LEFT VENTRICULAR HYPERTROPHY

IN END-STAGE RENAL DISEASE

A Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science

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ABSTRACT

Left ventricular hypertrophy is an important prognostic indicator in populations without renal failure, and it may regress with drug therapy. Although cardiovascular diseases are the leading cause of mortality and morbidity in patients being treated for end-stage renal disease, no longitudinal study has examined the prognostic importance of left ventricular hypertrophy in these patients. In this study an inception cohort beginning renal replacement therapy was identified and followed for up to 5 years. Using the Cox proportional hazards model, left ventricular hypertrophy was independently associated with survival. Based on comparison of upper- and lowermost quintiles of left ventricular mass index, the relative risk of dying was 3.7 for both cardiac and all-cause mortality.

The data were also used to examine the factors associated with hypertrophy. The design did not allow the effects of some factors to be reliably estimated. A relationship with anaemia was evident which suggested that anaemia contributes to the pathogenesis of hypertrophy in these patients. Whether reversal of anaemia will achieve regression of hypertrophy is the subject of ongoing research.

RESUME

L'hypertrophie ventriculaire gauche est un indicateur prognostique important chez les populations sans insufficance rénale, et il est possible qu'elle puisse régresser avec un traitement médicamenteux. Malgré que les maladies cardiovasculaires soient la cause principale de morbidité et de mortalité chez les patients avec insufficance rénale, l'importance prognostique de l'hypertrophie ventriculaire gauche chez ces patients n'a pas été étudiée. Dans cette étude, nous avons identifié une cohorte débutant un traitement de support rénal et l'avons suivie pendant cinq ans. Le modèle de "hasards proportionels de Cox" suggère que l'hypertrophie ventriculaire gauche est associée indépendamment à la survie des patients. La comparaison des quintiles supérieur et inférieur de l'index de la masse ventriculaire gauche démontre un risque relatif de décès de 3.7 pour la mortalité d'origine cardiaque et pour la mortalité totale.

Les données furent utilisés également pour examiner les facteurs associés avec l'hypertrophie. La formulation de l'étude n'a pas permis d'estimer de façon fiable l'effet de certains facteurs. Une corrélation avec l'anémie a été observée et suggère que l'anémie contribue à la pathogénèse de l'hypertrophie chez ces patients. La réversibilité de l'anémie peut-elle amener une régression de l'hypertrophie? Cette question est présentement à l'étude.

PREFACE

This is my own work. No longitudinal study of which I am aware has examined the prognostic importance of left ventricular hypertrophy in renal failure, while studies have examined various factors in relation to the development of hypertrophy. The hypothesis that hypertrophy was an adverse prognostic factor was Dr. Allan Sniderman's, the hypothesis that anaemia contributed to it's development was my own, and the pursuit of these should be considered contributions to original knowledge. The design and conduct of the study was my own, for which I alone am responsible.

Many people contributed in an important way to this work. Dr. Pierre Tousignant supervised the writing of this thesis, at a time when he was extremely busy yet did so graciously. Dr. Allan Sniderman was responsible for my coming to McGill and being able to participate in two programs jointly, gave invaluable professional and personal support throughout my stay, and clearly thought through the physiology with me. Dr. Maurice McGregor helped me through low periods with this work, Olli Miettinen taught me how not to lose sight of the question. Patti Groome taught me how to 'numbercrunch' and almost didn't mind when I 'prepared' the hard disk by accident. Dr. Tom Hutchinson provided his insights and made the services of his unit available to me. The Research Institute, the Department of Medicine and Divisions of Cardiology and Nephrology of the Royal Victoria Hospital provided financial support.

The most important thank you is to my wife Melinda for her unending support, willingness to be uprooted, and being a solo parent. My children Benjamin and Rebecca were asked to forego their father too much of the time, while Louis burped his way through the final draft.

