

The Clinical Epidemiology of Cardiac Disease in Chronic Renal Failure

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The annual mortality from cardiovascular disease in dialysis patients is substantially higher than in the general population (Figure 1) (1). The 5-yr survival of men >64 yr old starting dialysis is worse than that of men with colon cancer and prostate cancer (2). The 5-yr survival of women >64 yr old starting dialysis is worse than that of women with breast cancer and colon cancer (2). About half the deaths in dialysis patients are attributed to cardiovascular disease (2). Hospitalizations of dialysis patients occur frequently and about one-third are the result of cardiovascular disease (2). Despite enormous morbidity and premature mortality resulting from cardiovascular disease, it is only recently that the clinical epidemiology of cardiovascular disease in chronic renal failure has become a major focus of nephrology research.

A task force convened by the National Kidney Foundation has considered whether strategies for prevention and treatment of cardiovascular disease in the general population are applicable in patients with chronic renal disease. Two target conditions (coronary artery disease and left ventricular hypertrophy) and four target populations (chronic renal insufficiency, hemodialysis, peritoneal dialysis, and renal transplantation) were considered. Detailed reports are available in a supplement of the *American Journal of Kidney Diseases* (3). The major focus was on traditional cardiac risk factors identified in the general population, including hyperlipidemia, hypertension, diabetes mellitus, tobacco use, menopause, and physical inactivity. In addition, a recent volume of *Seminars in Dialysis* was devoted to consideration of potential uremia-related risk factors (4). These included risk factors altered by the uremic state, such as dyslipidemia, prothrombotic factors, hyperhomocysteinemia, and also risk factors characteristic of chronic uremia, such as hemodynamic overload, anemia, increased oxidant stress, hypoalbuminemia, and divalent ion abnormalities (Table 1).

Pathogenesis of Cardiac Disease

Manifestations of ischemic heart disease, such as angina pectoris or myocardial infarction, are caused by disorders of coronary vessel perfusion. Ischemic heart disease is usually the result of critical coronary artery disease, but in 27% of hemo-

dialysis patients ischemic symptoms are caused by nonatherosclerotic disease (5) (Figure 2). The latter is associated with the underlying cardiomyopathy, small vessel disease (caused by hypertension, diabetes mellitus, and calcium phosphate deposition), reduced capillary density, and abnormal myocyte bioenergetics (6). Left ventricular (LV) hypertrophy predisposes to ischemic symptoms by reducing coronary reserve.

Heart failure is the most common symptom of an underlying cardiomyopathy (Figure 2). LV structure and function alters as a result of LV pressure and volume overload, and of myocyte death (6) (Figure 3). LV pressure overload results from hypertension, arteriosclerosis, and occasionally aortic stenosis. It causes concentric LV hypertrophy, with increased myocyte thickness and little change in LV volume. LV volume overload results from salt and water overload, anemia, and the arteriovenous fistula. It causes eccentric LV hypertrophy, with increase in myocyte length and increase in LV volume. Initially, the LV hypertrophy is adaptive in both types of overload, and is beneficial because energy is spared by maintaining stable wall stress. However, the LV hypertrophy eventually becomes maladaptive, and is harmful because of myocyte death (resulting from continuing LV overload), decrease in capillary density, increase in myocardial fibrosis, diastolic dysfunction, and LV conduction abnormalities. The LV volume–LV pressure curve is displaced to the left, and altered in such a manner that small changes in LV volume result in large changes in LV pressure, predisposing to symptomatic LV failure (6).

Myocyte death induces LV dilation with compensatory LV hypertrophy. Eventually, systolic dysfunction occurs. In addition to continuing LV overload, myocyte death may be caused by decreased large and small coronary vessel perfusion, hyperparathyroidism, malnutrition, and other factors associated with severe uremia (6) (Figure 3).

Blood flow overload causes not only LV remodeling but also vascular remodeling. The latter results in arteriosclerosis with thickened, dilated, and noncompliant arteries (6). This is different from atherosclerosis, which is characterized by arterial plaques that are focal, intermittent in distribution, occlusive in nature, and with a predilection for arterial bifurcations. Arteriosclerosis predisposes to LV hypertrophy by diminishing arterial distensibility, and by enhancing arterial wave reflections, thus increasing the pulsatile work of the heart. There is a strong correlation between carotid artery intima-medial thickness and LV mass index (7). Arteriosclerosis also predisposes to ischemic heart disease by decreasing subendocardial coronary perfusion (6).

