SEMINARS IN
NEPHROLOGY

Sudden Cardiac Death and Acute Myocardial Infarction in Dialysis Patients: Perspectives of a Cardiologist

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Chronic renal failure is characterized by an increased risk for cardiovascular morbidity and mortality, including acute myocardial infarction (AMI). AMI is associated with poor long-term survival in dialysis patients; the 2-year survival rate of 25% has remained unchanged over the past 2 decades. Although underuse of appropriate therapies likely contributes to adverse outcomes, recent data suggest that dialysis patients with AMI are more likely to have clinical presentations atypical for acute coronary syndrome. The risk for cardiac arrest and in-hospital death are increased in dialysis patients with AMI compared with a nondialysis cohort. The phenomenon of increased AMI mortality in patients with chronic kidney disease is not restricted to end-stage renal disease because there is a gradient of mortality risk related to decreased renal function. Sudden cardiac death is the single largest cause of mortality in dialysis patients. Dialysis patients are vulnerable to sudden cardiac death, and myocardial ischemia likely plays a major role. Nevertheless, after percutaneous and surgical coronary revascularization dialysis patients remain at high risk for sudden cardiac death, implying that other factors besides myocardial ischemia are important. A randomized trial testing the efficacy of implantable cardioverter-defibrillators for the prevention of sudden cardiac death in dialysis patients is warranted.
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Dialysis patients are at extraordinarily high-risk for mortality. The death rate for prevalent dialysis patients in the United States in the period from 1999 through 2001 was 235 deaths/1,000 patient-years.[1] Cardiac disease is the major cause of death, accounting for 43% of all-cause mortality.[1] Dialysis patients have poor long-term survival rates after acute myocardial infarction (AMI). The 2-year mortality rate of US dialysis patients hospitalized for AMI is 74%; and the unadjusted survival rate of dialysis patients after AMI essentially is unchanged over the past 2 decades.[2,3] Approximately 20% of cardiac deaths occurring in dialysis patients are attributed to AMI in the United States Renal Data System (USRDS) database.[1] The single largest cause of death in dialysis patients according to the USRDS, however, is linked to arrhythmic mechanisms because 61% of all cardiac deaths are ascribed to "cardiac arrest/cause unknown"[1] or arrhythmia.

Chronic renal failure, a "vasculopathic state,"[4] is characterized by a propensity for accelerated cardiovascular morbidity and mortality, including AMI. Risk factors such as hypertension, dyslipidemia, hyperglycemia, smoking, physical inactivity, enhanced thrombogenicity, and perhaps hyperhomocystinemia and chronic inflammation fuel the atherosclerotic fire. The development of left ventricular hypertrophy (likely an important substrate for arrhythmic death) may be promoted by anemia and vascular noncompliance (the latter affected by calcium/phosphate abnormalities), and aortic stiffness is an independent predictor of death in dialysis patients.[5]

Dialysis patients are vulnerable to sudden cardiac death. Obstructive coronary artery disease (CAD), left ventricular hypertrophy, rapid electrolyte shifts in hemodialysis patients, and abnormalities in myocardial ultrastructure and function including endothelial dysfunction, interstitial fibro-

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sis, decreased perfusion reserve, and diminished ischemia tolerance[6-9] have been implicated in the increased risk for sudden cardiac death in dialysis patients. The nonphysiologic nature of conventional 3 times per week hemodialysis sessions may increase further the risk for sudden cardiac death; there is a 50% increased frequency of sudden and cardiac death on Monday (for patients dialyzing Monday, Wednesday, and Friday) and similar trends on Tuesday (for patients undergoing hemodialysis Tuesday, Thursday, and Saturday).[10] Although hyperkalemia may play a role in sudden cardiac death (particularly in medically noncompliant patients), it also is plausible that the rapid decrease in serum potassium level occurring during conventional hemodialysis is an arrhythmic substrate.

