

SCOPE OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH KIDNEY DISEASE

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Approximately 6 million Americans have combined chronic cardiovascular and kidney disease with growing epidemics of heart and kidney failure. This clinical intersection presents unique risks to the patient and unique challenges to the clinician. Observational studies have provided quantitative methods for estimating the risk of acute renal failure in patients undergoing percutaneous intervention and bypass surgery procedures. Fortunately, for the general cardiovascular population, these risks are small. On the other hand, patients with chronic kidney disease have increased risks of accelerated atherosclerosis, nonfatal myocardial infarction, congestive heart failure, atrial and ventricular arrhythmias, and cardiac death. Chronic kidney disease presents difficult scenarios in using conventional cardioprotective therapy. However, there are increasing bodies of evidence to suggest the kidney and the heart can be targeted with lines of therapy, specifically with renin-angiotensin system antagonism, which benefit both systems with respect to reduction in the progression of disease, and the prevention of hard kidney and cardiac endpoints. This paper will address the scope of cardiovascular complications in patients with chronic kidney disease and discuss the rationale for expanded basic and clinical investigation of the cardiorenal patient population. (*Ethn Dis.* 2002;12[suppl3]: S3-44-S3-48)

Key Words: Cardiovascular Disease, Chronic Kidney Disease, Atherosclerosis, Myocardial Infarction, Heart Failure, Microalbuminuria, End-Stage Renal Disease

AN EPIDEMIC OF KIDNEY AND CARDIOVASCULAR DISEASE

The modern day, first-world epidemics of obesity and hypertension are central drivers of an epidemic of combined chronic kidney disease (CKD) and cardiovascular disease (CVD) as depicted in Figure 1.¹ Among those with diabetes for 25 years or more, the prevalence of diabetic nephropathy in type 1 and type 2 diabetes is 57% and 48%, respectively.² Approximately half of all cases of end-stage renal disease (ESRD) are due to diabetic nephropathy, with most of these cases driven by obesity-related type 2 diabetes and hypertension. Both incident and prevalent cases of ESRD and congestive heart failure (CHF) are increasing at an alarming rate.³⁻⁴ African Americans have a 3- to 4-fold increased rate of all cardiovascular diseases, including CHF as shown in Figure 2. As internists, cardiologists, and nephrologists co-manage an increasing number of patients who fall in the clinical intersection (Figure 3), combined strategies, which provide accurate diagnosis and management of cardiorenal risk for benefits to both the heart and kidney, must be developed.

IS KIDNEY DISEASE A CARDIAC RISK FACTOR?

Epidemiologic studies and clinical trials have consistently reported an independent relationship between CKD, usually defined by an elevated serum creatinine (Cr), and cardiovascular death in a variety of settings.⁵⁻¹⁰ In a recent consensus conference, CKD was defined as the point in time when the steady-state serum creatinine rises to ≥ 1.2 mg/dL in a male and ≥ 1.4 mg/dL in a female, or when microalbumin-

uria is detected.¹¹ The recently published *Clinical Practice Guidelines for Chronic Kidney Disease* by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative refines the definition and outlines stages of CKD by estimated glomerular filtration rate: Stage 1 >90 mL/min/1.73 m² with CKD risk factors; Stage 2 60-89 mL/min/1.73 m²; Stage 3 30-59 mL/min/1.73 m²; Stage 4 15-29 mL/min/1.73 m²; and Stage 5 <15 mL/min/1.73 m² or on renal replacement therapy.¹² Microalbuminuria is a key marker of CKD and has been thought to occur as the result of hyperfiltration in the kidneys to diabetes- and hypertension-related changes in the glomeruli. There have been several definitions developed for microalbuminuria.¹³ A simple definition for microalbuminuria is 30-300 mg/L on a single voided casual specimen. Other definitions call for 24-hour urine sampling with 20-200 mg/min or 30-300 mg/24 hours of urinary albumin being considered microalbuminuria. In addition, the ratio of albumin to creatinine on a 24-hour urine specimen has been defined as microalbuminuria if the albumin/creatinine is 17-299 in a man, and 25-299 in a woman. Greater degrees of proteinuria on casual or 24-hour specimens have been described as macroalbuminuria, and finally, greater than 300 mg/L is usually considered gross proteinuria. Figure 4 displays the relationship between proteinuria and all-cause mortality in patients with CKD. The abnormal vascular biology of the CKD state is reflected by renal injury, proteinuria, and simultaneous cardiac injury with accrual of cardiovascular events, including death.

