

Cardiovascular Problems in Dialysis Patients: Impact on Survival

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Cardiovascular diseases, in their broad spectrum, are collectively the major cause of death in patients on dialysis. The population of patients treated with peritoneal and hemodialysis are not only subject to the traditional risk factors for heart disease, but also to certain uremia-associated risk factors that are unique in this population. Limited data are available on the effectiveness of routine interventions on cardiovascular outcomes in dialysis patients. Because most dialysis patients are excluded from clinical trials, data from randomized controlled trials regarding outcomes in patients undergoing peritoneal dialysis are almost absent. The present review discusses some of the major cardiovascular problems in the dialysis population, the impact of those problems on survival, and the available therapeutic strategies.

Key words

Hemodialysis, cardiovascular mortality, arrhythmia, heart failure

Introduction

Cardiovascular disease is the major cause of death in patients on dialysis (1). In the United States, the survival of patients on peritoneal dialysis (PD) at 1 year (excluding the first 90 days) is 87% as compared with 79% for patients on hemodialysis (HD) when adjusted for age, sex, race, ethnicity, and primary renal diagnosis. However, survival at 5 years is 35% on PD and 34% on HD. The specific causes of cardiovascular death are quite broad: Figure 1 summarizes those causes for PD and for HD patients ages 65 – 74 years.

Discussion

Coronary artery disease

The prevalence of angiographically significant coronary artery disease (CAD) varies between 25% in younger nondiabetic patients with end-stage renal disease (ESRD) and 85% in older dialysis patients with a long-standing history of diabetes mellitus (2). In addition, the incidence of acute myocardial infarction in the Medicare population with chronic kidney disease (CKD) is double that found in the population without CKD (1).

The traditional risk factors—which include advanced age, male sex, diabetes, hypertension, dyslipidemia, tobacco consumption, obesity, sedentary lifestyle, and family history of CAD—are highly prevalent in the end-stage renal disease (ESRD) population (3). Once patients are started on PD, they are subject to alterations in these traditional risk factors which may contribute to increased mortality from CAD as compared with the mortality of their counterparts on HD: 6% and 5% respectively (1).

Dyslipidemia is markedly prevalent in PD patients. As compared with patients not on PD, they have small, dense low-density lipoprotein (LDL), higher levels of lipoprotein a [Lp(a)], and low levels of high-density lipoprotein (HDL). Additionally, when compared with HD patients, they have high total and LDL cholesterol, high apolipoprotein B, high triglyceride levels, and reduced HDL (4).

The pathophysiologic mechanisms that exacerbate these dyslipidemias in individuals on PD are not well understood; however, a number of factors have been proposed to contribute to these findings. It is known that PD patients lose a substantial amount of protein in dialysate effluent; the protein losses resemble those observed in nephrotic syndrome (4). This protein loss may, in turn, stimulate hepatic production of albumin and cholesterol-enriched lipoproteins (4), thus leading to elevated concentrations of LDL cholesterol and Lp(a). In addition, absorption of glucose from dialysis