Montreal, February 1989

1. INTRODUCTION

Patients receiving replacement therapy for end-stage renal disease (ESRD) have a poor prognosis, the most frequent cause of death being cardiovascular disease (1). That atherosclerosis is common, with consequent coronary and cerebrovascular disease, is well recognised (2). However little attention has been paid to left ventricular hypertrophy (LVH) in these patients. In patients without renal failure, left ventricular hypertrophy is strongly related to cardiovascular morbidity and mortality (3,4,5,6,7). A cluster of cardiac deaths among patients being treated by chronic ambulatory peritoneal dialysis at the Royal Victoria Hospital suggested that LVH was prevalent in this population and might be associated with an adverse prognosis, as in patients without renal failure (8).

The study described herein was set up to examine, in a larger cohort treated by all modalities (haemodialysis, peritoneal dialysis and transplantation), whether left ventricular hypertrophy present at the commencement of dialysis was an adverse prognostic factor and secondarily, to examine the factors associated with the development of left ventricular hypertrophy in these patients.

Section 2 deals with background literature, Section 4 with methods (including statistical considerations). Section 5 (Results and Discussion) describes the cohort selection and the subpopulations studied in the various analyses, the primary analysis (left ventricular hypertrophy and survival) and the secondary analysis (factors associated with hypertrophy). Appendices 2-4 deal with certain theoretical considerations and alternative methods of analysis. There are 13 Tables and 9 Figures at the end of the text.

2. BACKGROUND LITERATURE

A. Survival in end-stage renal disease

Patients with end-stage renal disease (ESRD) are those in whom kidney dysfunction is severe enough to make survival for 12 months unlikely without treatment (9). Clinically, patients with renal failure are usually classified according to level of serum creatinine or endogenous creatinine clearance, with a creatinine clearance of less than 10 ml/min (less than 10% of normal renal function) indicating ESRD. At this level of creatinine clearance, symptoms are usually present and replacement therapy by haemodialysis, peritoneal dialysis, or transplantation is begun. Although it is often held that survival is improved by transplantation, it has been argued that the method of analysis (10) and selection of healthier patients for transplantation (11) are responsible for better survival with this treatment. There seems little to choose between dialysis modes in terms of survival (1).

In a study based on the experience of two Montreal hospitals (12), prognostic factors in patients beginning renal replacement therapy were examined. Those which appeared most important were age, duration of diabetes, and left heart failure. The latter characteristic reflects the final common pathway of many differing forms of cardiovascular disease, and was not more precisely examined in that study. These findings are consonant with those of the Canadian Renal Failure Registry (1) which indicated that in 1985, cardiovascular diseases (44%) were the leading cause of death in patients receiving renal replacement therapy, followed by infection (11%). Diabetic patients had poorer survival than other patients.

While atherosclerosis is common in ESRD, whether or not it is accelerated is controversial (13). Hypertension and diabetes are risk factors common to renal failure and atherosclerosis; a substantial proportion of dialysis patients smoke (14), and lipid abnormalities are prevalent (15). The relative contribution of these to the development of atherosclerosis has not been determined in patients with ESRD. The prevalence of asymptomatic coronary disease was 30% in young males being considered for transplantation (16) and is probably even higher among older patients.

B. Normal Left Ventricle

The left ventricle (LV) is a cone-shaped structure, with inlet (mitral) and outlet (aortic) valves at the base. It has a cavity whose volume varies during the cardiac cycle and walls of muscle which alternately contract and relax with each cardiac cycle. Ejection of blood occurs during systole as a result of muscle contraction, while cardiac filling occurs during diastole (both an active and a passive process). Clinical ventricular failure reflects a failure of either of these processes (usually abnormal systolic function due to intrinsic muscle disease or muscle injury).

The basic mechanisms that influence the contraction of isolated cardiac muscle affect the performance of the whole ventricle in a similar manner. The degree of stretch on ventricular muscle at the end of diastole (the 'preload': end-diastolic wall tension) is an important determinant of the quality of the contraction which follows. The second major determinant is 'afterload' which may be defined as the tension, force or stress (force per unit cross-sectional area) acting on the ventricular fibres after the onset of shortening. The determinants of wall stress are cavity size, peak systolic pressure, and wall thickness, with the

relationship between them defined according to the law of LaPlace. (The relation assumes a thin-shelled structure and it's limitations as a relation for LV wall stress have been pointed out (17).) The third determinant of ventricular performance is 'contractility', more precisely the slope of the ventricular developed pressure/volume relation, which refers to the intrinsic contractile properties of the myocyte independent of loading conditions.