How can we begin to unravel these important epidemiological observations into an approachable problem from a clinical and research perspective? One

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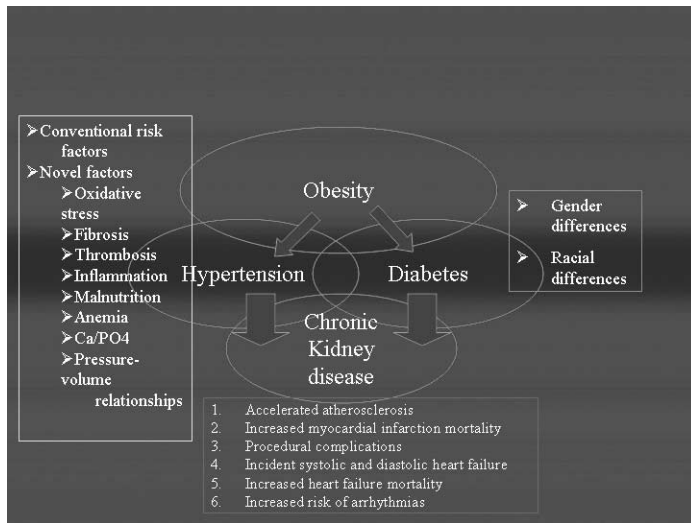


Fig 1. The first-world epidemic of obesity is driving an epidemic of diabetes and hypertension, which will result in a burgeoning population of patients with diabetic nephropathy and excess cardiovascular risk

approach is to divide the problem into four basic explanations: 1) excess comorbidities in CKD patients; 2) lower utilization of beneficial therapies in CKD patients, or therapeutic nihilism; 3) excess toxicities from conventional therapies used; and 4) special biology of the chronic renal failure state that leads

to accelerated and more severe cardiovascular disease.³

Excess Comorbidities

Population-based studies have demonstrated that there are higher rates of diabetes, poorly controlled hypertension, elevated triglycerides, lower HDL

cholesterol, and elevated Lp(a) levels in patients with CKD and ESRD.¹¹ However, there are lower rates of smoking in the same groups compared to the general population. Insufficient data exist regarding CVD family history or exercise to make conclusions regarding these contributory CVD risks to the CKD and ESRD populations. It is clear that age is a contributing factor to risk of CKD, but it is not for ESRD, where the mean age of patients on dialysis is 56 years old. Figure 5 demonstrates that microalbuminuria, as a diagnostic test, helps explain the graded risks from the general population with multiple risk factors, to diabetics with microalbuminuria, to diabetics with gross proteinuria, to finally, ESRD, the highest risk state in cardiovascular medicine.¹²⁻¹⁷

Underuse of Cardioprotective Therapies

Given the excess comorbidities in patients with CKD and ESRD, it is not unexpected that reduced rates of proven therapies may explain, in part, the outcomes observed. While data to support this hypothesis are limited, Beattie and coworkers have recently reported that in the setting of ST-segment myocardial infarction, there are graded decreases in the use of routine therapies including aspirin, beta-blockers, thrombolytics, and primary angioplasty as renal function declines.⁵ Quality programs that target these opportunities for improvement may make a difference in CKD outcomes. Importantly, blood pressure control, in both the inpatient and outpatient settings, is another important target for quality improvement in the cardiorenal risk field.¹⁸

Excess Toxicities of Therapies

It is clear that CKD and ESRD patients have worsened outcomes after angioplasty and bypass surgery, and this in part, can be considered a “toxicity” of the therapy offered. However, data on the drug toxicities and drug interactions, which result in poor outcomes in

