less progression of carotid IMT in the lacidipine group compared to the atenolol group (mean IMT change, .0359 vs .0579; $P < .009$). Moreover, the annual rate of progression (mm/yr) was slower among patients in the lacidipine group than among those in the atenolol group

At the end of the study, among those who completed the study, there was significantly less progression of carotid IMT in the lacidipine group compared to the atenolol group (mean IMT change, .0359 vs .0579; P < .009).

(.0087 vs .0145; $P = .0073$). These beneficial effects of lacidipine were noted despite the observation that lacidipine reduced blood pressure less than atenolol did.

As far as clinical cardiovascular events were concerned, the overall event rate was quite low, and no significant differences were observed between the lacidipine and atenolol groups, although the trend favored lacidipine. Thus, this long-term study showed that lacidipine slowed the progression of carotid IMT (and, by inference, atherosclerosis) better than atenolol did, even though lacidipine lowered blood pressure less than atenolol did, suggesting that this calcium channel blocker has a blood pressure–independent antiatherogenic effect. Similar results have been reported previously in smaller studies comparing calcium channel blockers to diuretics. ■

Renal Insufficiency

The Prognostic Value of Renal Function in Patients with Congestive Heart Failure and Acute Myocardial Infarction

Reviewed by Norman E. Lepor, MD, FACC, FAHA
The David Geffen School of Medicine at UCLA, Cedars-Sinai Medical Center, Los Angeles, CA
[*Rev Cardiovasc Med.* 2003;4(3):192–194]

This series of articles emphasizes the important role of renal function in the prognosis of patients with chronic congestive heart failure and acute myocardial infarction. The impact on prognosis is related to the metabolic syndrome associated with renal insufficiency, which includes insulin resistance and activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system. Of possibly equal importance are the less aggressive treatments, such as reperfusion therapies, that patients with renal insufficiency receive.

The Prognostic Value of Estimated Creatinine Clearance Alongside Functional Capacity in Ambulatory Patients with Chronic Congestive Heart Failure

Mahon N, Blackstone E, Francis G, et al.
J Am Coll Cardiol. 2002;40:1106–1113.

Over the last 2 to 3 years, our understanding of the importance of renal dysfunction in cardiovascular mortality and morbidity has become much clearer. Clinical studies by McCullough,[1] Berger,[2] and others as well as our improved understanding of the devastating consequences of contrast nephropathy have underscored the clear, inverse relationship between renal function and cardiovascular mortality. The estimation of creatinine clearance (CrCl) using the Cockcroft-Gault formula seems

The estimation of creatinine clearance using the Cockcroft-Gault formula seems to provide a much better assessment of renal function than does serum creatinine.

to provide a much better assessment of renal function than does serum creatinine. Using the Cockcroft-Gault formula, CrCl = [(140 − age in years) × weight in kg]/(serum creatinine in mg/dL × 72). For women, this number is multiplied by 0.85.

The study by Mahon and colleagues was designed to determine the prognostic significance of the CrCl calculation compared with a 6-minute walk test in ambulatory patients with chronic congestive heart failure. The authors divided the study patients into quartiles by their estimated CrCl: first quartile, 7.8 to 47.1 mL/min; second quartile, 47.1 to 63.8 mL/min; third quartile, 63.9 to 85.8 mL/min; and fourth quartile, 86.0 to 193.6 mL/min. Relevant patient information is presented in Table 1.

In this trial, despite no difference in ejection fraction across the quartiles of renal function as estimated by CrCl, a clear relationship between CrCl and mortality exists. Of note is that the quartiles where this relationship exists begin at serum creatinine levels in the 1.2- to

Table 1
Patient Information by Quartile of Estimated Creatinine Clearance

	1st (7.8–47.1)	2nd (47.1–63.8)	3rd (63.8–85.8)	4th (86.0–193.6)
6-min walk distance, m	272	307	336	359
Age, y	75	68	63	54
Body mass index	24	26	29	32
Ejection fraction	29	29	30	30
Serum creatinine, mg	1.6	1.3	1.2	1.0
Recent CHF hospitalization, %	39	36	23	27
Death during follow-up, %	37	29	18	21

CHF, congestive heart failure. Adapted from Mahon et al.

1.3-mg/dL range, levels that many would consider to be within "normal" ranges. A continuous decline in survival was seen with reductions of CrCl, with sharper declines observed as CrCl dropped below the 40- to 50-mL/min range. The direct and continuous relationship between mortality and renal dysfunction was independent of functional capacity as assessed in this trial by the 6-minute walk distance.

The mechanism for this relationship between renal dysfunction and mortality is not clear. Renal insufficiency is associated with activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, elevations of homocysteine and insulin levels, and chronic volume overload. Whether and how these and other abnormalities are responsible for the relationship between renal function and mortality in patients with chronic heart failure has yet to be determined.

The authors conclude, and I would agree, that in "ambulatory patients with chronic congestive heart failure, CrCl predicts all-cause mortality independently of established clinical, structural and functional prognostic variables." The now-established value of estimated CrCl using the Cockcroft-Gault formula would seem to mandate using this measure, rather than the much cruder serum creatinine, to assess renal function and to assist in assessing mortality risk in our patients with heart failure. Measures to preserve renal function would therefore seem to be important to reduce mortality risk in these patients; such measures would include avoidance of renal toxins such as non-steroidal anti-inflammatory agents and the judicious use of contrast agents, perhaps paired with a renal system-preserving agent such as fenoldopam and/or N-acetyl cysteine. The appropriate use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and beta-blockers such as carvedilol would certainly be recommended.

Association of Renal Insufficiency with Treatment and Outcomes after Myocardial Infarction in Elderly Patients

Shlipak M, Heindenreich P, Noguchi H, et al.
Ann Intern Med. 2002;137:555–562.

