Cardiorenal Risk Factors

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Abstract: The chronic renocardiac syndrome, in which chronic kidney disease (CKD) contributes to impairment of cardiac function or structure, is associated with an increased risk of adverse cardiovascular events. The prevalence of CKD in the U.S. population is approximately 11% and has been increasing over time. Numerous studies have demonstrated an association of CKD, defined by the presence of reduced glomerular filtration rate and/or albuminuria with adverse cardiovascular and renal outcomes. These data suggest that both albuminuria and glomerular filtration rate, which can be performed with minimally increased costs, should be included in the assessment of risk stratification for individual patients, in addition to traditional cardiovascular risk factors.

Key Indexing Terms: Chronic kidney disease; Albuminuria; Cardiovascular disease; Glomerular filtration rate. **[Am J Med Sci 2010;340(1):25–29.]**

Numerous epidemiologic studies have shown an association between cardiovascular morbidity and mortality and decreased kidney function, regardless of whether cardiac disease or kidney disease was the initial event.[1–6] The term cardiorenal syndrome has been applied to this relationship.[7–9] This discussion deals with cardiorenal syndrome type 4, also referred to as the chronic renocardiac syndrome in which chronic kidney disease (CKD) contributes to impairment of cardiac function or structure, leading to increased risk of adverse cardiovascular morbidity and mortality.[7]

Mechanisms by which CKD may lead to cardiovascular disease (CVD) are incompletely understood and have been the subject of a number of previous reviews.[9–15] CVD and CKD share traditional risk factors including hypertension, diabetes mellitus and left ventricular hypertrophy. In addition, CKD adds a number of nontraditional risk factors for the development of CVD, including albuminuria, abnormal calcium phosphate metabolism, anemia related to kidney disease and increased levels of homocysteine and asymmetric dimethylarginine. The net effect of these traditional and nontraditional risk factors is enhanced cardiovascular morbidity and mortality.[10–12]

The prevalence of CKD in the general U.S. population is approximately 11%, representing approximately 26 million people.[16–18] The prevalence of stages I and II CKD, defined as the presence of abnormal urinalysis or renal imaging studies with normal or near normal glomerular filtration rate (GFR), is approximately 6.6%. Epidemiologic studies have primarily used the presence of proteinuria (albuminuria) to identify the presence of stages 1 and 2 CKD.[16–18] An additional 4.3% have stage 3 CKD, defined as estimated GFR (eGFR) <60 mL/min/1.73 m^2 with or without proteinuria. Stages 1 and 2 CKD are rather uniformly distributed across the age groups, whereas stage 3 CKD is increasingly prevalent with advancing age.[2,18] There is a dramatically lower prevalence of patients with stages 4 and 5 CKD, approximately, 0.4% respectively.[16–18] During the time interval of 1988 to 1994 compared with 1999 to 2004, the prevalence of both albuminuria and decreased GFR increased in the United States, according to the most recent NHANE surveys.[18]

Association of CKD With Cardiovascular and All-Cause Mortality

Most CKD can be characterized as progressing from microalbuminuria to overt proteinuria, declining GFR and ultimately end-stage kidney disease.[19,20] The risk of CVD increases in association with each of these incremental changes in the progression of CKD. Approximately 50% of deaths in patients with CKD are attributable to CVD; mortality rate in the 2-year interval after acute myocardial infarction is about 50% in stage 5 CKD. In general, CKD patients have a 10- to 20-fold increased risk of cardiac death, when compared with age-/gender-matched controls, and this risk increases up to >100-fold in younger age groups. CKD patients with mild and moderate stages of CKD are 20 times more likely to die than to ever need renal placement therapy.[2] Even patients with severe CKD have an approximately 2-fold greater likelihood of death than to ever need renal replacement therapy.[2]

The powerful association of CKD with cardiovascular death underscores the importance of a precise definition of CKD. The National Kidney Foundation definition of CKD is shown in Figure 1.[19,20] Using this definition, the National Kidney Foundation has developed a staging system for CKD (stages 1–5), which is shown in Figure 2. GFR is estimated in most clinics and laboratories by standardized prediction equations. The most commonly used prediction equation is the Modified Diet in Renal Disease equation, which is based on serum creatinine and adjusted for age, gender and ethnicity.[21] The Modified Diet in Renal Disease equation, however, systematically underestimates true GFR for patients in the high normal range of kidney function.[22] This has led to the development of a new estimating equation, the Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) equation.[22] Use of the CKD-EPI equation has yielded a lower estimated prevalence of CKD, primarily because of reclassification of low-risk individuals into the normal kidney function category.[23] The diagnostic criteria for albuminuria are based on routine dipstick urinalysis and more sensitive assays for the identification of microalbuminuria.

