CLINICAL INTERVENTIONS TO REDUCE CARDIOVASCULAR RISK IN PATIENTS WITH KIDNEY DISEASE

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ABSTRACT

Although the specific mechanisms by which chronic kidney disease (CKD) and cardiovascular disease (CVD) compound the effects of one another have not been identified, there are practical therapies physicians can use to reduce the risk of mortality associated with these diseases. Clinical trial evidence suggests that treating modifiable risk factors can reduce the risks of CKD progression and of cardiovascular events. As patients progress through the stages of kidney disease, mortality risk dramatically increases, and the majority of these deaths are the result of cardiovascular events. The modifiable risk factors for the progression of CKD and of CVD have significant overlap. Among these risk factors, anemia has been shown to compound the problems of CKD and to confer significant additional cardiovascular risk. Studies suggest that correcting anemia in patients with CKD may provide cardiovascular benefit, such as improvements in detrimental cardiac remodeling. Correcting anemia in the early stages of kidney disease may provide additional cardiovascular protection by slowing the progression of kidney disease. Currently, there are 2 available pharmacologic treatments for anemia: recombinant human erythropoietin and darbepoetin alfa. Both treatments are safe and effective, and the long half-life of darbepoetin alfa potentially allows for less frequent dosing. Anemia is one of the more manageable risk factors in patients with CKD. Managing risk factors such as anemia may provide significant cardiovascular benefit for this high-risk population.

(Patients with chronic kidney disease (CKD) are at high risk for developing cardiovascular disease (CVD). Observational studies show a strong link between the diseases, but the specific mechanisms by which they compound one another’s detrimental effects have yet to be identified. Nevertheless, there are practical therapies that physicians can use to limit the risk of mortality from these diseases. For instance, risk factors, such as hypertension, dyslipidemia, proteinuria, and anemia, can be successfully treated. The National Kidney Foundation has issued the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease, which recommend that all patients with CKD should be considered in the highest risk category for developing CVD, regardless of the absence of traditional risk factors. The K/DOQI guidelines provide therapeutic targets for the risk factors associated with CKD, and clinical trial evidence suggests that treating modifiable risk factors can reduce the risk of CKD progression and the risk of cardiovascular events. The American Heart Association and the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) also recognize the contribution of CKD as an important cardiovascular disease risk factor.

MANAGING RISK FACTORS

HYPERTENSION

The K/DOQI guidelines recommend a target blood pressure for cardiovascular risk reduction of below 130/80 mm Hg, acknowledging that a multidrug regimen will be needed in most patients to lower their blood pressure to this level. Diuretics should be part of the antihypertensive regimen in most patients. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are recommended for patients with proteinuria or diabetes mellitus.)
**LIPIDS**

Low-density lipoprotein (LDL) cholesterol levels should be maintained below 100 mg/dL according to the K/DOQI guidelines, which for the most part follow the recommendations of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines. Although diet and lifestyle modification may be beneficial for some patients, LDL level reductions achieved are usually insufficient to obtain the desired LDL target. In most patients who do not achieve LDL levels below 100 mg/dL with lifestyle modification alone, statins are recommended as first-line therapy. In patients with advanced kidney disease, the initial doses of statins other than atorvastatin and pravastatin need to be reduced by 50%. Patients being treated with cyclosporine (and probably tacrolimus) also need to be treated with reduced doses of statins because cyclosporine increases blood levels of these drugs. Bile acid sequestrants are recommended as second-line therapy for patients who cannot tolerate statins and who do not have significant hypertriglyceridemia. Niacin is recommended for patients who cannot be treated with bile acid sequestrants. For patients with elevated triglycerides, therapy should include fibrates or niacin, with the caveat that fibrates and statins should not be used in combination because of musculoskeletal risk.

Prospective studies of statins in patients with CKD are few. However, a recent post hoc analysis of the pooled results from 3 pravastatin trials showed that the presence of moderate CKD, defined as a glomerular filtration rate (GFR) of 30 to 60 mL/min/1.73 m², was associated with a 26% increase in the risk of myocardial infarction (MI), coronary intervention, or coronary death compared with those patients who had normal kidney function. The use of pravastatin in patients with moderate CKD was associated with a 23% reduction in the risk of MI, coronary intervention, or coronary death and a 14% reduction in all-cause mortality. These data suggest that statins offer some degree of cardiovascular protection for patients with CKD.