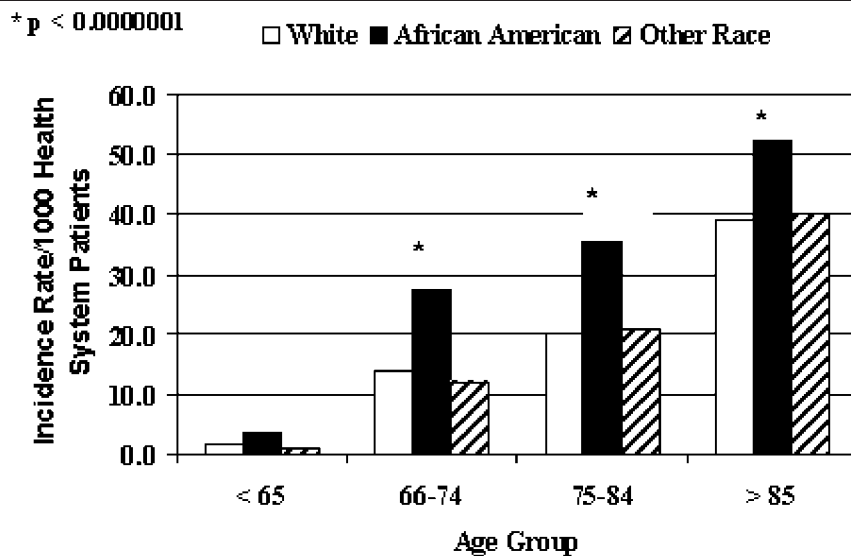


Fig 2. Increased burden of heart failure in African Americans from the Resource Utilization Among Congestive Heart Failure (REACH) study (adapted from reference 4)

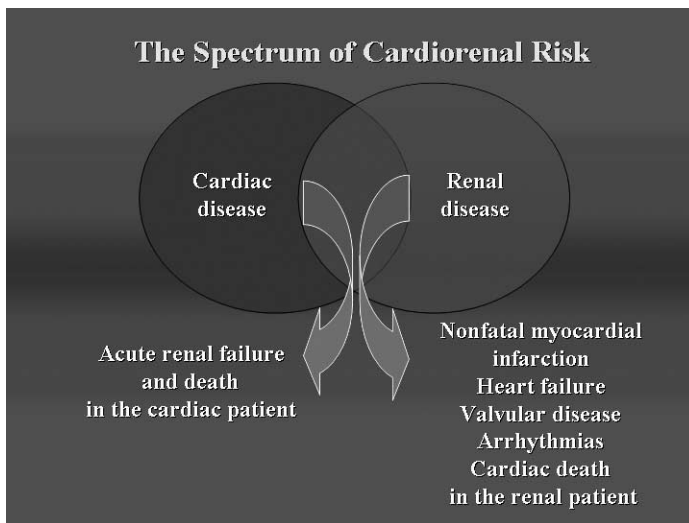


Fig 3. The cardiorenal intersection displayed as spectrum of risks and outcomes. The renal risks to cardiac patients are largely due to acute renal failure after percutaneous or surgical revascularization procedures. These risks can largely be anticipated, but rarely prevented. Cardiac risks to kidney patients are formidable, with increased independent risks for a variety of cardiovascular events

CKD and ESRD patients, are difficult to find. One explanation may be that CKD and ESRD are routinely excluded from randomized trials. In trials where analyses have been performed based on renal function, increased rates of bleed-

ing complications, which contribute to morbidity, have been found. Drugs, which have predictable problems with bleeding when the estimated glomerular filtration rate (calculated creatinine clearance [CrCl]) drops below 45 mL/

min, have included aspirin, non-anti-body glycoprotein IIb/IIIa inhibitors, unfractionated and low-molecular weight heparin, and in some studies, thrombolytics.¹⁹⁻²⁰ Other complications, including decreased clearance of anti-arrhythmics and inotropes, require dose adjustment. Lastly, the hastening of renal failure is a concern for CKD patients with CrCl <15 mL/min with the use of ACEI and angiotensin II receptor blockers (ARBs).

