Can We Prevent Sudden Cardiac Death in Dialysis Patients?

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End-stage renal disease (ESRD) patients are at high risk for mortality. The annual death rate for prevalent US dialysis patients in 2004 was 230 deaths per 1000 patient-years (1). Cardiac disease is the largest single cause of death for both hemodialysis and peritoneal dialysis patients, accounting for 43% of all-cause mortality (1). In the United States Renal Data System (USRDS) database, arrhythmic mechanisms account for 58% of cardiac deaths (25% of all deaths) among peritoneal dialysis patients, and 64% of cardiac deaths (27% of all deaths) among hemodialysis patients (1). In the Hemodialysis (HEMO) (2) and Die Deutsche Diabetes-Dialyse Study (4D) (3) trials, sudden death accounted for 25 to 26% of the observed total mortality. The USRDS Cardiovascular Special Studies Center estimated a sudden cardiac death rate among 2002 prevalent US dialysis patients of approximately 7% per year (1).

ESRD patients are particularly vulnerable to sudden cardiac death. Myocardial ischemia in the setting of obstructive coronary artery disease is likely an important contributor, but if it were the major contributor we would expect dialysis patients undergoing surgical coronary artery revascularization to be at low long-term risk for subsequent arrhythmic death. To the contrary, the annual mortality of dialysis patients ascribed to arrhythmic mechanisms after coronary artery bypass surgery was 7% per year, similar to the entire prevalent dialysis population, which implies that primary reliance on amelioration of myocardial ischemia may be an inadequate clinical strategy (4). Left ventricular hypertrophy (present in at least 75% of dialysis patients), rapid electrolyte shifts (and hyperkalemia) in hemodialysis patients, and abnormalities in myocardial ultrastructure and function such as endothelial dysfunction, interstitial fibrosis, decreased perfusion reserve, and diminished ischemia tolerance, may all contribute to the heightened vulnerability (5–10). The hazard of cardiac arrest after dialysis initiation is not uniform over time; longer dialysis vintage is associated with both a higher cardiac arrest rate and all-cause mortality (11,12). If the major hazard for sudden cardiac death were rapid electrolyte shifts, we would expect a markedly lower rate of cardiac arrest among peritoneal dialysis patients compared with hemodialysis patients. Although the monthly rate of cardiac arrest is about 50% higher for incident hemodialysis patients than for peritoneal dialysis patients three months after dialysis initiation, at three years after initiation the rate for peritoneal dialysis patients actually exceeds the rate for hemodialysis patients (1). Avoiding rapid electrolyte shifts (and dialysate very low in potassium) (13) is a sensible strategy to reduce the risk of cardiac arrest in hemodialysis centers, but it is unlikely to eliminate the hazard. The increased temporal hazard of sudden death associated with the long weekend interval (“skip day”) has been well documented by Bleyer and colleagues (14); quotidian hemodialysis might reduce the risk of cardiac arrest and deserves further study.

A brace of interesting papers by Middleton and colleagues (15,16) focuses on a special minority of potentially preventable sudden cardiac deaths: cardiac arrest occurring in outpatient hemodialysis clinics. Lehrich et al. (15) provide a pessimistic view of the utility of on-site automatic external defibrillators (AEDs) in dialysis centers, reporting a 1-yr Kaplan-Meier survival estimate of 9.5% after cardiac arrest in Gambro centers with AEDs on-site (n = 237 patients in 140 clinics) and 7.8% in sites without AEDs (n = 492 patients in 254 clinics). The 30-day survival estimate was 19% in centers with on-site AEDs and 15% in centers without AEDs. Of the 237 patients who experienced cardiac arrest in centers with AEDs on-site, 53.0% were receiving β-blockers, compared with 41.8% of the 492 patients at non-AED sites. After adjustment for baseline differences, including medical therapy, the authors found no association with survival and on-site availability of AEDs. In this issue of CJASN, Pun et al. (16), concentrating on the comparison of 24-h and 6-month survivors and nonsurvivors of cardiac arrest in the same 729-patient cohort, link β-blocker therapy to better immediate and long-term survival, and angiotensin-converting enzyme inhibitor or therapy with angiotensin receptor blockers and calcium-channel blockers to better long-term survival in a multivariate model.

Several issues complicate the interpretation of the paper by Pun et al. (16). It is not clear if AEDs, which were also associated with greater β-blocker use, were included in the survival model. The largest potential benefit of an AED would occur early, as demonstrated by Lehrich et al. (15). In clinical practice, unless end-of-life issues supervene, dialysis patients should be evaluated after cardiac arrest for ischemic heart disease (coronary angiography) as a population with intermediate or high probability of coronary artery disease, and appropriate candidates should be considered for implantable cardioverter-defibrillators (ICDs) (17). How were the 310 24-h survivors treated?
Did any receive coronary revascularization or an ICD, which could have altered outcome? Using a propensity model, we reported that an ICD is associated with improved long-term survival of dialysis patients who survived cardiac arrest (18). Finally, the authors rightly acknowledge the possibility of unmeasured confounding in their analysis.

Randomized placebo-controlled clinical trial data on the efficacy of cardioprotective medications in dialysis patients are sparse. The most persuasive evidence on β-blockers in dilated cardiomyopathy was reported by Cice et al. (19) in a prospective trial among 114 Neapolitan dialysis patients, showing improved 2-yr survival with carvedilol. The Fosinopril in Dialysis (FOSID-IAl) trial (n = 397) did not report a reduction in cardiovascular events with fosinopril, which is an angiotensin-converting enzyme inhibitor (20), but an even smaller Japanese trial (n = 80) found a reduction in mortality with candesartan, which is an angiotensin receptor blocker (21). Larger randomized clinical trials that assess cardioprotective agents for primary prevention of cardiovascular morbidity and mortality (including cardiac arrest) in ESRD patients would be welcome, but their successful design and implementation may be fraught with difficulty. For example, examining the benefit of cardioprotective agents such as β-blockers would be reasonable in dialysis patients without manifest heart disease (who, “unfortunately,” have a lower event rate, driving up the sample size needed for adequate power). On the other hand, from my admittedly idiosyncratic perspective as a cardiologist, it is difficult to imagine withholding β-blocker therapy in a placebo-controlled trial from dialysis patients known to have dilated cardiomyopathy with impaired left ventricular systolic function or symptomatic ischemic heart disease. For the former group, it is hard to dismiss data from Cice et al. (19), which are concordant with large-scale trials in non-ESRD patients, and for the latter group, who would be willing to claim equipoise for angina treatment for placebo versus β-blockers? Ironically, designing a primary prevention trial of ICDs for the prevention of sudden cardiac death may be easier, particularly among dialysis patients with left-ventricular ejection fractions >35% who do not meet current implant guidelines for primary prevention, and who comprise a high-risk population for sudden death. I have formally proposed such a trial (but that is grist for another editorial).

Clearly, however, sudden cardiac death remains a major clinical challenge in the care of dialysis patients. Middleton and colleagues are to be commended for focusing their attention on this vexing issue. We need to direct our efforts toward testing interventions that prevent cardiac arrest or reduce its lethality. Cardioprotective agents, including β-blockers, and ICDs merit further examination.

Disclosures

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References


See the related article, “Predictors of Survival after Cardiac Arrest in Outpatient Hemodialysis Clinics,” on pages 491–500.