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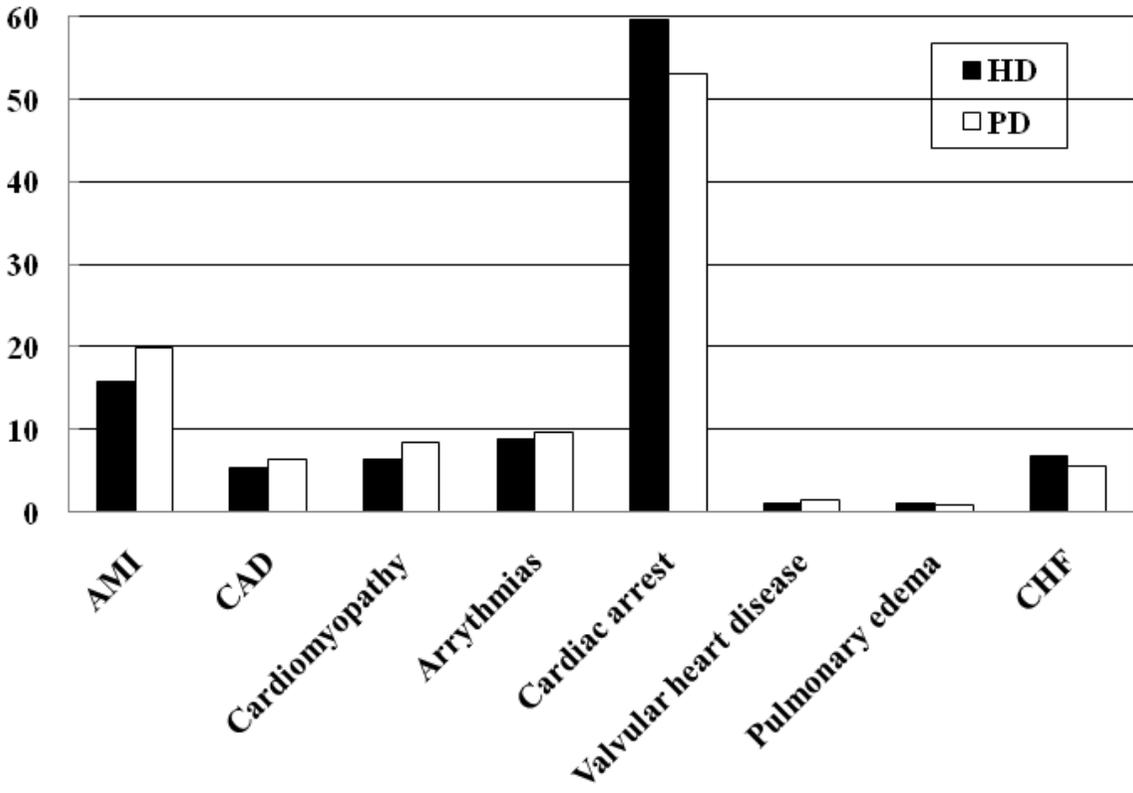


FIGURE 1 Causes of cardiovascular mortality (deaths per 1000 patient years). Data from the U.S. Renal Data System, 2008 (1). HD = hemodialysis; PD = peritoneal dialysis; AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure.

fluid and the resultant increase in insulin levels may enhance hepatic synthesis and secretion of very-low-density lipoprotein and other lipoproteins such as Lp(a). No direct correlation has been observed between peritoneal glucose absorption and serum lipid levels in PD patients, but recent studies indicate that reduction in the glucose load with the use of the less-absorbed icodextrin-containing solutions instead of glucose solution for the overnight dwell sufficiently reduces serum levels of total and LDL cholesterol and concentrations of triglycerides and small, dense LDL particles (4).

Very few data are available on the effect treating hyperlipidemia in PD patients, but recent lipid-lowering trials including patients with CKD demonstrated that intensive lipid lowering with statin medications was safe and even more effective in patients with CKD than in the general population (5).

Given that the traditional risk factors fail to fully account for the elevated cardiovascular risk seen in the PD patient population, there is significant interest in factors called “uremia-specific risk factors”: inflammatory markers, C-reactive protein, hyperphosphatemia, vascular calcification, electrolyte abnormalities, 25-hydroxy vitamin D deficiency, and anemia, among others. The hope is that modulation of those factors might improve outcomes in PD patients. Trials that examine the effectiveness of interventions on traditional risk factors or uremia-specific risk factors (or both) that may affect survival in PD patients are scarce and need to be pursued.

Because of the high prevalence of CAD in the entire ESRD population, early diagnosis and treatment is of paramount importance. Stress testing that includes physical exercise appears to be of limited value. The accuracy is low because angina and

dyspnea are frequently observed in ESRD patients, and physical capacity is significantly compromised because of associated comorbidities. Herzog *et al.* found dobutamine stress echocardiography to be most accurate stress test, with sensitivity and specificity exceeding 75% (6).

