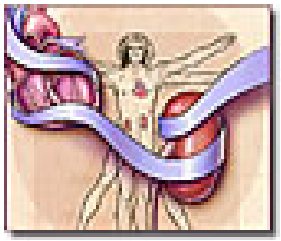
Chronic Renal Disease is a Risk Factor for CVD

Number 87 February/March, 2004

Chronic renal disease (CRD) is becoming increasingly prevalent in the US, with cardiovascular disease (CVD) as a major complicating factor. Kidney failure requiring treatment with dialysis or transplantation is the most visible outcome of CRD.



However, *CVD is also frequently associated with CRD*, which is important because individuals with CRD are more likely to die of CVD than to develop kidney failure[1]. CRD appears to be a risk factor for CVD. CVD in CRD is treatable and potentially preventable. Many strategies for CVD prevention also slow the parallel progression of CRD.

In this *Heartbeat* we will present data supporting the association of renal disease with CVD, identify traditional and non-traditional risk factors and outline some innovative treatment strategies to slow the parallel progression of CVD and CRD in these high-risk patients.

CRD high risk for CVD

Patients with CRD disease represent the population at greatest risk for cardiovascular morbidity and mortality, the American Heart Association (AHA) warns in a new Scientific Statement published in the October 28, 2003 issue of Circulation.[2] A 1998 analysis by the National Kidney Foundation found that *mortality from cardiovascular disease is 10-30 times higher in patients with renal disease than in the general population* (Figure 1). A lot of this mortality risk is obviously among the older long-term hemodialysis or peritoneal dialysis patients, but this CV risk is still very significant in patients with CRD before they need dialysis or renal transplantation.

"The presence of chronic kidney disease, whether it is manifested by proteinuria or reduced glomerular filtration rate, appears to be an independent risk factor for cardiovascular disease outcomes," write the authors of the Statement. They continue, "These findings are consistent with the National Kidney Foundation task force recommendation that *patients with chronic renal disease should be considered in the highest-risk group for cardiovascular disease events."* **This translates into the fact that these patients (with > 20% 10yr CHD risk) should receive the most aggressive CVD risk reduction strategies.**

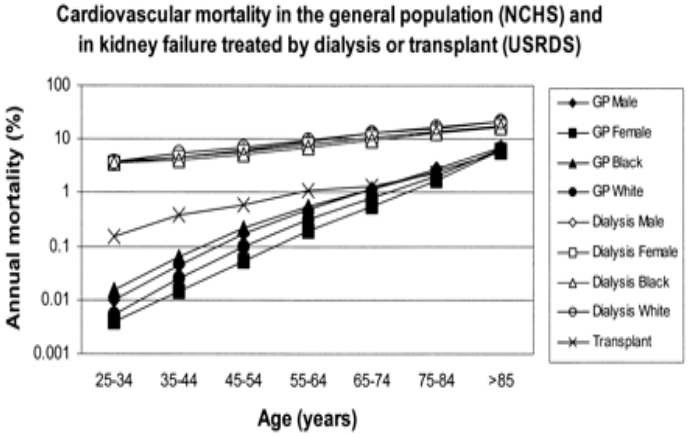


Figure 1. Cardiovascular mortality defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema in general population (GP; National Center for Health Statistics [NCHS] multiple cause of mortality data files International Classification of Diseases, 9th Revision [ICD 9] codes 402, 404, 410 to 414, and 425 to 429, 1993) compared with kidney failure treated by dialysis or kidney transplant (United States Renal Data System [USRDS] special data request Health Care Financing Administration form 2746 Nos. 23, 26 to 29, and 31, 1994 to 1996). Data are stratified by age, race, and sex. CVD mortality is underestimated in kidney transplant recipients owing to incomplete ascertainment of cause of death. Reproduced and modified with permission from Foley et al.[3]

The approximate prevalence of clinical ischemic heart disease is 8%-13% in the general population,

compared to 40% in patients on hemodialysis or peritoneal dialysis. CVD mortality is ~10-30 times higher in patients treated with dialysis compared to the general population despite stratification for sex, age, race or presence of diabetes (DM).

The prevalence of left ventricular hypertrophy is approximately 20% in the general population, versus 75% in patients on dialysis.

The approximate prevalence of clinical heart failure is only 3%-6% in the general population, compared to 40% in dialysis patients.

CVD accounts for 35% to 50% of all-cause mortality in kidney transplant patients.