The enumeration of cause-specific cardiac mortality in dialysis patients is a potentially treacherous area because classification schema may create rigid and misleading (from a clinician's perspective) causative categories. For example, a dialysis patient with anemia, left ventricular hypertrophy, and mild obstructive CAD shown by coronary angiography may report angina pectoris. If such a patient subsequently were to sustain a fatal cardiac arrest, how would such a death be characterized? Investigators of the hemodialysis (HEMO) study have implicated ischemic heart disease as the single largest cause of cardiac death,[11,12] but as our hypothetical patient shows, this is not a straightforward issue. In the HEMO study, our hypothetical patient would have fit the definition of ischemic heart disease as the primary cause of death; in the USRDS database I suspect that arrhythmic mechanisms would have been implicated for the same patient. It is extremely difficult to apportion accurately the contribution of CAD/ischemic heart disease to sudden cardiac death in dialysis patients. The identification of a putative ischemic cause for sudden cardiac death is not always meaningful clinically from a cardiologist's perspective. If treatment of myocardial ischemia were the only requirement to prevent sudden cardiac death in patients with ischemic cardiomyopathy, implantable cardioverter-defibrillators would play a minor role in the primary prevention of sudden cardiac death in these patients. As shown in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), implantable cardioverter-defibrillators provide better survival than medical therapy alone in patients with ischemic cardiomyopathy.[13]

Another troubling parallel issue is the survival of dialysis patients after coronary revascularization. Presumably, patients with ischemic heart disease have amelioration of their myocardial ischemia by successful coronary revascularization. Based on our preliminary data from the USRDS, the 2-year mortality rate of US dialysis patients hospitalized from 1999 to 2002 for coronary artery bypass surgery (CAB) with use of internal mammary grafts (patient population = 5,830) was 41%, 51% without internal mammary grafts (n = 2,919), 50% after percutaneous transluminal coronary angioplasty (PTCA) (n = 2,247), and 46% after coronary stenting (Stent) (n = 12,840).[14] The group with the best outcome (CAB with mammary grafting) still had a 2-year 41% mortality rate, and the 2-year cardiac mortality rate was 23% (ie, 56% of all-cause mortality). Surprisingly, arrhythmia/cardiac arrest was the single largest cause of death (13% for the 2-year mortality). For each type of coronary revascularization (CAB, PTCA, Stent), arrhythmia/cardiac arrest accounted for one third of all-cause mortality (ie, single largest cause).[15] The disturbing implication of these data are that even in patients with coronary revascularization (surgical or percutaneous) there remains a significant residual risk for arrhythmically mediated sudden cardiac death. These data suggest a potential role for implantable-cardioverter defibrillators for the primary prevention of sudden cardiac death after coronary revascularization in dialysis patients.

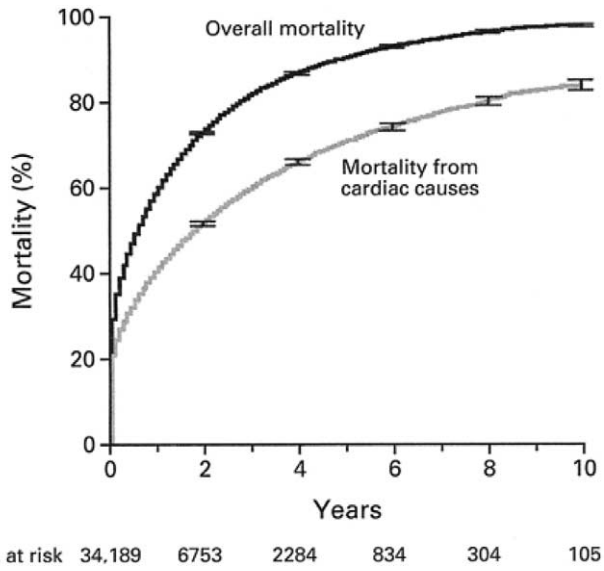

Figure 1 Estimated mortality of dialysis patients after AMI. Reprinted with permission from Herzog et al.[2]

Because it may be impossible to dissect the magnitude of importance of ischemic heart disease and AMI to sudden cardiac death, let us (arbitrarily) consider the high mortality rate of end-stage renal disease (ESRD) patients hospitalized for AMI as a separate clinical problem. AMI in dialysis patients is a catastrophic event associated with dismal long-term survival. Even in the modern treatment era of acute reperfusion therapy for AMI, only approximately 25% of dialysis patients are alive 2 years after AMI. The phenomenon of increased AMI mortality in chronic kidney disease (CKD) patients is not restricted to ESRD, and there is a gradient of risk associated with decreased renal function.[16-19] Figure 1 shows the mortality of dialysis patients hospitalized with AMI in the United States. Figure 2 shows the relationship of in-hospital mortality and renal function (ie, estimated creatinine clearance of <60 mL/min associated with excess mortality).

