The manifestations of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) are diverse. Studies have shown that even patients with mild kidney disease are at a greatly increased risk for cardiovascular events. This increased risk suggests that the threshold definition of kidney disease (a glomerular filtration rate of <60 mL/min/1.73 m²) may not be robust. It also suggests that CVD and CKD have complex interactions, consisting of chronic and acute processes that begin before patients become symptomatic of either disease. These processes produce many simultaneous metabolic imbalances, such as chronic inflammation, erythropoietin deficiency with resulting anemia, and a generalized metabolic disorder. Assessing CVD in patients with CKD has many pitfalls. The difficulty of evaluating these patients can be recognized in their mortality rates, which progressively increase with the severity of kidney disease. Nevertheless, patients with CKD should be assessed for coronary artery disease by traditional screening procedures, as well as some nontraditional tests, such as C-reactive protein and homocysteine determinations and perhaps computed tomography coronary calcium scoring. Similarly, patients presenting with CVD who have coexistent CKD have poorer outcomes than those without this comorbidity, underscoring the importance of early diagnosis and aggressive medical treatment of both conditions. Reliable indicators of early kidney disease, such as estimated creatinine clearance, are perhaps underutilized in identifying patients who have increased cardiovascular risk as a result of renal insufficiency.

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T he cardiologist’s interest in renal function stems from the observed impact of renal insufficiency on cardiovascular disease (CVD). Outcomes from the coexistence of these diseases are fairly well defined. Renal dysfunction complicates cardiac medical therapy and diagnostic and therapeutic procedures, and it decreases long- and short-term survival in patients with and without CVD. However, we have yet to identify the specific mechanisms by which renal insufficiency increases the mortality risk in patients with CVD. The manifestations of CVD in patients with chronic kidney disease (CKD) are diverse and include hypertension, pericardial disease, valvular disease, arterial stiffness, coronary artery disease (CAD), and arrhythmia. However, relatively little is known about the specific mechanisms by which CKD influences these conditions and how they—alone or in combination—affect the prognosis of patients with CKD.

EVIDENCE OF RISK

Studies measuring cardiovascular end points in patients with CKD have shown that this population is at greatly increased risk for cardiovascular events—even in the mild stage of kidney disease. However, the current treatment paradigm for patients with CKD suggests that these patients are not considered a high priority for cardiovascular evaluation until they either experience an event or become candidates for kidney transplants. Therefore, there appears to be a discrepancy between the need for screening and the current practice of screening patients with kidney disease for CVD. Perhaps this discrepancy reflects a lack of recognition of the relationship between CKD and increased risk of a cardiovascular event or a lack of clear guidelines for assessing this increased risk.

The evidence of increased risk for patients with mild disease suggests that our definition of kidney disease, a
glomerular filtration rate of below 60 mL/min/1.73 m², may not be robust. A study of patients with kidney disease who had an acute coronary syndrome (ACS) showed that even those patients with mild renal dysfunction had increased mortality.¹ Risk increased dramatically with worsening kidney disease (Figure 1). Patients presenting with acute myocardial infarction (AMI) have similar risk stratification with regard to renal function as those with ACS. In a retrospective cohort study by Wright et al, the in-hospital mortality risk for the dialysis patient was 15 times higher compared with patients who had normal renal function, defined as creatinine clearance of above 75 mL/min (Table 1).² Patients with mild CKD were at 3 times increased risk, and those with moderate CKD were at 7 times increased risk. In a Medicare population presenting with AMI, 1-year mortality rates were nearly doubled for those patients with mild CKD and were nearly tripled for those with moderate CKD compared with the control population (Table 2).³ The progressive rates of mortality in patients with both CKD and CVD show that the interplay of these diseases is certainly a mortality multiplier. However, the evidence suggests that this interaction is complex, consisting of chronic and acute processes that begin long before these patients become symptomatic of either CKD or CVD.

**Table 1. In-hospital Mortality Rates Stratified by Kidney Disease Severity for Patients with AMI**

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2</td>
</tr>
<tr>
<td>Mild CKD</td>
<td>6</td>
</tr>
<tr>
<td>Moderate CKD</td>
<td>14</td>
</tr>
<tr>
<td>Severe CKD</td>
<td>21</td>
</tr>
<tr>
<td>Dialysis</td>
<td>30</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CKD = chronic kidney disease.
Data from Wright et al.²

**Table 2. 1-Year Mortality Rates Stratified by Kidney Disease Severity in Post-AMI Medicare Patients**

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>24</td>
</tr>
<tr>
<td>Mild CKD</td>
<td>46</td>
</tr>
<tr>
<td>Moderate CKD</td>
<td>66</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CKD = chronic kidney disease.
Data from Shlipak et al.³

Figure 1. Long-Term Survival Stratified by GFR for Patients with Acute Coronary Syndromes

