Cardiorenal Risk: An Important Clinical Intersection

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA

Section of Cardiology, Departments of Basic Science and Internal Medicine, University of Missouri-Kansas City School of Medicine, Truman Medical Center, Kansas City, MO

Approximately 6 million Americans have combined chronic cardiovascular and kidney disease. 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, that benefit both systems with respect to reduction in the progression of disease, and the prevention of hard kidney and cardiac endpoints. This article will focus on the cardiorenal intersection and highlight innovative diagnostic and therapeutic strategies concerning this high-risk patient group. [Rev Cardiovasc Med. *2002;3(2):71–76*]

Key words: Cardiovascular disease • Chronic kidney disease • Atherosclerosis • Myocardial infarction • Heart failure • Microalbuminuria • End-stage renal 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 II diabetes and hypertension. As internists, cardiologists, and nephrologists co-manage an increasing number of patients who fall in the clinical intersection (Figure 2), there are needs for combined strategies that provide accurate diagnosis and management of cardiorenal risk for benefits to both heart and kidney.

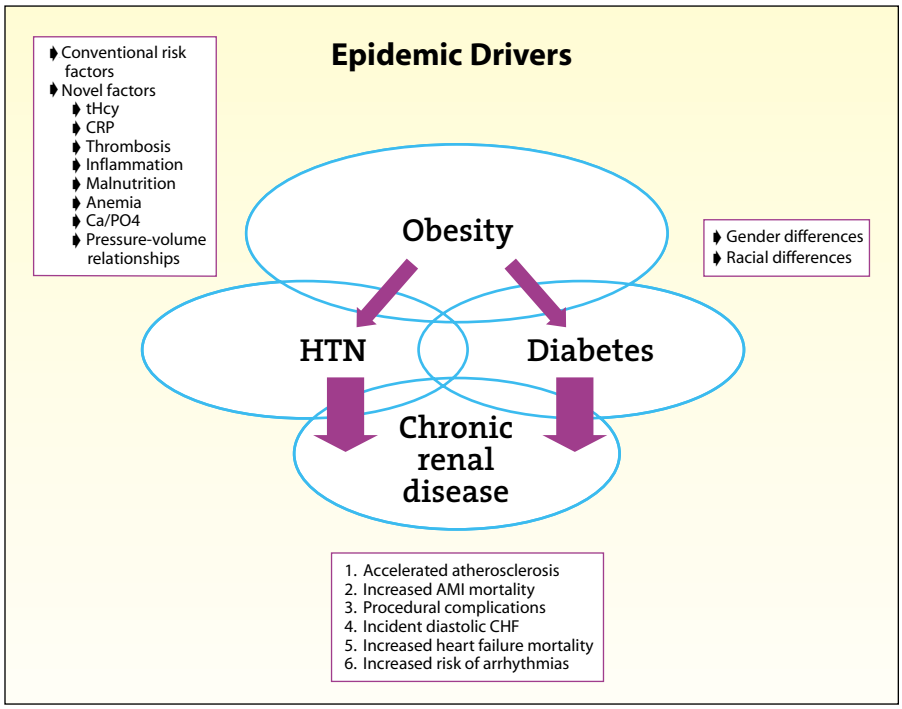


Figure 1. *The First World epidemic of obesity is driving a further epidemic of diabetes and hypertension that will result in a burgeoning population of patients with diabetic nephropathy and excess cardiovascular risk. tHcy, total serum homocysteine; CRP, c-reactive protein; Ca/P04, calcium-phosphate balance; HTN, hypertension; AMI, acute myocardial infarction; CHF, congestive heart failure.*

Chronic Kidney Disease as 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.[3–8] In a recent consensus conference, the following definition was agreed upon: CKD is defined as the point in time when the steady-state serum Cr rises to 1.2 mg/dL or higher in a male and 1.4 mg/dL or higher in a female, or when microalbuminuria is detected.[9] Microalbuminuria has been thought to occur as the result of hyperfiltration in the kidneys to diabetes and hypertension-related changes in the glomeruli. Several definitions have been developed for microalbuminuria.[10] One simple definition is 30 to 300 mg/L on a single voided casual specimen. Other definitions call for 24-hour urine sampling, with 20 to 200 μg/min or 30 to 300 mg/24 hours of urinary albumin being considered microalbuminuria. In addition, the ratio of albumin to Cr on a 24-hour urine specimen has been considered to define microalbuminuria if the albumin/Cr ratio is 17–299 in a man and 25–299 in a woman. Greater degrees of proteinuria in casual or 24-hour specimens have been described as macroalbuminuria, and finally, greater than 300 mg/L is usually considered gross proteinuria.

