Clinical Studies of Interventions to Mitigate Cardiovascular Risk in Peritoneal Dialysis Patients

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Summary: Cardiovascular disease (CVD) is highly prevalent in the peritoneal dialysis (PD) population, affecting up to 60% of cohorts. CVD is the primary cause of death in up to 40% of PD patients in Australia, New Zealand, and the United States. Cardiovascular mortality rates are reported to be approximately 14 per 100 patient-years, which are 10- to 20-fold greater than those of age- and sex-matched controls. The excess risk of CVD is related to a combination of traditional risk factors (such as hypertension, dyslipidemia, obesity, smoking, sedentary lifestyle, and insulin resistance), nontraditional (kidney disease–related) risk factors (such as anemia, chronic volume overload, inflammation, malnutrition, hyperuricemia, and mineral and bone disorder), and PD-specific risk factors (such as dialysis solutions, glycation end products, hypokalemia, residual kidney function, and ultrafiltration failure). Interventions targeting these factors may mitigate cardiovascular risk, although high-level clinical evidence is lacking. This review summarizes the evidence relating to cardiovascular interventions targeting modifiable CVD risk factors in PD patients, as well as highlighting the key recommendations of the International Society for Peritoneal Dialysis Cardiovascular and Metabolic Guidelines.

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Reduced kidney function (estimated or measured glomerular filtration rate <60 mL/min/1.73 m^2) and proteinuria are independent predictors of future coronary events.[1] There is considerable overlap between risk factors for the development of cardiovascular disease (CVD) and end-stage kidney disease (ESKD). It is no surprise therefore that CVD is highly prevalent in the dialysis population, affecting up to 60% of cohorts.[2] CVD remains the most common cause of death in this group, accounting for up to 40% of deaths in dialysis patients globally.[3–5] In Australia and New Zealand, the incidence rate of cardiovascular mortality in peritoneal dialysis (PD) patients is approximately 10 per 100 patient-years, some 20-fold greater than that of age- and sex-matched controls.[6] The most common causes of cardiovascular mortality are sudden cardiac death, myocardial infarction, cardiac failure, and stroke (Table 1).[6,7] However, traditional Framingham risk factors alone do not entirely explain the excess CVD-related mortality in this population. Nontraditional (kidney disease–related) CVD risk factors also have been identified (Figure 1, Table 2). PD patients may experience chronic inflammation and oxidative stress as a result of exposure to PD catheters, bioincompatible solutions, and PD-related peritonitis.[8] Serum potassium abnormalities, particularly hypokalemia, also disproportionately increase mortality risk in PD patients.[9] Excessive exposure to glucose in PD solutions (up to 200 g/d) also has been linked to atherogenic lipid profiles, metabolic syndrome, new-onset hyperglycemia requiring treatment, and, ultimately, increased CVD risk.[10,11] Jiang et al[12] noted that although approximately 22% of patients with ESKD met the diagnostic criteria for metabolic syndrome predialysis, this number increased to approximately 70% after commencement of PD. Similar results were reported by Johnson et al.[13] Metabolic syndrome is an independent predictor of cardiovascular mortality in the PD population.[14–16]

This review summarizes the evidence relating to the effectiveness of interventions targeting modifiable CVD risk factors in PD patients, as well as highlights the key recommendations of the International Society for Peritoneal Dialysis (ISPD) Cardiovascular and Metabolic Guidelines.

HYPERTENSION

Hypertension is highly prevalent in the PD population. In a study of 540 subjects across 27 centers belonging to the Italian Co-operative Peritoneal Dialysis Study Group, 88% of patients were hypertensive

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Table 1. Prevalence of Cardiovascular Pathology in PD Patients and Their Relative Contribution to Overall Mortality[3]

Cardiovascular Pathology	Prevalence	Contribution to All-Cause Mortality
Arrhythmia/SCA	19%	37%
AMI/ASHD	43%	7%
CHF	25%	6%
CVA/TIA	11%	3%
PAD	21%	-
Other cardiac	-	0.5%

AMI, acute myocardial infarction; ASHD, atherosclerotic heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; PAD, peripheral artery disease; SCA, sudden cardiac arrest; TIA, transient ischemic attack.