Double Threat-Traditional

According to the AHA Statement, patients with kidney disease may have both "traditional" and non-traditional risk factors for cardiovascular disease. *Traditional risk factors* for CVD, (as used in the Framingham study to estimate the risk of symptomatic ischemic heart disease, including diabetes, hypertension, older age, high levels of low-density lipoproteins etc.) are very common among patients with CRD and account for most of the excess risk of CVD among these patients.

This risk is magnified when hypertension occurs concomitantly with DM, which is already considered a coronary heart disease (CHD) equivalent. In addition, much of the clinical significance of hypertension and DM relates to its inextricable link to renal dysfunction. DM is the most common cause of end-stage renal disease (ESRD) in the US and Europe. The combination of DM and hypertension is associated with 6-times greater risk of ESRD than hypertension alone.[4] Each of these risk factors accelerates the other, and the cumulative burden exerts its ravages on the vascular system simultaneously with the ongoing loss of renal function.

Non-traditional

Data has shown that the traditional risk factors are insufficient to explain the tremendous burden of CVD in CRD[5 6]. The increased risk is independent of and additive to the risk of other associated risk factors. Patients with CRD have a higher prevalence of less established risk factors (*non-traditional risk factors*) for CVD, which include hyper-homocysteinemia, oxidant stress, dyslipidemia (low HDL-C, high triglycerides or elevated Lp(a)), elevated inflammatory markers (hs-CRP), high serum fibrinogen (pro-coagulant) and microalbuminuria. These factors may play an important role in promoting CVD in patients with CRD.[7]

Another possibility is that traditional risk factors may have a qualitatively and quantitatively different risk relationship with CVD in CRD compared with the general population. For example, individuals with CRD may have had a longer and more severe exposure to hypertension than subjects without CRD. In addition, subjects with CRD may have been treated for hypertension, and the Framingham risk equation does not take into account dose or years of treatment with antihypertensive medications.[8]

The most important point is that **each risk factor (traditional or non-traditional) and its duration or degree accelerates the other, and the cumulative burden damages the CV system simultaneously with the ongoing loss of renal function**. The patient presenting with CRD has already sustained considerable, often irreversible, loss of renal function. Less appreciated, however, is that the ***development of CVD begins during the early stages of renal disease. Increased CV risk is evident even in mild kidney disease.***[9]

Altered Renal Function and CV Risk

Microalbuminuria, an early sign of CRD, is consistently associated with an incremental risk of CV morbidity and mortality in patients with both DM and hypertension. A recent review concluded that the risk of CV events and mortality was estimated to be 2-8 times higher when microalbuminuria was present in patients with DM or hypertension.[10] This risk was higher for diabetes, especially T2DM, because of older age. Increased CV risk was noted to start at levels well below the widely reported microalbuminuria cut-off level of 300µg/dl., and CV risk increased as the level of microalbuminuria increased.

Mildly reduced glomerular filtration rate (GFR)—reflected by GFR < 60 -90 ml/min. or an elevated serum creatinine (>1.5mg/dl in men; >1.4mg/dl in women) has consistently been found to be an independent risk factor for CVD outcomes and all-cause mortality in high risk populations. This relationship is not as clear in low-risk populations.

Microalbuminuria and/or reduced GFR and subsequent progression to nephropathy and ESRD has been successfully lowered or slowed by various pharmacotherapies (ACE inhibitors, angiotensin receptor blockers and statins). It is important to note here that we don't stop these disease entities. We just postpone them. We are born to die.

Although microalbuminuria and reduced GFR are clearly risk factors for CV morbidity and mortality, the extent to which their reduction or slowing by drug therapy affects CV risk has not been definitively established. Further studies are in progress.

Preliminary evidence

(1) A II Blockade

A late-breaking trial presented in November at the American Heart Association Meeting, the Prevention of Renal Vascular End-Stage disease Intervention Trial (PREVEND IT), showed that treating microalbuminuria with an ACE inhibitor (fosinopril 20mg) reduced microalbuminuria by 23% **and CV and renal events by 44%.** This study which followed > 850 patients over a four-year period had patients who did not have hypercholesterolemia or hypertension. This information supports the information presented in a prior *Heartbeat* concerning the pathologic role of Angiotensin II (A II) in both renal and CV disease and the benefits of A II blockade.[11]

(2)Lipid- Lowering Therapy

From the Heart Protection Study (HPS) we know that treatment with simvastatin significantly reduced the decline in GFR in diabetic (n =5,943) and non-diabetic (n = 14,573) patients.[12]

In the secondary prevention Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study, diabetic patients treated with atorvastatin (n = 161) had a 10.9% increase in GFR, in contrast to a 4.9% reduction among the usual care diabetic subgroup.[13]

Both of these studies document improved CV outcomes—and improved GFRs. It's obviously logical to assume that "renal and CV disease progress in parallel, and that statins are beneficial to both organs."

