

## Assessing Cardiovascular Disease in the Dialysis Patient

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*Cardiac causes account for nearly half of all deaths in patients with end-stage renal disease (ESRD). Coronary artery disease (CAD) is present in 38%–40% of patients starting dialysis. Both traditional and chronic kidney disease–related cardiovascular risk factors contribute to this high prevalence rate. In patients with ESRD, CAD—particularly acute myocardial infarction—is underdiagnosed. Dobutamine stress echocardiography and, to a lesser extent, stress myocardial perfusion imaging have proved useful in screening for CAD in such patients. Coronary artery calcium scoring is less useful. Acute myocardial infarction is associated with high short- and long-term mortality in dialysis patients. Cardiac troponin I appears to be more specific than cardiac troponin T or CK-MB in the diagnosis of acute myocardial infarction.*

### Key words

End-stage renal disease, cardiovascular, coronary artery disease, myocardial infarction

### Introduction

More than 320,000 patients with end-stage renal disease (ESRD) in the United States are treated with chronic dialysis (1–10). The mortality rate of patients with ESRD is higher by a factor of 15–20 than that of the general population (1–10). Cardiac causes account for nearly half of all deaths of patients receiving chronic dialysis (1–10). Cardiovascular disease is the single best predictor of death in patients with ESRD (1–10).

### Discussion

#### *Scope of the problem*

Between 1998 and 2000, the mortality rate in dialysis patients in the United States was 23.6% per year (6). Cardiac disease accounted for 45% of those deaths (6). Of the deaths from cardiac disease, 20%

were attributed to acute myocardial infarction (MI) and 60% to sudden cardiac death (6).

The prevalence of coronary artery disease (CAD) in patients with ESRD at the start of dialysis is 38%–40% (5). In younger patients with diabetes, this prevalence can be as low as 24%; in older patients with diabetes, it may be as high as 70%–75% (5). In fact, these statistics likely underestimate the true prevalence of CAD in the ESRD population (5). In patients receiving chronic dialysis, CAD—especially acute MI—is underdiagnosed and undertreated despite its high prevalence (2–5). The incidence of new-onset atherosclerosis per 1000 patient–years was reported by Parekh *et al.* (10) to be 147 in white and 119 in African American dialysis patients in the United States. A lower incidence of acute MI in African American as compared with white dialysis patients was reported by Young and colleagues (11).

Ganesh *et al.* (12) reported the relative risk of death in 107,922 patients with and without CAD and diabetes mellitus starting dialysis between 1 May 1995 and 30 June 1997, based on data from the Centers for Medicare and Medicaid Services and the U.S. Renal Data System (USRDS). In diabetic patients with CAD, the relative risk of death was 23% higher in peritoneal dialysis (PD) patients than in hemodialysis (HD) patients. In nondiabetic patients with CAD, the relative risk of death was 20% higher in PD patients than in HD patients.

The prognosis for all forms of CAD—particularly acute MI—is significantly worse in ESRD patients on dialysis than in the general population. The incidence of acute coronary syndrome was 2.9% per year among 3374 incident dialysis patients followed for 2 years (USRDS Wave II) (6). The Hemo study (13) noted that nearly 40% of 1846 patients were described as having ischemic heart disease at the onset of dialysis. During the 2.8-year follow-up period, angina pectoris and acute MI accounted for 43% of all cardiac hospitalizations. Altogether, ischemic heart disease caused 62% of hospitalizations.

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### *Cardiovascular risk factors*

The high prevalence of cardiovascular disease in ESRD is attributable primarily to the large number and high prevalence of cardiovascular risk factors in these patients (7,14–19). Traditional cardiovascular risk factors that occur in ESRD patients include older age, male sex, hypertension, elevated low-density lipoprotein cholesterol, decreased high-density lipoprotein (HDL) cholesterol, diabetes mellitus, cigarette smoking, physical inactivity, psychosocial stress, menopause, and a family history of early cardiovascular disease (7,14,17). Risk factors related to chronic kidney disease (CKD)—that is, nontraditional risk factors that contribute to the high prevalence of cardiovascular disease—include CKD itself, increased activity of the renin–angiotensin–aldosterone system, abnormal calcium and phosphate metabolism (leading to vascular calcification), dyslipidemia, inflammation, thrombogenic factors, increased oxidative stress, and possibly hyper-homocysteinemia (15–19).

The Choices for Healthy Outcomes in Caring for ESRD study demonstrated that many dialysis patients have high prevalence rates of traditional risk factors for cardiovascular disease (14). The average age of onset of dialysis in that study was 66 years. Diabetes mellitus was present in 54% of the patients, low HDL cholesterol was present in 33%, and hypertension was present in 96%. In the 38% of patients with both diabetes mellitus and hypertension, the risk of cardiovascular disease was increased by a factor of 5 – 6 as compared with the risk in patients having neither condition.

