CARDIAC COMPLICATIONS OF END-STAGE RENAL DISEASE: IDENTIFICATION OF RISK FACTORS AND DESIGN OF CLINICAL TRIALS

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INTRODUCTION: THE BURDEN OF CARDIAC DISEASE IN ESRD.

End-stage renal disease seems to be inextricably tied to cardiac disease. Clyde Shields, the first patient with end-stage renal disease sustained on dialysis over a long period, died of myocardial infarction in 1970, at age 50, after 11 years of hemodialysis therapy (1). Approximately half of all deaths seen in end-stage renal disease (ESRD) patients are attributed to cardiovascular disease; this figure is remarkably similar throughout the world (2,3,4,5,6,7,8,9,10). Cardiovascular disease is frequently already present in patients reaching end-stage renal disease and undoubtedly contributes heavily to the excessive cardiovascular morbidity and mortality seen in patients on renal replacement therapy (2,3,4,6). For example, in the United States Renal Data System (USRDS) Special Study of Case Mix Severity of 3,399 patients starting chronic hemodialysis, coronary artery disease was already present in 40.8% of patients; for cardiac failure, the corresponding figure was 41.1% (2). In patients beginning renal replacement therapy in Canada in 1992, 21.9% had a history of angina pectoris, 17.5% myocardial infarction, 29.0% pulmonary edema, 8.3% cerebrovascular accident, while 14.8% had peripheral vascular disease (4). Pre-clinical cardiovascular abnormalities are even commoner. Non-invasive studies, principally using echocardiography, have consistently shown that up to 80% of patients starting renal replacement therapy have structural or functional abnormalities of the left ventricle (11,12,13,14) as was seen in the current study (15).

There is a high incidence of de novo cardiovascular disease in ESRD patients. A recent Japanese study followed 1609 dialysis patients prospectively for 3 years. Using the age-matched general population as reference category, the relative risk of cerebral infarction was 2.0, cerebral hemorrhage 10.7, subarachnoid hemorrhage 4.0 and acute myocardial infarction 2.1 (16). In the

Canadian Hemodialysis Morbidity Study, the annual incidence of myocardial infarction and congestive heart failure were both 10% per year (17).

The high burden of disease, and the need for high quality clinical studies were strongly highlighted in a recent consensus document from the United States National Institute of Health (18).

Between 1982 and 1991, a cohort of 433 inception dialysis patients was followed prospectively for an average of 41 months. All these patients survived for greater than 6 months on ESRD therapy, and had an echocardiogram within a year of starting therapy. The primary purpose of this study were to delineate the prevalence, natural history, prognosis and risk factors for the different manifestations of cardiac disease in ESRD. The ultimate aim of this study was to identify areas amenable to intervention, preferably by means of randomised controlled trials.

OVERVIEW OF METHODS

PATIENTS. This prospective study was started in the Royal Victoria Hospital, Montreal, Quebec in 1982, in the Health Sciences Centre St. John's, Newfoundland in 1984, and in the Grace Hospital, St. John's, Newfoundland in 1985. Patients were eligible for entry to the study if (a) they had survived for 6 months and (b) they had a technically satisfactory echocardiogram within a year of initiating renal replacement therapy. Patient recruitment at all 3 centers finished in June 1991.

Of 518 patients who survived at least 6 months from the start of end-stage renal disease therapy a cohort of 433 (83.6% of those screened) entered the study. 85 patients were excluded from the study for the following reasons : failure to obtain a technically satisfactory echocardiogram within a year of starting therapy - 71 patients; started therapy elsewhere - 7 patients ; patients' charts mislaid - 5 patients; 2 patients did not wish to participate in the study.

Baseline echocardiography was performed at a mean (standard deviation) interval of 3.3 (3.9) months from the time of first dialysis. The mean (standard deviation) duration of total follow-up was 41.1 (25.7) months. Hemodialysis, peritoneal dialysis and renal transplantation accounted on average for 18.8, 12.8 and 9.5 months respectively of the total follow-up.

The clinical and demographic characteristics of the patient cohort, at the time of study entry, are shown in Table 1. Overall, the age and proportion of diabetic patients were similar to other Canadian end-stage renal disease programs (17). Compared to a typical program in the United States there were more males (64% vs.52%) and fewer diabetics (27% vs. 32%) (2). The study group was almost entirely Caucasian.

DATA COLLECTION. At baseline, and at yearly intervals thereafter, a clinical assessment was undertaken to detect risk factors for and the presence of cardiovascular disease. Baseline and annual echocardiography was performed using M-mode and 2-dimensional ultrasonography. Left ventricular mass index was calculated using the Penn convention (19). Left ventricular cavity volume was calculated by the formula of Pombo et al. (20) Left ventricular mass and cavity volume were indexed to body surface area, presented in g/m^2 and ml/m^3, respectively. Where possible, imaging was carried out when the patient had achieved "dry weight", the weight below which hypotension or symptoms such as muscle cramps occur.

DEFINITIONS. The following definitions were used.

Coronary artery disease: history of myocardial infarction, coronary artery bypass surgery or percutaneous transluminal angioplasty.

Angina pectoris: precordial chest pain, precipitated by exertion or stress, relieved by rest or nitrates.

Ischemic heart disease: angina pectoris or coronary artery disease.

Cardiac failure: dyspnea plus 2 of the following - raised jugular venous pressure, bibasalar crackles, pulmonary venous hypertension or interstitial edema on chest X-ray.

Peripheral vascular disease: symptoms of, or surgery for peripheral vascular disease.

Dysrhythmia: atrial or ventricular rhythm disorder requiring therapy.

Arterial pulse pressure: systolic minus diastolic blood pressure.

Mean arterial pressure: diastolic blood pressure + 1/3(arterial pulse pressure).

LV dilatation: cavity volume > 90 ml/m^2 (20).

LV hypertrophy by mass index : mass index > 100g/m^2 in females, mass index > 131 g/m^2 in males (21).

Concentric LV hypertrophy: hypertrophy with normal cavity volume (22), fractional shortening greater than 25%.

Eccentric left ventricular hypertrophy: hypertrophy with LV dilatation, fractional shortening greater than 25% (22).

Systolic dysfunction: fractional shortening less than or equal to 25% on echocardiography.

Abnormal left ventricle: any of the following - LV hypertrophy, LV dilatation or systolic dysfunction.

Cardiac mortality: death recorded as "myocardial infarction", "sudden death" or "other cardiac causes".

ANALYSIS. Patient follow-up started with the first dialysis treatment. The primary outcome measure was death on dialysis therapy. Overall mortality and death after 2 years were assessed. We chose the latter end-point for the following reasons: firstly, because a time interval between exposure to a risk factor and subsequent mortality might be needed, and secondly, because we felt it likely that the independent hazards associated with different variables might not remain constant in time frames as long as those seen in this study. For the analyses in this report, patients were censored at the time of renal transplantation or at final follow-up. The survival analyses presented here used the day of first dialysis as entry point. Using 6 months on dialysis as entry point led to almost identical results. Cardiac mortality was a secondary end-point. Clinical episodes of cardiac

failure and ischemic heart disease following the initiation of ESRD therapy were analyzed similarly.

Normally distributed continuous variables were compared using t-tests. Categorical variables were compared using chi-squared analysis. Stepwise logistic regression analysis was used to assess the associations of the different left ventricular abnormalities present on first and follow-up echocardiography. Stepwise multiple linear regression was used to assess the independent associations of continuous variables, such as left ventricular mass index, cavity volume and fractional shortening. Univariate survival analysis was carried out using the product-limit method . The independent power of different variables to predict death, ischemic heart disease and cardiac failure was assessed using Cox's regression analysis. The suitability of this model was assessed by split validation, in which data derived from a randomly generated sample of 2/3rds of all patients (test sample) were used to predict the survival of the remaining 1/3rd (validation sample). The Cox's regression model accurately predicted the actual survival of both the test sample (suggesting high a degree of goodness of fit) and the validation sample (suggesting the ability of the model to predict future mortality.

Additionally, because variables such as mean calcium level could vary directly as a function of time on dialysis and could lead to a spurious association between calcium levels and mortality, we examined this possibility by testing these parameters as time-dependent variables given by the formula : $[X]_{adj} = [X].\ln(\text{survival time})$, where X is the level of the variable being tested (23). Such an adjustment procedure gives more weight to an abnormal variable which has been present for a

longer time period. All statistical tests are 2-tailed, with a p-value of less than 0.05 taken to indicate statistical significance.

RESULTS

PRINCIPAL OUTCOMES DURING THE STUDY (Table 2).

The overall median survival for the patient cohort was 50 months. The 149 deaths observed during the study period were attributed to: myocardial infarction-10.1%, sudden death-25.5%, other cardiac causes-11.4%, other vascular disease-10.7%, infection-14.0%, treatment withdrawal-12.1% and other causes-15.4%. The other major clinical and echocardiographic outcomes are shown in Table 2, which shows a very large burden of cardiac disease, both clinical and echocardiographic.

CLINICAL AND ECHOCARDIOGRAPHIC ABNORMALITIES AT BASELINE: PREVALENCE AND PROGNOSIS (Tables 1 to 3).

Abnormalities of left ventricular structure and function were very frequent on baseline echocardiography: 73.9% had left ventricular hypertrophy, 35.5% had left ventricular dilatation and 14.8% had systolic dysfunction.

Initial Cox's models were constructed to assess overall mortality and mortality after 2 years (Table 3, basic models). In these models left ventricular fractional shortening showed an inverse association and systolic dysfunction a direct association with all-cause mortality, independently of age, diabetes, coronary artery disease, angina pectoris, cardiac failure and baseline serum albumin. For patients who survived more than 2 years, left ventricular mass index, eccentric as opposed to concentric left ventricular hypertrophy, left ventricular cavity volume, left ventricular dilatation, fractional shortening and systolic dysfunction were all associated with late mortality. Systolic dysfunction, left ventricular cavity volume and left ventricular mass were all directly correlated

with each other. When these 3 variables were added together to the basic Cox's model, only left ventricular cavity volume retained its statistical significance in the prediction of late mortality.

When cardiac mortality was chosen as end-point the conclusions were virtually identical to those for all-cause mortality: cardiac left ventricular fractional shortening, systolic dysfunction and, in addition, left ventricular cavity volume, were associated with cardiac mortality in all time frames, whereas left ventricular mass index was independently associated with death after 2 years (data not shown).

LV GEOMETRY: THEORETICAL FRAMEWORK AND PROGNOSTIC IMPACT.

(Tables 4 to 6).

LV dilatation is commonly observed in states of LV volume overload whereas pressure overload leads primarily to an increase in left ventricular mass, with normal cavity volume. The Law of Laplace, whereby wall tension is directly proportional to wall radius and inversely proportional to wall thickness, would suggest that an increase in LV wall thickness would be an appropriate physiological response to LV dilatation. Many patients with LV dilatation also have increased LV mass (eccentric LV hypertrophy, 22). Failure to increase LV wall thickness may be pathological because wall tension increases and leads to increased oxygen utilization. This may be revealed on echocardiography by an increased left ventricular cavity volume and a low mass-to-volume ratio. In states of LV pressure overload the resultant increase in wall tension is offset by an increase in left ventricular wall thickness, reflected on echocardiography by hypertrophy with normal cavity volume (concentric hypertrophy 22), and a high mass-to-volume ratio.

Dialysis patients have many risk factors for both LV volume and pressure overload. Furthermore, the clinical importance of LV hypertrophy may be critically effected by LV geometry, as has been demonstrated in essential hypertensive patients (24). Our hypotheses in this study followed directly from the Law of Laplace: we postulated that in concentric hypertrophy the major adverse prognostic impact would be associated with increased LV mass and high mass-to-volume ratios, while in states of LV dilatation, an adverse prognosis would be associated with high cavity volume and low mass-to-volume ratios. Ultimately, we speculated that in-depth consideration of left ventricular geometry would enhance our ability to prognosticate on future adverse events. Patients with systolic dysfunction were excluded from the mortality analyses that follow.

All Patients. Considered as continuous variables, no single echocardiographic abnormalities was independently associated with overall mortality, after adjustment was made for baseline age, diabetes mellitus and ischemic heart disease (Table 4, all subjects). In contrast, both LV mass (adjusted RR 1.010 per g/m^2) and cavity volume (adjusted RR 1.015 per ml/m^2) were associated with mortality after 2 years. These results were virtually identical when echocardiographic valvular disease was added as a covariate; the latter covariate had no independent association with overall or late mortality.

Patients With Normal Cavity Volume. Considered as continuous variables, only LV mass-to-volume ratio (adjusted RR 1.307 per g/ml) was independently associated with mortality in all time frames, although this trend did not quite reach statistical significance (Table 4, subjects with normal cavity volume). Both high LV mass (adjusted RR 1.009 per g/m^2) and high mass-to-volume ratio (adjusted RR 1.664 per g/ml) were associated with mortality after 2 years on dialysis therapy. LV

cavity volume was of no prognostic significance in this group. In models that included all three parameters, only mass-to-volume ratio (adjusted RR 1.304 per g/ml, p = 0.076) predicted overall mortality, while left ventricular mass index (adjusted RR 1.009 per g/m^2, p = 0.045) was the only predictor of death after 2 years. These results were virtually identical when echocardiographic valvular disease was added as a covariate; the latter covariate had no independent association with overall or late mortality.

Patients With LV Dilatation. Considered as continuous variables, no single echocardiographic parameter showed a statistically significant, independent association with overall mortality (Table 4, subjects with LV dilatation). In contrast, both high cavity volume (adjusted RR 1.030 per ml/m^2) and low mass-to-volume ratio (adjusted RR 0.204 per g/ml) were strongly associated with late mortality. In models that included all three parameters, no single echocardiographic parameter predicted mortality in all time frames; only left ventricular cavity volume (adjusted RR 1.031 per ml/m^2, p = 0.001) was associated with mortality after 2 years. These results were virtually identical when echocardiographic valvular disease was added as a covariate; the latter covariate had no independent association with overall or late mortality.