Although outcomes research certainly indicates that CKD and CVD are a deadly combination, the pathophysiologic mechanisms by which the former influences death remain poorly defined, especially those associated with mild or moderate CKD. There is, however, some insight into the etiologies of death in patients with end-stage renal disease (ESRD). A study of mortality in these patients showed that 20.4% died of ischemic heart disease, 10.4% died of arrhythmia or conduction disorders, 8.6% died of stroke, and 7.7% died of nonaccess infection.⁴ For patients in less severe stages of CKD, the numbers are not firm. However, mortality is attributed to a wide range of cardiovascular events, including AMI from atherosclerosis, vulnerable plaques, or thrombosis; arrhythmia from hyperkalemia, autonomic dysfunction, or drug toxicity; and heart failure. The variety of car-
cardiovascular conditions in patients with CKD suggests that kidney disease does not affect the cardiovascular system through a single mechanism. Rather, the effects of CKD resemble a metabolic disorder that produces many simultaneous imbalances.

**Assessing Risk**

There are many pitfalls in the assessment of CVD in patients with CKD. Chest pain may occur with minimal epicardial obstructions in these patients because they have tendencies toward hypertension, ventricular hypertrophy, and anemia—all of which may contribute to myocardial hypoxia. Similarly, these factors, with the addition of fluid overload and deconditioning, may result in signs and symptoms of congestive heart failure in the absence of systolic dysfunction. Patients with diabetes mellitus present quite the opposite problem because neuropathy may mask chest pain associated with ischemia, even in the presence of severe CAD and AMI.

Despite these caveats, patients with CKD should be assessed for CAD using the traditional screening procedures, which include: a history, physical examination, and electrocardiogram; laboratory tests, including lipid profile, glucose and perhaps homocysteine, and C-reactive protein levels; and consideration of a coronary calcium score obtained by computed tomography (CT) evaluation. Provocative testing is usually reserved for patients with symptoms suggestive of ischemic disease and should include an imaging modality in addition to electrocardiographic monitoring; such tests include the dobutamine stress echocardiogram or exercise scintigraphy. Provocative testing may also be indicated in certain asymptomatic patients with a high-risk profile who are subject to significant physical exertion or are to undergo a major surgical procedure. If provocative testing is positive or equivocal, one should consider coronary angiography, which remains the gold standard for establishing the nature and severity of obstructive coronary disease and is required if revascularization is to be considered.

It should be recognized that coronary angiography has limitations. It provides in actuality a 'lumenogram', that is, a picture of contrast passing through the vessel. Thus it is capable of indicating whether there is an obstruction relative to the rest of the vessel but not whether there is disease in the wall of a positively remodeled artery or whether there is diffuse disease in an artery without a focal narrowing. Thus, patients with a 'normal' coronary angiogram may have considerable coronary disease. Because of the aggressive nature of CAD in CKD, it would seem that early detection and aggressive treatment are necessities in this population. While angiography very reliably identifies focal obstruction, it is not as reliable a detector of CAD that is in the preobstruction stage. By contrast, calcium scoring by CT is a reliable indicator of the presence of early CAD and a predictor of long-term prognosis. In a study of CAD burden in patients with ESRD, increased calcium score was strongly correlated with coronary obstruction confirmed by angiography, duration of dialysis, and the chronic inflammation associated with uremia. Since the calcium scoring test does not require contrast material and is a reliable indicator of CAD, it may become an important screening tool for patients with CKD. The recent introduction of noninvasive coronary imaging by CT angiography may prove even more informative by detecting not only hard calcified plaque, but also soft plaque. It should be noted, however, that iodinated contrast necessary for traditional coronary angiography and CT angiography is nephrotoxic and its use carries with it the risk of acute renal failure, which is inversely related to baseline renal function.

Calcification is not limited to the coronary arteries. It occurs in the aorta and peripheral arteries (increasing the overall stiffness of the vascular system) as well as the heart valves and fibroskeleton. Calcium deposition in the valves may produce significant valve disease and predispose to endocarditis, either of which may require valve replacement that may itself be complicated by dystrophic cardiac calcification.

The importance of early diagnosis and aggressive medical treatment of CVD in patients with CKD is underscored by their poor outcomes after cardiovascular events as well as their relatively high risk for coronary revascularization. For patients undergoing angioplasty, renal failure was second to cardiac shock as a comorbid predictor of in-hospital mortality (Table 3). In a study of patients with moderate kidney disease who underwent angioplasty, 3-year mortality rates were more than 5 times higher for patients with a baseline creatinine of above 2 mg/dL compared with patients whose baseline creatinine was 1 mg/dL or below (Figure 2). One-year follow-up for patients with ESRD who underwent angioplasty showed a 10-fold increase in mortality. The short- and long-term outcomes of CKD patients who
develop acute renal failure associated with angioplasty are even worse. It is not entirely clear why the CKD patient does poorly post-revascularization. There is some evidence to suggest that this is not due to restenosis as was originally thought, but alternative explanations—such as increased propensity for thrombotic events—have yet to be proven.