### *Clinical manifestations*

Coronary artery disease can present with the typical symptoms of angina pectoris on exertion, with exposure to cold or emotional stress, and after meals. Angina pectoris during dialysis (particularly HD) may be more common than are the traditional presentations. Zawada *et al.* (20) reported an incidence of 6% for stable angina pectoris and 11% for unstable angina pectoris in HD patients. Koch and colleagues (21) reported a sensitivity and specificity for angina pectoris of 43% and 83% respectively in patients on renal replacement therapy (RRT). Up to 25% of ESRD patients may have symptoms of angina pectoris without coronary artery stenosis; these incidents may be secondary to microvascular disease (22).

Silent myocardial ischemia may also be prevalent in this population (23–25). Ohtake *et al.* reported that 53.3% of 30 asymptomatic Japanese patients beginning RRT had more than 50% stenosis of at least one major coronary artery on coronary angiography (23). Charytan *et al.* (24) reported that 42% of 67 asymptomatic HD patients had 50% or greater stenosis in at least one major coronary artery on angiography, and 29% had stenosis of a proximal coronary artery. Conlon and co-workers (25) reported that 23 of 67 dialysis patients had asymptomatic ST segment depression during 48-hour ambulatory monitoring. After 2 years of follow-up, no relationship of silent ischemia to adverse cardiovascular outcomes (like that seen in the general population) was observed in the dialysis patients.

Who, then, among ESRD patients should be screened for CAD?

The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend that all patients about to start dialysis should be screened (1,17). Renal transplant candidates should be screened initially and then every 1 – 3 years. Diabetic candidates for renal transplant should be screened annually, nondiabetic patients at high cardiovascular risk should be screened every 2 years, and nondiabetic patients at low risk should be screened every 3 years.

### *Laboratory evaluation for CAD in ESRD patients*

#### ELECTROCARDIOGRAM

The signs of CAD on a resting electrocardiogram include pathologic Q waves, horizontal or downsloping ST depression, T wave inversion, and ST segment elevation. Left bundle branch block should also elicit a search for CAD. Electrocardiographic signs mimicking myocardial ischemia or MI may also occur in ESRD patients. For example, ST depression and T wave inversion may be caused by left ventricular hypertrophy (LVH) or electrolyte abnormalities and shifts. Elevation of the ST segment may occur with pericarditis or LVH. In addition, Q waves may be caused by LVH resulting from septal hypertrophy.

#### TRANSTHORACIC ECHOCARDIOGRAPHY

There are multiple echocardiographic and cardiac Doppler signs of CAD. Regional left ventricular wall motion abnormalities, including left ventricular aneurysm (with or without mural thrombus), are the most

common of these. Also, regional thinning of the myocardium and increased brightness of the left ventricular wall may signify loss of myocardium and scar formation. Coronary artery stenosis is sometimes observed with this technique. Evidence for myocardial ischemia, MI, or viability may be detected with dobutamine stress echocardiography (DSE) (26–31). Regional abnormalities of stress and strain may be detected with tissue Doppler. Contrast echocardiography may detect perfusion defects in some cases.

#### STRESS TESTING

According to the K/DOQI guidelines, DSE is more sensitive and specific than are other techniques in diagnosing significant CAD in ESRD patients (1,17). In a study by Karagiannis *et al.* (27), involving 2292 patients with known or suspected CAD and with normal renal function or with mild, moderate, or severe renal impairment, an abnormal DSE predicted adverse cardiac outcomes in all groups. The severity of the renal dysfunction was associated with an additional significant prognostic value.

Sharma and colleagues (28) studied 125 renal transplant candidates. Logistic regression analysis identified an abnormal electrocardiogram (pathologic Q waves, potentially ischemic ST–T wave abnormalities) and a positive DSE or exercise stress echocardiogram as independent predictors of severe CAD. In a study by Herzog and co-workers (29) of 50 renal transplant candidates undergoing DSE and coronary angiography, the DSE-related sensitivities and specificities for CAD were 52% and 74% respectively for more than 50% stenosis, 75% and 71% for more than 70% stenosis, and 75% – 76% for more than 75% stenosis.

Rakhit *et al.* (30) performed DSE in 224 CKD patients, including 169 on dialysis. Risk stratification was accomplished using the Framingham, Portland, and Brisbane risk scores. Follow-up was 4 years. In high-risk patients, 39% – 50% had an abnormal DSE, and 25% – 44% of patients with an abnormal DSE had a cardiac event. In low-risk patients, cardiac events occurred in 2.0% – 9.7%, and DSE did not add to the risk evaluation. Independent DSE-related risk factors for cardiac events were low diastolic blood pressure, chest pain during the test, and ischemic plus left ventricular systolic dysfunction.

