

ADDRESSING CARDIOVASCULAR DISEASE IN PATIENTS WITH RENAL DISEASE

It is well-established that patients with renal disease are at increased risk of cardiovascular disease (CVD) death. Despite better understanding of CVD in endstage renal disease (ESRD) patients and more rigid guidelines addressing the major risk factors for CVD in this population, CVD continues to be the number one cause of death in patients with ESRD. Moreover, higher rates of CVD are seen in patients with moderate, and even mild, renal dysfunction and in patients with albuminuria (micro and macroscopic). Few studies with CVD endpoints have included patients with renal disease. There is sufficient evidence to support appropriate blood pressure reduction as having a beneficial effect on CVD morbidity and mortality in patients with renal disease (especially for patients with diabetes). Data supporting the benefit of modification of other CVD risk factors is not as strong, but current recommendations do stress aggressive control of lipids, smoking cessation, and maintenance of adequate nutritional status. Inclusion of patients with renal disease in studies with CVD endpoints is necessary. Until then, it is generally recommended that CVD risk stratification and modification strategies be applied to this high-risk population. (*Ethn Dis.* 2002;12[suppl3]:S3-1–S3-4)

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INTRODUCTION

It is well-established that patients with renal disease are at increased risk of cardiovascular disease (CVD) death.^{1,2} Many years ago the concept of “accelerated atherosclerosis” in chronic renal failure (endstage renal disease, [ESRD]) was developed by pioneers in dialysis who recognized that patients with chronic renal failure have a 20-fold increased risk of CVD death when compared to age- and sex-matched controls.³ Despite better understanding of CVD in ESRD patients and more rigid guidelines addressing the major risk factors for CVD in this population, CVD continues to be the number one cause of death in patients with ESRD⁴ and is approximately 3 times that seen in non-uremic controls.⁵ Moreover, higher rates of CVD are seen in patients with moderate and even mild renal dysfunction.^{6–9}

It is reasonable to hypothesize that treatment aimed at modifying CVD risk factors in patients with chronic renal disease will be beneficial. This topic was addressed by a task force of the National Kidney Foundation^{10,11} It is interesting to note that at the time of that review and formulation of recommendations, there was a paucity of data from randomized controlled trials that included renal patients. Part of the recommendation of that task force was to conduct trials that specifically addressed the appropriate therapy for modification of CVD risk in patients with renal disease. To date, there has not been much more data available addressing this specific question, but there are ongoing studies that should provide some important information in the future. In addition, because disturbances in renal function,

such as decreased estimated and measured GFR, mildly elevated (or high normal) serum creatinine, and the presence of microscopic and gross albuminuria are all strongly associated with CVD,^{12,13} renal risk factors have been included in almost all studies looking at CVD.

In this review, we will examine whether treatments targeted at modifiable risk CVD factors have a beneficial effect in patients with renal disease. When addressing this question, one must consider data in both the pre-ESRD and ESRD population. The National Kidney Foundation has devised a staging system¹⁴ for chronic kidney disease (CKD). This system includes 5 stages ranging from those with albuminuria but without decreased glomerular filtration rate (GFR) in the first stage, progressive declines in GFR in stages 2–4, and chronic kidney failure/ESRD in stage 5. Unfortunately, few studies that have CVD endpoints have included patients with renal disease at any stage. Fewer still have included patients with stages 3–5.

PRIMARY PREVENTION VS SECONDARY PREVENTION

In some cases, it is necessary to consider whether one is devising a treatment plan aimed at primary prevention or secondary prevention of CVD. In patients with renal disease, especially those with ESRD, there is an extremely high prevalence of CVD and secondary treatment strategies are necessary. A detailed discussion of secondary treatment strategies for coronary artery disease (revascularization and medical therapy) is beyond the scope of this manuscript.

There is a high mortality rate for ESRD patients with coronary arterial lesions. In some series, the one-year mortality for these patients approaches 50%.^{15,16} This mortality rate is significantly higher than seen in the general population, and similar findings have been made with stroke.¹⁶ Data that predicts fatality rates after ischemic events in patients with severe renal disease is sparse, but age appears to be the biggest determinant in the ESRD population.¹⁷ In the non-ESRD population creatinine is a strong determinant of survival after myocardial infarction and stroke.^{18,19} In general, it is recommended that patients with renal disease have revascularization procedures like one would perform in the general population,^{10,11} as these patients may do slightly better with revascularization.¹⁵ However, patients with severe CKD and ESRD experience high rates of complications and high morbidity and mortality rates for coronary artery bypass grafting and percutaneous transluminal angioplasty.^{15,17}

DOES ADDRESSING MODIFIABLE RISK FACTORS REDUCE CVD IN PATIENTS WITH RENAL DISEASE?