Prospective studies of the effect of statins on CKD progression are limited. A 1-year study of atorvastatin showed that patients with CKD who received the statin in combination with ACE inhibitors or ARBs and other antihypertensive drugs had a greater reduction in urinary protein excretion. Likewise, the patients with CKD who received the statin showed a much smaller decrease in creatinine clearance, a signal of slower decline in kidney function. Ongoing studies will hopefully provide more information about this important topic in the near future.

**HOMOCYSTEINE**

Hyperhomocysteinemia has been associated with a variety of types of CVD, such as coronary artery disease, peripheral vascular disease, and stroke. Homocysteine levels are also inversely related to GFR. Consequently, most dialysis patients have elevated homocysteine levels. In the general population, elevated homocysteine levels can usually be managed easily with folic acid supplementation. However, in patients with CKD, elevated homocysteine levels can rarely be normalized, even with high-dose (5-20 mg) folic acid supplements. Although elevated homocysteine levels are associated with poorer cardiovascular outcomes, studies have yet to show that correcting hyperhomocysteinemia in patients with CKD confers a reduction in cardiovascular risk.

**CALCIUM-PHOSPHORUS METABOLISM**

The Dialysis Outcomes and Practice Patterns study analyzed the relationship between calcium levels, phosphorous levels, and the calcium-phosphorous product and mortality in dialysis patients. Both cardiovascular and all-cause mortality were associated with higher calcium and phosphorous levels and a higher calcium-phosphorous product. There was a significantly increased mortality risk above a calcium-phosphorous product of approximately 65 mg²/dL², a finding that is consistent with earlier studies.

Although data in patients with CKD who are not undergoing dialysis are limited, the K/DOQI guidelines recommend maintaining total serum calcium between 8.4 and 9.5 mg/dL and limiting calcium intake to 2 g/day. This daily limit on recommended intake could be easily exceeded, particularly in dialysis patients, through the normal dietary intake of calcium with the addition of calcium from phosphate binders. The guidelines also recommend that serum phosphorous levels be maintained between 2.7 and 4.6 mg/dL in CKD stages 3 to 4 and between 3.5 and 5.5 mg/dL in stage 5 CKD by using dietary phosphorous restriction and judicious use of phosphate binders when needed. The K/DOQI recommendations also indicate that the calcium-phosphorous product should be maintained at below 55 mg²/dL² through control of the serum phosphorous level.
Although unproved as a predictor of cardiovascular events in patients with CKD, coronary calcification is increasingly recognized as a common finding in these patients and may at least in part be the result of inadequately controlled calcium and phosphorous levels or excessive total calcium intake. The Dallas Heart Study recently analyzed coronary artery calcification scores by electron-beam computed tomography (EBCT) scanning in a variety of patients. Figure 1 shows that patients in progressively more advanced stages of CKD had progressively higher coronary artery calcification scores. This was particularly dramatic in subjects with CKD and diabetes mellitus, in whom coronary artery calcification scores were markedly elevated compared with patients who did not have diabetes mellitus. Although a recent study did report an association between coronary artery calcification and the extent of angiographically demonstrated coronary atherosclerosis in patients with CKD, it remains to be proven whether coronary artery calcification is associated with greater risk of cardiovascular events or that maintaining tight calcium-phosphorus control reduces cardiovascular risk in patients with CKD.

**TREATING THE CKD-CVD ENTITY**

Patients with CKD are more likely to die than to progress to end-stage renal disease. Figure 2 shows the 5-year follow-up results from a study of patients with CKD. For patients at each progressively higher stage of kidney disease, the risk of death was dramatically higher. Patients in this study who had stage 4 kidney disease had a mortality rate over 5 years exceeding 45%. These data suggest that preventing the progression of CKD may confer cardiovascular benefit. Many of the risk factors for progression of CKD are also risk factors for CVD, and many of these, such as hypertension, albuminuria/proteinuria, dyslipidemia, smoking, and anemia, are modifiable. Perhaps then, physicians should be thinking about treatments to slow the progression of CKD in terms of the potential of these treatments to also slow the progression of CVD.