Association of Albuminuria With Cardiovascular Outcomes

Microalbuminuria is most commonly assessed in early morning spot urine samples rather than timed urine collections.[19,20] Albuminuria, typically measured as the urinary albumin creatinine ratio (ACR), is categorized as normal albuminuria (<30 mg/g creatinine), microalbuminuria (30–299 mg/g creatinine) or macroalbuminuria (>300 mg/g creatinine).[19,20] Urinary dipstick analysis is not sensitive enough to detect microalbuminuria but will typically be positive in pa-

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Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*:
• **Pathological abnormalities; or**
• **Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests**
2. GFR <60 mL/Min/1.73m^2 for ≥3 months, with or without kidney damage

Abbreviation: GFR glomerular filtration rate

FIGURE 1. National Kidney Foundation definition of CKD.

tients with macroalbuminuria. Epidemiologic studies have typically used proteinuria (albuminuria) and eGFR to define the presence and severity of CKD.[16–18]

Multiple studies have shown a strong association of cardiovascular events and death rates with reductions in GFR.[1–6] An observational study by Go et al[1], involving more than 1 million subjects, demonstrated an association between progression in cardiovascular event and death rates and progressive reductions in GFR, especially when GFR was below 45 mL/min/1.73 m^2. Additional studies have documented an increased risk of death from cardiovascular causes in association with progressive reductions in GFR.[2–6] These early studies did not consistently consider the contribution of albuminuria.[2–6]

Microalbuminuria is associated with an approximately 2-fold increase in the mortality rate related to both cardiovascular and noncardiovascular causes.[24–30] In a high-risk population of type 2 diabetics, microalbuminuria has been shown to increase the likelihood of death from coronary heart disease, stroke and all cardiovascular causes.[25,28] Overt proteinuria (macroalbuminuria) adds another increment in death rates from these causes. Although microalbuminuria has been defined categorically, it is actually a continuous variable, and the risk associated with increments in urinary albumin excretion occur even in the "high normal" range of albuminuria, as early as 10 mg/g creatinine.[26,27]

Association of Reduced GFR and Albuminuria With Cardiovascular and Renal Outcomes

The fact that both reduced GFR and albuminuria are independent predictors of the development of end-stage renal disease (ESRD) and of cardiovascular and all-cause mortality has been highlighted in several additional studies reviewed below.[31–38] The effect of the stage of CKD on cardiovascular events and mortality was analyzed in the PREVEND study.[37] This study involved 8500 subjects with a median follow-up of 7.5 years in a community-based cohort in the Netherlands. Estimated GFR and albuminuria were used to define the stage of CKD. Cardiovascular events were more frequent in subjects with all stages of CKD than in subjects with normal kidney function. Patients with stage 1 or 2 CKD had an increased risk for adverse cardiovascular and renal outcomes that was similar in magnitude to the risk seen in patients with stage 3 kidney disease. Subjects with both reduced GFR and microalbuminuria had the highest cardiovascular event rates. Stage 3 patients with no albuminuria, representing approximately two thirds of the stage 3 patients, had only a minimally increased risk for CVD or renal endpoints.