Abnormal Vascular Biology

A growing body of literature supports the notion that CKD, manifested by decreased glomerular filtration and proteinuria, is an abnormal state of vascular biology. As renal function declines, there are a host of abnormalities that develop including changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium/phosphorus balance, and many other factors related to CVD (Table 1). All of these factors are subjects of active investigation, which is beyond the scope of this article. The most developed therapeutic target, with respect to reduction in cardiorenal risk, is the renin-angiotensin system (RAS). This powerful regulatory system has complicated inter-relationships between the juxtaglomerular complex, mesangium, proximal and distal tubules, sympathetic nervous system, adrenal glands, myocardium, vascular endothelium, lungs, and virtually every solid tissue organ in the body. Of note, angiotensin II has been demonstrated to promote vasoconstriction and salt and water retention via the angiotensin II type 1 receptor. In addition, angiotensin II causes important trophic effects including smooth muscle cell proliferation and chemotaxis via the type 2 receptor. Clinical trials in cardiology clearly have proven that antagonism of the RAS with ACEI prevents adverse left ventricular remodeling and CHF in those at risk. In addition, ACEI have been proven to reduce hospital admissions and death in CHF. In CKD, randomized trials have

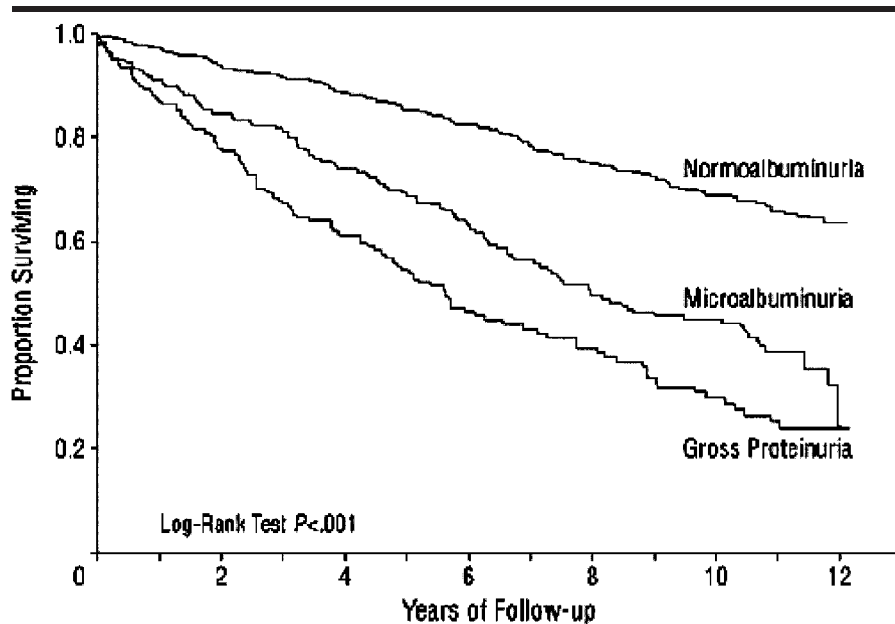


Fig 4. All-cause mortality stratified by levels of proteinuria in patients with type 2 diabetes and CKD (adapted from reference 13)