When CVD risk assessment is performed in patients with CKD, almost all of these patients fall into the highest risk category. This is in large part due to the consequences of the disease(s) that cause renal disease such as hypertension and diabetes. Therefore, it would be prudent to lower CVD through interventions of proven benefit. As mentioned, there is a paucity of data that "proves" that modification of the same CVD risk factors addressed in the general population has benefit in patients with renal disease. Conversely, there is significant data now that addresses the role of these CVD risk factors on the progression of renal disease.¹⁴ In general, many risk factors for

CVD are associated with progression of renal disease including: hypertension, diabetes, obesity, microalbuminuria, proteinuria, age, gender, race, hyperlipidemia, tobacco use, anemia, and nutritional status.¹⁴

It stands to reason, therefore, that treatments aimed at the modifiable risk factors will have a benefit on CVD and renal disease progression. Conventional wisdom was that, in patients with renal disease, aggressive intervention targeted at some CVD risk factors would not be of benefit because of the severity of the already-established CVD, the high mortality rate in this group, and the possibility of increased side effects on pharmaceutical agents in renal patients. In fact, most interventional studies targeting modifiable risk factors in patients without significant renal disease demonstrate that the benefit of intervention occurs early such that patients with CKD should benefit. Secondly, many risk factors can be modified in patients with CKD in a safe manner as described below.^{10,11,14}

Blood Pressure

Hypertension is one of the leading causes of renal failure and is highly prevalent in CKD. It is strongly associated with the development of CVD in patients with CKD and it is known to be associated with, and sometimes the cause of, left ventricular hypertrophy (LVH), which is also highly prevalent in patients with CKD. In turn, LVH is strongly associated with CVD events in this population. Numerous studies have demonstrated that blood pressure control has a beneficial effect on CVD in the general population.

It has been demonstrated that lowering of blood pressure to appropriate levels in patients with CKD will slow the progression of renal disease,²⁰ especially in those with proteinuria. However, we do not have similar data regarding CVD in this population. The Hypertension Optimal Treatment (HOT) Study²¹ demonstrated that low-

ering of blood pressure was associated with significant reduction in CVD morbidity and mortality. In this study of more than 18,000 patients, an estimated creatinine clearance (by Cockcroft Gault formula) of <60 mL/min was associated with significantly higher CVD risk and total CVD mortality.⁷ This study set 3 therapeutic targets for reduced diastolic blood pressure. In those with normal renal function, CVD events were lowered with blood pressure reduction. However, in those with renal insufficiency, the incidence of major CVD events did not differ among the 3 blood pressure target groups. This observation is disconcerting as it suggests that control of blood pressure in patients with CKD may not reduce the risk of reduced renal function. Similarly, the role of hypertension is not clear in those undergoing dialysis. In fact, there are reports that the presence of hypertension is associated with a favorable outcome in hemodialysis patients when compared to those with lower blood pressure.²²

Lipids

Lipid abnormalities are common in patients with renal disease and are associated with risk factors that are correlated with CVD morbidity and mortality in patients with and without renal disease.²³ In patients with renal disease, low HDL and elevated triglycerides and Apo B are more commonly seen than other lipid abnormalities. However, it is not known if therapy targeted at dyslipidemia will affect CVD in CKD. The answer to this question becomes more difficult with the observation that ESRD patients with lower cholesterol have worse survival rates.²⁴ This paradox may demonstrate that cholesterol is a surrogate for nutritional status, which is a determinant of CVD mortality in the ESRD population.

Treatment with a variety of lipid lowering agents has proven to be efficacious and safe in CKD. Unfortunately, the numerous trials examining the safety and effectiveness of these lipid

lowering agents in CKD have been short term and have not had CVD endpoints. While there is an ongoing study addressing this question in renal transplant patients, the largest published study that examines this question is retrospective. Seliger et al²⁵ used data from the United States Renal Data System to examine the effects of statins on CVD death and total mortality in ESRD patients. They found that <10% of ESRD patients were on statins at baseline. Total mortality was lower in the statin group, and statin use was independently associated with CVD mortality. In contrast, similar findings were not observed for fibrates.