Patients with chronic uremia have multiple risk factors pre-

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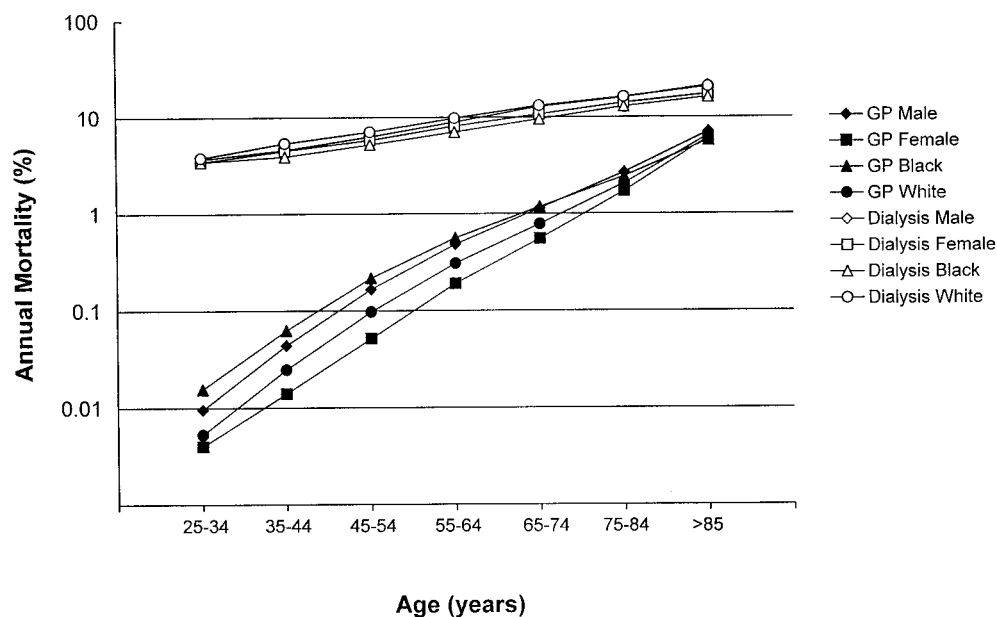


Figure 1. Cardiovascular disease mortality by age, race, and gender in the general population and in dialysis patients. Cardiovascular mortality is defined as death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema. Data from the general population are from the National Center for Health Statistics multiple cause of mortality files 1993. Data from dialysis patients include hemodialysis and peritoneal dialysis combined from USRDS 1994–1996. Reprinted with permission from *Am J Kidney Dis* 32[Suppl 3]: S115, 1998.

Table 1. Cardiac risk factors in chronic uremia

| Traditional Cardiac Risk Factors | Risk Factors Altered by Uremia | Uremia-Related Risk Factors |
|---|---|---|
| Hypertension ^a Hyperlipidemia ^a Diabetes mellitus ^a Tobacco use ^a Physical inactivity | Dyslipidemia High lipoprotein(a) ^a Prothrombotic factors Hyperhomocysteinemia | Hemodynamic overload Anemia ^a Increased oxidant stress Hypoalbuminemia ^a Inadequate dialysis Divalent ion abnormalities Metabolic acidosis Hypo/hyperkalemia |

^a Evidence available from longitudinal studies that demonstrated a significant risk for future cardiac events in chronic uremia.

disposing to disorders of coronary perfusion and to atherosclerosis. They also have multiple risk factors predisposing to abnormalities of LV structure and function and to arteriosclerosis. Disorders of coronary perfusion predispose to cardiomyopathy and *vice versa*. The presence of symptomatic ischemic heart disease and the presence of heart failure on starting dialysis predict earlier death. However, the impact of ischemic heart disease is not independent of that of heart failure, suggesting that the final cardiac pathway to death is via LV dysfunction (8).

Diagnosis

The gold standard for diagnosis of coronary artery disease is coronary angiography. Most of the noninvasive tests for coronary disease are not sensitive in dialysis patients, although dobutamine echocardiography may be (9). Recently, combined

dipyridamole-exercise thallium imaging was shown to be an accurate method for detecting coronary artery disease and for predicting future coronary events (10). It is usually not possible to use coronary arteriography in longitudinal studies and clinical trials of dialysis patients. Therefore, symptomatic ischemic heart disease has been the usual marker for coronary artery disease in longitudinal studies (8).

M-mode echocardiography is an accurate diagnostic test for the diagnosis of concentric LV hypertrophy, LV dilation, and systolic dysfunction (11). LV mass index and LV volume index can be calculated. However, LV volume fluctuates in hemodialysis patients (12). Therefore, it is necessary to perform echocardiography at the patient's dry weight, preferably the day after dialysis. There is substantial variability over time in measurements of LV mass index and LV volume index.

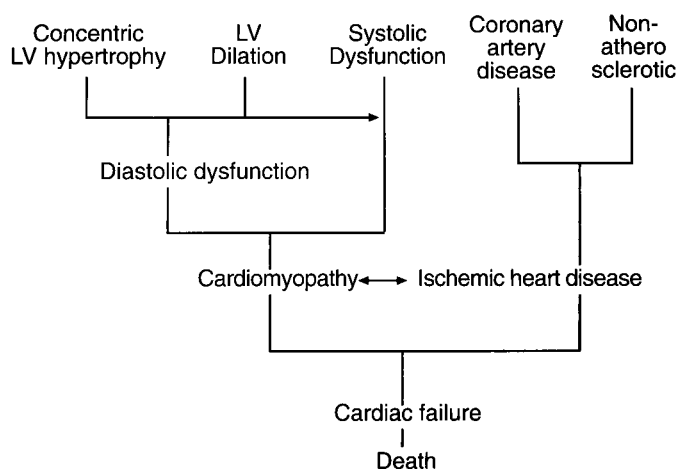


Figure 2. Cardiomyopathy and ischemic heart disease in chronic uremia.