Echocardiographic parameters were assessed as continuous variables in the analyses presented above. Assuming a linear relationship between the level of a given risk factor and subsequent mortality, the potential impact of different variables on late mortality can be conveniently compared by computing the relative risk of a subject at corresponding percentiles for each variable. For example, for patients with normal cavity volume the 25th and 75th percentiles for mass index were 116 and 163 respectively. The computed relative risk in this situation would be

$(1.009)^{163 - 116}$, or 1.524. For mass-to-volume ratio the corresponding figure is $1.664^{2.72 - 1.89}$, or 1.526. This suggests that in patients with normal cavity volume, LV mass index and mass-to-volume ratios show similar abilities to predict late mortality. For subjects with dilated left ventricles at baseline, the corresponding figures was 1.821 for high cavity volume and 2.675 for low mass-to-volume ratio, suggesting that mass-to-volume ratios may be a more sensitive marker of late mortality than cavity volume.

The previous analyses assumed a linear relationship between the level of a given risk factor and subsequent mortality. This assumption was checked by systematically testing different dichotomous cut-off values in patients with normal and elevated LV cavity volume. In patients with normal cavity volume, patients with higher LV mass index had a higher adjusted relative risk of death as cut-off points were increased in 10 g/m^2 increments from 90 through 160 g/m^2. However, increased late mortality was most clearly observed when LV mass index was > 120 g/m^2, equivalent to 125 g/m^2 for males and 112 g/m^2 for females in this cohort (adjusted RR 3.291, p = 0.029). For mass-to-volume ratio, there was a clear increase in late mortality when this ratio exceeded 2.0 g/ml (adjusted RR 2.24, p = 0.041). For patients with cavity volume > 90 ml/m^2 at baseline, late mortality increased stepwise with rising cavity volume and falling mass-to-volume ratio. Cavity volume > 120 ml/m^2 (adjusted RR 4.146, p = 0.01) and mass-to-volume ratio less than 1.8 (adjusted RR 4.27, p = 0.030) were clearly associated with an increased risk of late mortality.

AN ECHOCARDIOGRAPHIC PROGNOSTIC CLASSIFICATION SYSTEM (Table 5).

Patients were subdivided into 4 groups on the basis of their baseline echocardiograms : normal cavity volume, LV mass ≤ 120 g/m^2 (group I,N = 62), normal cavity volume, LV mass > 120 g/m^2

(group II, N = 165), LV dilatation, LV volume 90-120 ml/m^2 (group III, N = 86) and LV dilatation, LV volume > 120 ml/m^2 (group IV, N = 28). Each group was compared separately to group I as a reference category. After adjusting for age, diabetes and ischemic heart disease, the relative risk of death after 2 years was 3.29 ($p < 0.001$) for group II, 2.5 (p not statistically significant) for group III, and 17.14 ($p < 0.001$) for Group IV. Thus patients in groups II and IV clearly had a poorer prognosis than those in group I. Looked at in this way, 193 of 341 patients (57%) with normal systolic function fell into a high-risk echocardiographic classification (II or IV).

We wondered how this LV geometric classification impacted on mortality in more expanded multivariate models, applied to all groups (Table 5), including patients with systolic dysfunction. The baseline factors independently associated with overall mortality in these analyses were age, diabetes mellitus, cardiac failure and echocardiographic systolic dysfunction. The association with mortality was strongest for cardiac failure, followed by age, diabetes mellitus and systolic dysfunction. The baseline factors independently predictive of mortality after 2 years were age, diabetes mellitus, systolic dysfunction and LV geometry, based on LV mass and cavity volume. As judged by its associated χ^2 value, LV geometry was the strongest predictor of later mortality, followed by age, diabetes mellitus and systolic dysfunction. In otherwise identical models in which both left ventricular hypertrophy (no/yes) and left ventricular dilatation (no/yes) were used instead of this classification system, only left ventricular dilatation was independently associated with late mortality (adjusted RR 1.659, $p = 0.048$), with a c^2 value = 3.904. Similarly, when LV mass index and cavity volume were added as continuous variables, only cavity volume was independently associated with late mortality (RR 1.011, $p = 0.010$), with an associated χ^2 value

of 6.231. In a similar model in which risk was stratified as I - No hypertrophy or dilatation, II - hypertrophy, normal cavity volume, III - LV dilatation, χ^2 value was 4.539 (RR 1.302 per stratum, $p = 0.033$). The proposed classification system, with a χ^2 value of 15.972, was clearly superior in its ability to predict late mortality than considerations of mass and volume alone.

It has been shown in essential hypertensive patients that prognosis can be stratified as : I - LV mass index < 125 g/m^2, relative wall thickness < 0.45, II - LV mass index < 125 g/m^2, relative wall thickness > 0.45, III - LV mass index > 125 g/m^2, relative wall thickness < 0.45 and IV - LV mass index > 125 g/m^2 and relative wall thickness > 0.457 (24). We compared the ability of the 2 classification systems to independently predict different events in patients free of symptomatic heart disease at baseline, with fractional shortening > 25% on initial echocardiography (Table 6). According to the standard classification system (25), the 246 subjects were distributed as follows : Group I - 23.6%, Group II - 13.4%, Group III - 44.4% and Group IV - 38.6%. Using the system proposed in this study, the patients were distributed as follows : Group I - 23.5%, Group II - 23.9%, Group III - 44.8%, Group IV - 7.8% There were 52 deaths (31 after 2 years, 26 cardiac in nature) in this subgroup. In addition, there were 23 de novo episodes of ischemic heart disease (myocardial infarction or angina pectoris) and 55 de novo episodes of cardiac failure. The classification system proposed here was independently associated with each event. The geometric classification proposed by Koren et al.(24) showed a statistically significant association with cardiac death and an association bordering on statistical significance with de novo ischemic events. In patients with symptomatic cardiac disease at baseline neither classification system was independently associated with any of the outcomes studied (data not shown).

ASSOCIATIONS OF ECHOCARDIOGRAPHIC ABNORMALITIES PRESENT AT BASELINE (Table 7).

Compared to patients with normal cavity volume and LV mass less than 120 g/m^2, patients with mass > 120 g/m^2 and normal cavity volume were more likely ($p < 0.05$) to be older, diabetic, have a history of chronic hypertension and anemia at first dialysis; male gender ($p = 0.062$) and ischemic heart disease ($p = 0.071$) were of borderline significance in this analysis.

Using patients with normal mass and cavity volume as reference category, patients with LV dilatation were more likely ($p < 0.05$) to be older, male, to have low initial hemoglobin and blood urea levels, and to have higher inorganic phosphate levels; low serum albumin ($p = 0.062$) levels were of borderline statistical significance. The independent associations of more severe degrees of LV dilatation (cavity volume > 120 ml/m^2) were similar; ischemic heart disease (OR 6.7, $p = 0.038$) and wide pulse pressure (OR 1.48, $p = 0.076$) were also associated with this abnormality. Low serum albumin levels were unassociated with more severe LV dilatation.

Using an identical analytic strategy, systolic dysfunction on baseline echocardiography was associated with older age, female gender, coronary artery disease and low serum albumin levels.

ECHOCARDIOGRAPHIC ABNORMALITIES WHILE ON DIALYSIS THERAPY

(Tables 8 to 12).

Of the 432 patients who entered into the study, 298 patients remained on dialysis at one year, the remainder having died or received a renal transplant. A total of 275 patients had a second echocardiogram while on dialysis therapy, a median of 13 months following the baseline study. This patient subset was very similar to the parent study population at baseline, from a clinical and echocardiographic perspective (Table 8). The following potential predictors of echocardiographic abnormality on the second echocardiogram were assessed: age, gender, diabetes mellitus, ischemic heart disease prior to second echocardiogram, as well as the mean hemoglobin, blood pressure albumin and calcium levels, obtained at monthly intervals between the first and second echocardiogram.

Echocardiographic Outcome (Table 9). A total of 245 patients had adequate data to enable a categorical diagnosis to be made on baseline and follow-up echocardiography. It can be seen that most patients had abnormal LV structure both at baseline and on follow-up, although there was quite a high degree of interchange between abnormal categories.

Associations of Echocardiographic Abnormalities (Tables 10 to 12). In multiple logistic regression models, in which patients with normal left ventricles were used as reference category (Table 10), the presence of concentric hypertrophy was weakly associated with older age and female gender, LV dilatation with ischemic heart disease, anemia and hypertension, while systolic dysfunction was associated with previous ischemic heart disease. In similar multiple linear regression models (Table 10), the degree of concentric LV hypertrophy was associated with older

age, anemia and hypertension, the degree of LV dilatation with ischemic heart disease, anemia, hypertension and hypoalbuminemia, while the degree of systolic dysfunction was associated with ischemic heart disease and anemia.

ECHOCARDIOGRAPHIC ABNORMALITIES BEFORE AND AFTER RENAL TRANSPLANTATION

(Tables 13 to 15).

102 subjects had an echocardiogram within 1 year prior to renal transplantation, as well as another study at an interval greater than 1 year following successful renal transplantation. Where subjects had more than on one echocardiogram following transplantation, the last study was chosen for the current study. Selected pre-transplantation characteristics are shown in Table 13.

Renal transplantation was associated with dramatic echocardiographic changes (Tables 14 and 15). Decreases in LV mass index and cavity volume and increases in fractional shortening were seen. The most dramatic observation was the normalization of fractional shortening in all 12 subjects with systolic dysfunction prior to transplantation.

Although all echocardiographic parameters tended to improve, on average, most (76%) subjects had abnormal echocardiograms at final follow-up. In multivariate models, the only potentially reversible factor was the strong relationship between mean arterial blood pressure following transplantation and the failure of left ventricular hypertrophy to regress (data not shown).

ISCHEMIC HEART DISEASE

(Tables 17 and 18).

BURDEN OF DISEASE.

22% of patients had a history of clinically apparent ischemic heart disease at inception of dialysis therapy. 40 of 337 (11.9%) patients free of ischemic heart disease at baseline were subsequently admitted for ischemic heart disease while on dialysis therapy.

PROGNOSIS.

When adjustment was made for age and the presence or absence of diabetes mellitus, patients with ischemic heart at baseline were more likely to have systolic dysfunction on repeat (OR 4.36, p = 0.004) echocardiography, more likely to be admitted for recurrent cardiac failure (RR 2.03, p = 0.003) while on dialysis therapy and more likely to die early (RR 1.48, p = 0.026). Ischemic heart disease at baseline was unassociated with concentric LV hypertrophy on follow-up echocardiography and de novo cardiac failure). Most of the impact on mortality was via the occurrence of cardiac failure: in a similar prognostic model that also included cardiac failure as a covariate, ischemic heart disease was no longer independently associated with mortality.

ASSOCIATIONS (Tables 17 and 18).

In stepwise logistic regression models (Table 17), patients starting ESRD therapy with ischemic heart disease were more likely to older, diabetic, less anemic and to have systolic dysfunction on initial echocardiogram.

Using the Cox's model (Table 18), applied to subjects without ischemic heart disease at baseline, the independent predictors of new ischemic heart disease were : at baseline - older age, diabetes, smoking and in particular, the presence of concentric LV hypertrophy, LV dilatation or systolic dysfunction on baseline echocardiography; while on dialysis therapy - hypertension and hypoalbuminemia.

CARDIAC FAILURE (Tables 19 to 21).

BURDEN OF DISEASE

31% of all patients had a history of cardiac failure at the time of inception of dialysis therapy. Of these 133 patients 75 (56.4%) went on to have at least one clinical recurrence while on dialysis therapy. Of the 299 patients free of cardiac failure at baseline, 76 (25.4%) had an episode of new-onset cardiac failure while on dialysis therapy.

PROGNOSIS

Cardiac failure at baseline carried a very poor prognosis. Patients with cardiac failure died 2.6 times more quickly than those without cardiac failure ($p < 0.0001$). After adjustment for baseline age, diabetes and ischemic heart disease using the Cox model, the excess mortality remained very high (RR 1.93, $p < 0.001$).

ASSOCIATIONS (Tables 19 and 20).

Using logistic regression analysis (Table 19), the independent discriminating characteristics of patients with baseline cardiac failure were older age, diabetes mellitus, ischemic heart disease and the presence of LV dilatation or systolic dysfunction on baseline echocardiography.

Using the Cox model (Table 20), the independent predictors of de novo cardiac failure among those free from the condition at baseline were: at baseline - older age and the presence of concentric LV hypertrophy, LV dilatation or systolic dysfunction; while on dialysis therapy - anemia, hypoalbuminemia and hypertension.

The independent predictors of recurrent cardiac failure (Table 21) were ischemic heart disease at baseline, as well as anemia and hypoalbuminemia ($p = 0.06$) while on dialysis therapy.

THE IMPACT OF ANEMIA (Tables 22 to 24).

LEVELS OBSERVED AND ASSOCIATIONS (Table 22).

The mean hemoglobin level while on dialysis was 89 ± 15 g/l, higher in peritoneal dialysis (96 ± 15 g/l) than hemodialysis patients (84 ± 14 g/l, $p < 0.0001$). The mean transfusion rate during the study was 5.2 ± 7.5 transfusions per year. Erythropoietin was first used in this patients sample in 1989. 26% of patients received erythropoietin at some stage during the study.

We divided patients into 4 time intervals according to year of study entry: 1982 - 1984 (20.3%), 1985 - 1986 (17.3%), 1987 - 1988 (27.5%) and 1989 - 1991 (34.9%). Mean hemoglobin levels - 84 ± 16, 88 ± 19, 89 ± 16 and 91 ± 12 (p for trend 0.003) - rose progressively with year of study entry, as did the proportion of patients receiving erythropoietin - 10.2%, 23.0%, 22.0% and 41.2% (p for trend 0.04). The mean hemoglobin levels observed were not a function of time spent on dialysis therapy.

We divided patients according to tertile of mean hemoglobin level (Table 22). Patients with adverse prognostic features at baseline - diabetes, ischemic heart disease and cardiac failure- were maintained at higher hemoglobin levels.

PROGNOSTIC IMPACT OF ANEMIA (Tables 23 and 24).

After adjustment for baseline age, diabetes, ischemic heart disease as well blood pressure and serum albumin levels measured serially, anemia was independently associated with the following outcomes : LV dilatation on follow-up echocardiography, de novo cardiac failure,

recurrent cardiac failure and death. It was also independently associated with systolic dysfunction on follow-up echocardiography in hemodialysis patients.