Bergeron and colleagues (31) performed DSE on 485 dialysis patients and followed them for  $2.3 \pm 1.8$

years. During follow-up, 39% died. Survival rates at 1 and 3 years were 77% and 45% for those with ischemia in more than 25% of myocardial segments, 83% and 52% in those with ischemia in 25% or fewer myocardial segments, and 88% and 70% in those with a normal DSE. Multivariate analysis showed that the percentage of ischemic segments was an independent predictor of all-cause mortality.

Radionuclide stress myocardial perfusion imaging (MPI) may also provide useful information regarding the presence prognosis of CAD in ESRD patients (32–35). In studies by Dahan *et al.* (33,34), 42 chronic HD patients received dipyridamole plus exercise  $^{201}\text{Tl}$  MPI and coronary angiography. In 11 patients, the MPI was positive, with an associated sensitivity of 80% and specificity of 73%. Kim *et al.* (35) determined the factors predicting a positive  $^{201}\text{Tl}$  single-photon-emission computed tomography MPI in 277 continuous ambulatory PD patients. The composite of age above 60 years, diabetic nephropathy, and elevated high-sensitivity C-reactive protein predicted a positive MPI (43%); absence of those factors was not similarly predictive (4%). Diabetic nephropathy and age over 60 years were predictive of mortality; a positive MPI was not.

#### CORONARY ARTERY CALCIUM SCORING

Coronary artery calcium scoring is another noninvasive modality that can be used to detect CAD in dialysis patients (36–39). Coronary artery calcification detected by electron-beam computed tomography (EBCT) or multislice computed tomography (MSCT) has been shown to record coronary calcium scores above 400 in up to 69% of PD patients. In patients with normal renal function, coronary calcium scores above 400 are strongly associated with coronary artery atherosclerosis and total atherosclerotic burden, but they do not necessarily predict the severity of atherosclerosis or the likelihood of coronary events. In patients with ESRD, coronary artery calcification by EBCT or MSCT is closely associated with calcium and phosphate abnormalities and inflammation.

The American College of Cardiology and the American Heart Association do not currently recommend routine screening for CAD with coronary artery calcium scoring, even in high-risk patients. The K/DOQI guidelines suggest that further study is needed before using this modality to screen for CAD in patients with ESRD (17).

## CORONARY ANGIOGRAPHY

Coronary angiography remains the most definitive way to diagnose CAD. Coronary angiography should be used in dialysis patients with signs and symptoms of CAD or in those with a positive stress test who are candidates for myocardial revascularization (1,17). Coronary angiography is also indicated in patients with refractory stable angina pectoris, acute MI, and post-infarction angina pectoris or ischemia, and in patients with angina or ischemia after percutaneous coronary intervention or coronary artery bypass graft (1,17). In dialysis patients with residual renal function, *N*-acetylcysteine and iso-osmolar radiocontrast media should be used (1,17). Hydration before angiography may be associated with risk because of expansion of intravascular volume (1,17).

Despite the aforementioned recommendations, some studies evaluating the effect of radiocontrast media on residual renal function in PD patients undergoing contrast angiography do not show deterioration of renal function (40,41). In a study by Weisbord *et al.*, residual renal function was measured in 23 of 29 PD patients (40). This residual renal function declined at a rate similar to the rate seen in PD patients not undergoing angiography. There was 1 case of anuria among the 6 patients in whom residual renal function was not measured. Similarly, Moranne *et al.* reported no accelerated decline of residual renal function in 36 PD patients 2 weeks after they received iodinated contrast media (41).

*Acute MI in ESRD*

Acute MI is underdiagnosed in dialysis patients (42,43). Compared with non dialysis patients with acute MI, dialysis patients with acute MI were less likely to be diagnosed on admission (55% vs. 79%), to present with chest pain (44% vs. 68%), and to have ST segment elevation (19% vs. 36%) (42). Reasons for the underdiagnosis include atypical symptoms such as dyspnea, silent MI (perhaps related to diabetes mellitus), baseline ST and T wave abnormalities misdiagnosed as attributable to LVH or pericarditis, and decreased specificity of biomarkers (troponins, CK-MB).

In-hospital mortality after acute MI was studied by Wright *et al.* (43) in 3106 patients with varying degrees of renal function. Mortality rates were 2% in patients with normal renal function, 6% in patients with mild CKD, 21% in patients with severe CKD, and 30% in dialysis-dependent patients.

Short- and long-term mortality rates were reported by Herzog *et al.* for 34,189 long-term dialysis patients with acute MI who were hospitalized between 1977 and 1995. Mortality rates were 26% in hospital, 59% at 1 year, 73% at 2 years, and 90% at 5 years (44,45). Cardiac mortality rates were 41% at 1 year, 52% at 2 years, and 70% at 5 years. Thus, it appears that both short- and long-term mortality after acute MI are extremely high in dialysis patients.

