

Cardiovascular Mortality in Dialysis Patients

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In their broad spectrum, cardiovascular diseases are, collectively, the major cause of death in patients on dialysis. The population of patients treated with peritoneal dialysis 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. In the dialysis population, data regarding the effectiveness of routine pharmacologic and procedural interventions on cardiovascular outcomes are limited. Most dialysis patients are excluded from clinical trials, and so data from randomized controlled trials investigating outcomes in patients undergoing peritoneal dialysis or hemodialysis are almost absent. In this review, we discuss some of the major cardiovascular problems in the dialysis population, the impact of those problems on survival, and when data are available, the impact of therapeutic strategies.

Key words

Myocardial stunning, hemodialysis

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 and adjusted for age, sex, race, ethnicity, and primary renal diagnosis) is 87% compared with 79% for patients on hemodialysis (HD). However, survival at 5 years is 35% on PD and 34% on HD.

The specific causes of cardiovascular death in the dialysis population span quite a broad spectrum. Figure 1 summarizes those causes for PD and HD patients 65–74 years of age. Mortality in new dialysis patients is also increased in age-matched patients

not on dialysis (2). In the present review, we address the major cardiovascular conditions responsible for increased mortality in the dialysis population.

Discussion

Coronary artery disease

The prevalence of angiographically significant coronary artery disease 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 (1). 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).

Go and colleagues (3) showed that impaired renal function (CKD stage 3) is a strong predictor of coronary artery disease in patients presenting with stable angina. Between 2003 and 2005, Hage *et al.* (4) showed that cardiovascular causes were responsible for 45% of the mortality in HD patients. The total mortality from specific cardiovascular causes was divided as follows: 26% sudden cardiac death, 9% myocardial infarction, 4% cerebrovascular disease, and 6% other cardiovascular

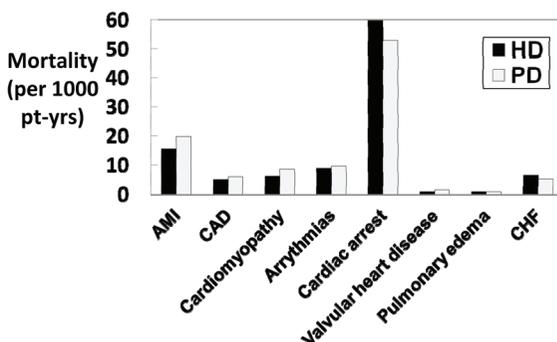


FIGURE 1 Causes of cardiovascular mortality (deaths per 1000 patient-years). Data from the U.S. Renal Data System, 2008. HD = hemodialysis; PD = peritoneal dialysis; AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure.

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causes. The severity of renal dysfunction correlated with the severity of increased cardiovascular risk from multiple causes, including the risk of myocardial infarction, sudden death, stroke, and cardiovascular mortality in general (5).

The traditional risk factors for development of atherosclerotic heart disease, including advanced age, male sex, diabetes, hypertension, dyslipidemia, tobacco consumption, obesity, sedentary lifestyle, and family history of coronary artery disease are highly prevalent in the ESRD population (4). Other risk factors, including the presence of heart valve calcification and high C-reactive protein, high interleukin 6, and low fetuin-A are associated with a significant decrease in cumulative survival over a 48-month follow-up period. Further, this worsened mortality was not seen in patients lacking those factors (6).

Badve and colleagues (7) undertook a meta-analysis and systemic review of the beneficial effect of beta adrenergic antagonists in patients with CKD. Eight trials met their criteria for inclusion: six placebo-controlled trials involving 5972 participants with chronic systolic heart failure and two angiotensin converting-enzyme inhibitor comparator trials involving 977 participants not known to have heart failure. They reported that optimal treatment was associated with a reduction in all-cause and cardiovascular mortality in patients with CKD. Nonetheless, increased incidences of bradycardia and hypotension were observed. The patient population in the analyzed trials consisted primarily of those with CKD. In patients on dialysis, the foregoing side effects may worsen outcomes for some.

Tsai and colleagues (8) reported that, in CKD patients, those receiving drug-eluting stents had a lower incidence of myocardial infarction and lower mortality rates than did those receiving bare metal stents. However, patients on long-term dialysis did not see the same benefit with respect to reduced incidence of myocardial infarction. That finding may be a result of a reduced effect of clopidogrel on anti-platelet reactivity (9).