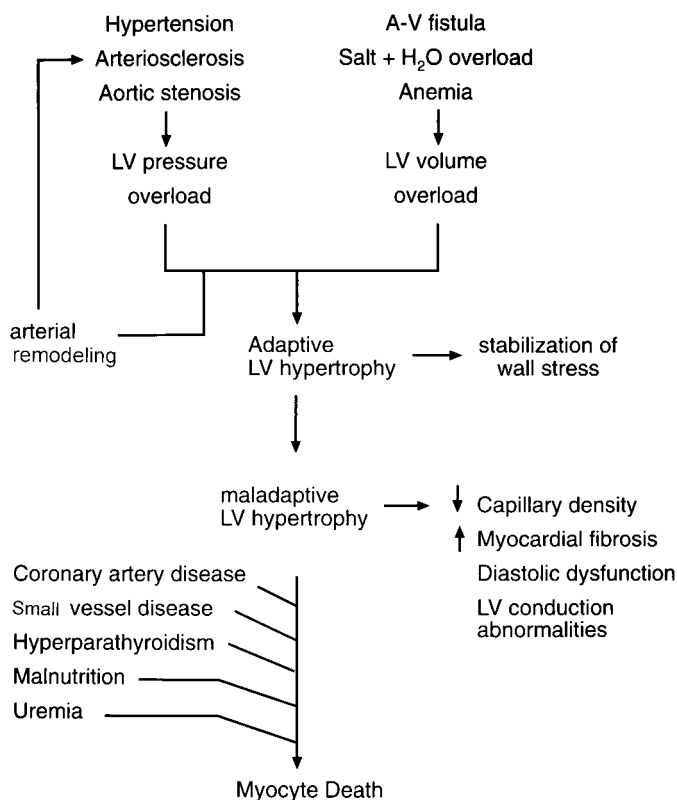


Figure 3. Left ventricular (LV) pressure overload, LV volume overload, and myocyte death in chronic uremia.

Nonetheless, it is a useful test for use in longitudinal studies and clinical trials (11).

The diagnosis of LV failure is not difficult—dyspnea with signs of heart failure on clinical examination (bilateral basal crepitations and raised jugular venous pressure) and/or on chest x-ray (interstitial edema, pulmonary vascular redistribution) (13). The interpretation of these clinical signs is more problematic—Are they the result of salt and water overload or of primary heart disease? It may not be critical (or possible) to

answer this question in most studies, because the presence of clinical heart failure on starting dialysis, regardless of whether it is caused by salt and water overload or of primary heart disease, is a very strong independent predictor of mortality.

Chronic Renal Insufficiency

Prevalence

The prevalence of coronary artery disease in the general population is 5 to 12%, of LV hypertrophy 20%, and of heart failure 5% (1). In patients with chronic renal insufficiency, there are no data on coronary disease or heart failure (14). The prevalence of LV hypertrophy varies according to GFR: 27% in those with GFR ≥ 50 ml/min, 31% in those with GFR 25 to 49 ml/min, and 45% in those with GFR < 25 ml/min (15).

Young patients (mean age 10 yr) with chronic renal insufficiency have increased LV mass index and diminished E/A ratio (suggestive of diastolic dysfunction) compared with normal control subjects (16).

Incidence

There are few longitudinal studies in this population. Data abstracted from the Modification of Diet in Renal Disease Study indicated three first hospitalizations per 100 patient years due to cardiovascular disease (14). In Canada, 246 patients with GFR 25 to 75 ml/min had serial echocardiography. Twelve months after enrollment, LV mass index increased by $>20\%$ above baseline or >20 g/m² in 25% of the group (17).

Risk Factors

In one cross-sectional study, lower GFR, higher systolic BP, and lower hemoglobin level were associated with LV hypertrophy (15). In a cross-sectional study of 32 children with chronic renal failure, higher BP and higher serum creatinine were associated with higher LV mass (16). In the Canadian longitudinal study, increase in LV mass index, 12 mo after enrollment in the study, was associated with anemia, hypertension, and lower baseline LV mass index. The odds ratio was 1.32 for each 5 g/L fall in hemoglobin ($P = 0.004$) and 1.11 for each 5 mmHg rise in systolic BP ($P = 0.01$) (17).

Patients Starting Dialysis

Prevalence

The prevalence of ischemic heart disease on starting dialysis, as reported by the national registries, was 41% in the United States, 36% in Australia and New Zealand, and 28% in Canada (14–18). In the United States, the prevalence of heart failure on starting dialysis was 40% (18).

A Canadian multicenter longitudinal study followed 822 patients in 11 centers from the day of starting dialysis in 1993–1994 (19). A detailed evaluation of comorbidity was performed at that time. Eighty percent of the patients were Caucasian and 29% were diabetic. The prevalence of angina pectoris was 21%, of myocardial infarction 18%, of heart failure 35%, and of peripheral vascular disease 16%.

Another Canadian study followed 432 patients who survived at least 6 mo on dialysis. Enrollment occurred from 1983–1991. Echocardiography at baseline revealed concentric LV

hypertrophy in 42%, eccentric LV hypertrophy in 23%, isolated LV dilation in 4%, and systolic dysfunction in 16% (11). Only 16% had a normal echocardiogram (Figure 4). In this cohort, the prevalence of heart failure on starting dialysis was 31% and the prevalence of ischemic heart disease on starting dialysis was 22% (Figure 4).

Risk Factors

The high prevalence of cardiovascular disease on starting dialysis suggests that the predialysis phase of chronic renal disease is a state of high cardiac risk. Part of this risk can be attributed to the contribution of diabetes mellitus and hypertension in the etiology of end-stage renal disease (ESRD). In the United States in 1996, 42% of new cases resulted from diabetes mellitus and 26% from hypertension (2). Diabetes is associated with more severe and extensive coronary artery disease than that observed in nondiabetic patients (20). LV mass index is higher in hypertensive diabetic patients than in matched essential hypertensive patients (21). At autopsy, LV hypertrophy is associated with more extensive fibrosis in hypertensive diabetic patients than in hypertensive nondiabetic patients, or nonhypertensive diabetic patients (22). On starting dialysis in the Canadian echocardiographic study, diabetic patients ($n = 116$) had more concentric LV hypertrophy (50%

versus 38%, $P = 0.04$), symptomatic ischemic heart disease (32% versus 18%, $P = 0.003$), and cardiac failure (48% versus 24%, $P < 0.00001$) when compared to nondiabetic patients ($n = 317$) (23).

