understood.^{1,49}

Common pathologic findings in uremic hearts include calcifications of the coronary arteries, valves, and myocardial tissue, as well as diffuse myocardial fibrosis.⁵⁰ Animal studies have shown that parathyroid hormone (PTH) increases the cellular burden of calcium and activates fibroblasts. Primary and secondary hyperparathyroidism have been associated with increased myocardial calcium content in humans, but the clinical consequences of secondary hyperparathyroidism are less clear. The improvement in cardiac function after parathyroidectomy has not been consistently demonstrated in studies.⁵⁰

Excessive plasma PTH probably plays a prominent role in diffuse arterial media calcification and is one factor among many others in the pathogenesis of patchy intimal and subintimal calcification.^{41,50} No data are available linking increased PTH concentrations to primary endpoints such as survival and cardiovascular morbidity.

In contrast to the absence of a direct link between PTH and prognosis, hyperphosphatemia has been found to be strongly associated with mortality in dialyzed ESRD patients.⁵¹ The adjusted relative risk of death was found to be greater at serum phosphate levels greater than 6.5 mg/dL and when the calcium and phosphate product was greater than 72 mg²/dL². The increased mortality in hyperphosphatemic patients was shown to be due to an increase in cardiac deaths. There are no interventional data yet available on treat-

ment of hyperphosphatemia and primary endpoints. However, a recent study demonstrated less progression of coronary and valvular calcifications in patients randomized to sevelamer (a noncalcium polymer that also has a lipid-lowering effect) as the primary binder than in those randomized to calcium carbonate or acetate.⁵²

These data implicate the urgency of treating hyperphosphatemia to prevent cardiac death during the early stages of chronic renal failure. Similarly, treatment of secondary hyperparathyroidism also may afford some cardiovascular benefit. Efforts should be made to reduce PTH secretion through strict phosphorus control (diet and binders) and judicious use of vitamin D derivatives. Use of a noncalcium-containing binder (eg, sevelamer) may have additional benefits from a cardiovascular standpoint.

EMERGING RISK FACTORS

Growing evidence supports the role of vessel wall inflammation and malnutrition in the initiation and progression of atherosclerosis—the so-called *malnutrition-inflammation-atherosclerosis syndrome*.⁵³ Stenvinkel et al⁵⁴ found a higher prevalence of malnutrition in patients with chronic renal failure compared with healthy controls. Malnourished patients in turn had increased levels of C-reactive protein, higher calculated carotid intima media areas, and a higher prevalence of carotid plaques compared with well-nourished patients. Zimmermann et al⁵⁵ found age and C-reactive protein to be powerful independent predictors of both overall death and cardiovascular death in hemodialysis patients. Pecoits-Filho et al⁵⁶ analyzed other markers of chronic inflammation and found that patients with the highest levels of interleukin-6 at initiation of dialysis had an increase in mortality after an average of 3.1 years of follow-up, and this effect was independent of multiple other risk factors. Though teleologically sound, it has not yet been determined that time-dependent improvement in nutritional status improves cardiovascular outcomes.

Metabolic waste products accumulating in chronic renal failure may contribute to elevated cardiovascular risk. The endogenous competitive nitric oxide synthase inhibitor, asymmetric dimethyl arginine, has been shown to accumulate in chronic renal failure and inhibits nitric oxide-induced vasodilatation, thereby contributing to hypertension and cardiovascular disease.⁵⁷ More studies are needed to understand how this factor may be modified.

Activation of the sympathetic nervous system has long been documented in patients with CKD.⁵⁸ However, it was not until recently that a prognostic relevance

of this hyperactivity was demonstrated. Zoccali et al⁵⁹ showed that hemodialysis patients with plasma nor-epinephrine levels above the 75th percentile of the distribution had a nearly 2-fold increase in relative risk of cardiovascular complications.

Sleep apnea is also a common complication of ESRD and has been associated with increased left ventricular mass⁶⁰ as well as increased risk for cardiovascular events.⁶¹ Because more intensive dialysis has been shown to improve dialysis-associated sleep-disordered breathing,⁶² future research will be needed to independently demonstrate the value of such intervention on improvement of outcomes. Because sleep apnea in ESRD patients is a combination of central and obstructive components, it is not clear what value noninvasive positive-pressure ventilation would have on a large scale.

CONCLUSION

In conclusion, patients with CKD have both traditional and nontraditional (ie, uremia-related) risk factors for cardiovascular disease, and early intervention may reduce the burden of disease in these patients. Cardiovascular disease should be a concern even in the early stages of CKD, long before patients are referred to nephrologists or considered for renal replacement therapy. The primary care provider should seek to identify and modify those risk factors that will significantly affect the cardiovascular morbidity and mortality of CKD patients. While some risk factors cannot be easily modified, the risks from hypertension, smoking, physical inactivity, hyperlipidemia, anemia, and hyperparathyroidism could be reduced with early intervention. **HP**

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