Coronary angiography still represents the “gold standard” for the diagnosis of CAD, and it allows for direct treatment using percutaneous methods [percutaneous coronary intervention (PCI)]. However, because of contrast use and other risks, PCI is still underused in this highly vulnerable patient group (7). Underutilization of these therapies may be a reflection of “therapeutic nihilism” or attributable to a lack of evidence for benefit in this patient group, given that dialysis patients are excluded from nearly all clinical trials. However, Hemmelgarn *et al.* (8) compared patients receiving either coronary artery bypass surgery (CABG) or PCI, or no revascularization after coronary angiography and found that, in dialysis patients, survival was significantly higher after CABG or PCI.

Congestive heart failure

The incidence of congestive heart failure (CHF) in the Medicare population with normal kidney function is 5.6% per patient–year; in patients with CKD stages 3–5, it is 17.6% per patient–year (1). The median overall survival of dialysis patients with CHF is 36 months compared with 62 months in those without CHF (9).

Exacerbation of CHF symptoms in patients with ESRD can occur through multiple mechanisms. By itself, ESRD is known to be associated with a high burden of sympathetic activity and activation of the renal angiotensin–aldosterone system (RAAS). Angiotensin II (AII), one of the key components of RAAS, leads to activation of nicotinamide adenine dinucleotide phosphate (NADPH)–oxidase, which in turn leads to formation of reactive oxygen species (ROS). Furthermore, AII activates nuclear factor κ B, which is a potent stimulator of chemotactic and adhesion molecules. Nitric oxide, which is vital to endothelial function and regulation of extracellular fluid balance, is inhibited in the milieu of AII–induced ROS production (10). Thus, ESRD in itself is a high oxidative stress and inflammatory state unfavorable for the myocardium. Also, the circulating toxins associated with chronic ESRD can exert direct negative inotropic effects and contribute to overwhelming variations in preload and afterload. These untoward events lead to

myocyte necrosis and a “feed forward” loop that promotes accelerated cell death and failure.

Several factors unique to the dialysis population lead to increased left ventricular afterload and preload. The potential swings in volume from one dialysis cycle to another can exacerbate symptoms. Further, long-standing hypertension and vasculopathy may result in increased arterial stiffness and noncompliance of the left ventricle. The heart may compensate with left ventricular hypertrophy, but over time, chronic unfavorable myocardial oxygen consumption and abnormal autoregulation by the heart may result in the development of CHF.

Based on studies of patients whose central venous pressure was measured at the time of transplantation, patients on PD experience elevated intravascular volume. This volume elevation can contribute to elevations in blood pressure, worsening CHF and affecting survival. In the ADEMEX trial, investigators showed that volume removal was associated with patient survival; they also observed a strong independent direct association of baseline N-terminal prohormone brain natriuretic peptide with cardiovascular mortality (11). Optimizing volume status by carefully matching the PD prescription to the transport category of an individual patient’s peritoneal membrane is therefore critical. Angiotensin converting-enzyme inhibitors and AII receptor blockers are preferred for use in PD patients because of their beneficial effects for CHF, their protective effect on residual renal function, and their possible effect on the peritoneal membrane.

Valvular heart disease

Cardiac valvular and perivalvular abnormalities are increasingly recognized as both causes and markers of morbidity and mortality in ESRD. Premature and accelerated calcific degeneration of the mitral annulus and aortic valve in ESRD most commonly manifest as mitral annular calcification and aortic stenosis (12). Valvular calcifications (aortic, mitral) are present in approximately one third of patients at the start of PD. Presence of these calcifications carries a high risk for morbidity and mortality, with the 1-year survival being 70% for patients with valvular calcification as compared with 93% for those without ($p < 0.001$). The hazard ratio for cardiovascular death if valvular calcifications are present at the start of PD is 5.39 ($p = 0.0003$) independent of age, male sex, dialysis duration, C-reactive protein, diabetes, and atherosclerotic vascular disease (13).

