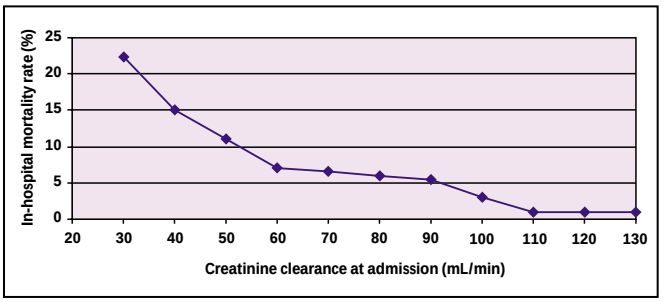


**Figure 1.** *In-hospital mortality rates by level of renal dysfunction. Adapted from Wright et al with permission.*

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

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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

that vascular calcification occurs by the same mechanism as bone formation.[2] In 1906, Bunting reported bone marrow elements within the arterial wall.[3] In recent years, various bone matrix proteins, as well as osteoclast and osteoblast-like cells, have also been described in vascular lesions. Coronary calcification is not benign. Almost 20 years ago, Margolis and colleagues demonstrated that in patients undergoing cardiac fluoroscopy, the presence of coronary calcification was associated with a 5-year survival of 58%, compared with 87% for patients without calcification. Furthermore, the prognostic significance of coronary artery calcification was independent of information obtained by cardiac catheterization.[4] Since then, multiple studies have been published that demonstrate a linear correlation between the extent of coronary calcification and risk of cardiac events. Coronary calcification is not an inevitable part of aging. Indeed, 9% of octo- and nanogenerians do not have detectable coronary calcium by electron beam computed tomography (EBCT).[5]

C-reactive protein (CRP), a nonspecific marker of inflammation, has emerged as one of the most powerful predictors of vascular events, including myocardial infarction (MI), stroke, and vascular death. Elevated levels of CRP predict future cardiovascular events in apparently healthy men and women and also portend the vulnerability of an atherosclerotic plaque toward rupture.[6–8] Hardly an innocent bystander, CRP actively promotes inflammation via attenuation of nitric oxide production and augmentation of the endothelium-derived constrictor, ET-1.[9] CRP facilitates the atherothrombotic process by enhancing intercellular and vascular adhesion molecule expression, chemokine (monocyte chemoattractant protein 1 production, and macrophage low-density lipoprotein (LDL) uptake and tissue factor expression, resulting in a prothrombotic, proinflammatory, and proatherogenic milieu.[10–12]

In various pathologic processes, inflammation and calcification are a continuum of the same process. However, this may not be the case with CRP and coronary calcium. Redberg and colleagues[13] demonstrated lack of correlation between high-sensitivity (hs)CRP and calcium score by EBCT, thus raising the possibility that hsCRP and EBCT calcium score may reflect different pathologic processes.

## Combined Use of Computed Tomography Coronary Calcium Scores and C-Reactive Protein Levels in Predicting Cardiovascular Events in Nondiabetic Individuals

Park R, Detrano R, Xiang M, et al.
*Circulation.* 2002;106:2073–2077.

The South Bay Heart Watch (SBHW) study was designed to evaluate the relative value of coronary calcium, as well as both traditional and nontraditional risk factors, for predicting cardiovascular outcomes and calcium progression in asymptomatic adults. As described by Park and coworkers,[14] the SBHW cohort of nondiabetics was evaluated prospectively with the combined use of CT coronary calcium scores and hsCRP to predict cardiovascular events. This cohort consisted of 1461 asymptomatic participants who were more than 45 years of age and had a greater than 10% 8-year risk for developing coronary heart disease by Framingham risk score stratification. Diabetic patients were excluded because of previous observations that calcium scores have little prognostic value in diabetics. Patients were followed for 7 years after their initial EBCT. Endpoints of the study included MI/coronary death, and the composite occurrence of nonfatal MI, coronary death, stroke, or coronary revascularization.