There are several possible explanations for the increased AMI mortality in ESRD patients. Prior publications have reported the underuse of therapies in patients with CKD,[16,18-22] including in dialysis patients with acute coronary syndrome (ACS), which have been shown to improve survival in clinical trials in nonrenal patients with ACS. The exclusion of CKD patients from ACS clinical trials unwittingly may have abetted an approach of therapeutic nihilism in the past because

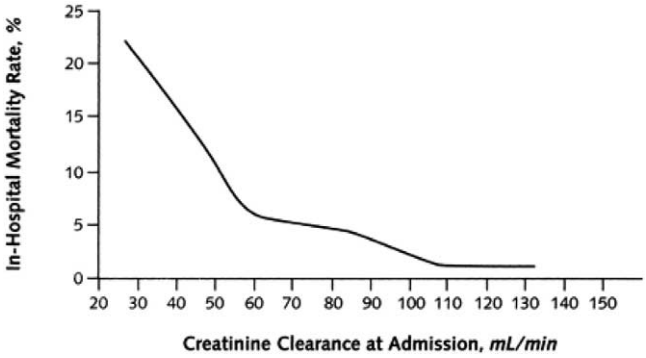

Figure 2 In-hospital mortality as a function of creatinine (Cr) clearance ($P < .001$). Reprinted with permission from Wright et al.[16]

there are a paucity of evidence-based practice guidelines for treatment of ACS in CKD patients. Recent data suggest that the excess mortality of dialysis patients sustaining AMI also may reflect atypical clinical presentations (ie, lower frequency of chest pain), and a lower proportion of patients qualifying for acute reperfusion therapy by standard electrocardiographic criteria (ie, ST-segment increase MI).[23] Dialysis patients hospitalized for AMI are at greater risk for in-hospital cardiac arrest; a preliminary analysis from the USRDS/National Registry of Myocardial Infarction 3 database of dialysis patients with AMI found that 11% of 3,049 dialysis patients hospitalized for AMI had an in-hospital cardiac arrest versus 5% of the 534,395 AMI patients in the nondialysis cohort.[23] Finally, as shown in Figure 3, anemia (with hemoglobin values <10 g/dL) is associated with an increased mortality rate after AMI in dialysis patients.[1]

Cardiac arrest is a devastating clinical event in dialysis patients. The 30-day mortality of dialysis patients hospitalized for cardiac arrest is 32%, and the 1-year mortality rate is 85%.[3] Because many patients who die of cardiac arrest are not resuscitated successfully and subsequently are hospitalized, the actual mortality rate likely is much higher. Prior publications have reported poor survival after cardiopulmonary resuscitation (CPR): 92% in-hospital death and 97%

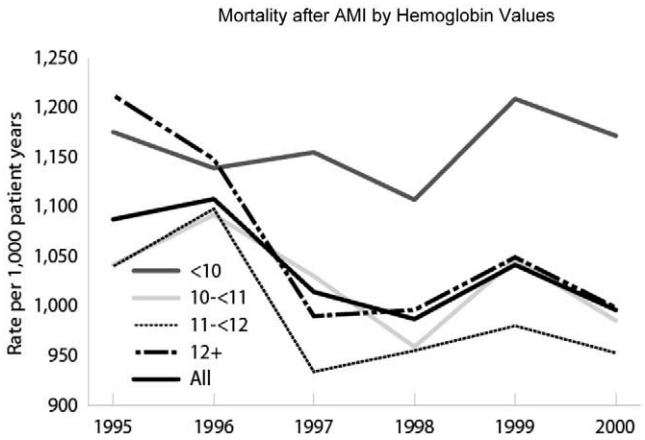

Figure 3 Mortality after AMI by hemoglobin values. ___, less than 10; ‾‾, 10 to less than 11; ----, 11 to less than 12; ___, 12+; ___, all. Reprinted with permission from U.S. Renal Data System.[1]