THE IMPACT OF HYPERTENSION (Tables 25 to 28).

LEVELS OBSERVED AND ASSOCIATIONS (Table 25).

The average mean arterial blood pressure level while on dialysis was 101 ± 11 mm Hg, similar in peritoneal dialysis (101 ± 11 mm Hg) and hemodialysis patients 102 ± 11 mm Hg, p = 0.35). On average patients received 1.2 ± 2.1 antihypertensive medications while on dialysis therapy (10th percentile - zero, median - 0.9, 90th percentile -3.0). Calcium channel blockers (3,147 patient months) were the most frequently used agent, followed by beta blockers (2,707 patient months), ACE-inhibitors (1,546 patient months), vasodilators (1,457 patient months) and centrally acting agents (520 patient months).

We divided patients into 4 time intervals according to year of study entry: 1982 - 1984 (20.3%), 1985 - 1986 (17.3%), 1987 - 1988 (27.5%) and 1989 - 1991 (34.9%). Mean arterial blood pressure levels - 103 ± 9, 101 ± 10, 101 ± 12 and 101 ± 11 (p for trend 0.42) were similar in the four time periods. The mean arterial blood pressure levels observed were not a function of time spent on dialysis therapy.

We divided patients according to tertile of mean arterial blood pressure level (Table 25). Patients with adverse prognostic features at baseline - older age, ischemic heart disease, cardiac failure and hypoalbuminemia- exhibited lower mean arterial blood pressure levels.

PROGNOSTIC IMPACT OF MEAN ARTERIAL BLOOD PRESSURE LEVELS (Tables 26 to 28).

After adjustment for baseline age, diabetes, ischemic heart disease as well as hemoglobin and serum albumin levels measured serially, higher mean arterial blood pressure levels were

independently associated with the following outcomes : concentric LV hypertrophy, LV dilatation, increased mass index and cavity volume on follow-up echocardiography, de novo ischemic heart disease, and de novo cardiac failure.

Paradoxically, low, not high, average mean arterial blood pressure levels were associated with mortality. It is likely that this observation reflected the occurrence of cardiac failure prior to death: 65% of all deaths in dialysis patients were preceded by an episode of cardiac failure; mean arterial blood pressure levels fell from 103 ± 10 mm Hg before to 98 ± 13 mm Hg ($p < 0.0001$) following the occurrence of cardiac failure. Among patients admitted for cardiac failure while on dialysis therapy, low blood pressure was the major independent predictor of death (adjusted RR 1.43 per 10 mm Hg fall in mean arterial blood pressure, $p < 0.001$).

THE IMPACT OF HYPOALBUMINEMIA (Tables 29 to 31)

LEVELS OBSERVED AND ASSOCIATIONS (Table 29)

The mean serum albumin level while on dialysis therapy was 37 ± 15 g/l, higher in hemodialysis (39 ± 5 g/l) than peritoneal dialysis patients (35 ± 5 g/l, $p < 0.0001$). There were no differences in mean serum albumin level according to year of entry into study or according to time spent on dialysis therapy.

One third of patients had mean serum albumin levels less than or equal to 36 g/l, one third between 36 and 39 g/l and one third had levels greater 39 g/l. The characteristics of patients in the different tertiles are shown in Table 29. Patients with lower albumin levels while on dialysis therapy had adverse prognostic features at baseline - older age ($p = 0.0002$), diabetes ($p = 0.0005$) and ischemic heart disease ($p = 0.02$).

PROGNOSTIC IMPACT OF HYPOALBUMINEMIA (Tables 30 and 31).

After adjustment for age, diabetes and ischemic heart disease at baseline, as well as mean arterial blood pressure levels and hemoglobin levels while on dialysis therapy, hypoalbuminemia was independently associated with each of the following outcomes: LV dilatation on follow-up echocardiography, de novo cardiac failure, recurrent cardiac failure, de novo ischemic heart disease, cardiac mortality, non-cardiac mortality and overall mortality.

ABNORMALITIES OF CALCIUM-PHOSPHATE HOMEOSTASIS (Tables 29 to 31).

LEVELS OBSERVED.

22.6% of patients had mean calcium levels below 2.2 mmol/l (18.8% in HD vs. 29.9% in PD, p = 0.008). After adjustment for mean serum albumin levels, mean calcium levels were below 2.2 mmol/l in 9.0% (11.7% in HD vs. 5.5% in PD, p = 0.03).

There was no impact of study entry period on mean calcium, phosphorus or alkaline phosphatase levels. The percentages with hypocalcemia were 20% for patients enrolled up to 1984 (N=84), 23% for 1985 to 1986 (N=74), 26% for 1987 to 1988 (N=118) and 22% for patients enrolled from 1989 on (N=148) (p=0.79). For high mean inorganic phosphorus levels the corresponding figures were 43%, 45%, 49% and 43% (p=0.72). For high alkaline phosphatase levels the figures were 30%, 24%, 25% and 22% (p=0.59). There was a clear association between time on dialysis and calcium levels: in patients with mean serum calcium levels less than 2.2 mmol/l, 40% were on dialysis ≤1 year, 32% were on dialysis 1 to ≤2 years, 14% were on dialysis 2 to 3 years, 8% were on dialysis 3 to ≤ 4 and 4% were on dialysis > 4 years (p = 0.0001). 43.9% had inorganic phosphorus levels greater than 1.9 mmol/l (51.6% in HD vs. 34.1% in PD, p < 0.001). 24% had alkaline phosphatase levels greater than 120 U/l (23.0% in HD vs. 26.9% in PD, p = 0.36). There was no relationship between mean inorganic phosphorus and alkaline phosphatase levels and time on dialysis therapy.

PROGNOSTIC IMPACT OF CALCIUM, PHOSPHATE AND ALKALINE PHOSPHATASE LEVELS (Tables 32 and 33)

On univariate analysis, applied to the entire cohort, patients with mean serum calcium levels below 2.2 mmol/l had a relative risk of death 2.90 ($p < 0.001$) times that of patients with values above 2.2 mmol/l. Alkaline phosphatase levels above 120 U/l (RR 1.63, $p = 0.004$) were also associated with early mortality, while inorganic phosphorus levels had no impact. The impact of both low mean calcium levels and high alkaline phosphatase levels persisted when adjustment was made for multiple possible confounding factors, including mean serum albumin level. The conclusions were identical when albumin-adjusted calcium was instead of actual calcium levels in similar multivariate models. Hypocalcemia retained its independent prognostic significance in patients treated predominantly with hemodialysis and in patients treated with peritoneal dialysis. Adding mean interdialytic weight gain as a covariate had no impact on the results obtained in hemodialysis patients. High phosphorus levels were of prognostic significance in neither group. High alkaline phosphatase levels were of borderline statistical significance in hemodialysis patients only (adjusted RR 1.78, $p = 0.063$).

In otherwise-identical analyses in which mean calcium, phosphorus, alkaline phosphatase, albumin, hemoglobin and mean arterial blood pressure levels were included as time-dependent covariates, hypocalcemia was independently associated with mortality in the overall group (adjusted RR 1.28, $p = 0.004$), in hemodialysis patients (adjusted RR 1.33, $p = 0.005$) and in peritoneal dialysis patients (adjusted RR 1.36, $p = 0.028$). In these analyses, high alkaline phosphatase levels were associated with mortality in the combined group of hemodialysis and peritoneal dialysis patients (adjusted RR 1.13, $p = 0.019$), and in hemodialysis patients alone

(adjusted RR 1.18, p = 0.040), but were not associated with mortality in peritoneal dialysis patients alone. High phosphorus levels had no impact on mortality in these models.

Using Cox's regression analysis, calcium levels below 2.2 mmol/l were associated with each of the following outcomes: de novo ischemic heart disease (adjusted RR 5.23, $p < 10^{-4}$), recurrent ischemic heart disease (adjusted RR 2.46, p = 0.006), de novo cardiac failure (adjusted RR 2.64, $p < 10^{-4}$) and recurrent cardiac failure (adjusted RR 3.30, $p < 10^{-4}$). High phosphorus levels and high alkaline phosphatase levels had no independent association with any of these outcomes.

In otherwise-identical analyses in which mean calcium, phosphorus, alkaline phosphatase, albumin, hemoglobin and mean arterial blood pressure levels were included as time-dependent covariates, hypocalcemia was independently associated with de novo ischemic heart disease (adjusted RR 1.49, p = 0.025), de novo congestive heart failure (adjusted RR 1.34, p = 0.010) and recurrent congestive heart failure (adjusted RR 1.31, p = 0.038). High mean inorganic phosphorus and alkaline phosphatase levels had no association with any of these outcomes.

DISCUSSION

LEFT VENTRICULAR ABNORMALITIES IN ESRD

DIAGNOSIS. Echocardiography has been the most widely-used cardiac non-invasive cardiac imaging test in the general population, because of accuracy, simplicity, lack of radiation and relatively low cost (25). In the general population, left ventricular mass, measured by echocardiography, is a stronger predictor of cardiovascular morbidity than blood pressure or other classical risk factors, with the exception of age; this has been shown in patients with hypertension, in patients with or without angiographically determined coronary artery disease or heart failure, as well as in the general population (24,26,27,28,29,30,31,32).

In dialysis patients, M-mode echocardiography has been shown to have high reliability and validity (33). Ventricular diameters, however, increase with fluid reaccumulation following dialysis, as one would expect; this effects the calculated left ventricular mass index (33). A practical consequence of this observation is that the time period when the study is performed and fluid gains need to be standardized in echocardiographic studies on dialysis patients. In our current studies, echocardiograms are carried out the day after a hemodialysis session, with the patient at dry weight and a maximum allowable weight gain of 1 kg following the dialysis session. The assessment of dry weight, frequently defined as the weight at the termination of dialysis below which the patient is likely to become hypotensive (34) is problematic in dialysis patients; none of the echocardiographic studies on ESRD patients have employed methods (such actual central venous pressure measurement or non-invasive techniques such as bioimpedance monitoring or inferior vena caval echocardiography (35,36,37)) that accurately measure blood volume. In practical terms,

the impact of hypervolemia on calculated mass index is small, of the order of 9 g/m^2 for each litre of fluid accumulated (33); this observation partially reflects the fact that both the numerator (calculated mass) and the denominator (calculated body surface area) used to calculate mass index (mass/surface area) tend to increase in parallel with fluid accumulation.

BURDEN OF DISEASE. Abnormalities of cardiac structure or function are very much the rule in ESRD patients. In our study we defined systolic dysfunction as echocardiographic fractional shortening ≤ 25%, left ventricular dilatation as cavity volume > 90 ml/m^2 (20), and left ventricular hypertrophy as mass index > 131 g/m^2 in males and > 100 g/m^2 in females (21). On baseline echocardiography only 14.8% of patients had normal left ventricles; 14.8% had systolic dysfunction; 39.0% had hypertrophy with normal cavity volume ("concentric hypertrophy" (22); 27% had left ventricular dilatation; among patients with left ventricular dilatation 88% also had left ventricular hypertrophy ("eccentric hypertrophy"(22)). Several cross-sectional studies have shown a high prevalence of left ventricular abnormalities in ESRD patients (11,12,13,38,39,40,41,42,43).

RISK FACTORS. Left ventricular abnormalities can occur in response to both LV volume overload and pressure overload. LV volume overload leads to proliferation of sarcomeres in series, chamber dilatation and augmented cardiac output (44). In this situation, the trade off for increased LV volume is an increased wall tension (and oxygen consumption), by the Law of Laplace (Tension = Pressure x Radius/2Wall Thickness). In situations of pressure overload, sarcomeres proliferate in parallel with existing sarcomeres, leading to wall thickening, leading to increased cavity pressure. This increased cavity pressure allows cardiac output to be maintained. The trade off in this situation is increased wall stiffness (44). ESRD are exposed to many factors leading to

volume overload, such as anemia, arteriovenous connections and chronic fluid overload. They are also frequently exposed to factors which lead to pressure overload, such as hypertension and occasionally aortic stenosis.

In this study, the independent associations of systolic dysfunction on baseline echocardiography were older age, female gender, coronary artery disease and hypoalbuminemia. On repeat echocardiography, 13 months later, the independent associations were ischemic heart disease and anemia. LV dilatation at baseline (with normal systolic function) was associated with older age, male gender, anemia low blood urea levels and high inorganic phosphorus levels. LV dilatation on follow-up echocardiography was associated with ischemic heart disease, hypertension, anemia and hypoalbuminemia. Concentric LV hypertrophy was associated with older age, diabetes mellitus, chronic hypertension and anemia at baseline. On follow-up echocardiography, concentric LV hypertrophy was independently associated with older age, hypertension, female gender and anemia.

Anemia. It is very likely that anemia is a major player in the cardiac abnormalities seen in ESRD. Several epidemiological surveys, including the current study (15) have suggested that anemia leads to left ventricular dilatation and/or left ventricular dilatation (11,14,41). There have been several studies that have examined the effect of partial correction of renal anemia with recombinant human erythropoietin (rHuEpo) on echocardiographic abnormalities. Most of these studies have included small numbers of patients, and have compared mass before and after rHuEpo therapy, in the absence of an untreated control group. In spite of these limitations, the studies have shown that treating anemia leads to a decrease in hypoxia- induced vasodilatation, an increased peripheral

resistance, reduced cardiac output, and partial reversal of left ventricular dilatation and hypertrophy (45,46,47,38,49,50,51,52,53,54,55,56,57). None of the published literature to date has adequate patient numbers and follow-up to test the hypothesis that improvement of echocardiographic parameters will reduce cardiac morbidity or mortality. To date, there has been no study to assess the risks and benefits of complete normalization of hematocrit in ESRD patients. The studies completed to date have shown that partial correction of anemia leads to only partial reversal of echocardiographic abnormalities. Whether complete correction of anemia leads to further regression of these abnormalities, and the cost of such an approach in terms of finances, hypertension (58,59), seizures (58,59), and access loss (58,60,61,62,63,64) is currently unknown. One study showed that hypertension abrogated the impact of anemia correction on left ventricular hypertrophy (65).