The simplest measure of systolic performance is the left ventricular ejection fraction, which is the ratio of the volume ejected with each beat (the stroke volume) to the volume of the ventricle at enddiastole (the enddiastolic volume). The endsystolic volume is probably a better index, but calibration problems limit the value of measurements derived by most imaging techniques.

While measurement of ventricular volumes provide information about physiology, ventricular mass is an anatomic measure. Measured at autopsy, it's use predated in vivo measurement of volumes, when the precedent was set for it's use as an index of cardiac status.

Absolute measures of volume or mass need to be standardised to body size. This is conventionally done to body surface area (estimated from a weight/height algorithm), thus left ventricular mass index (g/m^2). It has recently been argued that with regard to the influence of obesity on left ventricular mass, standardisation to height (as g/m) may be more appropriate (18).

C. Left Ventricular Hypertrophy

1. Pathophysiology

The pathophysiology of LVH has been extensively studied (19,20). When the primary insult is a pressure overload (as in hypertension or aortic valve stenosis), systolic wall stress rises, with adverse effects on contraction and

myocardial oxygen requirements. The ventricle responds by increasing wall thickness in order to normalise wall stress; muscle cells enlarge in parallel, so called 'concentric' hypertrophy, with wall thickening at the expense of the cavity. In contrast, when the primary insult is volume overload (as in aortic or mitral valve regurgitation, loss of pump function through infarction, or any state associated with an increased venous return and increased enddiastolic volume), muscle cells enlarge in series, so called 'eccentric' hypertrophy: cavity size is not reduced, and absolute thickness may not be above 'normal'. While these two states are physiologically distinct, they often coexist, and in disease, either type of hypertrophy may predominate.

The distinction between hypertrophy and dilatation must be made. As described above, a dilated ventricle must hypertrophy if wall stress is to be normalised and systolic function preserved. In patients with clinical heart failure, the most common finding is progressive left ventricular dilatation with impaired systolic function. Although left ventricular mass (LVM) is increased, it is postulated that hypertrophy is 'inadequate' and systolic performance consequently impaired (21,22). An inverse relation has been described between wall stress and left ventricular ejection fraction (23). Although a primary volume or pressure overload is not always evident (as in idiopathic dilated cardiomyopathy), a degree of wall thickening is to develop if wall stress is to be normalised in relation to it's two other major determinants, cavity dimension (enddiastolic volume) and peak systolic pressure. It has been postulated that a threshold level may be reached where the ability of the muscle cells to hypertrophy is exhausted and systolic performance deteriorates (24).

At the other end of the spectrum, the walls may thicken at the expense of the cavity (concentric hypertrophy). If peak systolic pressure is normal, wall

stress is low, and hypertrophy is held to be 'inappropriate'. An example is 'hypertrophic cardiomyopathy' in which wall thickening may be uniform or asymmetrical.

The ratio of enddiastolic radius to wall thickness has been suggested as a measure of the 'adequacy' of hypertrophy in relation to cavity size, and the product of this term and peak systolic pressure, a proxy for wall stress, as an index of 'appropriateness' of hypertrophy (25). Conceptually similar to the radius/thickness ratio is the mass/volume ratio (24).

2. Consequences

Although it is believed that hypertrophy develops in order to normalise wall stress, considerable evidence exists that the ventricle is not well suited to longstanding hypertrophy: in some patients microvascular changes may develop (26), in others, although resting myocardial blood flow may be adequate, under conditions of increased work, vasodilator reserve may be reduced (27,28). These result in intermittent ischaemia (29) and ventricular arrhythmias (30,31). Furthermore the hypertrophied ventricle may be less compliant than normal and operate at an increased filling pressure ('diastolic dysfunction'): this may result in left heart failure or pulmonary hypertension.