and, of these, 90% were maintained on regular antihypertensive therapy.[17] Volume and sodium overload, often aggravated by loss of residual kidney function (RKF) and ultrafiltration failure, are the predominant mechanisms underpinning hypertension in PD patients.[18] Other reported mechanisms include increased arterial stiffness,[19] renin-angiotensin-aldosterone system activation,[20] sympathetic hyperactivity,[21,22] endothelial dysfunction,[23,24] sleep apnea,[25] and use of erythropoiesis-stimulating agents (ESAs).[26,27]

Defining hypertension and the targets for its treatment is difficult because the relationship between blood pressure (BP) and mortality remains unclear in PD patients. For example, in a retrospective study of 2,770 incident adult PD patients with a median follow-up period of 3.7 years, Udayaraj et al[28] found that higher baseline systolic and diastolic BP were associated paradoxically with lower mortality (adjusted hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.78-0.92; and HR, 0.78; 95% CI, 0.67-0.91, respectively) within the first year of dialysis. However, after 6 years on PD, higher baseline systolic BP was associated with increased mortality (HR, 1.10; 95% CI, 1.01-1.19). On the other hand, prospective data from The Netherlands Cooperative Study on the Adequacy of Dialysis study of 118 incident adult PD patients with a mean follow-up period of 25 months reported that a 10-mm Hg increase in systolic BP at 1 year correlated with a 42% increase in mortality (relative risk [RR], 1.42; 95% CI, 1.17-1.73).[29] Although there is no universally accepted definition of hypertension in the PD population and no randomized controlled evidence to provide guidance regarding appropriate BP targets, the ISPD Cardiovascular and Metabolic guidelines currently advocate targeting a BP less than 140/90 mmHg, with therapy recommended in patients who are consistently above this target.[30] It is

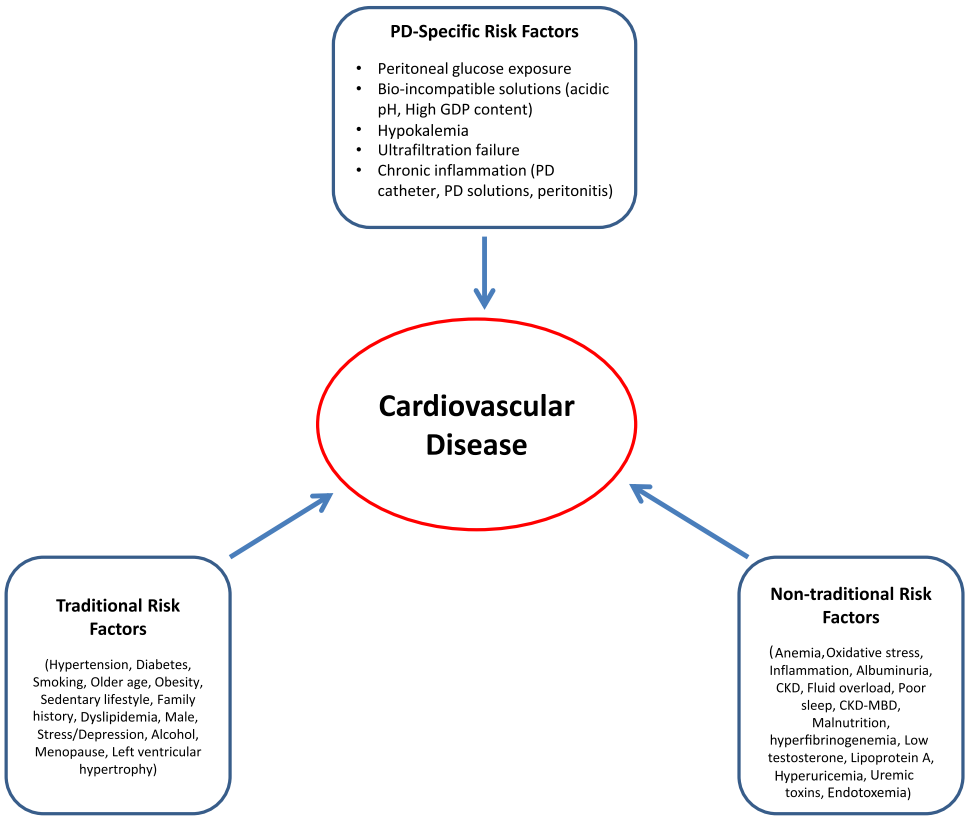

Figure 1. Risk factors for cardiovascular disease in PD patients.