Age and Gender. Several studies, including the current study (15), have implicated age as a risk factor for echocardiographic abnormalities in ESRD (39,66,67). There are no data from other investigators, to date, to suggest that gender influences the development of cardiomyopathy in ESRD. In the normal population, the effects of ageing include an increase in myocyte size, increased rate of degenerative change, fibrosis, loss of myoctyes, amyloidosis and calcification (68,69). The specific effects of age on the uremic heart are unknown.

Hypertension. Several studies have shown that left ventricular hypertrophy is commoner in ESRD patients with hypertension (14,15,67). In general, the correlation between left ventricular hypertrophy and blood pressure has been relatively weak. For example, in the study of Greaves and co-workers, variability in systolic blood pressure could explain 10.3% of the variability in left

ventricular posterior wall thickness, while variability in diastolic blood pressure could explain 6.7% of the variability in left ventricular wall thickness (14). The current study clearly shows that hypertension is associated with LV ventricular abnormalities in end-stage renal disease patients.

Diabetes Mellitus. There is evidence for a specific diabetic cardiomyopathy in diabetic patients without ESRD. This is usually manifested by left ventricular diastolic dysfunction, in the absence of large vessel disease, and may be associated with microvascular coronary disease (70,71,72,73,74,75,76,77,78). Left ventricular hypertrophy is found more frequently in hypertensive diabetics than hypertensive non-diabetics (76,77). In a post-mortem study, hypertensive-diabetic hearts were heavier and had more fibrosis than diabetic-non-hypertensive and hypertensive-non-diabetic hearts (78). We found an association between concentric left ventricular hypertrophy and diabetes, while Greaves and co-workers found an association with the presence of diabetic nephropathy and left ventricular hypertrophy(14).

Ischemic Heart Disease. It is well known that poor systolic function is a major complication and is the principal determinant of outcome following myocardial infarction. In our patient cohort (15) as well as in the cross-sectional study of Greaves and co-workers (14), patients with a history of myocardial infarction were much more likely to have echocardiographic systolic dysfunction. Antecedent ischemic heart disease was independently associated with

Uremia and Malnutrition. There is direct evidence from animal studies to suggest that the uremic environment is detrimental to the myocardium. Induction of uremia in Sprague-Dawley rats leads to increase deposition of interstitial ground substance, followed by collagen deposition, as well as a reduction in capillary surface density. These effects appear to be independent of blood pressure

(79,80). Uremic serum is a direct myocardial depressant (81,82). The specific factors responsible for this effect have not been identified. Some authors believe that the depressant factors are water soluble and filterable, with a molecular weight between 10,000 and 30,000 daltons (83).

There is indirect evidence that uremia is cardiotoxic in human ESRD. In the National Co-operative Dialysis Study there were more clinically important cardiac events in patients who were randomized to receive less intensive dialysis (84). In chronic renal failure left ventricular echocardiographic abnormalities are commoner in dialysis patients than in predialysis patients (14). Churchill and co-workers found that more intensive dialysis ameliorated cardiac abnormalities in a randomized crossover trial (85).

Renal transplantation is a convenient, though extreme, natural experiment that allows one to assess the impact of uremia. There have been a number of case reports documenting dramatic improvements in cardiac function in patients with severe dilated cardiomyopathy (86,87). In our study, a total of 102 patients had an echocardiogram within 1 year prior to transplantation as well as a year or more following transplantation. In this population, which was largely free of coronary artery disease the following changes were observed: left ventricular mass index fell from 175 g/m^2 to 148 g/m^2 ($p < 0.0001$); left ventricular cavity volume fell from 86 ml/m^2 to 77 ml/m^2 ($p = 0.003$); left ventricular fractional shortening rose from 35% to 37% ($p = 0.036$). Multivariate analysis suggested that patients with high left ventricular mass index prior to transplantation and those with better blood pressure control following transplantation were most likely to have a fall in left ventricular mass index. The most dramatic changes were seen in the 12 patients with systolic dysfunction (fractional shortening less than 25%) immediately prior to transplantation. Systolic

dysfunction reversed in all these patients, with fractional shortening increasing from a mean of 22% to 34% ($p < 0.0001$). These data suggest that renal transplantation can have a profound impact on dilated cardiomyopathy, at least in patients without coronary artery disease. Indirectly, therefore, these data suggest a role for uremia in the pathogenesis of uremic cardiomyopathy.

Hyperparathyroidism is a major component of ESRD and the uremic syndrome. The current study was unable to directly test the hypothesis that hyperparathyroidism is a major etiological factor in the development of uremic cardiomyopathy, as other authors have suggested (88).

It is not clear how malnutrition might lead to cardiomyopathy in dialysis patients. Malnutrition can have pronounced effects on cardiac structure and function in non-uremic individuals. For example, "brown atrophy" of the heart was seen in autopsy studies of individuals who died of starvation in the Warsaw ghetto in World War II (89). Low cardiac output, cardiac fibrosis, fatty infiltration and myofibrillar atrophy leading to frank cardiac failure have been seen in individuals with kwashiorkor (90-92). Both cardiac atrophy and cardiac hypertrophy (93) are seen in marasmus. The diets of many ESRD patients show similarities to those that result in kwashiorkor (inadequate protein intake, with adequate caloric intake) and marasmus (inadequate intake of both protein and calories). In this study serial albumin levels were inversely associated with the extent of LV dilatation in hemodialysis patients and the presence of concentric LV hypertrophy in peritoneal dialysis patients on follow-up echocardiography . The vast majority of ESRD patients already have left ventricular abnormalities at the time they start dialysis therapy (15). Very large patient numbers with long-term follow-up, would be needed to show that low albumin levels predate the development of LV abnormalities in patients free of LV abnormalities at baseline.

PROGNOSIS. There has been very little prospective research on the prognostic impact of left ventricular abnormalities in ESRD patients, although Silberberg et al. (94) showed a strong, independent relationship between left ventricular hypertrophy and subsequent mortality on dialysis therapy. In this study systolic dysfunction on baseline echocardiography was independently associated with the subsequent development of de novo ischemic heart disease, de novo cardiac failure and death. The prognostic impact of left ventricular index and cavity volume was critically dependent on the underlying state of the left ventricle: mass index was of prognostic impact only in those without left ventricular dilatation; mass index was of no prognostic impact in the latter patients - in these patients left ventricular cavity volume was the critical prognostic variable. Looked at in this way, it was clear that subclinical abnormalities of the left ventricle were harbingers of ischemic heart disease, cardiac failure and death, even in the absence of systolic dysfunction.

ISCHEMIC HEART DISEASE IN ESRD

DIAGNOSIS. In mechanical terms, myocardial ischemia could be the result of disorders at several levels : large and medium size arterial disease (including luminal narrowing and/or inability to dilate when required); small vessel disease; an inappropriately small density of vascular channels relative to myocardial mass; Ischemia can also occur in the absence mechanical problems, if blood is delivered too slowly, has inadequate nutrients for energy production, or the myocardial machinery for energy production is inadequate even though substrate delivery is adequate. Adequate sensory mechanisms are needed for myocardial ischemia to be perceived as pain.

Ischemic heart disease is not a homogeneous entity, especially in ESRD patients. At least 4 factors make the delineation of the natural history of ischemic heart disease difficult:

1. Many ESRD patients have non-atherosclerotic ischemic heart disease, with typical symptoms of angina pectoris but patent coronary arteries (95,96,97). For example Rostand and co-workers found that about 25% of patients with typical anginal symptoms had either no disease or trivial disease on coronary arteriography. These patients were more likely to be African-American, anemic and to have severe left ventricular hypertrophy (96,97).

2. It is also known that many ESRD patients with advanced anatomical coronary artery stenosis are asymptomatic, without typical electrocardiographic changes. The reported frequency of silent ischemia in ESRD patients (diagnosed by continuous ST segment monitoring), seen most often during, or just after, dialysis, ranges from 15 to 37% (98,99,100,101,102).

3. The non-invasive tests used to diagnose coronary artery disease in the general population are problematic in dialysis patients. Creatinine phosphokinase, including its MB fraction, and lactate dehydrogenase levels are elevated in renal failure, which makes the diagnosis of acute myocardial infarction more difficult (103,104). The limited data concerning the use of stress testing in ESRD patients have generally been disappointing. The physical condition of many ESRD patients, the frequent use of drugs effecting heart rate, and the frequent occurrence of non-specific ST segment changes limit the usefulness of standard exercise stress testing in ESRD patients. Rostand and co-workers, for example, reported that 80% of ESRD patients failed to reach a target heart rate of 85% of predicted maximum (97). The use of dipyridamole and dobutamine as stressing agents, and the use of other diagnostic techniques, such as echocardiography to detect regional wall motion abnormalities, or thallium scintigraphy have shown mixed results in ESRD patients (104,105,106,107,108,109) and cannot yet be fully endorsed. Larger studies are needed, where selection bias is minimised, and patients are stratified by diabetic status and symptoms of ischemic heart disease.

RISK FACTORS FOR ISCHEMIC HEART DISEASE IN ESRD. 20% of the patient cohort we studies were admitted with an episode of ischemic heart disease, (angina pectoris, coronary artery revascularization or myocardial infarction) while on dialysis therapy. Half of these episodes were de novo episodes, in patients who had not had ischemic heart disease at the inception of dialysis therapy. The independent associations of baseline ischemic heart disease included older age, diabetes, echocardiographic systolic function and higher initial hemoglobin levels. The last observation most likely reflects physician practice to maintain higher hemoglobin levels in those

with symptomatic ischemic heart disease. The independent risk factors for de novo ischemic heart disease were older age, diabetes, the presence of concentric hypertrophy, LV dilatation or systolic dysfunction on initial echocardiogram, as well as high blood pressure, low serum albumin and low calcium levels averaged over the total time on dialysis therapy. The study also illustrates that many of the risk factors (age, diabetes, hypertension and echocardiographic abnormalities) for ischemic heart disease are common to the general and ESRD populations. It also suggests that factors related to the uremic state, such as hypocalcemia and hypoalbuminemia, may be important in the pathogenesis of ischemic heart disease in ESRD.

Age. Advancing age is associated with an increased risk of coronary artery disease in the general public (110,111). The vascular changes associated normally with advancing age include atheroma deposition, increased intimal heterogeneity and subendothelial hardening (68,69). Age has been associated with arteriographic coronary artery disease in the general ESRD population as a whole (15,112) and in asymptomatic diabetic patients (113).

Hypertension. Hypertension is a well established risk factor for coronary artery disease in the general population (114). Hypertension is very prevalent in ESRD populations (115,116,117) hemodynamic studies have shown that the sustained hypertension of ESRD is due to elevations of peripheral resistance (118). Suggested factors leading to inappropriately high peripheral resistance in ESRD include inability to excrete salt and water (119,120), activation of the renin angiotensin system, increased production of the vasoconstrictor endothelin (121), and activation of the sympathetic nervous system (122,123). The relationship between hypertension and ischemic heart disease in end-stage renal disease has long been suspected, though the amount of supporting data is

sparse. In a retrospective study of 320 patients high diastolic blood pressure levels at first dialysis were independently associated with subsequent ischemic heart disease while on renal replacement therapy (124).

Diabetes Mellitus. Diabetes mellitus is an independent risk factor for the development of coronary artery disease in the non-ESRD population, although these also patients have an excess burden of other risk factors, such as hypertension and dyslipoproteinemia (125,126). Our study defined ischemic heart disease on the basis of clinical symptoms. Such an approach almost certainly underestimates the degree of coronary artery disease in diabetic patients, in whom there is a very marked prevalence of ischemic heart disease. It has been estimated that about a third of asymptomatic diabetic patients on renal replacement therapy have 50% or more stenosis of at least one coronary artery (127,128,129,113). The prevalence of ischemic heart disease rises markedly with age. For example Manske and co-workers found that 88% of asymptomatic diabetics undergoing pre-transplant screening coronary angiography had significant arterial stenosis. In patients under 45 years of age, only patients with each of the following - diabetes less than 5 years, normal ST segments on arteriography and a smoking history less than 5 pack years- could be predicted not to have angiographic coronary artery disease with any degree of confidence (sensitivity 97% and negative predictive accuracy 96%) (113). These latter studies are likely subject to selection bias; it is highly likely that the true prevalence of asymptomatic coronary artery disease is much higher when the diabetic-ESRD population is considered in its entirety.

Smoking. Smoking is a powerful risk factor for coronary artery disease in the general population, approximately doubling the risk of cardiovascular disease in the Framingham Study (130). In the

USRDS Special Study of Case Mix Severity (N=3,399) smoking was associated with an excess mortality of 26%, even after extensive covariate adjustment, among incident hemodialysis patients (131). The independent effect of smoking appears to be especially marked in diabetics with ESRD, in whom it more than doubles mortality rates (132).

Dyslipidemia. Increased low density lipoprotein (LDL), decreased high density lipoprotein (HDL), a high ratio of total cholesterol to HDL cholesterol and high lipoprotein(a) levels are clearly associated with coronary artery disease in the general population (132,133,134,135). It is less clear whether high triglyceride levels are associated with coronary artery disease. Recent evidence suggests that hypertriglyceridemia may be a powerful risk factor when it coincides with a high LDL to HDL cholesterol ratio (136).

ESRD is associated with quantitative lipid disturbances. High triglyceride levels and decreased HDL levels are typical of both hemodialysis and peritoneal dialysis, while peritoneal dialysis patients may also have high LDL levels (137,138). Several studies have shown that ESRD patients tend to have higher lipoprotein Lp(a) levels than in the general population (139,140,141,142,143,144,145). Qualitative abnormalities are also common in ESRD. Remnant particles of chylomicrons and very low density lipoproteins (VLDL) are very atherogenic, as are oxidized LDL. Some of the defects seen in ESRD patients include (a) a profound defect in postprandial lipid disposal, which exposes the vasculature to high chylomicron remnant concentrations (146), (b) elevated intermediate density lipoprotein levels (147), (c) increased heterogeneity of LDL and HDL apoproteins (147), (d) abnormalities of size and composition of

LDL and HDL particles (147). (e) increased LDL susceptibility to oxidation (148) and (f) altered cell surface LDL epitope recognition (149).