3. Prognostic importance

Hypertrophy is a frequent finding in victims of sudden (unexpected) death when coronary disease is not responsible (7). The Framingham study demonstrated the prognostic importance of electrocardiographic LVH in asymptomatic persons, with an estimated relative risk of cardiovascular events of 2.3 in males and 2.6 in females (5). The relative risk was as great as that seen with unrecognised myocardial infarction. More recently echocardiographic LVH has been reported to predict coronary disease events independent of the standard

risk factors in a subset of the Framingham cohort (6), with relative risks (based on comparison of upper- and lowermost quintiles of left ventricular mass index) of 7.8 in males and 3.4 in females. Other studies have described LVH as a risk factor for both morbid and fatal cardiovascular events in patients with hypertension, and able to predict events more accurately than the absolute level of blood pressure (3,4). Not surprisingly, prevention or regression of LVH has become one of the goals of therapy in hypertension management (32).

4. Detection

Prior to the advent of echocardiography, the diagnosis of LVH (present/absent) was made by electrocardiography, which has low sensitivity and is unable to estimate LV mass (33).

The gold standard for the assessment of left ventricular hypertrophy is the weight of the LV at autopsy. Two components- the walls and cavity of the LV- contribute to it's weight, and both can be measured by M-mode and 2-dimensional echocardiography (echo). Echocardiographic methods for estimating left ventricular mass have been validated against autopsy-determined LV mass (34), with a close correlation (r=.92) but a systematic tendency for mass to be overestimated by echocardiography. In 52 patients, LVH (defined as left ventricular mass exceeding the 95th centile in apparently normal subjects) was classified by echocardiography with a sensitivity of 100% and specificity of 56%, for an overall accuracy of 71% (35). It is usual to correct for this overestimation with a regression equation (35). This correction should improve on the reported specificity, but this has not yet been tested. Further considerations regarding the echocardiographic estimation of LV mass are dealt with in Appendix 4.

D. Left ventricular hypertrophy in end-stage renal disease

In ESRD, the prognostic importance of LVH has received comparatively little attention. A high prevalence was observed in patients treated by Chronic Ambulatory Peritoneal Dialysis, with an apparent high mortality during a short followup period (8). One study reported a high prevalence among patients selected for the absence of known cardiac disease (36); another reported a prevalence of 48% in a cross-section of patients maintained on haemodialysis (37); the significance of this hypertrophy was not examined.

Estimation of LV Mass

The echo estimation of LV mass has not been validated in patients with ESRD. The method includes a correction factor for the specific gravity of cardiac muscle (1.05 in non-renal failure). Based on studies in experimental uraemia, it has been suggested that the increase in LV mass may reflect increases in interstitial matrix rather than changes in myocytes (70); furthermore a clinical study has reported increased myocardial calcium content in ESRD (38). The specific gravity term may thus be inappropriate.

Effects of transplantation

Recently, regression of LVH following renal transplantation was reported (39). 41 patients were studied by echocardiography before and a mean of 1.5 years after renal transplantation. Both posterior wall thickness and cavity dimension reduced following successful transplantation; in these patients, in addition to the reversal of the uraemic state, blood pressure and anaemia were improved. The population studied was a selected group, of similar 'baseline' characteristics to their overall renal transplant population.

E. 'Explaining' hypertrophy

In the literature, simple and multiple linear regression have been used to examine the relationship between measured left ventricular mass index (LVMI) and patient characteristics of interest. Based on the product-moment correlation coefficient, authors have commented how little variation in LVMI is explained by measured blood pressure, and have pursued other factors in both clinical and laboratory research (40,41). Left ventricular hypertrophy is no doubt a multifactorial phenomenon: however even if only one factor were responsible, what would satisfy a critical 'r' value is not clear. In order for all the observed variation in LVMI to be explained by variation in systolic blood pressure, both would have to be measured without error and be precise markers of their biologic counterparts (myocyte hypertrophy and ventricular afterload). No other factors could modify the relationship, and random variation could not be present. The rationale of explaining variance as a means of examining cause-effect relationships has been questioned (42).