This study used data from the Cooperative Cardiovascular Project for all Medicare beneficiaries (age ≥ 65 years) who were admitted to an acute-care hospital with the diagnosis of acute myocardial infarction (AMI) between April 1994 and July 1995. Patients with serum creatinine levels of at least 4.0 mg/dL were excluded from this study. Patients were stratified by serum creatinine levels representing normal renal function (< 1.5 mg/dL), mild renal insufficiency (1.5–2.4 mg/dL), and moderate renal insufficiency (2.5–3.9 mg/dL). Of the elderly patients presenting with AMI in this sample, 28% met the definition of mild renal insufficiency and 8% met the definition of moderate renal insufficiency.

At 1 year, almost three times as many patients with moderate renal insufficiency had died than had patients without renal insufficiency.

Patients with renal insufficiency were more likely than patients with normal renal function to be black and male with a higher prevalence of diabetes, hypertension, heart failure, peripheral vascular disease, and dementia. They presented with a higher Killip class, were less likely to receive aspirin and beta-blockers, and were more likely to receive angiotensin-receptor inhibitors. Patients with normal renal function were twice as likely to undergo coronary angiography and angioplasty.

One month after hospitalization, mortality for patients with moderate renal insufficiency was 44% versus 13% for patients with "relatively" normal renal function. At 1 year, almost three times as many patients with moderate renal insufficiency had died than had patients without renal insufficiency. Mild renal insufficiency was also associated with an increase in mortality. The relationship

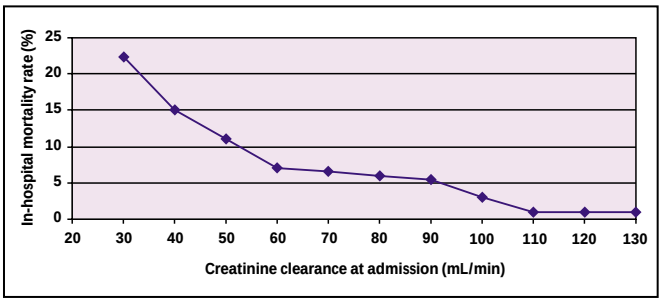

Figure 1. *In-hospital mortality rates by level of renal dysfunction. Adapted from Wright et al with permission.*

between mortality and renal insufficiency was most profound in the first 6 months following an AMI, as about half of the patients with moderate renal insufficiency died within that time period. Therefore, it is mandatory that treatments such as beta-blockers, antiplatelet therapies, and reperfusion be made available to these patients early in their presentations. The authors conclude that "renal insufficiency as defined by serum creatinine or estimated creatinine clearance is an independent risk factor for death in elderly patients after myocardial infarction."

Acute Myocardial Infarction and Renal Dysfunction: A High-Risk Combination

Wright R, Reeder G, Herzog C, et al.
Ann Intern Med. 2002;137:563–570.

Using the coronary-care-unit database at the Mayo Clinic, 3106 patients with a diagnosis of AMI between 1988 and 2000 were evaluated. The authors compared outcomes in patients with varying degrees of renal function. Patients were stratified into five categories of renal function as defined by estimated CrCl using the Cockcroft-Gault formula: normal (> 75 mL/min), mild renal insufficiency (50–74 mL/min), moderate renal insufficiency (35–49 mL/min), severe renal insufficiency (< 35 mL/min), and end-stage renal disease (on dialysis).

Patients with any degree of renal dysfunction were more likely than patients with normal renal function to present with symptoms of heart failure and more likely to experience atrial fibrillation.

Primary reperfusion therapies were used less frequently in patients with any degree of renal insufficiency. The use of heparin, aspirin, and beta-blockers was less frequent in patients with moderate and severe renal dysfunction. In-hospital mortality increased with worsening renal function (Figure 1).

Predictors of in-hospital mortality included mild, moderate, severe, and end-stage renal dysfunction, congestive heart failure on admission and during hospitalization, diabetes, and advanced age. Perhaps a surprise to some, the presence of moderate, severe, and end-stage renal dysfunction exposed patients presenting with AMI to higher mortality risk than did the presence of congestive heart failure, Killip class > 1, mechanical complications, or diabetes.

The authors conclude that "even mild degrees of renal insufficiency confer poor MI outcomes. Clinicians should use reperfusion therapy, aspirin, and beta-blockers aggressively in patients with renal insufficiency."

What is clear from these articles is that, in patients with chronic congestive heart failure and ischemic heart disease, as renal insufficiency progresses or renal function deteriorates, cardiovascular risk increases. This increased risk occurs at levels of serum creatinine that are often referred to as "normal." The relationship between renal function and cardiovascular risk makes the case for both identifying those patients at risk and implementing strategies for renal preservation, including the use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. Unfortunately, with the epidemic of obesity-related hypertension and diabetes, the most common causes of renal insufficiency, the prevalence of renal insufficiency and its associated cardiovascular risk is expected to reach epidemic proportions as well. ■

Myocardial Infarction

Coronary Calcium and C-Reactive Protein: Another Tip of the Iceberg

Reviewed by Wojciech Mazur, MD,* Mark McCracken, MD,† Dean J. Kereiakes, MD‡
**The Lindner Center for Research and Education, †The Christ Hospital, ‡Ohio Heart Health Center, Cincinnati, Ohio*
[*Rev Cardiovasc Med.* 2003;4(3):194–196]

For centuries, vascular calcification was widely regarded as merely a rare, end-stage, passive, degenerative, and inevitable process of aging. The fact that this process is not degenerative but rather regenerative was noted more than 300 years ago by Morgagni: "the left coronary artery appeared to have been changed into a bony canal from its very origin."[1] In 1863, Virchow postulated