*Statistical analysis revealed C-reactive protein and coronary calcium score to be independent predictors of cardiovascular events.*

The EBCT calcium score was a statistically significant predictor of all endpoints ($P < .005$). CRP was a marginally significant predictor of MI or coronary death ($P = .09$) and a statistically significant predictor of any cardiovascular event ($P = .03$). Further statistical analysis revealed CRP and coronary calcium score to be independent predictors of cardiovascular events.

For the coronary calcium score, risk groups were defined by tertiles as low (<3.7), medium (3.7–142.1), and high (> 142.1). For CRP, risk groups were stratified by the 75th percentile as normal (≤ 4.05 mg/L) and abnormal (>4.05 mg/L). Compared with subjects in the low-risk CRP and calcium score group, an increased risk for MI or death was observed in the low-risk CRP and high-risk calcium score cohort (relative risk [RR] = 4.9) as well as the high-risk CRP and either medium- or high-risk calcium groups (RR = 4.3 and 6.1, respectively). For the composite cardiovascular endpoint, increased risk was observed in the low-risk CRP and both medium- and high-risk calcium groups (RR = 2.8 and 4.4, respectively), as well as the high-risk CRP and both medium- and high-risk calcium groups (RR = 3.4 and 7.5, respectively).

The combination of hsCRP and EBCT calcium score defined an approximately six-fold increment in risk for MI or cardiac death and a seven-fold increment in risk for any cardiovascular event between the lowest- and the highest-risk cohorts. Patients in the highest tertile of

coronary calcium score were at significantly increased risk for vascular events regardless of their hsCRP levels.

The implications of this study are quite significant. Two relatively inexpensive and noninvasive tests will permit identification of a much larger population at risk than can be identified by current National Cholesterol Education Program (NCEP) guidelines. Although more than 50% of all MIs occur in patients with normal cholesterol levels, primary prevention trials have demonstrated a 30% risk reduction in MI. How do we prevent the remainder events? First, the population at risk needs to be better identified using both traditional (cholesterol fractions, blood pressure, smoking, age, etc) and nontraditional (hsCRP and coronary calcium score) markers. Second, treatments that modify the disease process must be employed. For example, statins have been demonstrated to normalize hsCRP levels within 2 weeks of therapy, independent of their LDL-lowering effect.[15] Is coronary artery calcification reversible? Interestingly, osteoclast-like cells are responsible for constant remodeling similar to the process that exists in skeletal bones. In an elegant study, Achenbach and colleagues[16] demonstrated that aggressive LDL lowering by statin therapy led to a regression of coronary calcium score by 3.4% as compared with an average annual progression rate of 25%. Current NCEP guidelines fail to identify more than 40% of the population at risk for vascular events.[17] Interestingly, more than 40% of the coronary artery calcium score cannot be ascribed to traditional risk factors and appears to be heritable.[18] Both hsCRP and coronary calcium scoring are rapidly becoming part of the global cardiovascular risk assessment. These two relatively inexpensive and readily available tests will likely have a profound impact on the early detection of atherosclerosis and subsequent prevention of its complication. Many questions remain, such as who should be screened. A likely candidate would be that population at intermediate risk for cardiovascular events, which constitutes almost one third of the entire U.S. population.[19] If this sounds too aggressive, remember that 17% of American teenagers already have evidence of coronary atherosclerosis by intravascular ultrasound evaluation. Furthermore, if hsCRP and coronary calcium score uncover another tip of the "iceberg" represented by atherosclerotic cardiovascular disease and thus facilitate earlier administration of effective medications and dietary and life-style modifications, this proverbial "ounce of prevention" may be indeed be worth a "pound of cure." ■

*Two relatively inexpensive and noninvasive tests will permit identification of a much larger population at risk for myocardial infarction than can be identified by current National Cholesterol Education Program guidelines.*

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