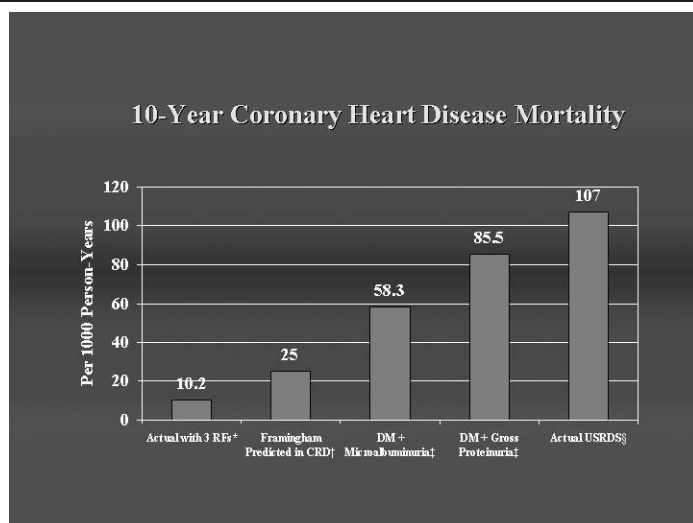


Fig 5. Sequential increased coronary heart disease risk in the general population, those with CKD and ESRD

proven ACEI to delay the progression of renal failure, reduce proteinuria, and reduce the incidence of ESRD.²¹ Recently, a convergence of randomized trials of ARBs, as an isolated attempt at RAS blockade, found again, that there are reductions in microalbuminuria, and delayed progression of renal disease.^{22–25} Lastly, studies that have combined the

use of ACEI and ARBs, in general, have demonstrated synergistic effects and have had even greater renal protection with the potential for improved cardiovascular outcomes, especially in CHF patients. Today, it is clear that leaving the RAS unabated in patients with diabetes, hypertension, CKD, or CVD leads to the progression of renal failure,

adverse left-ventricular remodeling, incident heart failure, and perhaps accelerated atherosclerosis and incident diabetes.

In addition in the RAS, there are multiple therapeutic targets for treatment of CVD in CKD patients. Multiple intervention trials are underway to address lipid reduction, homocysteine, and other atherosclerotic risk factors in CKD patients. With respect to heart failure, the erythropoietin deficiency and chronic anemia in CKD has been considered as a potential target, and at least one small randomized trial suggests that correction of anemia with exogenous erythropoietin may be beneficial.²⁶ It is currently unknown whether newer therapies including nesiritide (B-Type natriuretic peptide) or fenoldopam (dopamine-1 receptor agonist) will be useful for the acutely decompensated patient with combined heart and renal failure. Studies are currently being planned with these agents. As more hypotheses mature, we can expect a greater investment in the CKD population with high-quality prospective cohort studies and randomized, controlled, intervention trials.

Selected factors and physiological phenomenon, which contribute to the pathobiology of vascular disease in patients with chronic kidney disease

Abnormal Vascular Biology in Patients with Chronic Kidney Disease

Pathogenesis of heart failure (systolic and diastolic dysfunction)

- Altered cardiomyocyte function
- Altered intercellular matrix
- Unique volume-pressure relationships—chronic volume overload
- Adverse LV remodeling related to anemia/erythropoietin deficiency

Accelerated atherosclerosis

- Endothelial dysfunction (NO)
- Homocysteine, folate, B12, and B6 metabolism
- Lipoprotein metabolism
- Hyperinsulinemia
- Coagulation
- Fibrinolysis
- Inflammation (CRP, IL-6)
- Overactivation of the renin-angiotensin system
- Oxidative stress
- Abnormal collagen metabolism and cardiac and renal fibrosis
- Advanced vascular calcification

Accelerated valve disease

Increased risk of arrhythmias

Renal artery stenosis as a special atherosclerotic syndrome

CONCLUSION

Cardiorenal risk is an important clinical intersection warranting clinical attention and innovative strategies for diagnosis and treatment. The single greatest opportunity for improving cardiorenal risk at present is blockade of the RAS at one or multiple levels. Recognition of renal dysfunction and its unique vascular pathobiology has led to translational research yielding new therapeutic targets currently being tested in randomized trials. This growing base of information will be needed to address the consequences of the chronic heart and renal failure epidemics we witness today.

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AUTHOR CONTRIBUTIONS

Design and concept of study: McCullough
Acquisition of data: McCullough
Data analysis and interpretation: McCullough
Manuscript draft: McCullough
Statistical expertise: McCullough
Acquisition of funding: McCullough
Administrative, technical, or material assistance: McCullough
Supervision: McCullough