Table 1 lists the independent risk factors for death after primary angioplasty from the New York State angioplasty registry. Both baseline Cr and ESRD are independent poor prognostic factors, and this has been consistently reported in observational and clinical trial databases that include patients with CKD. There are four basic explanations for the cardiorenal risk relationship: 1) excess comorbidities in CKD patients; 2) lesser use 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, which leads to accelerated and more severe cardiovascular disease.[3]

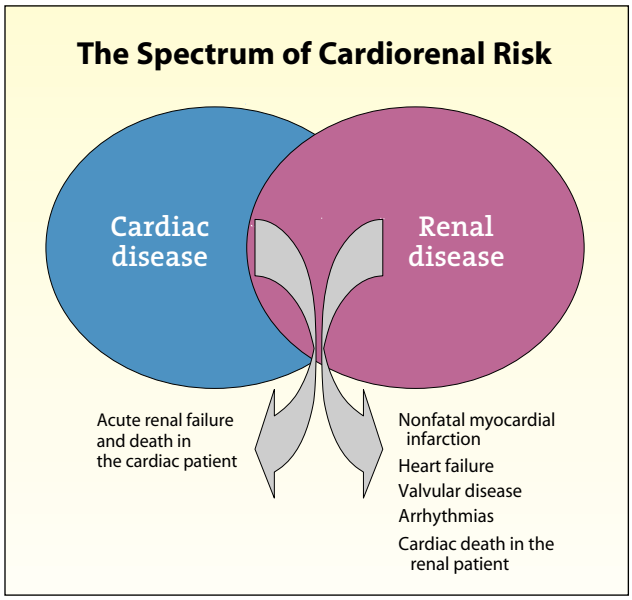


Figure 2. *The cardiorenal intersection displayed as spectrum of risks and outcomes. The renal risks to cardiac patients are largely due to acute renal failure after percutaneous or surgical revascularization procedures. These risks can be largely anticipated but rarely prevented. Cardiac risks to kidney patients are formidable, with increased independent risks for a variety of cardiovascular events.*

Excess Comorbidities

Population-based studies have demonstrated that there are higher rates of diabetes, poorly controlled hypertension, elevated triglycerides, lower high-density lipoprotein cholesterol, and elevated Lp(a) levels in patients with CKD and ESRD.[9] However, there are lower rates of smoking in the same groups compared to the general population. There are insufficient data 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. Figure 3 demonstrates that microalbuminuria as a diagnostic test helps explain the graded risks in the general population with multiple risk factors, diabetics with microalbuminuria, diabetics with gross proteinuria, and patients with ESRD, the highest-risk state in cardiovascular medicine.[10–14]

Table 1
Multivariate Predictors of Death After Primary Angioplasty for Acute Myocardial Infarction

Predictor	Relative Risk*
Shock	4.66
ESRD	3.44
Cr > 2.5 mg/dL	2.00
LM Dz	2.88
CHF	2.11
EF < 20%	2.08

Note only cardiogenic shock confers a higher risk state than the chronic kidney disease or ESRD patients. ESRD, end-stage renal disease; Cr, serum creatinine; LM Dz, left main disease; CHF, congestive heart failure; EF, ejection fraction. Data from Hannan et al.[19]
*All $P < .05$.