Outcome

The presence of concentric LV hypertrophy, LV dilation, or systolic dysfunction on starting dialysis was associated with about a threefold increase in the risk of subsequent heart failure, independent of age, diabetes, and ischemic heart disease (11). The median survival of patients with systolic dysfunction on starting dialysis was 38 mo (Figure 5), with an odds ratio for mortality, compared to those with normal echocardiogram, of 1.88 (independent of age, gender, diabetes, and ischemic heart disease) (11). The late mortality (after 2 yr of dialysis) for both concentric LV hypertrophy and LV dilation was worse than for those with a normal echocardiogram (Figure 3) (11,24).

The presence of heart failure on starting dialysis was associated with a 93% increased risk of death, independent of age, diabetes, and ischemic heart disease (Figure 6) (8,13). The presence of symptomatic ischemic heart disease was associated with a 48% increased risk of death, independent of age and diabetes. However, when cardiac failure was included in the multivariate Cox regression model, ischemic heart disease was no longer an independent predictor of death (8).

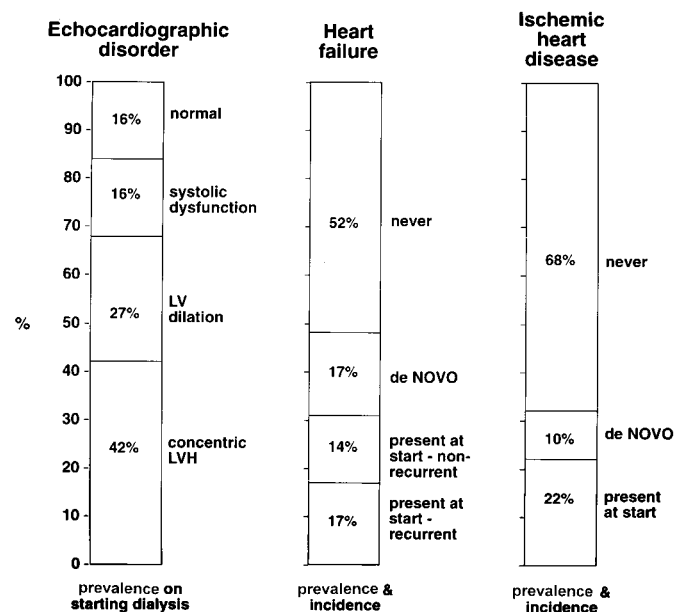


Figure 4. The prevalence and incidence of cardiac disease in a cohort of 432 Canadian dialysis patients followed from the start of dialysis for a mean of 41 mo (8,11,13). Consecutive patients were enrolled and followed if they survived 6 mo on end-stage renal disease (ESRD) therapy. prevalence = disease present at start of ESRD therapy. incidence = *de novo* disease developed during follow-up on dialysis therapy. recurrent = heart failure present at start of therapy and recurred during follow-up. nonrecurrent = heart failure present at start of therapy but did not recur. *de novo* = disease not present at start of therapy but occurred during follow-up while on dialysis therapy. never = disease not present at start of therapy and never occurred during follow-up.

Hemodialysis Prevalence

London and Fabiani (25) in the 1980s in France observed a prevalence of 38% for LV dilation (LV end diastolic diameter >5.8 cm) and 20% for systolic dysfunction (fractional shortening $<20\%$). After 10 yr of hemodialysis, the prevalence of LV hypertrophy was 75% and the prevalence of low ejection fraction was 12%.

The prevalence of heart failure in the United States has increased slightly from 52% in 1986–1987 to 55% in 1990

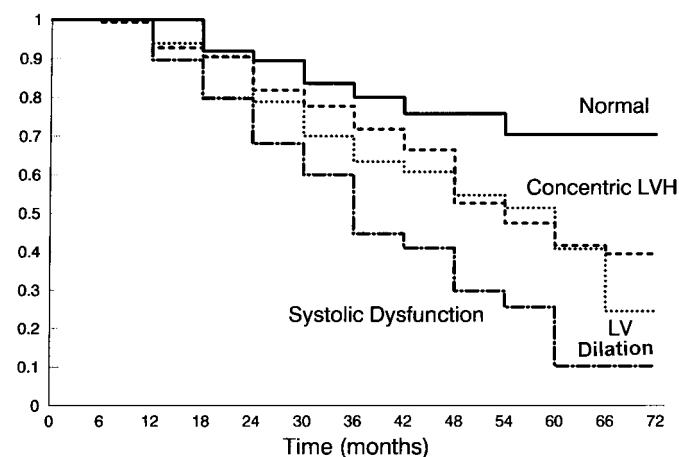


Figure 5. Cumulative percent survival in patients with systolic dysfunction, concentric LV hypertrophy, LV dilation, and normal echocardiogram on starting dialysis therapy (11). Reprinted with permission from *Nephrol Dial Transplant* 11: 1277–1285, 1996.