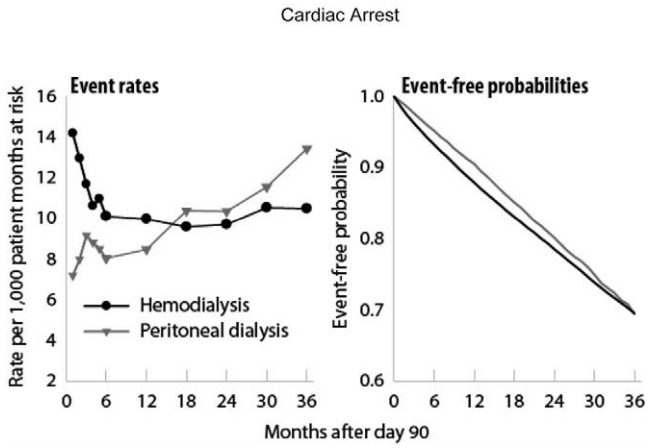

Figure 4 Cardiac arrest. Incident Medicare dialysis patients, from 1998 to 2000 combined, age 20 and older; adjusted for age, sex, race, and primary diagnosis. Monthly event rates during the first 6 months, and mean monthly event rates during each following 6-month interval. Reprinted with permission from U.S. Renal Data System.[29]

6-month mortality rate in 74 patients[24] and 100% in-hospital mortality rate in 24 patients.[25] A notable exception to these depressing statistics has been provided by Linda Becker, who generously shared with me the unpublished dialysis-specific cardiac arrest data in her publication on cardiac arrest in Seattle and King County from 1990 to 1996.[26] There were 47 cardiac arrests in dialysis centers, with an annual incidence of 0.75 (and consistent with the cardiac arrest rate of 7 per 100,000 hemodialysis sessions reported by Karnik et al[27] in their case-control study, patients with cardiac arrest were nearly twice as likely to have been dialyzed against a 0 or 1.0 mEq/L potassium dialysate on the day of cardiac arrest). There were 41 witnessed events, and bystander CPR was administered to these patients. In 29 patients (62%) the cardiac rhythm was ventricular tachycardia or ventricular fibrillation. The overall survival to hospital discharge was 30%, and it was 38% in patients with ventricular tachycardia/ventricular fibrillation. These data provide a compelling case for the availability of defibrillators in all dialysis centers. In the general population, the mortality rate is 10% per minute in the first 5 minutes after cardiac arrest (with CPR); without on-site defibrillators, the response time never will be sufficiently swift. Automatic external defibrillators are a cost-effective means of providing on-site defibrillator capability in dialysis centers.[28]

Unfortunately, most cardiac arrests do not occur in dialysis centers (and many are unwitnessed). In an incident (1995-1999) dialysis cohort of 295,913 patients surviving for at least 1 year, a cardiac arrest rate of 93 events/1,000 patient-years 2 years after dialysis initiation and increasing to 164 events/1,000 patient-years 5 years after dialysis initiation has been reported; in diabetic ESRD patients the 2- and 5-year arrest rates were 110 and 208 events/1,000 patient-years, respectively.[3] The initiation of hemodialysis is a time of immediate increased vulnerability to cardiac arrest, but the same is not true for peritoneal dialysis. Figure 4[29] shows a

cardiac arrest rate of 14 events/1,000 patient-months in the first month after hemodialysis initiation, decreasing progressively to about 10 events/1,000 patient-months 6 months after initiation. In peritoneal dialysis patients the cardiac arrest rate is 8 to 9 events/1,000 patient months during the entire first year after dialysis initiation.

Dialysis patients are at high risk for cardiac mortality. Sudden cardiac death is an important contributor to the overall mortality risk for ESRD patients. Although the cause of the heightened vulnerability of ESRD patients to sudden cardiac death is complex, the end result, cardiac arrest, is not. From my perspective as a cardiologist, a randomized trial testing the efficacy of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death is warranted.

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