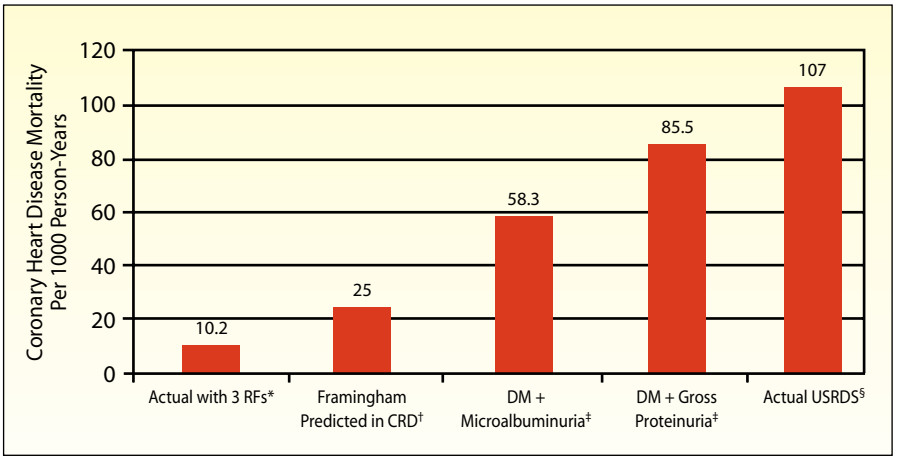
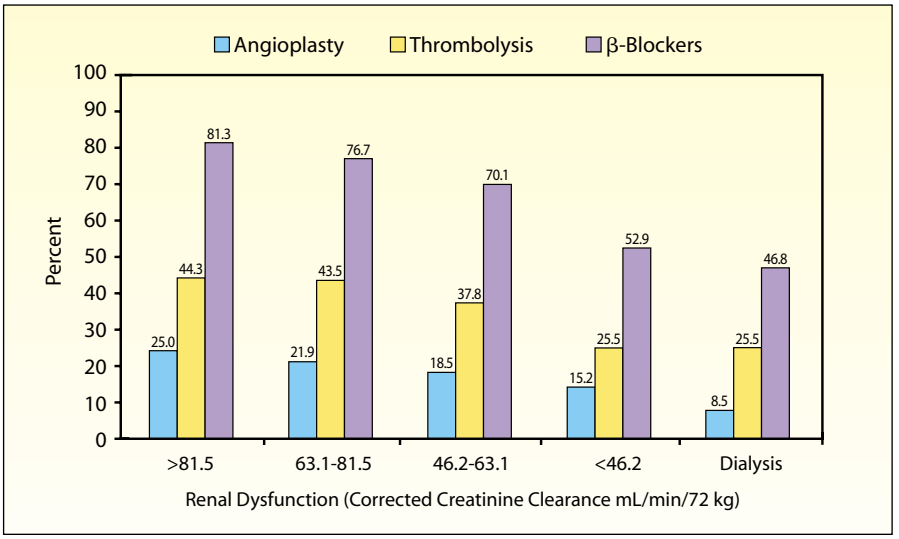


Figure 3. *Sequential increased coronary heart disease risk in the general population, patients with chronic kidney disease, and patients with end-stage renal disease. RFs, risk factors; CRD chronic renal disease; DM, diabetes mellitus; USRDS, U.S. Renal Data System. *, data from Lowe et al[20]; †, data from Wilson et al.[21]; ‡, data from Valmadrid et al.[22]; §, data from Port et al.[23]*

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 in part explain the outcomes observed. Although 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 as renal function declines (Figure 4).[3] It is certainly conceivable that quality programs may target these opportunities for improvement, especially with respect to the use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and reperfusion therapy. In addition, chronic blood pressure control in CKD and ESRD populations is another target for quality improvement in the cardiorenal risk field.[15]

Figure 4. *Decreased rates of cardioprotective drug utilization in patients with ST-segment elevation myocardial infarction. Reproduced, with permission, from Beattie et al.[3]*



SELECTED FACTORS AND PHYSIOLOGICAL PHENOMENA THAT CONTRIBUTE TO THE SPECIAL BIOLOGY OF CARDIORENAL RISK

- Pathogenesis of heart failure (systolic and diastolic dysfunction)
  - Altered cardiomyocyte function
  - Altered intercellular matrix
  - Unique volume–pressure relationships—chronic volume overload
  - Adverse left ventricular remodeling related to anemia/erythropoetin deficiency
- Accelerated atherosclerosis
  - Endothelial dysfunction
  - Homocysteine, folate, B12, and B6 metabolism
  - Lipoprotein metabolism
  - Hyperinsulinemia
  - Coagulation
  - Fibrinolysis
  - Inflammation (c-reactive protein, cytokines)
  - Angiotensin system (via PAI-1 or endogenous TPA)
  - Oxidative stress
  - Advanced vascular calcification
- Accelerated valve disease
- Increased risk of arrhythmias
- Renal artery stenosis as a special atherosclerotic syndrome

Table 2
Outcomes of Leaving the Renin–Angiotensin System Unabated or Unchecked in Patients in Patients with Diabetes, Hypertension, Chronic Kidney Disease, or Cardiovascular Disease

- ► Leads to progression in renal disease, worsened levels of proteinuria, and ultimate need for dialysis
- ► Leads to adverse remodeling and symptomatic congestive heart failure
- ► May lead to accelerated atherosclerosis and the development of diabetes in those with existing vascular disease