*Clinical implications of cardiac biomarkers in ESRD*

## CARDIAC TROPONINS AND CK-MB

Persistently elevated cardiac troponin (cTn) is frequently observed among patients with ESRD (46–48). Repeated early measurements are necessary to detect peaks in patients with suspected MI (46–48). The prevalence rate may be as high as 53% according to Apple *et al.* (49). Elevated cTnT levels may be present in patients without evidence of myocardial ischemia or MI; cTnI is less likely to be elevated (46–49).

In acute coronary syndrome patients with and without CKD, both troponins have been associated with increased short- and long-term morbidity and mortality. Apple *et al.* reported troponin-associated relative risks for death in 733 ESRD patients followed for 2 years or until they died. Adjusted risks were 3.9 for cTnT and 2.1 for cTnI (50). Morton and colleagues reported a specificity of 100% for cTnI and 94.6% for CK-MB in asymptomatic dialysis patients without evidence of muscle trauma (51). Willging and co-workers studied 20 continuous ambulatory PD and 42 HD patients without acute coronary syndrome or evidence of muscle injury (52). The specificity for cTnI was 100% in both groups patients. The specificity for cTnT was 95% in continuous ambulatory PD patients and 75% in HD patients. The enzyme CK-MB was less specific than was cTnT, and myoglobin was less specific than was cTnT.

Frankel and colleagues studied 96 patients without acute coronary syndrome (53). Cardiac troponin T was elevated in 71% of HD patients, 57% of PD patients, 30% of CKD patients not on dialysis, and 18% of cardiomyopathy patients without CKD. Wood *et al.* followed 98 CKD patients for 2 years or until death (54). Death rates were 42% for patients with elevated cTnT and 14% for those with normal cTnT levels. One third of deaths were the result of vascular

events, with 64% occurring in the cTnT-positive group and 24% occurring in the cTnT-negative group.

Duman and co-workers followed 65 continuous ambulatory PD patients for 4 years or until death (55). The 35% mortality rate in this group was 70% attributable to vascular causes. Elevated cTnT was an independent predictor of death. Cardiac troponin T correlated positively with left ventricular mass index. In one study of 222 chronic PD patients without MI, Wang *et al.* found that elevated cTnT predicted cardiovascular congestion and that increments in cTnT level predicted increasing left ventricular mass index and decreasing left ventricular ejection fraction (56). In another study by Wang *et al.* of 238 chronic PD patients followed for 3 years or until death, elevated cTnT independently predicted long-term mortality, cardiovascular death, cardiovascular events and non cardiovascular death independent of inflammation, residual renal function, LVH, and left ventricular function (57). Han and colleagues studied 107 asymptomatic PD patients without apparent cardiovascular disease (58). Elevated cTnT predicted cardiovascular events independent of inflammatory markers and age.

Porter and co-workers studied 94 asymptomatic CKD patients who were being screened for CAD. In patients with positive scans, cTnT (but not cTnI) was elevated (59). Lowbeer *et al.* followed 76 PD patients without MI for 4 years or until death (60). Cardiac troponin T was an independent predictor of all-cause mortality, and it correlated positively with high-sensitivity C-reactive protein; cTnI and CK-MB had no predictive value.

Ninan and colleagues studied 75 maintenance dialysis patients 45 years of age or older (61). Cardiac troponin I levels were 0.1 ng/mL or less in 92% of patients. Needham *et al.* conducted a meta-analysis of 39 studies of 349 CKD patients and 3899 HD patients without acute coronary syndrome (62). The specificity for cTnI was 97% in CKD patients and 96% in HD patients; for cTnT, it was 85% in CKD patients and 71% in HD patients. Bueti and co-workers reported that the 30-day risk of major adverse cardiac events was increased (odds ratio: 15.2) among 149 dialysis patients with an elevated cTnI in the emergency department (63).

#### NATRIURETIC PEPTIDES

Natriuretic peptides also have prognostic significance in ESRD patients (64–68). Plasma B-type natriuretic

peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) levels are elevated in heart failure patients without CKD. Recent studies have identified elevated plasma levels of BNP and NT-pro-BNP as independent predictors of short- and long-term cardiovascular events in non CKD patients with acute coronary syndrome (64,65). The kidney metabolizes both BNP and NT-pro BNP (65,67). Plasma levels of these natriuretic peptides may be chronically elevated in patients with CKD, including those treated with dialysis (64–67). In a study by Mallamaci *et al.*, BNP was identified as an independent predictor of death in 246 dialysis patients (68). Suna *et al.* identified BNP and NT-pro BNP as sensitive and specific predictors of cardiovascular events in 217 HD patients (64). The role of natriuretic peptides as a cardiovascular risk predictor in dialysis patients presenting with acute coronary syndrome has not been extensively studied.

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