The ADVANCE trial evaluated the effects of GFR and albuminuria on the risk for cardiovascular and renal endpoints in a population of 10,460 subjects with type 2 diabetes mellitus with an average follow-up of 4.3 years[34]; 8.8% experienced a cardiovascular event and 1% a renal event. Fully adjusted models for cardiovascular events demonstrated a 2.48 hazard ratio for every 10-fold increase in albuminuria and 2.2 hazard ratio for every halving of GFR. Albuminuria and low GFR were independent risk factors for both cardiovascular and renal end points. The effects of albuminuria and GFR were independent both of each other and of other known risk factors, including systolic blood pressure. The magnitude of the risk attributable to low GFR and albuminuria was comparable with that of traditional cardiovascular risk factors. Subjects with both albuminuria and stage 3 kidney disease were at the greatest risk for all outcomes. In stage 3 kidney disease, the risk for cardiovascular and renal outcomes was lower in patients without microalbuminuria (albuminuria <30 mg/g).

The NHANES data from approximately 15,000 U.S. community-dwelling adults with approximately 13 years of follow-up demonstrated that estimated GFR and albuminuria independently predicted cardiovascular and all-cause mortality in this population.[35] Reduced GFR was associated with an increased risk of cardiovascular and all-cause mortality over all and within every category of proteinuria. Similarly, proteinuria was associated with increased cardiovascular and all-cause mortality within every category of estimated GFR. The presence of both of these abnormalities was associated with an even greater

Stage	Description	GFR (ml/min/1.73 m^2)	Prevalence*	
			N (1000s)	%
1	Kidney Damage with Normal or ↑ GFR	≥ 90	5,900	3.3
2	Kidney Damage with Mild ↓ GFR	60-89	5,300	3.0
3	Moderate ↓ GFR	30-59	7,600	4.3
4	Severe ↓ GFR	15-29	400	0.2
5	Kidney Failure	< 15 or Dialysis	300	0.1

*Stages 1-4 from NHANES III (1988-1994). Population of 177 million with age ≥20. Stage 5 from USRDS (1998), includes approximately 230,000 patients treated by dialysis, and assuming 70,000 additional patients not on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For Stage 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio ≥17 mg/g in men or ≥25 mg/g in women in two measurements.

FIGURE 2. Prevalence of CKD and estimated number of adults with CKD in the United States (NHANES data 88–94). (Adapted from Coresh J, Aston BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12.)

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increased risk. During comparable time intervals (1988–1994 to 1999–2004), the prevalence of both albuminuria and decreased GFR increased in the United States, according to the most recent NHANE surveys.[18]

Similar findings were noted in a community-based cohort study from a single province in Alberta, Canada.[38] In this study, approximately 920,000 adults had estimated GFR and albuminuria measured and had an average follow-up of about 3 years. In the fully adjusted model, all-cause mortality was higher in subjects with lower GFR and quantitatively greater proteinuria. In addition, the risk of myocardial infarction and progression to kidney failure associated with a given level of GFR was independently increased in patients with higher levels of proteinuria. The study also demonstrated that stages 1 and 2 kidney diseases are major risk factors for CVD. Their risk was equal to or greater than that of patients with stage 3 CKD who did not have albuminuria.

Reduced creatinine clearance was independently associated with an increased risk of developing ESRD in a large Japanese population reported by Iseki et al.[31] Subjects with a low creatinine clearance who had proteinuria on dipstick urinalysis had a significantly higher risk of developing ESRD than patients with a low creatinine clearance not associated with proteinuria.[31] Reduced eGFR and microalbuminuria were risk factors for cardiovascular death, independent of each other and of traditional risk factors, in the HUNT II study.[33] In patients with vascular disease, both decreased eGFR with normal albumin excretion and microalbuminuria with normal eGFR were independent predictors of future vascular events. The combination of decreased eGFR with albuminuria was associated with the highest risk of vascular events and all-cause mortality.[32]

Reduction of Albuminuria as a Potential Modifiable Risk Factor

Despite the numerous studies demonstrating that albuminuria is an important and independent predictor of mortality, cardiovascular events and adverse renal outcomes, there are very few studies that conclusively demonstrate that reduction of albuminuria reduces these risks. This is a critical question. The following studies show evidence that albuminuria is a modifiable risk factor.