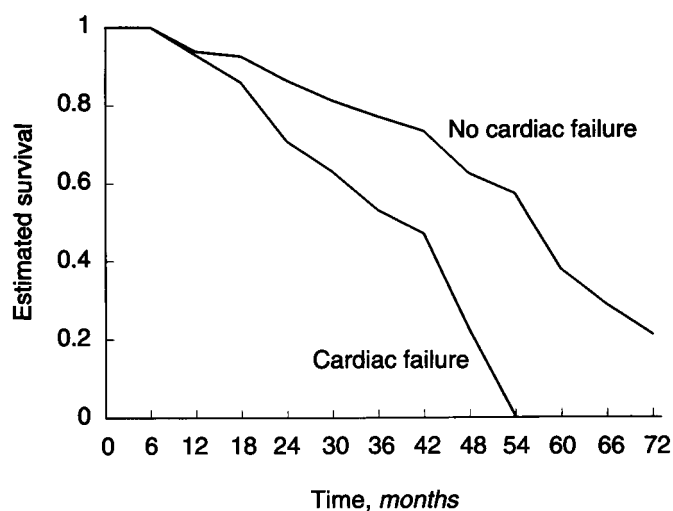


Figure 6. Cumulative percent survival in patients with and without heart failure on starting dialysis therapy (13). Reprinted with permission from *Kidney Int* 49: 1428–1434, 1996.

(26). During the same time, the prevalence of ischemic heart disease increased from 48 to 52% (26).

Natural History and Incidence

LV dilation with compensatory hypertrophy continues after starting dialysis. A self-selected subgroup of dialysis patients from the Canadian echocardiographic study had four consecutive annual echocardiograms from the start of dialysis (27). LV cavity volume index was 73 ml/m² at baseline (2 mo after start of dialysis), increased by 13 ml/m² at 18 mo from start of dialysis, by a further 5 ml/m² at 30 mo, and fell by 2 ml/m² at 43 mo follow-up from start of dialysis. LV mass index at baseline was 128 g/m², increased by 18 g/m² on first follow-up, fell by 1 g/m² on second follow-up, and increased by 9 g/m² on third follow-up.

The Canadian Hemodialysis Morbidity Study reported an 8% per year probability of having myocardial infarction or angina requiring hospitalization in a cohort followed from the start of hemodialysis (28). The probability of developing pulmonary edema requiring hospitalization or extra ultrafiltration was 10% per year.

The incidence of *de novo* ischemic heart disease in another Canadian cohort of dialysis patients without ischemic heart disease on starting dialysis was 12% during a follow-up of 41 mo, giving an annual incidence of 3.6% (8) (Figure 4). The incidence of *de novo* heart failure was 26% in the patients who did not have heart failure on starting dialysis, an annual incidence of 7.6% per year (13) (Figure 4).

In the United States, the annual cardiovascular disease mortality in the general population is 0.27%, whereas in hemodialysis patients it is 35 times higher, at 9.5% (1) (Figure 1). This very substantially increased mortality occurred in males, females, blacks, whites, and diabetic patients (Figure 1).

The incidence of death due to ischemic heart disease varies according to country. Southern European countries have a lower incidence of coronary artery disease than northern Eu-

ropean countries in the general population. This translates into the dialysis population (29). For example, the annual adjusted death rates for ischemic heart disease for male hemodialysis patients 55 to 64 yr per 1000 patient years were 14 in Italy and 32 in the United Kingdom. Comparable rates for females were 9 and 34.

Outcome

Patients on dialysis who present with acute myocardial infarction have high mortality from cardiac causes and poor long-term survival (30). In 34,189 U.S. patients on long-term dialysis, overall mortality after acute myocardial infarction was 59% at 1 yr, 73% at 2 yr, and 90% at 5 yr. Older patients and diabetic patients had higher rates of mortality. These data are compatible with the belief that a decrease in coronary perfusion in patients with overload cardiomyopathy would be catastrophic. The median survival following the development of *de novo* heart failure during the course of dialysis was 18 mo (13).

Peritoneal Dialysis

Comparison of rates between patients treated with peritoneal dialysis and hemodialysis is fraught with difficulty because of selection bias in the choice of ESRD modality. For example, in Canada comorbidity scores that influence survival, present on starting dialysis, are substantially higher in hemodialysis than in peritoneal dialysis patients (19,31).

The hemodynamic milieu of hemodialysis favors the development of LV dilation and compensatory LV hypertrophy, whereas in peritoneal dialysis patients the absence of a fistula, less anemia, and constant blood volume do not (27). In 70 patients treated exclusively with peritoneal dialysis, LV cavity volume decreased by 5 ml/m² during the first year of follow-up from start of dialysis. In 229 patients maintained exclusively on hemodialysis, LV cavity volume increased by 7 ml/m² and LV mass index increased by 36 g/m² during the first year of follow-up (32). In the group of patients treated only with peritoneal dialysis, 16.5% developed *de novo* heart failure versus 28.1% of those treated with hemodialysis ($P = 0.02$) (32). In this study, hemodialysis had a late survival advantage over peritoneal dialysis because of the adverse impact of hypoalbuminemia in the latter group. Mean serum albumin in peritoneal dialysis patients in the first 2 yr of therapy accounted for 65% of the increase in subsequent mortality (32). It appears that the path to cardiac death is different for hemodialysis and peritoneal dialysis patients.