In general the design of studies relating outcome to dyslipidemia in ESRD has been less than optimal. However recent reports have associated dyslipidemia with cardiac death in diabetic ESRD patients (150,151), lipoprotein(a) levels with cardiovascular disease (152) and vascular access loss (153) in ESRD patients.

Other Factors. Other factors suggested as risk factors for vascular disease in ESRD patients include chronic endothelial activation and injury with activation of prothrombotic factors (154), high homocysteine levels (155), high aluminum levels (156) and defective clearance of advanced glycosylation end-products (157,158).

In our study hypocalcemia was strongly related to both de novo and recurrent ischemic heart disease, even after adjusting for age, diabetes, blood pressure, hemoglobin and several other possible confounding variables. The effect was as marked in peritoneal dialysis patients as in hemodialysis patients, and could not be explained away by the clear (direct) relationship between mean serum calcium and time spent on dialysis therapy. Another group has shown that low calcium levels are independently associated with mortality in a very large cross-section of dialysis patients (159,160). Hypocalcemia induces hyperparathyroidism, which may lead to profound disturbances of myocardial bioenergetics and myocardial ischemia (161) Hyperparathyroidism has also been associated with dyslipidemia (162) and LV hypertrophy (163).

We observed a very strong relationship between hypoalbuminemia and ischemic heart disease in this study. In the cohort without ischemic disease at baseline, the association between

hypoalbuminemia and the subsequent occurrence of ischemic disease suggests that hypoalbuminemia is an important predisposing risk factor. How hypoalbuminemia could cause ischemic heart disease is unclear, but some possible mechanisms are suggested

(i) Low albumin levels lead to a hypercoagulable state. In elderly, non-uremic patients, malnutrition is associated with heparin co-factor II and antithromin III deficiency, which attenuates the ability to inhibit thrombin generation (164). It is interesting that low serum albumin levels were the single factor most predictive of access thrombosis in the Canadian Hemodialysis Morbidity Study, leading to speculation that low oncotic pressure associated with hypoalbuminemia leads to a hypercoagulable state, as in the nephrotic syndrome (17). Low albumin levels reflect more severe uremia; uremia leads to atherogenesis. As discussed above, quantitative and qualitative lipid abnormalities are common in ESRD patients, and probably influence prognosis. The contribution of malnutrition and low serum albumin levels to these abnormalities is unclear. In this study, the inverse association between serum albumin levels and ischemic heart disease was independent of total cholesterol levels. The association between hypoalbuminemia and ischemic heart disease could be a surrogate marker for a more severe uremic state with endothelial cell activation, as discussed above. Uremia and its therapy may be a chronic, low-grade inflammatory state. There is accumulating evidence that inflammation may play a major role in atheroma formation (165). It is of interest that Helicobacter pylori, Chlamydia pneumoniae and Cytomegalovirus infections have been associated with an excess incidence of coronary artery disease in non-uremic patients (166,167,168). It is well known that low serum albumin levels may be a response to inflammation, independent of protein intake. Whether such mechanisms may explain the recently reported

excessive mortality seen with pro-inflammatory, bio-incompatible hemodialysis membranes (169) is unknown. (iii) Low albumin levels are associated with other nutritional deficiencies that lead to ischemic heart disease. Recent evidence suggests that hyperhomocysteinemia is a risk factor for atherothrombotic cardiovascular disease in the general (170) and ESRD populations (155). Homocysteine levels are markedly elevated in chronic renal failure (171). In the general population, dietary deficiencies of pyridoxine ,folic acid, pyridoxal 5'-phosphate and vitamin B_{12} are thought to be the major determinants of high plasma homocysteine levels (172).

PROGNOSIS. The natural history of ischemic heart disease in ESRD patients has not been well studied. In the USRDS Special Study of Case Mix Severity, ischemic heart disease at baseline was independently associated with an excess mortality of 22% (131). In a retrospective study, we found that both the presence and severity of ischemic heart disease in patients starting maintenance dialysis therapy were strongly associated with 6-month mortality rates (6). In the current prospective cohort study, patients were followed from inception of ESRD therapy, but had to have survived for 6 months to be included in the study. After adjusting for baseline age and diabetes mellitus, patients with ischemic heart disease were 70% more likely to have an admission for cardiac failure, 50% more likely to die, and 70% more likely to have a cardiac death. In these patients most of the excess mortality associated with ischemic heart disease appeared to be via the development of cardiac failure.

CARDIAC FAILURE IN END-STAGE RENAL DISEASE

DIAGNOSIS AND BURDEN OF DISEASE. In general, cardiac results form systolic dysfunction or diastolic dysfunction. Ischemic heart disease can lead to either functional abnormality; to further complicate the situation, myocardial ischemia can also be the result of systolic or diastolic dysfunction. Cardiac failure is always a clinical diagnosis: it occurs when cardiac function is inadequate for bodily needs. There is no diagnostic test for cardiac failure, because it can result from several different mechanisms, which can often coexist in a given individual.

The clinical epidemiology of cardiac failure in ESRD is very incomplete. The burden of disease appears to be very high. In both our retrospective study (6) and the current cohort prospective study (15) clinically defined cardiac failure was present in approximately one third of subjects. Approximately one quarter of patients initially free of cardiac failure went on to have an episode of cardiac failure while on dialysis therapy.

RISK FACTORS. To our knowledge, there has been no prospective study concerning the risk factors for cardiac failure in ESRD patients. In this study older age (baseline and de novo cardiac failure), ischemic heart disease (baseline and recurrent), diabetes mellitus (baseline), systolic dysfunction (baseline and de novo), concentric LV hypertrophy (de novo), LV dilatation (de novo), hypertension (de novo), anemia (de novo), hypoalbuminemia (de novo and recurrent) and hypocalcemia (de novo and recurrent) were all independently associated with cardiac failure. It was impossible to say whether these risk factors are connected to cardiac failure via coronary artery disease or via myocardial abnormalities per se.

PROGNOSIS. The presence of cardiac failure was strongly, and independently associated with early demise, underscored by the observation that 60% of all deaths seen in this study were preceded by an episode of cardiac failure. Similar findings have been reported retrospectively by Hutchinson et al (173), as well as prospectively by the USRDS (131).

THE FUTURE.

It is clear from this study that many epidemiological questions need answers:

1. What is the target hemoglobin level for dialysis patients ?; will normalization (as compared to partial correction) ameliorate echocardiographic abnormalities ?; if so, will this be translated into a reduction in cardiac morbidity and mortality ?

2. Will intensification of dialysis delivery have an impact on echocardiographic and clinical cardiac disease?

3. What is the target blood pressure level that minimizes echocardiographic and clinical cardiac disease? What are the most appropriate antihypertensive agents to achieve this? Is the inverse relationship between blood pressure and mortality a marker for underlying cardiomyopathy and/or drug therapy? If the latter is true, is iatrogenic hypotension predisposing to death?

4. Is the association between malnutrition and cardiac disease causal, or dose it mark for some other factor? Will intensification of nutritional intake have an impact on echocardiographic and clinical cardiac disease?

5. What is the target calcium level for dialysis patients? Does hypocalcemia predispose to death via hyperparathyroidism, or via other mechanisms?

6. What is the relationship between total lipid levels, lipid subfractions and lipid turnover and cardiac disease in ESRD patients ?

With the possible exception of #6, these questions are probably best answered by means of randomized controlled clinical trials. The following chapter focuses on the design of 2 clinical trials

which may help determine the optimum hemoglobin and dialysis intensity levels necessary to treat the various manifestations of cardiomyopathy in chronic uremia.

NORMALIZATION OF HEMOGLOBIN LEVEL.

Question 1 is probably the most easily studied given the efficacy of recombinant human erythropoietin. A large multicentre clinical trial is currently underway in the United States to study the impact of full normalization of hematocrit, in patients with symptomatic cardiac disease. Mortality is the primary outcome for this study, which is being sponsored by the Amgen Corporation. Secondary end-points include the changes seen in left ventricular mass index. Data from our cohort study have been used in the trial design.

The following Canadian multicentre trial is proposed.

OBJECTIVES. The primary objective of the study is to assess the effect of hemoglobin normalization compared to partial correction of anemia, using epoetin alfa in hemodialysis without symptomatic cardiac disease who have either left ventricular hypertrophy or left ventricular dilatation on echocardiography.

RATIONALE. Anemia is an independent risk factor for LV dilatation and concentric hypertrophy in ESRD patients, as shown in this and other studies.

DESIGN. This is an open label study to assess the effect of two target hemoglobin levels, 100 g/l and 135 g/l on cardiomyopathy. Patients will be stratified according to whether or not they have left ventricular dilatation. Essentially, there are two studies: (1) to assess the extent of regression of LV mass in patients with concentric LV hypertrophy and (2) to assess the extent of regression of LV cavity volume in patients with LV dilatation.

PATIENTS. Patients entering the study must fulfil the following principal criteria:

1. Age > 18 years.

2. On hemodialysis > 3 months.

3. No myocardial infarction, admission for angina or cardiac failure within the last 12 months.

4. On epoetin alfa >3 months, with hemoglobin between 95g/l and 105 g/l in the previous month.

5. Stable vascular access for the last 3 months.

6. Life expectancy > 18 months.

INTERVENTION. Patients will be randomly assigned to either the high (130 - 140 g/l) or normal (95 - 105 g/l) hemoglobin target group. Patients in the high target group will have their hemoglobins ramped upwards using a pre-set epoetin dosing schedule. The ramping will take place over a six months period.

OUTCOMES. Echocardiography will be performed at baseline, 12 months and at 18 months. The change in mass index (component 1 above) or cavity volume (component 2 above) at 12 months will be the primary outcome.

Secondary outcomes will include the change in LV parameters at 18 months, morbidity, mortality, safety, quality of life and pharmacoeconomic effects.

SAMPLE SIZE CALCULATIONS.

Study 1: Assuming a = 0.05 (2-tailed), b = 0.80 and that the standard deviation of the change in mass index at 1 year is 37 g/m^2 (as was seen in this study), the number of patients needed to detect

a 27 g/m^2 difference between the low and high hemoglobin groups is 30 per treatment arm (174). Assuming a dropout rate of 12.5%, 35 subjects per patient arm are required.

Study 2: Assuming a = 0.05 (2-tailed), b = 0.80 and that the standard deviation of the change in cavity volume at 1 year is 31 ml/m^2 (as was seen in this study), the number of patients needed to detect a 24 ml/m^2 difference between the low and high hemoglobin groups is 27 per treatment arm (174). Assuming a dropout rate of 12.5%, 35 subjects per patient arm are required.

ANALYSIS. The intention to treat principle will be used primarily, where patients will be analyzed according to the group they were randomized to, regardless of whether or not they achieved the hemoglobin level. Pure efficacy analyses will also be performed where only patients who reached their target hemoglobin will be assessed.

The change in mass index (study 1) and cavity volume (study 2) in the two treatment groups will be compared using a parametric test. Multivariate analysis of variance may be used should any imbalances between patient groups occur during the study, in terms of blood pressure levels or dialysis intensity.

INTENSIFIED DIALYSIS THERAPY

OBJECTIVES: To test the hypothesis that increased amounts of dialysis will improve diminished contractility in patients with end-stage renal disease.

DESIGN. This is a multicentre, cross Canada, randomised, open-label, controlled clinical trial. 70 chronic hemodialysis patients with echocardiographic systolic dysfunction (fractional shortening less than or equal to 30%) will be randomly assigned to receive either standard dialysis intensity (KT/V 1.2 -range 1.1 to 1.3 inclusive) or intensified therapy (KT/V 1.6 -range 1.5 to 1.7 inclusive) for a total of 15 months. 3 months will be used to ramp dialysis intensity to the target range; patients will be maintained at target range for a further 12 months. Echocardiography will be repeated at 6 and 12 months of the maintenance period.

PATIENTS. All patients with the following characteristics are eligible:

1. On hemodialysis therapy for at least 3 months.
2. Stable arteriovenous access.
3. Predicted survival > 1 year.
4. Technically satisfactory echocardiogram within 6 months of randomization.
5. No myocardial infarction or unstable angina within the previous year.
6. Absence of Class IV NIHAU congestive heart failure.
7. Not pregnant or judged capable of becoming pregnant.

INTERVENTION. Random assignment to either standard KT/V (1.2) or intensified KT/V (1.6). Dialysis will be intensified by increasing time on dialysis, and by increasing the performance of the patients dialyzer membrane.

OUTCOME. The primary outcome measure will be the change in fractional shortening between the baseline echo, and that performed at 12 months into the study.

Secondary outcomes will be (i) the change in fractional shortening between the baseline echo, and that performed at 6 months into the study, (ii) time to death or congestive heart failure.

SAMPLE SIZE. 78 patients in our prospective study had fractional shortening less than or equal to 30% on initial echocardiography, and had a second echo one year later. The fall in fractional shortening was 4.2%, with a standard deviation of 7.3%. To detect a change of 5%, with a 2-tailed a of 0.05 and a b of 0.1, the required sample size is 28 subjects per group. Assuming a 25% loss to follow-up (to death or change in mode of ESRD therapy) during the 15 months of the study the required sample size is 35 per treatment arm.

ANALYSIS. The intention to treat principle will be used primarily, where patients will be analyzed according to the group they were randomized to, regardless of whether or not they achieved the hemoglobin level. Pure efficacy analyses will also be performed where only patients who reached their target KT/V will be assessed.

The change in fractional shortening in the two treatment groups will be compared using a parametric test. Multivariate analysis of variance may be used should any imbalances between patient groups be present at baseline or occur during the study, in terms of hemoglobin or blood pressure levels.

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TABLES

Table 1. Baseline Characteristics[a] (N=432).

Age (years)	51 ± 17
Male/Female (%)	64/36
Diabetes mellitus (%)	27
Coronary artery disease (%)	14
Angina pectoris (%)	19
Cardiac failure (%)	31
LV hypertrophy (%)	74
Systolic dysfunction (%)	15
Renal disease(%):	
Glomerulonephritis	31
Diabetic nephropathy	21
Nephrosclerosis	11
Genetic	7
Other	18
Unknown	7
Hypertension > 10 years	29
Current smoker (%)	35
Serum cholesterol (mmol/l)	5.3 ± 1.6

Table 2. Echocardiographic and Clinical Outcomes.