AORTIC VALVE CALCIFICATION AND AORTIC STENOSIS

Aortic valve calcification and aortic stenosis occur more commonly in patients with ESRD than in the general population (12). The incidence of aortic valve calcification in patients with ESRD ranges from 30% to 55% as compared with 21% to 29% in the U.S. adult general population over the age of 65 (12). Multivariate analysis has identified Ca×P product and duration of dialysis as independent predictors of aortic valve calcification in patients with ESRD. By contrast, age at initiation of renal replacement therapy, systemic hypertension, and cause of renal failure do not independently predict valvular calcification in patients undergoing either HD or PD.

The incidence of clinically significant aortic stenosis in members of the general population older than 65 years is 1% – 2% compared with 3.3% in patients with ESRD (12). Ureña *et al.* (14) reported an annual decrement in aortic valve area of 0.23 cm² in HD patients as compared with 0.05 – 0.1 cm² in the general population. However, among all subjects, the variation in the rate of progression of aortic stenosis was wide. The natural history of aortic stenosis in ESRD has not been well defined. The accelerated progression of this condition in ESRD patients and the high frequency of comorbidities may worsen the prognosis, but this hypothesis has not been tested. To date, no effective treatment has been identified to retard the development of valvular calcification or progression of aortic stenosis in ESRD. Medical therapy is of little value, and aortic valve replacement is the only effective therapy in most cases.

MITRAL ANNULAR CALCIFICATION

The incidence of mitral annular calcification (MAC) is higher in patients with ESRD than in age-matched control subjects (12). The reported prevalence of MAC is 32% in patients with ESRD. Age and duration of renal replacement therapy seem to be important factors contributing to the development of MAC. However, the high incidence of MAC in ESRD is thought to relate directly to altered Ca and P metabolism (12). The Ca×P product directly correlates with the incidence of MAC. Mitral regurgitation is commonly encountered in patients with MAC. Mitral stenosis has been reported in patients with the most severe forms of MAC. Furthermore, MAC may serve as a nidus for infection, and infective endocarditis can also complicate MAC.

VALVE SURGERY

Reported operative mortality rates in patients receiving dialysis are 17% for isolated aortic valve replacement, 22% for isolated mitral valve replacement, 25% for aortic valve replacement with CABG, and 36% for mitral valve replacement with CABG—all significantly higher than the rates observed in the population with normal renal function (12). Significant controversy still exists as to whether mechanical prosthetic valves are superior to bioprostheses (porcine aortic and bovine pericardial) in patients with ESRD. Mechanical valves are favored by clinicians who are concerned about comorbidities (hypertension, accelerated calcification) in patients with a bioprosthesis. However, a recent prospective study by Umezu *et al.* showed that, compared with patients having bioprosthetic valves, patients with mechanical valves experienced significantly higher early mortality ($p=0.03$). However, mechanical- and bioprosthetic-valve patients both had similar survival and event-free rates in mid-term results. As would be expected, the need for chronic anticoagulation led to the mechanical-valve group having a higher rate of bleeding events, but that group also experienced no structural valve deterioration up to 5 years of follow-up (15).

Arrhythmias

Arrhythmias are frequently observed in patients undergoing dialysis. These events are a significant cause of mortality in the dialysis population (Figure 1).

The incidence of atrial fibrillation (AF) in patients with ESRD is between 1 and 4.1 per 100 patient-years (16). The prevalence and incidence rates show substantial differences across studies—variations that can be attributed to several factors, such as differences in the ages of the studied populations, differences in the type and documentation of the recorded AF episodes, and differences in the time on dialysis. Vazquez *et al.* extended previous observations to report on the prevalence and incidence of AF in a cohort of patients who started dialysis at that group's center and who were followed for a mean period of 2 years. The AF prevalence was noted as 12.1%, and the incidence, as 5.9 per 100 patient-years (17). Multiple mechanisms have been proposed for the development of AF in ESRD, but most appear to be attributable to the atrial stretch caused by hemodynamic (pressure and volume) overload.