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). In dialysis patients, the presence of CHF markedly reduces median overall survival to 36 months compared with 62 months in those without CHF (10). In the setting

of chronic heart failure, renal function predicts outcomes. In one study, the glomerular filtration rate of a patient was inversely proportional to the likelihood of hospitalizations and cardiovascular death (11).

Multiple mechanisms can exacerbate CHF symptoms in patients with ESRD. By itself, ESRD is known to be associated with a high burden of sympathetic activity and activation of the renin–angiotensin–aldosterone system (RAAS). Angiotensin II, one of the key components of the RAAS, leads to activation of NADPH oxidase, which in turn leads to formation of reactive oxygen species. Furthermore, angiotensin II 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 angiotensin II–induced production of reactive oxygen species (12).

Thus, ESRD in itself is a state of high oxidative stress and inflammation 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. Those untoward events lead to myocyte necrosis and a “feed-forward” loop that promotes accelerated cell death and failure. The potential swings in volume from one dialysis cycle to another can exacerbate symptoms.

Further, longstanding 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 increased blood pressure, worsening CHF and ultimately contributing to poorer survival.

Atrial fibrillation

Arrhythmias are frequently observed in patients undergoing dialysis. These events are a significant cause of mortality in the dialysis population. The incidence of atrial fibrillation (AF) in patients with ESRD is between 1 and 4.1 per 100 patient-years (13). The variation in incidence across reports can be attributed

to several factors, such as differences in the ages of the studied populations, type and documentation of the recorded AF episodes, and differences in the duration of dialysis. Vazquez and colleagues reported the prevalence and incidence of AF in a cohort of incident center dialysis patients who were followed for a mean of 2 years. The prevalence of AF was 12.1%, and the incidence was 5.9 per 100 patient–years (14).

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.

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 (15). The mechanisms that underlie SCD in dialysis patients are complex. In addition to the traditional risk factors associated with SCD in the general population, 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 (15). A recent study comparing the survival of HD and PD patients showed an early survival advantage for those receiving PD. That initial advantage may be attributable to PD patients having fewer comorbidities at initiation of dialysis therapy and higher residual renal function during dialysis. However, there was no apparent difference with regard to SCD between patients on PD and those on HD (15).

Cannizzaro and colleagues (16) reviewed the effect of device therapy in CHF patients with CKD. They noted that, of all the major trials evaluating implantable cardio-defibrillator treatment of heart failure, only one trial (MADIT-II) analyzed results based on renal function. In the MADIT-II trial, no difference in 2-year all-cause mortality was observed for a glomerular filtration rate less than 35 mL/min/1.73 m². In addition, those authors reported that cardiac resynchronization therapy for heart failure showed no benefit for symptom reduction or all-cause mortality in patients with CKD. A major limitation of this analysis is that, in all the trials reviewed, only

a small number of the evaluated patients had CKD, and outcomes in patients with CKD and heart failure appeared to be dismal.

Dialysis-induced myocardial stunning

Recently, McIntyre and colleagues (17) demonstrated the presence of dialysis-induced regional wall motion abnormalities in 4 patients assessed by echocardiography during HD. This effect was associated with a reduction in myocardial blood flow. In a more recent trial, Foley and colleagues (18) showed that, compared with a more traditional short interdialytic interval, a long interval was associated with increased mortality. That finding may be related to increased time on dialysis, which has been associated with myocardial stunning. Burton and colleagues (19) were able to replicate the study performed by McIntyre, but illustrated that the dialysis-induced regional wall motion abnormality can progress to left ventricular failure over a period of 12 months after initial identification by echocardiography. In one study, Jefferies and colleagues (20) subsequently described the benefit of more frequent dialysis on left ventricular function and regional wall motion. Those authors followed four groups of patients on HD (traditional 3 times weekly, 5–6 times weekly, home dialysis, and home nocturnal dialysis) for more than 3 months. They found that more frequent dialysis was associated with a decreased incidence of myocardial stunning.

Dialysis-induced myocardial stunning may be contributing to increased mortality in this specialized population. Future studies should include measurement of morbidity and mortality in patients that do and do not develop myocardial stunning during HD. In addition to clinical outcomes, further investigation into the mechanisms of stunning may lead to approaches that can prevent this potentially adverse effect.

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 disappointing. 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

include this population will lead only to continued attempts by the medical community to extrapolate clinical evidence into practice for a markedly different patient population.

Disclosures

The authors have no financial conflicts of interest to disclose.

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