OUTCOME	#EVENTS/# AT RISK
Diagnosis on follow-up echocardiography:	
Normal	35/259 (14%)
Concentric left ventricular hypertrophy	102/259 (39)%
Left ventricular dilatation	65/259 (25%)
Systolic dysfunction	57/259 (22%)
Cardiac failure:	
De novo	72/299 (24%)
Recurrent	71/133 (53%)
Ischemic heart disease:	
De novo	40/337 (12%)
Recurrent	46/95 (48%)
Death:	137/432 (35%)
Cardiac	67/432 (16%)
Non-cardiac	70/432 (16%)

Table 3. Prognosis. Adjusted[a] Relative Risk of Overall Mortality and Late Mortality (> 2 Years). Using Cox's Regression.

Basic Model	Overall Mortality		Late Mortality	
#Deaths/# At Risk	145/420		70/290	
	RR	p	RR	p
Age (years)	1.031	$< 10^{-4}$	1.035	0.0009
Diabetes mellitus	1.952	0.0002	1.915	0.009
Cor artery dis	1.022	0.931	1.156	0.697
Angina Pectoris	1.218	0.409	1.034	0.923
Cardiac failure	1.846	0.0006	1.790	0.015
Albumin (g/dl)	0.744	0.079	0.674	0.046
Covariates added[b]				
Atrial dysrhythmia	1.403	0.391	1.390	0.353
PVD	1.825	0.014	2.718	0.004
Left ventricular:				
Mass (g/m^2)	1.003	0.107	1.009	0.0007
Hypertrophy	0.853	0.555	1.779	0.214
Volume (ml/m^2)	1.009	0.071	1.011	$< 10^{-4}$
LV dilatation	1.375	0.093	1.858	0.019

Table 3. cont

FS(%)	0.978	0.047	0.961	0.013
LV systolic dysfunction	1.596	0.027	2.034	0.015

a. Adjusted for age, diabetes, coronary artery disease, angina pectoris, cardiac failure, serum albumin.

b. Added one at a time to basic model.

Table 4. Patients Without Systolic Dysfunction. Prognostic Importance of Left Ventricular Parameters, Estimated Separately For All Subjects (N=343), Those With Normal Cavity Volume (N=229) and Those With Left Ventricular Dilatation (N=114)[a].

	OVERALL MORTALITY		LATE MORTALITY	
	RR[b]	p	RR[b]	p
	ALL SUBJECTS			
Mass index (g/m^2)	NA	NA	1.011	0.002
Volume (ml/m^2)	1.006	0.085	1.017	0.002
Mass/Vol (g/ml)	NA	NA	NA	NA
	NORMAL CAVITY VOLUME			
Mass index (g/m^2)	NA	NA	1.014	0.005
Volume (ml/m^2)	NA	NA	NA	NA
Mass/Vol (g/ml)	1.418	0.004	1.777	0.024

	LV	DILATATION		
	RR[b]	p	RR[b]	p
Mass	NA	NA	NA	NA
index (g/m^2)				
Volume (ml/m^2)	1.010	0.080	1.028	0.001
Mass/Vol (g/ml)	NA	NA	0.185	0.019

a. I V, RR and NA denote "left ventricular", "relative risk" and "not associated".

b. Adjusted for baseline age, diabetes and ischemic heart disease.

Table 5. Impact of Echocardiographic Classification on Overall Mortality and Late Mortality in Expanded Multivariate Models.

OVERALL MORTALITY

Step	Variable	De^2	RR	p
1	Cardiac failure	29.1	1.85	< 0.001
2	Age (years)	16.6	1.03	< 0.001
3	Diabetes	17.5	2.19	< 0.001
4	Systolic dysfunction	3.5	1.52	0.062

LATE MORTALITY

Step	Variable	De^2	RR	p
1	LV geometry[b]	16.0	1.80	< 0.001
2	Diabetes	11.8	2.87	0.001
3	Age (years)	12.8	1.04	< 0.001
4	Systolic dysfunction	5.9	2.10	0.015

Table 5, continued.

a. The variables included in each Cox's Regression analysis were LV geometry, age, gender, diabetes mellitus, coronary artery disease, angina pectoris, cardiac failure, hypertension ' · 10 years, baseline serum albumin and hemoglobin levels.

b. Entered as 1: Normal LV volume, mass £ 120 g/m^2; 2: LV dilatation, volume £ 120 ml/m^2; 3: Normal LV volume, mass > 120 g/m^2; 4: LV dilatation, volume > 120 ml/m^2.

The relative risk is that associated with a change of 1 stratum. The relative risk of death for patient in stratum 4 would be 1.802^3, or 5.85 times that of an otherwise comparable patient in stratum 1.

Table 6. Prognostic Impact of Proposed Classification System (II) Compared to the Classification System of Koren et al[7].(I), In Patients Free of Symptomatic Heart Disease at Baseline[a]

	SYSTEM I		SYSTEM II	
EVENT	RR[d]	p	RR[d]	p
Death	1.00	0.98	1.51	0.029
Late death	1.15	0.4	2.33	0.003
MI or angina	1.62	0.06	1.83	0.044
Cardiac failure	1.08	0.56	1.50	0.015

a. RR denotes relative risk. MI myocardial infarction.

b. Entered as 1: LV mass ≤ 125 g/m^2, relative wall thickness ≤ 0.45; 2: LV mass ≤125 g/m^2, relative wall thickness > 0.45; 3: LV mass > 125 g/m^2, relative wall thickness ≤ 0.45; LV mass > 125 g/m^2, relative wall thickness > 0.45. The relative risk is that associated with a change of 1 stratum.

c. Entered as 1: Normal LV volume, mass ≤ 120 g/m^2; 2: LV dilatation, volume ≤ 120 ml/m^2; 3: Normal LV volume, mass > 120 g/m^2; 4: LV dilatation, volume > 120 ml/m^2.

The relative risk is that associated with a change of 1 stratum.

d. Adjusted for baseline age and diabetes mellitus.

Table 7. Associations[a] of (I) Concentric LV Hypertrophy (LV Mass Index > 120 g/m^2, Cavity Volume ≤ 90 ml/m^2, Fractional Shortening > 25%) (II) LV Dilatation (Cavity Volume > 90 ml/m^2, Fractional Shortening > 25%), and (III) Systolic Dysfunction (Fractional Shortening £ 25%) Using Patients With Normal LV as Reference Category[b].

ABNORMALITY	ASSOCIATIONS	OR	P
Concentric LVH	Age (years)	1.03	< 0.001
	Male gender	2.23	0.062
	Diabetes mellitus	2.40	0.027
	Coronary artery disease	2.65	0.071
	Hypertension > 10 yrs	2.25	0.033
	Hemoglobin	0.98	0.032
LV Dilatation	Age (years)	1.03	0.010
	Male gender	4.52	< 0.001
	Hemoglobin (g/l)	0.96	< 0.001
	Urea (mmol/l)	0.99	0.046
	Phosphate	1.21	0.042
	Albumin (g/l)	0.94	0.062

Table 7, continued.

ABNORMALITY	ASSOCIATIONS	OR	p
Systolic dysfunction	Age (years)	1.06	< 0.001
	Female gender	4.45	0.003
	Coronary artery disease	7.25	0.007
	Albumin (g/l)	0.93	0.05

a. The covariates included in each analysis were age, gender, diabetes mellitus, coronary artery disease, angina pectoris, hypertension > 10 years, arterial pulse pressure, mean arterial blood presssure, hemoglobin, blood urea, serum creatinine, inorganic phosphate, calcium , alkaline phosphatase and serum albumin levels. The global p-value was < 0.001 for each analysis.

b. LV denotes "left ventricular", OR "odds ratio" .

Table 8. Patient Characteristics. All Patients (Group I, N = 432) and Patient Subset with Repeat Echocardiograms (Group II, N=278)[a].

BASELINE DATA	GROUP I	GROUP II
Age (years)	51 ±	54 ±
Male/Female (%)	64/36	63/37
Renal disease (%):		
Glomerulonephritis	31	30
Diabetic nephropathy	20	18
Tubulointerstitial	11	12
Genetic	7	8
Nephrosclerosis	7	8
Other	18	19
Unknown	7	7
Hypertension > 10 years (%)	29	32
Ischemic heart disease (%)	22	25
Cardiac failure (%)	31	33
SERIAL DATA		
Mean arterial BP (mm Hg)	101 ± 11	101 ± 11
Serum albumin (g/l)	37 ± 5	37 ± ±
Hemoglobin (g/l)	89 ±	90 ±

Table 8, continued.

a. Continuous variables are expressed as mean plus or minus standard deviation.

There were no statistically significant differences between Group I and Group II.

Table 9. Echocardiographic Diagnosis on Baseline and Follow-Up Echocardiography, Performed At A Median Interval of 13 months[a].

		2nd ECHO			
1st ECHO	Normal	Concentric LVH	LV Dilatation	Systolic Dysfnction	TOTAL
Normal	15	10	5	1	31
Concentric LVH	11	58	21	8	98
LV Dilatation	5	20	29	15	69
Systolic Dysfunction	2	11	9	25	47
TOTAL	33	99	64	49	245

a. LV denotes "left ventricle", LVH "left ventricular hypertrophy".

Table 10. Associations of The Presence of Concentric LV Hypertrophy[a] and LV Mass Index[b] in Patients With Concentric LV Hypertrophy (N=102) or Normal LV (N=35) on Follow-Up Echocardiography[c].

OUTCOME	ASSOCIATIONS	OR	p
Concentric LV hypertrophy	Systolic BP (mm Hg)	1.03	0.02
	Female gender	2.6	0.03
		b	p
LV mass index (g/m^2)	Systolic BP (mm Hg)	+0.92	0.002
	Age (years)	+ 0.57	0.005
	Hemoglobin (g/l)	- 0.52	0.005

a. Using multiple logistic regression.

b. Using multiple linear regression.

c. The covariates used in each model were age, gender, diabetes mellitus, ischemic heart disease and mean hemoglobin, systolic blood pressure, serum albumin and calcium levels up to the the second echocardiogram.

Table 11. Associations of The Presence of LV Dilatation[a] and LV Cavity Volume[b] in Patients With LV Dilatation (N=65) or Normal LV (N=35) on Follow-UpEchocardiography[c]

OUTCOME	ASSOCIATIONS	OR	p
LV dilatation	Ischemic heart disease	5.1	0.008
	Hemoglobin (g/l)	0.96	0.02
	Diastolic BP	1.04	0.06
		b	p
Cavity volume (ml/m^2)	Ischemic heart disease	+ 24.1	0.009
	Hemoglobin (g/l)	- 0.45	0.004
	Diastolic BP (mm Hg)	+ 0.8	0.04
	Serum albumin (g/l)	- 0.85	0.04

a. Using multiple logistic regression.

b. Using multiple linear regression.

c. The covariates used in each model were age, gender, diabetes mellitus, ischemic heart disease and mean hemoglobin, diastolic blood pressure, serum albumin and calcium levels up to the the second echocardiogram.

Table 12. Associations of The Presence of Systolic Dysfunction[a] and Fractional Shortening[b] in Patients With Systolic Dysfunction (N=57) or Normal LV (N=35) on Follow-Up Echocardiography[c].

OUTCOME	ASOCIATIONS	OR	p
Systolic dysfunction	Ischemic heart disease	5.2	0.001
		b	p
Fractional Shortening (%)	Ischemic heart disease	- 6.4	0.02
	Hemoglobin (g/l)	0.18	0.02

a. Using multiple logistic regression.

b. Using multiple linear regression.

c. The covariates used in each model were age, gender, diabetes mellitus, ischemic heart disease and mean hemoglobin, diastolic blood pressure, serum albumin and calcium levels up to the the second echocardiogram.

Table 13. The Impact of Renal Transplantation: Patient Characteristics (N=102)[a].

Age (years)	37 ±12
Male/female (%)	72/28
Duration of dialysis (years)	15 ± 15
Live-related graft (%)	49
Diabetic (%)	20
Myocardial infarction (%)	1
Cardac failure (%)	12
Hypertension (%)	81
Mean arterial blood pressure (mm Hg)	104 ± 10
Hemoglobin (g/l)	83 ± 16
Current smoker (%)	32

a. ± refers to mean plus or minus standard deviation.

Table 14. The Impact of Renal Transplantation on Echocardiographic Parameters (N=102)[a].

	PRE	POST	p
LV mass index (g/m^2)	175 ± 62	148 ± 43	< 0.001
LV hyertrophy (%)	86	71	< 0.001
Cavity volume (ml/m^2)	86 ± 35	74 ± 25	< 0.001
LV dilatation (%)	43	29	< 0.001
Fractional Shortening (%)	35 ± 9	37 ± 7	0.036
Diagnosis (%)			
Normal reference category	10	25	-
Conentric LVH	44	46	0.06
LV dilatation	34	30	0.03
Systolic dysfunction	12	0[b]	0.00008

a. ± refers to mean plus or minus standard deviation. LV denotes left ventricle, LVH left ventricular hypertrophy.

b. Total exceeds 100% due to rounding error.

Table 15. Echocardiographic Diagnosis Pre and Post Transplantation[a].

		POST			
PRE	Normal	Concentric LVH	LV Dilatation	Systolic Dysfnction	TOTAL
Normal	6	2	2	0	10
Concentric LVH	10	27	6	0	43
LV Dilatation	7	20	17	0	34
Systolic Dysfunctio n	2	6	4	0	12
TOTAL	25	45	29	0	99

a. LV denotes "left ventricle", LVH "left ventricular hypertrophy".

Table 16. The Prognostic Impact of Baseline Ischemic Heart Disease[a].

OUTCOME	Adjusted[d] OR	p
Diagnosis on follow-up		
Echocardiogram[b]:		
Normal (reference category)	-	-
Concentric LV hypertrophy	NA	NA
LV dilatation	NA	NA
Systolic dysfunction	4.36	0.004
	Adjusted[d]	p
De novo cardiac failure[c]	NA	NA
Recurrent cardiac failure[c]	2.03	0.003
Death[c]	1.48	0.026

a. OR, RR, and NA denote "odds ratio", "relatie risk" and "not associated".

b. Using multiple logistic regression.

c. Using Cox's regresssion.

d. Adjusted for baseline age and diabetes mellitus.