F. Factors associated with left ventricular hypertrophy

1. Without renal failure

LVH is most often encountered in patients with hypertension, although it's development is not universal. The strongest relationship reported has been with the use of continuous 24 hr blood pressure monitoring, with echocardiographic LVMI relating to mean systolic blood pressure with an estimated regression coefficient of 1.7 $mg/m^2/mmHg$ (r=.59) (43). Experimental work suggests that longstanding beta-adrenergic stimulation or exposure to angiotensin promotes myocyte hypertrophy, and in clinical studies regression of hypertrophy has been observed in hypertensive patients treated with beta-

adrenoreceptor blocking agents or angiotensin converting enzyme inhibitors, but not in those treated with agents in which reflex sympathetic activity is unopposed (44). Other factors invoked have been sex, race, and age, but the relationships are very weak (39).

Abnormalities of the mitral or aortic valves, with consequent pressure or volume overload, result in LVH, as does ischaemic heart disease with LV dilatation (45). Similarly any condition associated with LV dilatation will manifest a raised LV mass, although such hypertrophy may not be 'adequate' (46). Whether or not uraemia (47) or diabetes (48) are associated with specific cardiomyopathies has long been controversial. The distinction is in most ways unhelpful, as the term 'cardiomyopathy' refers widely to all primary disorders of heart muscle function and includes left ventricular hypertrophy with heart failure otherwise unexplained.

2. With renal failure

A weak relationship between LV mass and measured blood pressure has been observed in dialysis patients (49). There has been recent interest in Parathyroid Hormone, following a report that bone indices of hyperparathyroidism were inversely related to LVMI (36) although the relationship to serum PTH was less convincing (49). It is suggested that hyperparathyroidism prevents the development of adequate muscle hypertrophy. Although anaemia has never been examined in relation to LV mass, strong relationships between anaemia and LV cavity dimension (36) and increased cardiac work (50) with reversal by transfusion (51) have been shown, and as mentioned, LV cavity size is a major determinant of LV mass Other factors in renal failure which might be expected to contribute to the development of LVH are intravascular expansion associated with the fluid overloaded state (52), and

the effective LV volume overload of arteriovenous fistula flow. These are more likely to be encountered in haemodialysis patients than in those treated by CAPD or transplantation.

3. HYPOTHESES AND OBJECTIVES

Primary Hypothesis: Left ventricular hypertrophy is of independent prognostic importance in patients beginning replacement therapy for End-stage Renal Disease.

Objective: To estimate the risk associated with left ventricular hypertrophy, as measured by Left Ventricular Mass Index (LVMI).

Primary Outcome: All cause mortality

Secondary Outcome: Cardiac mortality

Secondary Hypothesis: The development of left ventricular hypertrophy in end-stage renal disease is multifactorial. Several clinically measurable factors relate to left ventricular mass. These include systolic and diastolic blood pressure, anaemia, parathyroid hormone, arteriovenous fistula flow, coronary artery disease, and diabetes mellitus.

Objective: To estimate the strength of the relationship between left ventricular hypertrophy and these factors.

4. PATIENTS AND METHODS

A. Cohort Assembly

Attached to McGill University, the Royal Victoria Hospital (RVH) is a tertiary referral centre which offers all forms of renal replacement therapy with the exception of home haemodialysis. In 1983, a protocol was established for the evaluation of patients beginning renal replacement therapy, which included routine echocardiography. Beginning in August 1987, dialysis records were examined to identify all patients being treated by dialysis after 1st January 1983. In order to assemble an incep'.on cohort, patients who began dialysis prior to 1983, patients rejoining after failed transplantation, and patients referred to the RVH after beginning dialysis elsewhere were excluded. Also excluded were patients with acute renal failure (as assessed by the attending medical officer at the time of admission) who either died or recovered renal function. Patients initially thought to be suffering from acute renal failure who did not recover function and who remained on dialysis longterm were included. Other exclusions were patients with haemodynamically significant heart valve disease (which might lead to LVH and be associated with an adverse outcome of it's own right) and patients with known preexisting malignant disease.