Excess Toxicities of Therapies

It is clear that CKD and ESRD patients have worse 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 that result in poor outcomes in CKD and ESRD patients are difficult to find. One of the reasons for this is that CKD and ESRD are routinely excluded from randomized trials. In trials where analyses have been performed based on renal function, there have been increased rates of bleeding complications, which contribute to morbidity (Figure 5). Drugs that have predictable problems with bleeding when the estimated glomerular filtration rate (calculated creatinine clearance [Cr Cl]) drops below 45 mL/min included aspirin, nonantibody glycoprotein IIb/IIIa inhibitors (epiphibatide and tirofiban), unfractionated and low-molecular-weight heparin, and, in some studies, thrombolytics.[16,17] Other complications, including decreased clearance of antiarrhythmics and inotropes, require dose adjustment. Lastly, the hastening of renal failure is a concern for CKD patients with Cr Cl under 15 mL/min with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Special Biology in the Cardiorenal Intersection

As renal function declines, a host of abnormalities develop, including changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium/phosphorus balance, and many other factors that have been related to CVD (see Sidebar). All of these factors are subjects of active investigations that are beyond the scope of this article. Far and away the most developed area of investigation with respect to reduction in cardiorenal risk is the renin–angiotensin system (RAS). This powerful regulatory system has complicated interrelationships between the juxtaglomerular complex, mesangium, proximal and distal tubules, sympathetic nervous system, adrenal glands, myocardium, vascular endothelium, lungs, and virtually every solid-organ tissue in the body.

As renal function declines, a host of abnormalities develop.

Of note is that angiotensin II has

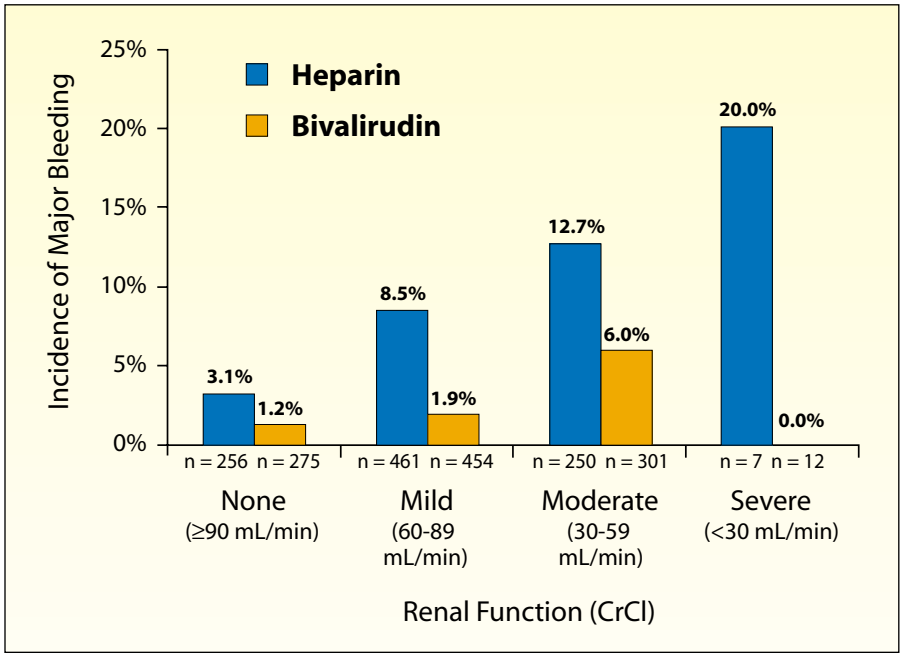


Figure 5. *Increased bleeding rates with unfractionated heparin when compared to bivalirudin in a randomized trial of elective antithrombotic therapy in elective angioplasty. CrCl, creatinine clearance (mL/min). Data from Robson et al.*[24]

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. In fact, there are at least six angiotensin II receptors and likely more to be discovered. Clinical trials in cardiology have clearly proven that antagonism of the RAS with ACE inhibitors prevents adverse left ventricular remodeling and congestive heart failure (CHF) in those at risk. In addition, ACE inhibitors have been proven to reduce hospital admissions and death in CHF. In CKD, randomized trials have proven ACE inhibitors to delay the progression of renal failure, reduce proteinuria, and reduce the incidence of ESRD.[18] Recently, a convergence of randomized trials of ARBs as an isolated attempt at RAS blockade showed that, again, there are reductions in microalbuminuria and delayed progression of renal disease. Lastly, studies that have combined the use of ACE inhibitors and ARBs have in general demonstrated synergistic effects and have shown 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 (Table 2). Future issues of *Reviews in Cardiovascular Medicine* will highlight the basic and clinical sources of data that support these statements and will explore new approaches to patients at risk.