In 55 normotensive continuous ambulatory peritoneal dialysis patients on treatment for 29 mo, a high prevalence of left atrial dilation and LV hypertrophy was observed, the latter mainly the result of septal thickening (33). The prevalence of LV hypertrophy was lower in those during the first 2 to 3 yr of treatment and higher in those treated for 5 yr (34).

In the United States, the prevalence of ischemic heart disease in peritoneal dialysis patients was about 40%, as was that of heart failure (18). The cardiovascular disease annual mortality is 9.7%, similar to that in hemodialysis patients (9.5%) (1). The relative risk of death from myocardial infarction was 30% higher in peritoneal versus hemodialysis patients in 1987–

1989. The death rate from acute myocardial infarction (1991–1993) was 31.5 per 100 patient years in peritoneal dialysis patients *versus* 24.8 per 100 patient years in hemodialysis patients (35).

Risk Factors for Cardiac Disease in Dialysis Patients

The most appropriate research design to identify risk factors for cardiac disease in dialysis patients is: (1) identify patients without the disease of interest on starting dialysis; (2) measure the potential risk factors; and (3) follow patients prospectively until *de novo* disease develops. There are few such longitudinal studies reported.

Cardiomyopathy

A nested case control with prospective follow-up identified high systolic BP as a risk factor for the subsequent development of LV hypertrophy (36). Progressive cardiac enlargement identified by serial echocardiography from the start of dialysis was associated with hemodialysis (compared with peritoneal dialysis) and anemia (27). Each g/dl fall in hemoglobin from the reference value was associated with a 10 g/m² rise in LV mass index. These data are compatible with the belief that systolic hypertension causes concentric hypertrophy, and that anemia and hemodynamic overload cause an increase in LV volume, with further compensatory hypertrophy.

When patients with LV dilation were compared to those with normal echocardiogram, significant independent associations with the degree of LV dilation included ischemic heart disease, anemia, hypertension, and hypoalbuminemia (11).

Heart Failure

Independent risk factors for the development of *de novo* heart failure in dialysis patients are shown in Table 2 (13). Potentially reversible uremia-related risk factors for *de novo* heart failure include anemia, hypertension, and hypoalbuminemia.

Ischemic Heart Disease

Independent risk factors for the development of *de novo* ischemic heart disease in dialysis patients are shown in Table 3 (8). Potentially reversible risk factors for *de novo* ischemic disease include the underlying cardiomyopathy, hypertension, hypoalbuminemia, but not anemia.

Hypertension

Hypertension is not always due to increased peripheral resistance, but may reflect increased cardiac output from anemia, salt and water overload, or arteriovenous fistula, or it may reflect arteriosclerosis. Hypertension is a risk factor for LV hypertrophy, LV dilation, heart failure, and ischemic heart disease, but hypotension is a risk factor for mortality (37) (Table 4). The latter, counterintuitive observation has been confirmed in multiple studies. It is probably explained by the fact that low BP is a marker for cardiac disease before death. This interpretation is supported by the following observations: (1) A high proportion of dialysis patients already have cardiac disease on starting dialysis. (2) In patients who develop cardiac failure on dialysis, the time to this event is shorter than the follow-up after the event. (3) BP falls after the development of heart failure. (4) Sixty-five percent of all deaths are preceded by cardiac failure (36).

Hypoalbuminemia

It is unclear how one should interpret hypoalbuminemia as a cardiac risk factor for cardiac failure and ischemic heart disease, because it may be a marker for malnutrition, inadequate dialysis, an associated prothrombotic state, dyslipidemia, chronic inflammation, or vitamin deficiency, all of which could potentially be pathogenic to the heart (38,39).

Anemia

In the therapeutic milieu of partial correction of anemia with blood transfusion in the 1980s and more recently with erythropoietin, anemia induces LV dilation and compensatory LV hypertrophy, and is a risk factor for *de novo* heart failure and earlier death (27,40). Pre-post studies of partial correction of anemia with erythropoietin have demonstrated improvement, but not normalization, of LV mass and volume (41).

Diabetes Mellitus

After adjusting for age and gender, diabetic dialysis patients had similar rates of progression of echocardiographic disorders and development of *de novo* heart failure, but higher rates of *de novo* ischemic heart disease, overall mortality, and cardiovascular mortality than nondiabetic dialysis patients (23) (Table 5). The excessive cardiac morbidity and mortality of diabetic patients seems to be mediated via ischemic disease, rather than progression of cardiomyopathy, while on dialysis therapy.

Table 2. Independent risk factors for the development of *de novo* heart failure in dialysis patients (13)

| Parameter | Adjusted Relative Risk | P Value |
|--|------------------------|---------|
| Age (per 10 yr) | 1.32 | 0.004 |
| Diabetes mellitus | 1.63 | 0.09 |
| Systolic dysfunction | 2.05 | 0.08 |
| Hemoglobin (per 10 g/L fall) | 1.49 | <0.0001 |
| Serum albumin (5 g/L fall) | 1.34 | 0.007 |
| Diastolic blood pressure (per 5 mmHg increase) | 1.32 | 0.0005 |

Table 3. Independent risk factors for the development of *de novo* ischemic heart disease in dialysis patients (8)^a

| Parameter | Adjusted Relative Risk | P Value |
|----------------------------------|------------------------|---------|
| Age (per year) | 1.05 | <0.001 |
| Diabetes mellitus | 3.97 | <0.001 |
| Echocardiographic diagnosis | | |
| normal reference group | | |
| concentric LVH | 5.92 | 0.01 |
| LV dilation | 5.35 | 0.02 |
| systolic dysfunction | 12.2 | 0.002 |
| Diastolic BP (per mmHg increase) | 1.04 | 0.03 |
| Serum albumin (per g/L increase) | 0.93 | 0.03 |
| Hemoglobin | NS | NS |

^a LVH, left ventricular hypertrophy; LV, left ventricular.