As an example, data from the Losartan Intervention for Endpoint Reduction (LIFE) trial showed a strong correlation between the risk of cardiovascular events and the severity of microalbuminuria (Figure 3). The severity of microalbuminuria can be modified through blood pressure control and the use of ACE inhibitors and ARBs. Reducing microalbuminuria in this way has been associated with slowing of the progression of CKD and may limit the associated cardiovascular risk.
Anemia has also been identified as a significant mortality risk factor, conferring about the same mortality risk in patients with CKD as the deadly combination of diabetes mellitus and congestive heart failure (CHF). Anemia in patients with CKD has been clearly associated with increased risk of stroke, cardiovascular events, CHF, hospitalization, and mortality. Figure 4 shows that for patients with decompensated CHF, the number of days spent in the hospital and in-hospital mortality were higher among patients with hemoglobin (Hb) levels below 11.4 g/dL compared with those with higher Hb levels. In the same study, mortality at 60 days and the combined end point of rehospitalization or death (60 days) were also higher in patients with lower Hb levels.

Anemia is a readily modifiable CVD risk factor that can be safely treated. Evidence suggests that anemia correction in patients with CKD may confer important cardiovascular benefits. A few small studies have suggested that treating moderately severe anemia results in reductions in left ventricular hypertrophy and left ventricular dilatation. One study of anemia correction with erythropoietin showed that raising baseline Hb from 8 g/dL to 10 g/dL was associated with a marked reduction in left ventricular mass index (LVMI) and end-diastolic volume over a 12-month period. Upon cessation of erythropoietin treatment, the patients became anemic again, and their improvements in LVMI and end-diastolic volume regressed (Figure 5). Another study in anemic patients with left ventricular hypertrophy examined the effects of raising Hb above 10 g/dL to 13.5 g/dL with erythropoietin treatment. This study did not show that achieving this higher level of Hb conferred additional cardiac benefits. Patients did, however, have improved quality of life.

A study of patients with severe, resistant CHF who underwent erythropoietin and iron treatment to raise their mean Hb from about 10.5 g/dL to 13 g/dL showed a statistically significant reduction in New York Heart Association functional class and scores on an index of symptoms such as fatigue and shortness of breath, and improved left ventricular ejection fraction. Hospitalizations were also significantly reduced, by more than 95%. Treatment of anemia had no adverse effects on GFR or blood pressure.

In addition to beneficial cardiac effects, treatment of anemia also appears to have beneficial effects in terms of slowing progression of CKD. A study exam-
ining the effects of early versus delayed erythropoietin treatment showed that patients with CKD who were treated earlier, with mild-to-moderate stages of anemia, had lower mortality and were less likely to require renal replacement therapy than patients whose treatment was delayed until they were more severely anemic. These studies suggest that correcting severe anemia may have a positive effect on measurable cardiovascular outcomes, such as left ventricular mass index. They also suggest that correcting anemia in the early stages of kidney disease may slow kidney disease progression, thereby reducing mortality risk.

There are 2 pharmacologic therapies approved in the United States for the treatment of anemia. Recombinant human erythropoietin has the same amino acid backbone as the native hormone. Darbepoetin alfa, a modified form of recombinant human erythropoietin, has a slightly different amino acid structure from the native hormone and a higher carbohydrate content than recombinant erythropoietin. Darbepoetin alfa offers the advantage of a longer serum half-life than recombinant human erythropoietin, allowing less frequent dosing. A comparative study of once-weekly darbepoetin and twice-weekly recombinant erythropoietin showed no difference in efficacy. Figure 6 shows that both treatment groups achieved the target Hb range of 11 g/dL to 13 g/dL within 6 to 7 weeks.

The K/DOQI guidelines recommend a target Hb level of 11 g/dL to 12 g/dL. This target is easily achievable with current therapies. Successful anemia treatment requires 2 agents at most: iron and either recombinant erythropoietin or darbepoetin alfa. Hypertension, by comparison, typically requires 2 to 3 agents or more to achieve adequate control. The efficacy of anemia treatment, coupled with the potential for infrequent dosing with darbepoetin alfa, make anemia one of the more easily treatable risk factors in patients with CKD. As stated earlier, all patients with CKD should be considered in the highest risk category for developing CVD. The appropriate management of risk factors, such as hypertension, proteinuria, dyslipidemia, calcium-phosphorous metabolism, and anemia, has the potential to reduce cardiovascular risk in patients with CKD.

**REFERENCES**