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. *Reviews in Cardiovascular Medicine* will explore the many aspects of cardiorenal risk as new data become available in the coming months to years. ■

References

1. Lewis CE, Jacobs DR Jr, McCreath H, et al. Weight gain continues in the 1990s: 10-year trends in weight and overweight from the CARDIA study. Coronary Artery Risk Development in Young Adults. *Am J Epidemiol*. 2000;151:1172–1181.
2. Bretzel RG. Effects of antihypertensive drugs on renal function in patients with diabetic nephropathy. *Am J Hypertens*. 1997;10(9 Pt 2):S208–S217.
3. Beattie JN, Soman SS, Sandberg KR, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis*. 2001;37:1191–1200.
4. Chertow GM, Normand SL, Silva LR, McNeil BJ. Survival after acute myocardial infarction in patients with end-stage renal disease: results from the cooperative cardiovascular project. *Am J Kidney Dis*. 2000;35:1044–1051.
5. Mangano CM, Diamondstone LS, Ramsay JG, et al. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med*. 1998;128:194–203.
6. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368–375.
7. Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. *Circulation*. 1997;95:878–884.
8. Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke*. 1997;28:557–563.
9. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis*. 1998;32:853–906.
10. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kidney Dis*. 1999;33:1004–1010.
11. Breyer JA, Bain RP, Evans JK, et al. Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. The Collaborative Study Group. *Kidney Int*. 1996;50:1651–1658.
12. Valmadrid CT, Klein R, Moss SE, Klein BE. The

risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med*. 2000;160:1093–1100.
13. Cirillo M, Senigalliesi L, Laurenzi M, et al. Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. *Arch Intern Med*. 1998;158:1933–1939.
14. Pinto-Sietsma SJ, Mulder J, Janssen WM, et al. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med*. 2000;133:585–591.
15. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med*. 1997;157:2413–2446.
16. Steiner RW, Coggins C, Carvalho ACA. Bleeding time in uremia: a useful test to assess clinical bleeding. *Am J Hematol*. 1979;7:107–117.
17. Gaspari F, Vigano G, Orisio S, et al. Aspirin prolongs bleeding time in uremia by a mechanism distinct from cyclooxygenase inhibition. *J Clin Invest*. 1987;79:1788–1797.
18. Kausz AT, Khan SS, Abichandani R, et al. Management of patients with chronic renal insufficiency in northeastern United States. *J Am Soc Nephrol*. 2001;12:1501–1507.
19. Hannan EL, Racz MJ, Arani DT, et al. Short- and long-term mortality for patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 2000;36:1194–1201.
20. Lowe LP, Greenland P, Ruth KJ, et al. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Arch Intern Med*. 1998;158:2007–2014.
21. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
22. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med*. 2000;160:1093–1100.
23. Port FK, Orzol SM, Held PJ, Wolfe RA. Trends in treatment and survival for hemodialysis patients in the United States. *Am J Kidney Dis*. 1998;32(6 suppl 4):S34–S38.
24. Robson R. The use of bivalirudin in patients with renal impairment. *J Invas Cardiol*. 2000;12(suppl F):33F–36F.

Main Points

- First World epidemics of obesity and hypertension are central drivers of a further epidemic of combined chronic kidney disease (CKD) and cardiovascular disease (CVD).
- 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.
- CKD is defined as the point in time when the steady-state serum Cr rises to ≥1.2 mg/dL in a female and ≥1.4 mg/dL in a male, or when microalbuminuria is detected.
- Population-based studies have demonstrated that there are higher rates of diabetes, poorly controlled hypertension, elevated triglycerides, lower high-density lipoprotein cholesterol, and elevated Lp(a) levels in patients with CKD and end-stage renal disease (ESRD). However, there are lower rates of smoking in the same groups compared to the general population.
- As renal function declines, a host of abnormalities develop, including changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium/phosphorus balance, and many other factors that have been related to CVD.
- In CKD, randomized trials have proven angiotensin-converting enzyme (ACE) inhibitors to delay the progression of renal failure, reduce proteinuria, and reduce the incidence of ESRD.
- Studies that have combined the use of ACE inhibitors and ARBs have in general demonstrated synergistic effects and have had even greater renal protection with the potential for improved cardiovascular outcomes, especially in CHF patients.