390 patients were screened, of whom 119 met the entry criteria and were included in the study. 109 were followed at RVH, while 10 were transferred elsewhere. All these patients were followed as to vital status. The breakdown of screened patients is shown in Figure 1.

B. Echocardiographic Data

The records of the department of echocardiography were examined to establish the dates of echocardiographic studies. All studies were performed using an ATL-600 apparatus (Advanced Technology Laboratories, Bothell, WA) and reported by one of two observers. Left ventricular wall thickness and cavity size (enddiastole and endsystole) and left atrial dimension were recorded and kept in a file separate from that used for the abstraction of the hospital record.

Left Ventricular Mass estimation

LV mass was determined by the method of Devereux and Reichek (34) using American Society of Echocardiography measurement criteria (53) and normalised to body surface area as left ventricular mass index (LVMI, grams/m^2). The method has been validated against autopsy LV mass in a wide range of normal and abnormal hearts. The method is less accurate in markedly distorted hearts (such as those with LV aneurysm following myocardial infarction), where it tends to underestimate LV mass (34, 35). Since such hearts function poorly, are at risk of arrhythmias, and adversely affect survival, using the method in such hearts would bias this analysis toward the null hypothesis.

C. Data abstraction

Demographic characteristics and information regarding possible confounding factors were abstracted from hospital records. These included age, height, duration and cause of renal failure, presence and duration of diabetes mellitus and hypertension, angina, known or suspected myocardial infarction, prior coronary artery grafting, smoking status, degree of renal failure at the time of pre-treatment echocardiography, systolic and diastolic blood pressure, serum haemoglobin, serum calcium, phosphate, alkaline phosphatase and parathyroid

hormone, and electrocardiographic findings. A single operator performed all abstraction according to a pre-designed form which included the date of echocardiographic examinations, but not the echocardiographic data. Wherever possible, the three blood pressure or laboratory values closest in time to the relevant echocardiographic study were noted. Electrocardiographic findings were classified according to the report in the hospital record.

D. Definitions

Definite Myocardial Infarction

An ECG report of definite myocardial infarction, an ECG report of probable infarction in a patient with angina, or an ECG report of possible infarction along with regional wall motion abnormality on the echocardiogram.

Coronary Artery Disease

Proven coronary disease by coronary angiography; ECG report of definite myocardial infarction; regional wall motion abnormality on echocardiography along with ECG changes consistent with ischaemia; chest pain suggestive of angina. The latter criterion, while of low specificity, was included so as to improve sensitivity in classifying this important prognostic variable. While angina may occur in hypertrophied ventricles without obstructive coronary disease, the misclassification so introduced would obscure, rather than enhance, the hypertrophy/survival relationship in multivariate analysis.

Hypertension

High blood pressure requiring drug treatment. In some patients, blood pressure was controlled without drugs once dialysis was begun. Such patients retained their original 'hypertensive' label. Patients with a high blood pressure

at first evaluation, who had not used antihypertensive drugs, and whose blood pressure normalised without therapy were not labelled hypertensive.

Left ventricular hypertrophy

In the logistic regression analysis with LVH as the Y-variate (Appendix 2), LVH was defined as left ventricular mass index greater than 131 g/m^2. This was the median of LVMI in the population, and such stratification maximised efficiency for fitting the logistic function. For testing the proportionality assumption in the Cox model survival analysis, and for constructing non-parametric survival curves, LVH was defined as LVMI > 125 g/m^2. This corresponds to the upper 95th centile of two normal populations reported in the literature (3).

E. Outcome Classification

Mode of death assignment

The attending physician was asked to describe the MODE of death according to criteria based on those used in the Lipid Research Clinics Coronary Primary Prevention Trial (54). The criteria used are listed in Appendix 1. Sudden death, death in heart failure refractory to ultrafiltration or death following a definite ischaemic event were considered to be cardiac. In view of the difficulty in assigning cause of death in patients with multisystem disease, all cause mortality was used as the primary endpoint for the survival analysis. Since the mode of death always includes a terminal cardiac event, LVH may be a contributor to 'noncardiac' mortality (by lowering the threshold for terminal cardiac arrest such as in the setting of hypoxia, acidosis or hypotension due to infection or blood loss. Clearly cancer deaths would be an exception.). Cardiac mortality was also examined, but was not a primary outcome of interest.