The relatively poor outcomes of patients with both CKD and CVD may be partially explained by an increased incidence of coronary risk factors and what appears to be less aggressive treatment for the cardiovascular conditions of patients with CKD. A study of patients with kidney disease who also had heart failure and CAD showed that patients with the lowest renal function also had higher incidence of traditional risk factors for CVD, such as hypertension, hyperlipidemia, diabetes mellitus, and smoking. These patients also received fewer prescriptions for agents that are beneficial in combating traditional risk factors. In a study of patients presenting with ACS, the percentage of prescriptions for aspirin, beta blockers, and angiotensin-converting enzyme inhibitors were highest for patients with the highest renal function and lowest for those patients with the lowest renal function. The same trend was observed for the use of therapeutic interventions; patients with lower renal function received fewer procedures.

The evidence presented above points in many directions. CAD may be silent in patients with CKD, and this silence may exacerbate what appears to be physician reluctance to perform diagnostic and therapeutic procedures on these patients. Little is known about the mechanism by which CKD increases the risk of cardiovascular events. However, the variety of cardiovascular events associated with CKD suggests that there are multiple underlying causes, which may include chronic inflammation, erythropoietin deficiency with accompanying anemia, and a generalized metabolic disorder. Evidence clearly shows that CKD is an independent risk factor for CVD. Cardiovascular risk is inversely proportional to creatinine clearance, which is perhaps underutilized as an indicator of early renal disease.

**DISCUSSION**

**Dr Lepor:** Because the long-term prognosis of patients who are predialysis and those who are on dialysis does not seem to be very different, is it appropriate to withhold certain diagnostic contrast-requiring procedures and interventions in a patient with a creatinine clearance of 12 mL/min because there is a concern about dialysis, or would this be a disservice?

**Dr Brinker:** Before the nephrologists answer these questions, I think I should bring up one point. When

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**Table 3. In-hospital Mortality Risk Following Angioplasty, Stratified by Comorbidity**

<table>
<thead>
<tr>
<th>Risk Parameter</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic shock</td>
<td>8.49</td>
</tr>
<tr>
<td>AMI</td>
<td>1.31</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.41</td>
</tr>
<tr>
<td>COPD</td>
<td>1.33</td>
</tr>
<tr>
<td>Left main CAD</td>
<td>2.04</td>
</tr>
<tr>
<td>Decreased LVEF</td>
<td>0.87-3.93</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3.04</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; LVEF = left ventricular ejection fraction.

Data from Shaw et al.®

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**Figure 2. 3-Year Mortality Stratified by Baseline Serum Creatinine in Postangioplasty Patients**

compared with medical therapy alone, coronary artery bypass graft surgery and angioplasty decrease symptoms and appear to increase survival in patients with CKD. However, in those with the worst renal function who are predialysis, bypass surgery seems to have a more beneficial effect than angioplasty. Thus, for the symptomatic patient with CKD, revascularization is indicated; however, for patients who are asymptomatic, especially those with very severe renal dysfunction, the issue becomes more complicated. There is a price to pay for revascularization in terms of renal function.

**Dr Atta:** What about asymptomatic dialysis patients? For instance, I have a patient who has ESRD, is on dialysis, is a diabetic, and had recurrent chest pain. She went for several angioplasties and is now pain-free.

**Dr Brinker:** It is clear that symptoms should be treated appropriately. Patients with chest pain are candidates for revascularization if a medical approach is not feasible. Hemodialysis patients are an easier matter because we are less concerned about damaging the kidneys with contrast. However, in a patient with a creatinine of 4 or 6 mg/dL who is doing fairly well as an outpatient, there is a reticence to perform a contrast study. We usually proceed on the basis of the results of a provocative test. If the test suggests significant coronary ischemia, we would perform angiography and coronary intervention if required. But suppose we take these steps and it decreases the patient's kidney function to the point it necessitates dialysis. I am not certain this course has been a major benefit to that patient.

**Dr Berns:** I would like to take exception with that approach to the hemodialysis patient with an indication for cardiac catheterization in that we know for at least a 1- or 2-year period after they start dialysis, residual renal function is probably very important. I think there has been a tendency among nephrologists as well as cardiologists to overlook the importance of residual renal function. So the caution we ought to take in performing interventions or contrast exposure in this 6 or 12 months prior to the development of the need for dialysis perhaps should also be extended into that 6- or 12- to 24-month period after the initiation of dialysis. We should also try to preserve kidney function in that timeframe.

**Dr Lepor:** But what is the benefit? It seems that the natural history of that patient is not too dissimilar from the patient who is on dialysis.

**Dr Berns:** I think the best data comes from the peritoneal dialysis [PD] literature that shows that looking at measures of clearance is not predictive of mortality. In 2 large international PD trials, the single best predictor of life expectancy was residual kidney function, suggesting a benefit to preserving residual function. There is also a convenience issue: if a patient produces a half mL or half liter of urine per day, that output increases dietary options. At least in the PD population—I am not sure whether this has been shown in the hemodialysis population—there is a life expectancy advantage to having some residual kidney function.

**REFERENCES**