Table 17. Associations[a] of Ischemic Heart Disease at Baseline[b].

ASSOCIATION	Adjusted[c] OR	p
Age (years)	1.06	< 0.001
Diabetes melitus	2.10	0.007
Hypertension > 10 years	NA	NA
Serum cholesterol (mmol/l)	NA	NA
Current smoking	NA	NA
Hemoglobin (g/l)	1.04	< 0.001
Serum albumin (g/l)	NA	NA
Echocardiographic diagnosis:		
Normal (reference category)	-	-
Concentric LV hypertrophy	NA	NA
LV dilatation	NA	NA
Systolic dysfunction	3.38	0019

a. Using multiple logistic regression.

b. LV, OR and NA denote "left ventricular", "odds ratio" and "not associated".

c. Adjusted for age, diabetes mellitus, hypertension > 10 years, smoking and cholesterol levels.

Table 18. Associations[a] of De Novo Ischemic Heart Disease[b].

ASSOCIATION	Adjusted[d] RR	p
BASELINE		
Age (year)	1.05	0.001
Diabetes mellitus	3.97	0.001
Serum cholesterol (mmol/l)	NA	NA
Current smoker	NA	NA
Echocardiographic diagnosis:		
Normal (reference category)	-	-
Concentric LV hypertrophy	5.92	0.014
LV dilatation	5.35	0.022
Systolic dysfunction	12.1	0.002
SERIAL[c]		
Hemoglbin (g/l)	NA	NA
Diastolic BP (mm Hg)	1.04	0.034
Serum albumin (g/l)	0.93	0.033

a. Using Cox's regression.

b. LV, RR and NA denote "left ventricular", "relative risk" and "not associated".

c. Averaged from the start of dialysis therapy until the development of ischemic heart disease.

Table 18, continued.

d. Adjusted for baseline age, diabetes, cholesterol, and smoking and serial diastolic blood pressure levels while on dialysis therapy.

Table 19. Associations[a] of Baseline Cardiac Failure[b].

ASSOCIATION	Adjusted[c] OR	p
Age (years)	1.04	< 0.001
Diabetes mellitus	2.71	< 0.001
Ischemic heart disease	3.17	< 0.001
Hemoglobin (g/l)	NA	NA
Serum albumin (g/l)	NA	NA
Echocardiographic diagnosis:		
Normal (reference category)	-	-
Concentric LV hypertrophy	NA	NA
LV dilatation	3.32	0.015
Systolic dysfunction	13.3	< 0.001

a. Using multiple logistic regression.

b. LV, RR and NA denote "left ventricular", "relative risk" and "not associated".

c. Adjusted for age, diabetes, ischemic heart disease and hypertension > 10 years.

Table 20. Associations[a] of De Novo Cardiac Failure[b].

ASSOCIATIONS	Adjusted[d] RR	p
BASELINE		
Age (years)	1.02	0.044
Diabetes mellitus	NA	NA
Ischemic heart disease	NA	NA
Echocardiographic diagnosis:		
Normal (reference category)	-	-
Concentric LV hypertrophy	3.58	0.002
LV dilatation	2.97	0.019
Systolic dysfunction	3.40	0.032
SERIAL		
Mean arterial BP (mm Hg)	1.03	0.026
Hemoglobin (g/l)	0.96	< 0.001
Serum albumin (g/l)	0.93	< 0.001

a. Using Cox's regression.

b. LV, RR and NA denote "left ventricular", "relative risk" and "not associated".

c. Averaged from the start of dialysis therapy until the development of cardiac failure.

d. Adjusted for baseline age, diabetes, ischemic heart disease and serial mean arterial blood pressure levels while on dialysis therapy.

Table 21. Associations[a] of Recurrent Cardiac Failure[b].

ASSOCIATIONS	Adjusted[d] RR	p
BASELINE		
Age (years)	NA	NA
Diabetes mellitus	NA	NA
Ischemic heart disease	2.03	0.003
Echocardiographic diagnosis:		
Normal (reference category)	-	-
Concentric LV hypertrophy	NA	NA
LV dilatation	NA	NA
Systolic dysfunction	NA	NA
SERIAL		
Mean arterial BP (mm Hg)	NA	NA
Hemoglobin (g/l)	0.98	0.013
Serum albumin (g/l)	0.95	0.064

a. Using Cox's regression.

b. LV, RR and NA denote "left ventricular", "relative risk" and "not associated".

c. Averaged from the start of dialysis therapy until the development of cardiac failure.

d. Adjusted for baseline age, diabetes, ischemic heart disease and serial mean arterial blood pressure levels while on dialysis therapy.

Table 22. Patient Characteristics According to Tertile of Mean Hemoglobin Level[a].

BASELINE	> 95 g/l	80 - 90 g/l	≤ 80 g/l	p
Age (years)	52 ± 16	53 ± 15	49 ± 18	0.08
M/F	66%34%	64%/35%	64%/37%	0.93
Diabetic	32%	28%	31%	0.03
Renal disease:				
GN	32%	29%	31%	
Diabetic	26%	19%	14%	
Tubulointerstitial	8%	12%	12%	
Genetic	9%	3%	8%	
Nephrosclerosis	9%	7%	7%	
Other	11%	22%	20%	
Unknown	4%	8%	8%	0.07
BP > 10 years	19%	23%	36%	0.005
Ischemic heart dis	34%	21%	12%	0.00001
Cardiac failure	38%	35%	21%	0.004
SERIAL				
MAP (mm Hg)	102 ± 10	100 ± 12	101 ± 11	0.25
Albumin (g/l)	37 ± 4	37 ± 5	37 ± 11	0.31

a. Continuous data are expressed as mean plus or minus standard deiation

Table 23. Independent Impact of Anemia (Expressed as the Effect of A Fall in Mean Hemoglobin Level of 10 g/l) on Echocardiographic and Clinical Outcomes in The Combined Group of Hemodialysis and Peritoneal Dialysis Patients and Hemodialysis Patients Only[a].

OUTCOME	HD and PD	HD
	Adjusted[b] OR (p)	Adjusted[b] OR (p)
Normal (reference category)	-	-
LV dilatation	NA	1.49 (0.039)
Systolic dysfunction	1.42 (0.018)	1.55 (0.048)
	Adjusted[b] OR (p)	Adjusted[b] OR (p)
Cardiac failure:		
De novo	1.28 (0.017)	1.24 (0.028)
Recurrent	1.20 (0.046)	1.31 (0.093)
Ischemic heart disease:		
De novo	NA	NA
Recurrent	NA	NA
Death	1.14 (0.024)	1.25 (0.037)

a. HD denotes hemodialysis, PD peritoneal dialysis, OR odds ratio, RR relative risk, and NA no statistical association . b. Adjusted for age, diabetes, ischemic heart disease (excluded for the outcomes de novo and recurrent ischemic heart disease) and the average monthly mean arterial blood pressure, serum albumin and hemoglobin level before the index event.

Table 24. Echocardiographic and Clinical Outcome According to Tertile of Mean Hemoglobin Level, in the Combined Group of Hemodialysis and Peritoneal Dialysis Patients[a].

OUTCOME	Adjusted[b] OR (p)
Concentric LV hypertrophy:	
> 95 g/l (reference category)	-
80 - 95 g/l	NA
£ 80 g/l	3.73 (0.056)(
LV dilatation:	
> 95 g/l (reference category)	-
80 - 95 g/l	NA
£ 80 g/l	2.88 (0.062)
Systolic dysfunction:	
> 95 g/l (reference category)	-
80 - 95 g/l	NA
£ 80 g/l	NA
Admission for cardiac failure:	
> 95 g/l (reference category)	-
80 - 95 g/l	1.70 (0.035)
£ 80 g/l	2.66 (< 0.0001)

Table 24. continued.

OUTCOME	Adjusted[b] OR (p)
Admission for ischemic heart disease:	
> 95 g/l (reference category)	-
80 - 95 g/l	NA
£ 80 g/l	NA
Death:	
> 95 g/l (reference category)	-
80 - 95 g/l	NA
£ 80 g/l	1.73 (0.056)

a. OR, RR and NA denote odds ratio, relative risk and no statistical association. The

b. Adjusted for age, diabetes, ischemic heart disease and the average monthly mean arterial blood pressure, serum albumin and hemoglobin level before the index event.

Table 25. Patient Characteristics According to Tertile of Mean Arterial Blood

BASELINE	≤98 mm Hg	98 - 106 mm Hg	> 106 mm Hg	p
Age (years)	56 ± 16	59 ± 17	48 ± 16	0.002
M/F	61%/39%	62%/38%	71%/2%	0.13
Diabetic	33%	23%	21%	0.10
BP > 10 years	37%	49%	19%	0.007
Ischemic heart dis	33%	21%	13%	0.0005
Cardiac failure	40%	30%	23%	0.006
SERIAL				
Hemoglobin (g/l)	87 ± 14	89 ± 15	89 ± 16	0.46
Albumin (g/l)	36 ± 5	37 ± 5	38 ± 4	0.03

a. Continuous data are expressed as mean plus or minus standard deiation

Table 26. Echocardiographic and Clinical Outcomes: Associated Mean Arterial Blood Pressure Levels .

OUTCOME	#EVENTS/#AT RISK	MAP (mm Hg)	p
Diagnosis on repeat Echocardiogram:			
Normal	35/259 (14%)	99 ± 15	-
Concentric LVH	102/259 (39%)	104 ± 10	0.02
LV dilatation	65/259 (25%)	103 ± 11	0.08
Systolic dysfunction	57/259 (22%)	97 ± 12	0.73
Cardiac failure:			
De novo			
No	227/299 (76%)	102 ± 11	-
Yes	72/299 (24%)	104 ± 9	0.27
Recurrent			
No	62/133 (47%)	101 ± 9	-
Yes	71/133 (53%)	101 ± 12	0.84
Death after admission			
No	47/133 (35%)	104 ± 11	-
Yes	86/133 (65%)	95 ± 13	0.0001

Table 26, continued.

OUTCOME	#EVENTS/#AT RISK	MAP (mm Hg)	p
Ischemic heart disease			
De novo			
No	297/337 (88%)	103 ± 11	-
Yes	40/337 (12%)	103 ± 11	0.58
Recurrent			
No	49/95 (52%)	98 ± 10	-
Yes	46/95 (48%)	101 ± 10	0.18
Death after admission			
No	23/73 (32%)	101 ± 10	-
Yes	50/73 (68%)	95 ± 13	0.10
Death			
No	282/432 (65%)	103 ± 10	-
Yes	150/432 (35%)	98 ± 8	< 0.0001

Table 27. Independent Association Between Blood Pressure (the Effect of A Rise in Mean Arterial Blood Pressure Level of 10 mm Hg) and Echocardiographic and Clinical Outcomes in the Combined Group of Hemodialysis and Peritoneal Dialysis Patients[a].

OUTCOME	Adjusted[b] OR (p)
Normal (reference category)	-
Concentric LV hypertrophy	1.48 (0.020)
LV dilatation	1.48 (0.063)
Systolic dysfunction	NA
Change in LV:	b (p)
Mass index (g/m^2)	+5.4 (0.027)
Cavity volume (ml/m^2)	+ 4.3 (0.048)
Fractional shortening (%)	NA
	Adjusted[b] RR
Cardiac failure:	
De novo	1.44 (0.007)
Recurrent	NA
Ischemic heart disease:	
De novo	1.39 0.051)
Recurrent	NA
Death	0.82 (0.009)

Table 27, continued.

a. OR denotes odds ratio, RR relative risk, and NA no statistical association.

b. Adjusted for age, diabetes, ischemic heart disease (excluded for the outcomes de novo and recurrent ischemic heart disease) and the average monthly mean arterial blood pressure, serum albumin and hemoglobin level before the index event.

Table 28. Independent Association Between Blood Pressure (the Effect of A Rise in Mean Arterial Blood Pressure Level of 10 mm Hg) on Echocardiographic and Clinical Outcomes Analyzed Separately in Hemodialysis and Peritoneal Dialysis Patients[a].

OUTCOME	HEMODIALYSIS	PERITONEAL DIALYSIS
	Adjusted[b] OR (p)	Adjusted[b] OR (p)
Normal (reference category)	-	-
Concentric LV hypertrophy	NA	2.16 (0.018)
LV dilatation	NA	NA
Systolic dysfunction	NA	NA
	b (p)	b (p)
Change in LV:		
Mass index (g/m^2)	+7.2 (0.048)NA	NA
Cavity volume (ml/m^2)	NA	NA
Fractional shortening (%)	NA	NA

Table 28, continued.

	Adjusted[b] RR	Adjusted
Cardiac failure:		
De novo	2.07 (0.004)	NA
Recurrent	NA	NA
Ischemic heart disease:		
De novo	NA	1.95 (0.
Recurrent	NA	NA
Death	0.73 (0.004)	NA

a. HD denotes hemodialysis, PD peritoneal dialysis, OR odds ratio, RR relative risk, and NA no statistical association .

b. Adjusted for age, diabetes, ischemic heart disease (excluded for the outcomes de novo and recurrent ischemic heart disease) and the average monthly mean arterial blood pressure, serum albumin and hemoglobin level before the index event.

Table 29. Patient Characteristics According to Tertile of Mean Serum Albumin Level[a].

BASELINE	≤ 36 g/l	36 - 39 g/l	> 39 g/l	p
Age (yrs)	54 ± 16	53 ± 16	46 ± 16	0.0002
Male/Female	59%/41%	69%/31%	68%/32%	0.10
Diabetic	34%	27%	14%	0.0005
Hypertension	30%	31%	26%	0.64
> 10 years				
Ischemic	26%	25%	13%	0.02
heart disease				
Cardiac failure	34%	35%	22%	0.06
SERIAL				
Hemoglobin (g/)	88 ± 17	88 ± 14	89 ± 15	0.91
MAP (mm Hg)	100 ± 11	101 ± 11	102 ± 10	0.19

a. Continuous variables are expressed as mean plus or minus standard deviation.

Table 30. Association Between Mean Serum Albumin (Expressed as the Effect of A Fall of 10 g/l) and Echocardiographic and Clinical Outcomes In The Combined Group of Hemodialysis and Peritoneal Dialysis Patients[a].