F. Miscellaneous

Stratification

In certain instances, continuous variables were stratified for categorical analysis. Age was dealt with as in the Canadian Renal Failure Registry: less than 45 years, 45-64 years, and 65 years and over. For haemoglobin and parathyroid hormone contrasts were established according to the value being below the 25th centile, between 25th and 75th centiles, and above the 75th centile for this population. These led to groupings for haemoglobin of less than 80 g/L, 80-110 g/L, and greater than 110 g/L, and for parathyroid hormone, of less than 60, 60 to 290, and greater than 290 mgeq/l (55).

'Explaining' hypertrophy: Cross-sectional approach

It has previously been suggested that hypertrophy tends to progress once dialysis is begun (7). In this study, not all patients were studied by echocardiography before the commencement of dialysis, despite the protocol which intended otherwise. Similarly not all patients studied had pairwise examinations. For the purpose of examining the factors associated with hypertrophy, the population was examined in cross-sectional fashion at two points in follow-up time: at the initiation of dialysis (the 'baseline' cross-section) and after a variable period of replacement therapy (the 'followup' cross-section). Several patients were common to both cross-sections. These patients were also studied separately.

G. Data management

Data were entered in d-Base III Plus (Ashton-Tate, 1984). Analysis was performed using SAS (Statistical Analysis Systems, Cary, N.C.) and BMDP (University of California, Berkeley) software.

H. Statistical Considerations

Survival Analysis

The Cox Proportional Hazards model (BMDP-2L) was used to estimate the survival function. Transplantation was treated as a time-dependent covariate (56), since it has been shown that this method minimises the effects of crediting survival time on dialysis toward transplantation (10). The proportionality assumption was tested using the log-minus-log rank method (BMDP-2L). Stepwise automated models were not used for multivariate analyses (see Appendix 2, where a part of the analysis is repeated using stepwise modelling). All p values reported are two-sided, even though the hypotheses are one-sided. For continuous variables, relative risks are presented as a comparison between upper- and lowermost quintiles of the variable (top 20% versus bottom 20%), as was done in the Framingham study (6). The term 'relative risk' is used in it's generic sense, since technically the model deals with hazard ratios. Confidence intervals are test-based (57).

'Explaining' hypertrophy

Simple and multiple linear regression were performed by the least-squares method with left ventricular mass index (*LVMI*) as the Y-variate. In this analysis, the emphasis is on the regression coefficient (beta) rather than the correlation coefficient (rho) as the measure of the strength of the relationship. When examining the components of LVMI, Spearman's Rank Correlation coefficient is used. In Appendix 3, the relationship between LVH (present or absent) and the variables of interest is examined using multiple logistic regression. The purpose of this analysis is to see in what way the qualitative

conclusions are affected by the choice of regression model. Here LVH was defined as Left Ventricular Mass Index (LVMI) greater than 131 g/m^2 and the multiple logistic model fitted to the same X-variates as in the multiple linear regression analysis. The use of the term 'effects' refers to statistical effects, with inference regarding biologic effects left to the reader.

5. RESULTS AND DISCUSSION

Patient populations

The overall population of 119 patients was divided into several subpopulations for these analyses. The breakdown is shown in Figure 2.

For the survival analysis (primary hypothesis), an inception cohort was identified. These were patients who had undergone echocardiographic study within the first two months of starting dialysis, of whom there were 91 in number. Six patients died before echocardiography could be performed (within the first two months of starting dialysis). The remaining 22 patients were studied for the first time when already established on dialysis or in some cases, post-transplantation. Since it has previously been suggested that LVH progresses on dialysis (7), rather than backdate echocardiographic data, these 22 patients were examined in a separate survival analysis, based on survival from the time of echocardiography. The characteristics and outcome of these three 'groups' (early, late only, no echo) are reported separately. (Part 1.)