The LIFE study involved approximately 8200 subjects with essential hypertension and left ventricular hypertrophy randomized to receive losartan or atenolol. Baseline albuminuria was a powerful predictor of CVD mortality. Patients receiving losartan had a greater sustained reduction in albuminuria than those receiving atenolol, and CVD outcomes were reduced in patients receiving losartan, when compared with those receiving atenolol, at all levels of albuminuria.[39]

In the RENAAL trial, which involved patients with diabetic nephropathy, the degree of albuminuria was the major predictor of adverse cardiovascular events.[40] Evaluation of albuminuria at the 6-month follow-up period demonstrated a positive relationship between the change in albuminuria from baseline levels and the risk of cardiovascular events. There was an approximately 20% reduction in the hazard ratio for cardiovascular and heart failure endpoints associated with a 50% reduction in albuminuria.[40] The IDNT diabetic nephropathy trial study group reported that a 50% reduction in albuminuria at the 12-month follow-up was associated with a halving of renal endpoints but no significant differences in cardiovascular endpoints.[41]

The PREVEND IT study was a randomized controlled trial designed to evaluate the effect of treatment of albuminuria on CVD outcomes in nonhypertensive individuals with persistent microalbuminuria.[42] Patients from the PREVEND cohort ($n = 864$) were randomized to receive fosinopril (20 mg daily) and/or pravastatin (40 mg daily) versus matching placebo using a 2×2 factorial design. Fosinopril reduced albuminuria by 26% and was associated with a 40% reduction in the primary cardiovascular endpoints. In patients with albuminuria >50 mg/d, fosinopril reduced the primary endpoint by 60%. Pravastatin did not reduce albuminuria and was associated with a nonsignificant 13% reduction in the primary endpoint. Only 3.4% of the participants had established CVD, and there was a low overall rate of cardiovascular events during the study. There are currently no published studies designed to directly determine the effect of albuminuria reduction on cardiovascular events in patients with established CVD.

However, there are other studies that have shown reductions in albuminuria that were not associated with decreased cardiovascular outcomes. The ON TARGET study compared combination therapy with telmisartan and ramipril to monotherapy with either telmisartan or ramipril.[43] Combination therapy resulted in greater reductions in albuminuria but was not associated with any further decrease in cardiovascular or renal outcomes. The AVOID trial evaluated the addition of either aliskiren or placebo to losartan therapy in patients with diabetic nephropathy, using a surrogate endpoint of reduction in proteinuria.[44] Treatment with aliskiren reduced ACR approximately 20%compared with the placebo effect. However, the study was not powered to evaluate cardiovascular outcomes. Based on the AVOID study results, an additional long-term study designed to evaluate cardiovascular and renal endpoints is now in progress in patients with type 2 diabetes and nephropathy (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints). Study completion is anticipated in 2012: http://www.clinicaltrials.gov, identifier NCT00549757.

Clinical Implications

Clinical decision making concerning initiation and intensity of treatment measures are frequently made on the basis of risk stratification. More aggressive therapy is initiated in patients at higher risk. The current studies that have been reviewed suggest that both albuminuria (ACR) and eGFR should be included in the assessment of risk stratification for individual patients, in addition to traditional cardiovascular risk factors. Albuminuria and reduced GFR are independent risk factors for both CVD and CKD. Determinations of eGFR and ACR can be performed with minimally increased cost. The presence of abnormal ACR identifies a higher risk profile in all age groups, even in the presence of normal or near normal eGFR (stages 1 and 2 CKD). The presence of moderate reductions in eGFR (stage 3 CKD) in the absence of abnormal ACR imparts only a modest increase in cardiovascular risk. This is particularly relevant to evaluation of elderly patients, as up to one half of the elderly with stage 3 CKD do not have microalbuminuria or macroalbuminuria. The combination of reduced eGFR and albuminuria confers the highest risk in all age groups studied. Previous studies have shown that a comprehensive approach to the treatment of modifiable risk factors is associated with improvements in both renal and cardiovascular outcomes.[45–49]

SUMMARY AND CONCLUSION

Both reduced GFR and albuminuria, particularly macroalbuminuria, are independently associated with adverse cardiovascular and renal outcomes. The presence of both factors is associated with an even greater increase in risk for adverse outcomes. The addition of eGFR and urine ACR improves risk stratification of adult patients while adding minimal cost to an office visit.

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