Table 4. Independent associations between blood pressure (the effect of a rise in mean arterial blood pressure level of 10 mmHg) and echocardiographic and clinical outcomes in dialysis patients (37)

| Outcome | Odds Ratio | P Value |
|--|---------------|---------|
| Echocardiogram in second year | | |
| normal LV (reference category) | | |
| concentric LVH | 1.48 | 0.02 |
| LV dilation | 1.48 | 0.06 |
| Change in LV from echo done on | β | |
| starting dialysis to echo in second year | | |
| LV mass index (g/m ²) | 5.4 | 0.03 |
| LV volume (ml/m ²) | 4.3 | 0.05 |
| | Relative Risk | |
| <i>De novo</i> ischemic heart disease | 1.39 | 0.05 |
| <i>De novo</i> cardiac failure | 1.44 | 0.007 |
| Death | 0.82 | 0.009 |

Table 5. Outcomes of diabetic relative to nondiabetic dialysis patients (23)

| Outcome | Diabetic (n = 116) (%) | Nondiabetic (n = 317) (%) | Adjusted Hazard Ratio ^a | P Value |
|---|------------------------------|---------------------------------|---------------------------------------|---------|
| <i>De novo</i> symptomatic ischemic heart disease | 24 | 8 | 3.2 | 0.0002 |
| <i>De novo</i> heart failure | 27 | 23 | 1.3 | NS |
| Overall mortality | 53 | 28 | 2.3 | <0.0001 |
| Cardiovascular mortality | 22 | 14 | 2.0 | 0.006 |

^a Adjusted for age and gender.

Dyslipidemia

The prevalence of hyperlipidemia in chronic renal disease is higher than in the general population, but varies depending on the type of lipid, target population, cause of renal disease, and level of renal function (42). The prevalence of increased total or LDL-cholesterol is highest in patients with chronic renal insufficiency and nephrotic syndrome, patients treated by peritoneal dialysis, and renal transplant recipients (45 to 55%). All target populations have a high prevalence of increased triglyc-

erides, usually with a low HDL-cholesterol (35 to 65%). Hypercholesterolemia in chronic uremia is confounded by the impact of malnutrition, which lowers serum cholesterol. Chronic uremia is associated with higher lipoprotein(a) levels, chylomicron remnants, and altered lipoprotein particles, which are potentially atherogenic (43). A longitudinal study has demonstrated that a high lipoprotein(a) level is a risk factor for future cardiac events (44). In Germany, 196 diabetic patients were followed from the start of dialysis. Diabetic patients

subsequently dying from myocardial infarction had significantly higher median cholesterol than survivors, and higher LDL-cholesterol, LDL/HDL ratio, and apolipoprotein B (45). There are no longitudinal studies reported for large numbers of patients followed from the start of dialysis, which unravel the degree of cardiac risk associated with the various lipid abnormalities prevalent in chronic uremia.

Other Risk Factors

Potential uremia-related cardiac risk factors include salt and water overload, excess fistula flow rates, inadequate dialysis, hyperhomocysteinemia, increased oxidant stress, inflammation, increased prothrombotic factors, divalent ion abnormalities, hyperparathyroidism, metabolic acidosis, hypokalemia, and carnitine insufficiency (4). However, there are no longitudinal studies with an appropriate design and large numbers of patients that have quantified the extent of cardiac risk associated with each of these potential risk factors.

Risk Factor Intervention

The highest level of evidence, to determine the efficacy of an intervention, is derived from randomized controlled clinical trials. A small randomized controlled clinical trial has demonstrated that the angiotensin-converting enzyme inhibitor perindopril induced regression of LV hypertrophy (46). A Canadian multicenter study of 146 patients compared the effect of complete *versus* partial correction of anemia with erythropoietin on LV structure in asymptomatic hemodialysis patients with concentric LV hypertrophy or LV dilation (47). Complete correction of anemia failed to induce regression of concentric LV hypertrophy or LV dilation, but it appeared to prevent LV dilation in patients with normal LV volumes. In the latter group, there was a strong correlation between change in LV volume and change in hemoglobin level at 12 mo after the start of the study.

Trials of interventions, powered to detect improvements in clinical outcomes, have been few. The Amgen trial examined the effects of normalization of hematocrit with erythropoietin compared with low hematocrit values in patients with symptomatic cardiac disease, who were receiving hemodialysis (48). A total of 1233 hemodialysis patients with either symptomatic heart failure or ischemic heart disease was enrolled. The primary end point was death or first nonfatal myocardial infarction. The trial was prematurely halted because of excess deaths (Figure 7) and significantly increased vascular access loss in the group allocated to complete correction of anemia. These data, together with the Canadian data, suggest that it is too late to intervene and totally correct anemia late in the course of cardiac disease, by the time at which LV dilation has already developed or clinical symptoms from either ischemia or heart failure have occurred. Whether early intervention to normalize hemoglobin in the predialysis phase or on starting dialysis can prevent subsequent development of cardiac disease is unknown.