Diabetes/Glycemic Control

Diabetes is strongly associated with increased mortality in patients with CKD. In fact, it is one of the strongest predictors of CVD disease in CKD.^{10,11,24,25} While the association between glycemic control and reduction of the development of microvascular complications of diabetes is established, the association with CVD risk is not as strong. Similarly, in patients with CKD, there is a lack of data demonstrating that glycemic control reduces CVD. However, even in those with CKD, glycemic control may reduce the severity of retinopathy and neuropathy.^{10,11,14} Therefore it is prudent to strive for glycemic control in those with CKD.

In diabetics, the goals for blood pressure control are lower than in the general population, especially if renal disease is present.^{14,26} These blood pressure reduction goals are largely based on the effects of blood pressure reduction on renal disease. However, in diabetics with nephropathy, there is compelling data that reducing blood pressure lowers CVD events.²⁷⁻³⁰ In normotensive²⁸ and hypertensive²⁷ persons with type 2 diabetes and nephropathy, the beneficial effects of blood pressure lowering on stroke and retinopathy was independent of antihypertensive agents (ACE inhibitor [enalapril] or calcium antagonist

[nisoldipine]). However, there is data to show that ACE inhibitors may lower fatal and non-fatal myocardial infarction in patients with hypertension, type 2 diabetes and nephropathy.²⁹

Proteinuria and Microalbuminuria

Both proteinuria and microalbuminuria have been demonstrated to be significantly associated with CVD. Therapy that lowers albuminuria has been shown to reduce renal disease progression in persons with or without diabetes.^{14,20,26} However, we do not know if lowering of albuminuria is associated with lower CVD risk and mortality. Some insight was gained into this question as losartan use in persons with type 2 diabetes and nephropathy lowered albuminuria and was associated with reduced first-time CHF hospitalizations.³⁰ Similarly, ramipril use in patients with risk for CVD lowered albuminuria and improved CVD morbidity and mortality.³¹ Future studies should be focused on whether albuminuria is truly a modifiable risk factor for CVD in those with CKD.

Nutrition/Obesity/Other Factors

As mentioned above, nutritional status is associated with CVD in ESRD patients. For example, creatinine, a marker of nutritional status, is inversely correlated with mortality in ESRD patients.^{23,24} Therefore, in patients with severe renal disease, it is important that nutritional status is followed as they approach ESRD. Dietary intervention to slow the rate of renal disease progression should not be so aggressive as to lead to worsening of overall nutritional status.²⁰ Another marker of nutritional status in African Americans with CKD and ESRD may be obesity. Obesity is now recognized as a major CVD risk factor. However, in African-American ESRD patients, higher BMI was associated with improved survival.³²

An elevated plasma homocysteine

level is an independent risk factor for atherosclerosis in ESRD patients, as well as in the general population.²³ In ESRD patients, plasma homocysteine level might also be a surrogate for nutritional status as it correlates with plasma albumin. Similar to what was seen with cholesterol, lower mortality was observed in ESRD patients with higher plasma homocysteine.³³

Finally, race is a determinant of CVD in the general population, with African Americans having higher rates than Whites. In addition, African Americans also have significantly higher rates of renal disease. However, in ESRD patients, African-American race is associated with better survival rates compared to Whites. The reason behind this survival advantage for African Americans with ESRD is not clear, but deserves further study.

CONCLUSION

CVD and CVD risk factors are common in patients with CKD. While few studies with CVD endpoints have included patients with CKD, it is reasonable to follow current guidelines for treatment strategies targeted at modifiable risk factors.^{10,11} Chief among these is the control of blood pressure, lipid abnormalities, prevention of diabetes, glycemic control in those with diabetes, and smoking cessation. There may also be a role for addressing elevated plasma homocysteine. Clinicians should pay attention to nutritional status of patients with severe CKD, as it is strongly associated with CVD and total mortality in ESRD patients. Finally, it is of utmost importance that patients with CKD be included in studies with CVD endpoints. Ongoing studies that address CKD should consider analysis of data that examines the effect of modifiable CVD risk factors in patients with CKD.

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