The management of AF in patients with ESRD is more complex and problematic. Heart rate control can

usually be achieved with beta-blockers and diltiazem. Digoxin should be avoided because of the potential for accumulation and toxicity. If digoxin is needed to assist in rate control, careful monitoring for level and non-cardiac toxicity are necessary. For rhythm control, propafenone seems to be effective in the setting of ESRD, without proarrhythmic effects. However, the use of propafenone should be avoided in significant structural heart disease, especially heart failure or substantial left ventricular hypertrophy. Amiodarone is acceptable for sinus rhythm restoration and maintenance, but its side-effect profile is significant. For acute cardioversion, ibutilide (an intravenous pure class III agent) can be used in patients with ESRD, but because of its prominent proarrhythmic risk, it should be avoided if the patient has hypokalemia or hypomagnesemia.

Even though anticoagulation is a well-established strategy for reducing thromboembolic risk in general population, data in ESRD patients are limited. Considering the uncertainties about stroke phenotype, bleeding risk, and vascular calcification risk induced by warfarin, it becomes exceedingly difficult to determine the risk–benefit profile of anticoagulation therapy in patients with ESRD who are undergoing dialysis (18). However, using the annual bleeding rates from the systematic review by Elliott *et al.* (19), the outpatient risk-of-bleeding index can be crudely modified (see Table I) to be more applicable to the ESRD population (18). If the minimum score obtained by the patient with ESRD is 2, then the approximate annual bleeding risk is 32%, far exceeding the 8% annually for the general population. Other confounding

factors such as dietary needs may tip the decision in favor of not using anticoagulation.

Sudden cardiac death

Approximately 60% of all cardiac deaths and 25% of all-cause mortality in patients on dialysis are the result of sudden cardiac death (SCD). Those rates were confirmed by several large and recent survival trials in dialysis patients (20). The mechanisms that underlie SCD in dialysis patients are complex; many factors are involved. In addition to the traditional risk factors associated with SCD in the general population (such as ischemic heart disease), several factors and circumstances more specific to dialysis patients may contribute to the risk of SCD. Those factors include heightened adrenergic state, left ventricular hypertrophy, rapid electrolyte and fluid shifts (in HD patients), and abnormalities in myocardial ultrastructure and function, including endothelial dysfunction and interstitial fibrosis (20). A recent study compared the survival of HD and PD patients in the Netherlands. An early survival advantage was seen for PD as compared with HD. This initial advantage may be attributable to PD patients having a fewer comorbidities at initiation of dialysis therapy and better residual renal function during dialysis. Overall, however, there was no apparent difference with regard to SCD between patients on PD and those on HD (20).

Summary

Patients on dialysis—PD and HD alike—are subject to multiple cardiovascular maladies that contribute to higher mortality. The paucity of trials examining the effectiveness of various interventions on cardiovascular outcomes in PD patients is astonishing. To discern how to optimally manage these complex and high-risk patients, it is critical that well-designed clinical trials include patients on dialysis. Failure to do so will lead only to continued attempts by the medical community to extrapolate clinical evidence into practice for a markedly different patient population.

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TABLE I Modified outpatient risk-of-bleeding index (18)

Score ^a	Risk group	Annual risk of bleeding (%)	
		No ESRD	ESRD
0	Low	3	10
1–2	Moderate	8	Approximately 32 ^b
3	High	30	54

^a Scoring system: 2 points for the combination of current and previous stroke; 1 point each for age greater than 65 years, current or previous stroke, history of gastrointestinal bleed, creatinine concentration greater than 133 mol/L, recent myocardial infarction, severe anemia, diabetes mellitus, and atrial fibrillation.

^b The midpoint of risk between the high-risk and the low-risk groups [(high – low)/2 + low].

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