The ongoing HEMO study in the United States, comparing a high quantity of dialysis to a conventional dose, should be able to: (1) determine the interrelationship between quantity of

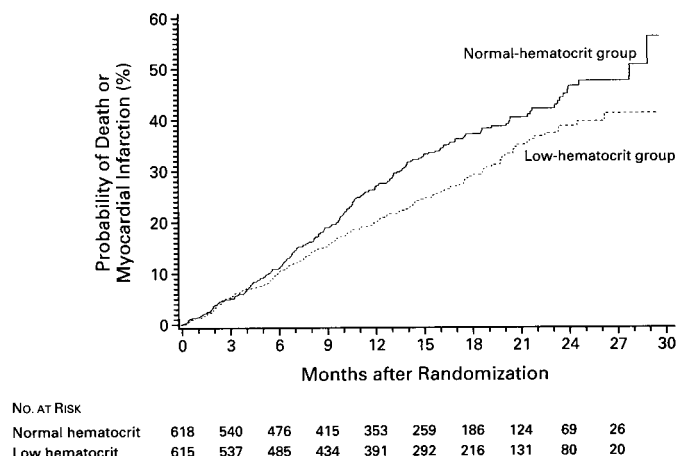


Figure 7. Cumulative percent survival in hemodialysis patients with preexisting cardiac disease, randomly allocated to normalization of hematocrit compared to partial correction of anemia with erythropoietin. There were 183 deaths and 19 first nonfatal myocardial infarctions (total = 202 events) in the normal hematocrit group ($n = 618$) *versus* 150 deaths and 14 nonfatal myocardial infarctions (total = 164 events) in the group assigned a hematocrit of 30 ($n = 615$) ($P = 0.03$). Reprinted with permission from *N Engl J Med* 339: 584–590, 1998.

dialysis, hypoalbuminemia, and cardiac events; (2) recommend the optimal target dose of dialysis; and (3) assess whether achievement of the optimal target dose of dialysis can prevent cardiac events.

In the absence of randomized controlled trials in chronic uremia, it seems reasonable to apply several strategies for prevention and treatment of cardiovascular disease in the general population to patients with chronic uremia (1). These include:

- The guidelines of the Sixth Joint National Committee for Prevention, Detection, Evaluation and Treatment of High BP, which define the optimal and target BP for antihypertensive therapy to reduce the risk of cardiovascular disease outcomes.
- The guidelines of the National Cholesterol Education Program Adult Treatment Panel II for initial classification, treatment initiation, and target cholesterol levels for diet or drug therapy, taking into account that patients with chronic renal disease are at high risk of developing cardiac disease.
- Use of aspirin to reduce the risk of subsequent cardiovascular disease in patients with coronary artery disease or in those who are at high risk of developing coronary disease.
- Cessation of smoking.
- Moderate level of physical activity for 30 min per day for most days of the week.

Renal Transplantation

Patients who receive renal transplants are a select subgroup of the dialysis population in that they are younger and have little cardiac comorbidity. In the Canadian echocardiographic study, only 11% of the subgroup of dialysis patients who were transplanted had previous heart failure and 1% had myocardial

infarction (49). Nonetheless, many of them had abnormal LV structure and/or function before transplantation. After transplantation, LV mass index regressed in those with concentric LV hypertrophy. Both LV mass index and LV volume improved in those with LV dilation. However, in many patients LV structure did not normalize. It was striking that all 12 patients with systolic dysfunction (fractional shortening <25%) normalized (49).

Renal transplantation is a state of chronic renal insufficiency and thus constitutes a state of high cardiac risk. The prevalence of LV hypertrophy is between 50 and 70% (14). The incidence of myocardial infarction is 3 to 5 times that of the general population (50). Type I diabetic patients comprise a high-risk group. A high prevalence of coronary artery disease, often diffuse, has been observed in type I diabetic transplant candidates (51). The risk of vascular events was 4 times higher in those with coronary disease compared to those without. Kasiske *et al.* (52) reported on the incidence of ischemic heart disease in 706 renal transplant recipients whose transplants functioned for >6 mo from 1976 to 1991. Twelve percent developed major ischemic heart disease, and the 15-yr cumulative incidence rate was 23%. Nineteen percent of deaths were due to ischemic heart disease. These data, together with the observations that this young population has an annual cardiovascular mortality of 0.57% (1) and cause of death was attributed to cardiac disease in 32% of deaths, (53) suggest that long-term cardiac disease is a major problem. This problem will increase in magnitude because there has been a substantial reduction in graft loss during the past decade and a substantial growth in the number of surviving renal transplant recipients.

Conclusion

The clinical epidemiology of cardiac disease in chronic renal disease has become a major area of research during the past 8 years. The U.S. Renal Data System work on the epidemiology of cardiac disease in the U.S. population of dialysis patients has provided invaluable information on the burden of disease. The pathophysiologic basis of cardiovascular disease in chronic uremia has been explored superbly by London and colleagues in France. The importance of LV disorders in the etiology of cardiac symptoms and of some risk factors for cardiac disease has been demonstrated by the Canadian longitudinal studies. Nonetheless, there is a deficit in several important areas, including: (1) the clinical epidemiology of cardiac disease in predialysis chronic renal insufficiency, peritoneal dialysis, and renal transplant recipients; (2) the clinical importance of uremia-related risk factors; and (3) the clinical efficacy of risk factor intervention, as proven by randomized controlled trials. Research investment in these areas is necessary, together with translation of research conclusions concerning therapy into practice, because the potential for improving longevity and quality of life in patients with chronic renal disease is great.

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