OUTCOME	Adjusted[b]
Degree of :	b (p)
Concentric LV hypertrophy[c] (g/m^2)	NA
LV dilatation[d] (ml/m^2)	+18.8 (0.036)
Systolic dysfunction[e] (% FS)	NA
	OR (p)
Presence of:	
Normal (reference category)	-
Concentric LV hypertrophy	NA
LV dilatation	NA
Systolic dysfunction	NA

Table 30, continued.

	Adjusted[b] RR (p)
Cardiac failure:	
De novo	1.82 (0.007)
Recurrent	1.80 (0.03)
Ischemic heart disease:	
De novo	2.22 (0.037)
Recurrent	NA
Death:	
Cardiac	2.54 (< 0.001)
Non-cardiac	2.23 (< 0.001)

a. LVH denotes left ventricular hypertrophy, NA no statistical association, FS fractional shortening, OR odds ratio and RR relative risk.

b. Adjusted for age, diabetes, ischemic heart disease (excluded for the outcomes de novo and recurrent ischemic heart disease) and the average monthly mean arterial blood pressure, serum albumin and hemoglobin level before the index event.

c. In the group with either normal LV or concentric LVH.

d. In the group with either normal LV or LV dilatation

e. In the group with either normal LV or systolic dysfunction.

Table 31. Association Between Mean Serum Albumin Level (Expressed as the Effect of A Fall of 10 g/l) and Echocardiographic and Clinical Outcomes Analyzed Separately in Hemodialysis and Peritoneal Dialysis Patients[a].

OUTCOME	HEMODIALYSIS	PERITONEAL DIALYSIS
	Adjusted[b] b (p)	Adjusted[b] b (p)
Concentric LVH[c] (g/m^2)	NA	NA
LV dilatation[d] (ml/m^2)	+29.7 (0.031)	NA
Systolic dysfunction[e] (% FS)	NA	NA
	Adjusted[b] OR	Adjusted[b] OR
Presence of:		
Normal (reference category)	-	NA
Concentric LV hypertrophy	NA	+4.26 (0.014)
LV dilatation	NA	NA
Systolic dysfunction	NA	NA

Table 31, continued.

OUTCOME	HEMODIALYSIS	PERITONEAL DIALYSIS
	Adjusted[b] RR	Adjusted[b] RR
Cardiac failure:		
De novo	2.22 (0.001)	4.16 (0.003)
Recurrent	3.84 (0.003)	NA
Ischemic heart disease:		
De novo	5.29 (0.001)	NA
Recurrent	4.24 (0.005)	NA
Death:	4.33 (< 0.001)	2.06 (< 0.001)
Cardiac	5.60 (0.001)	NA
Non-cardiac	3.58 (< 0.001)	3.52 (< 0.001)

a. HD denotes hemodialysis, PD peritoneal dialysis, LVH left ventricular hypertrophy, NA no statistical association, FS fractional shortening, OR odds ratio and RR relative risk.

b. Adjusted for age, diabetes, ischemic heart disease (excluded for the outcomes de Table 31, continued.novo and recurrent ischemic heart disease) and the average monthly mean arterial blood pressure, serum albumin and hemoglobin level before the index event.

c. In the group with either normal LV or concentric LVH.

d. In the group with either normal LV or LV dilatation

e. In the group with either normal LV or systolic dysfunction.

Table 32. Association Between Mean Serum Calcium, Inorganic Phosphorus and Alkaline Phosphatase Levels and Mortality.

	Adjusted[b] RR (p)
ALL PATIENTS:	
Serum calcium ≤ 2.2 mmol/l	2.10 (0.006)
Phosphorus > 1.9 mmol/l	NA
Alkaline phosphatase > 120 U/l	1.55 (0.02)
HEMODIALYSIS PATIENTS:	
Serum calcium ≤2.2 mmol/l	2.21 (0.01)
Phosphorus > 1.9 mmol/l	NA
Alkaline phosphatase > 120 U/l	1.78 (0.063)
PERITONEAL DIALYSIS PATIENTS:	
Serum calcium ≤2.2 mmol/l	2.67 (0.034)
Phosphorus > 1.9 mmol/l	NA
Alkaline phosphatase > 120 U/l	NA

a. Adjusted for age, diabetes mellitus, ischemic heart disease, smoking status and cholesterol level at baseline, and serial albumin, mean arterial blood pressure, hemoglobin, calcium, phosphorus and alkaline phosphatase levels.

Table 33. Morbidity: Association Between Mean Serum Calcium, Inorganic Phosphorus and Alkaline Phosphatase Levels And Admission for De Novo Ischemic Heart Disease, Recurrent Ischemic Heart Disease, De Novo Cardiac Failure and Recurrent Heart Failure[a].

	Ca 2.2 mmol/l	Pi > 1.9 mmol/l	AP > 120 mmol/l
	Adjusted[b] RR (p)	Adjusted[b] RR (p)	Adjusted[b] RR (p)
Ischemic heart disease:			
De novo	5.23 (< 0.0001)	NA	NA
Recurrent	2.46 (0.006)	NA	NA
Cardiac failure:			
De novo	2.64 (< 0.0001)	NA	NA
Recurrent	3.30 (< 0.0001)	NA	NA

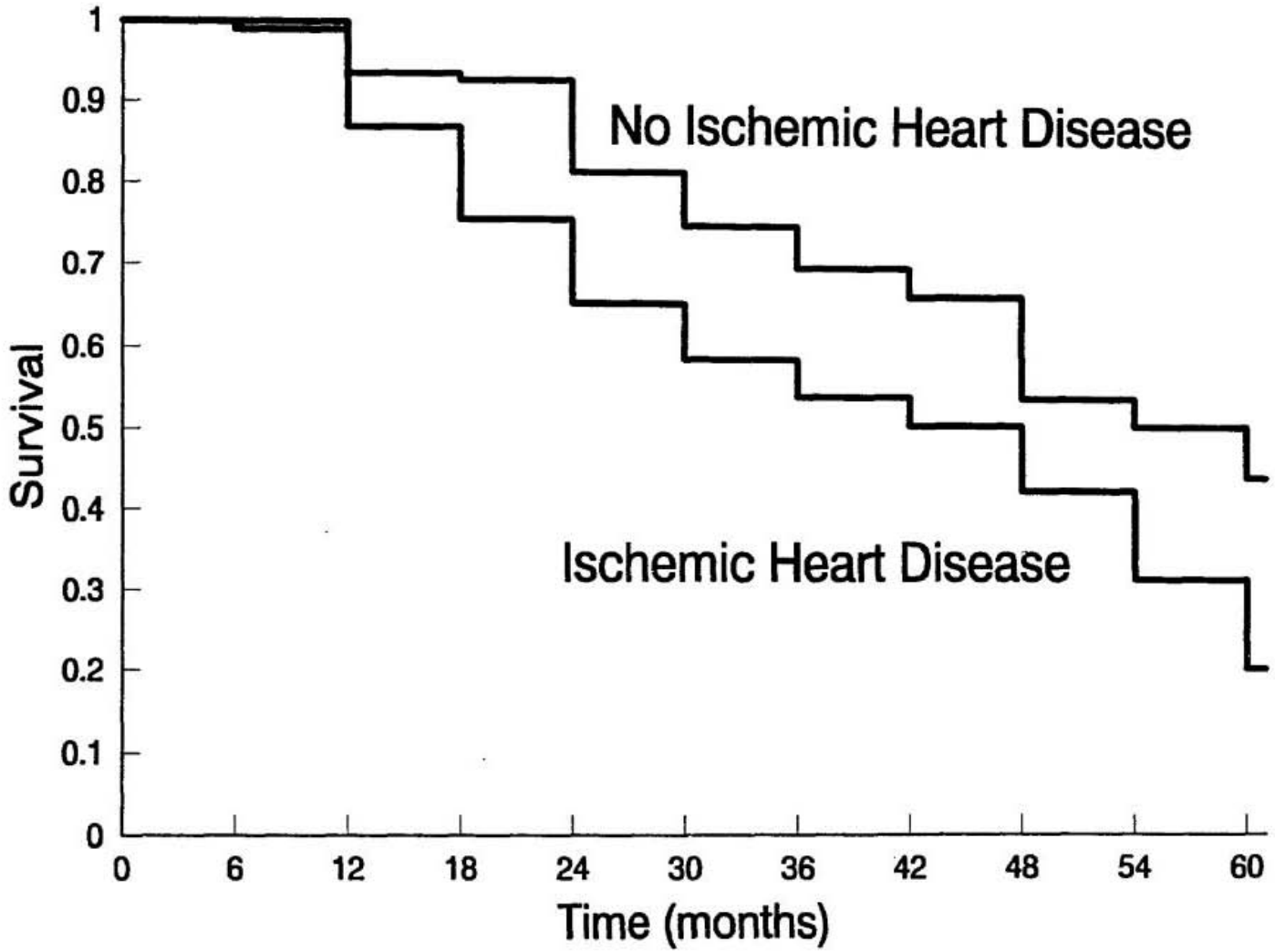
a. Ca, Pi AP and RR denote serum calcium, inorganic phosphorus, alkaline phosphatase and relative risk respectively.

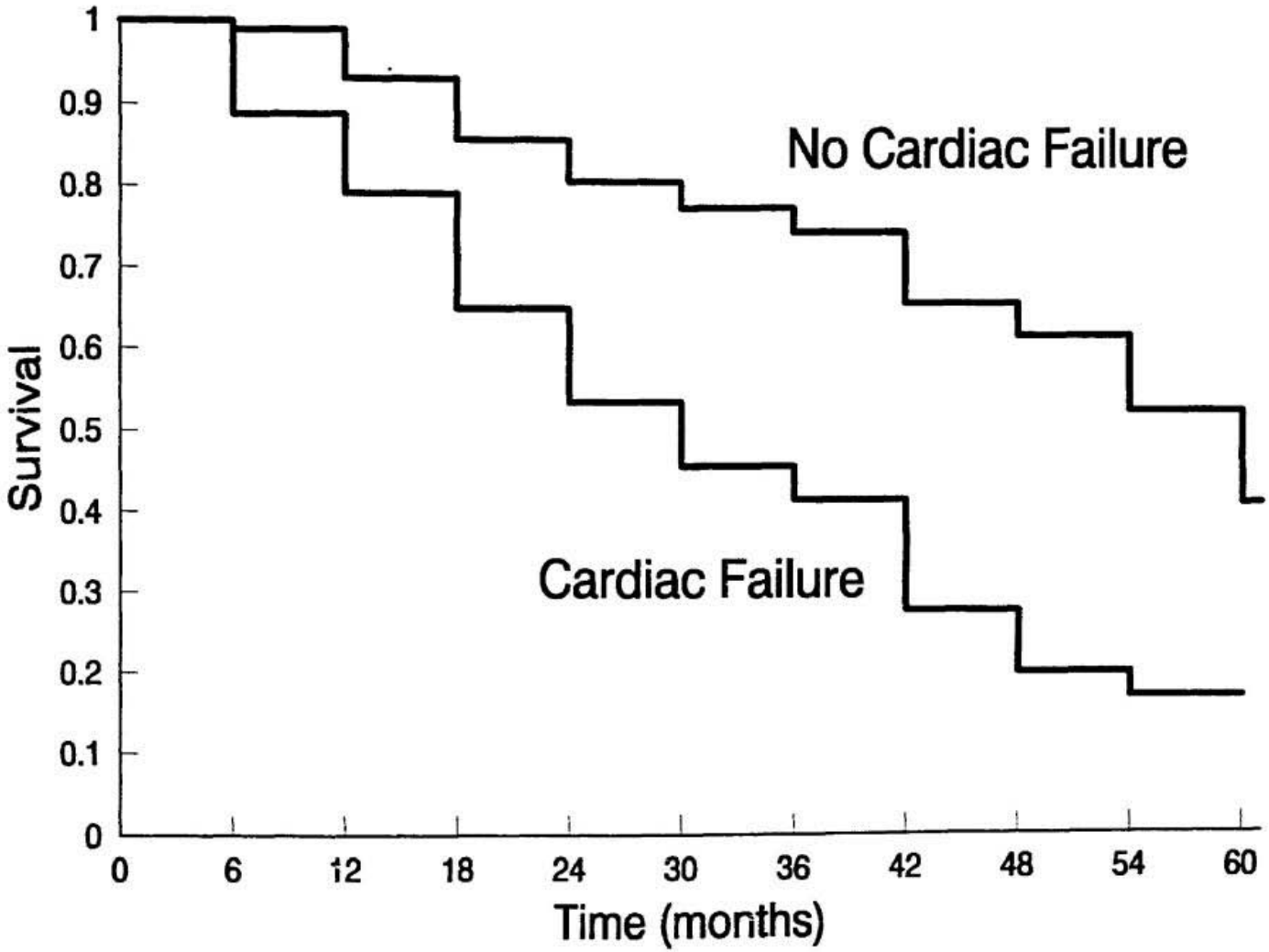
b. Adjusted for age, diabetes mellitus, smoking status and cholesterol level at baseline, and serial albumin, mean arterial blood pressure, hemoglobin, calcium, phosphate and alkaline phosphatase levels.

Table 34. Summary of Principal Results. All Associations Are Derived From Multivariate Analysis Presented in Previous Tables.

	RISK FACTORS				***PREDICTOR OF***				
for	**ANEMIA**	**HTN**	**LOW ALB**	**CLVH**	**LVD**	**SDF**	**HHD**	**HF**	**DEATH**
CLVH	yes	yes	no	-	-	-	yes	yes	yes
LVD	yes	yes	yes	-	-	-	yes	yes	yes
SDF	yes	no	no	-	-	-	yes	yes	yes
HHD	no	yes	yes	-	-	yes	-	yes	yes
HF	yes	yes	yes	-	-	-	-	-	yes
DEATH	yes	inverse relation	yes	-	-	-	-	-	-

FIGURES


No Ischemic Heart Disease
Ischemic Heart Disease
Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
6
12
18
24
30
36
42
48
54
60
Time (months)


1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Survival
No Cardiac Failure
Cardiac Failure
0
6
12
18
24
30
36
42
48
54
60
Time (months)