Pearls for Practice

***** Preventive care means more than assessing *traditional risk factors* (older age, male sex, hypertension, high LDL-C, low HDL-C, DM, smoking, FH, physical inactivity and LVH). *Non-traditional risk factors* (albuminuria, homocysteine, Lp[a], *hs*-CRP [cardiac] and thrombogenic factors) may be the missing link that explains the excessive risk of CVD in CRD.

***** *Microalbuminuria is consistently associated with increased CV and renal risk* across different patient populations (even without DM or hypertension). It is important to measure it, and when present, it should raise a flag. The presence microalbuminuria should prompt more aggressive treatment to reduce CV risk in addition to slowing the progression of renal disease. The new AHA statement recommends that patients with CVD or those at high risk for CVD—in addition to those with DM or hypertension—be checked for renal impairment (microalbuminuria or reduced GFR).

***** Elevated *hs*-CRP, homocysteine and Lp(a) are *markers* of higher risk for CVD and CRD. and *indicators* that more aggressive treatment may be necessary.

***** The presence of CRD, whether it is manifested by microalbuminuria, mildly reduced GFR, or ESRD on dialysis, appears to be an independent risk factor for CVD outcomes. This information supports the National Kidney Foundation task force recommendation that patients with CRD should be considered in the highest-risk group for CVD events.

***** Based on guidelines and what we know, all these higher-risk patients should be on:

Statins--(regardless of LDL-C levels) with goal LDL-C <100mg/dL—maybe lower based on new information—(April Heartbeat).

AII blockade—at doses documented effective in the studies (ACE inhibitors or angiotensin receptor blockers)—[***NOT*** *ramipril 2.5mg*].

Aspirin.

Water to Prevent Syncope

Syncope is experienced by 1/5 of the population at some time in their lives, frequently more than once and the most common type is vasovagal (or neurally mediated)—usually occurring after prolonged standing, alcohol use or emotional stress. The simple act of drinking two glasses of water (16 ounces) could significantly improve tolerance of orthostatic stress based on a recent study.[14]

The potential clinical implications of just drinking water are obvious, especially in those with a known propensity to vasovagal syncope, in settings where risk is high and all the syncope of undetermined origin. Further study of the water intervention's clinical efficacy could be invaluable, and in the mean time, push water in these clinical situations—not much downside risk, and most people don't take in enough fluids or drink the wrong kind (caffeinated).

Mario L Maiese, DO, FACC, FACOI
Associate Professor of Medicine, UMDNJSOM

Heartbeats can be found @ www.sjhg.salu.net
Under Patient Education—From Your Physician.
Mailto: maiese1@comcast.net

[1] Shulman NB, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension 1*989; 13 (5 Suppl): I80–I93.

[2] Sarnak MJ, et al. A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* October 2003; 108: 2154-2169.

[3] Foley RN, et al.Clinical epidemiology of CVD in CRD. *Am Kidney Dis.* 1998; 32: S112-S119.

[4] Bakris GL, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis.* 2000; 36: 646-661.

[5] Longenecker JC, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol.* 2002; 13: 1918–1927.

[6] Sarnak MJ, et al. Cardiovascular disease risk factors in chronic renal insufficiency. *Clin Nephrol.* 2002; 57: 327–335.

[7] Muntner P, et al. The prevalence of nontraditional risk factors for CAD in patients with chronic kidney disease. *Ann Intern Med* January 2004; 140: 9-17.

[8] Uhlig K, et al. Traditional cardiac risk factors in individuals with chronic kidney disease. *Semin Dial.* 2003; 16: 118–127.

[9] Fox CS, et al. Predictors of new-onset kidney disease in a community-based population. *JAMA* February 18 2004; 291: 844-850.

[10] Park HY, et al. A structured review of the relationship between microalbuminuria and CV events in patients with DM and hypertension. *Pharmoacotherapy* December 2003; 23: 1611-1616.

[11] Pitone JM, Maiese ML. Optimizing cardiovascular and renal risk-reduction. *Heartbeat* January 2002; 65.

[12] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study (HPS) of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7–22.

[13] Mikhailidis DP, et al. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2002 18: 4 215-219.

[14] Lu CC, et al. Water ingestion as prophylaxis against syncope. *Circulation* November 25 2003; 108: 2660-2665.