For the analysis of factors associated with hypertrophy (secondary hypothesis), two populations were defined. The 'baseline' cross-section comprised 87 patients who had echocardiography performed prior to, or within the first month of, starting dialysis (median 2 months pre-dialysis, range 30 months pre- to 1 month post-dialysis). The 'followup' cross-section comprised 85 patients who were studied after a variable period of replacement therapy (median 21 months, range 4 to 56 months after beginning dialysis). 59 patients had at least two paired studies and were common to both 'baseline' and 'followup' cross-sections. (Part 2.)

Part 1. Hypertrophy and survival

A. Clinical characteristics

The characteristics of the patients in the three groups are shown in Table 1.1. By echocardiographic criteria, over half the patients studied had LVH (defined as left ventricular mass index (LVMI) exceeding the 95th centile of a 'normal' population). In contrast, LVH as detected by ECG was less common, in keeping with it's lower sensitivity. Four of the six patients who died before echocardiography could be performed had ECG-LVH. A history of hypertension was common in all three groups, although mean systolic and diastolic blood pressure was only mildly raised. No patient with prior myocardial infarction or angiographically confirmed coronary disease was angina-free. Several patients, however, suffered from angina without confirmed coronary disease. Definite myocardial infarction was most common in the group studied early, and less so in those studied late only; the prevalence of angina, however, was similar. In all other respects the three groups were reasonably similar. Consistent with progression of hypertrophy on dialysis, mean LVMI was higher in the patients who were studied for the first time late in the course of replacement therapy.

B. Followup

Vital status was determined for all patients eligible for the study, who were followed until February 1st 1988 (median followup 19 months, range 2 days to 61 months). Actuarial survival for the whole cohort (119 patients) is shown in Figure 3. This survival is similar to that of all patients in Canada as described in the Canadian Renal Failure Registry (1), and that reported from two Montreal hospitals over a ten-year period ending in 1982 (12). There were 45 deaths, 34 among the 91 patients included in the major analysis (Section C.1). 19 of these 34 were 'cardiac' deaths.

C. Cohort studied 'Early'

1. Cox model survival analysis

Crude Associations

The crude associations between all-cause and cardiac mortality and the factors of interest are given in Tables 1.2 and 1.3, respectively. For continuous variables, relative risks are displayed as a comparison between upper- and lowermost quintiles. The relative risk (RR) of dying associated with LVMI was 3.7 for both all-cause and cardiac mortality. Endsystolic dimension, which is a measure of left ventricular systolic function (and has been proposed as the 'best' predictor of survival after myocardial infarction (58)) predicted mortality with similar ability. Age was a very powerful predictor of mortality (RR 26 for all-cause and 15 for cardiac mortality), as was angina (RR 4.9 and 9.2 respectively) and diabetes mellitus (RR 2.3 and 3.6 respectively). Only one transplanted patient died during the followup period, from a non-cardiac cause; for all-cause mortality, the confidence limits about the estimate for transplantation are thus very wide, and the coefficient for cardiac mortality is inestimable. Neither sex, underlying kidney disease (other than diabetes) nor the level of systolic blood pressure was significantly associated with mortality. There was a trend toward greater cardiac mortality in patients with a diagnosis of hypertension, but this was not conventionally significant.

Actuarial survival curves according to high and low indices of left ventricular mass index are shown in Figure 4. The cutpoint of 125 g/m^2 corresponds to the upper 95th centile for two normal populations (3). Patients with hypertrophy fared worse, the curves separating early in the course of treatment.

Adjusted associations (Tables 1.4 and 1.5)

Since endsystolic dimension (ESD) is the major determinant of enddiastolic dimension (EDD), and since EDD forms part of the calculation of LVMI, the effects of LVMI on survival were not examined conditional on ESD in the full model. Although hypertension was not significantly associated with survival in the univariate analysis (see Table 1.2), this variable was included in the adjusted analysis so that the estimated effect of LVH would be conditional on prior hypertension.

The adjusted RR associated with LVMI was 2.9 (all-cause mortality) and 2.7 (cardiac mortality). The adjusted RR for age was still substantial, although lessened (12.0 for all-cause, and 5.7 for cardiac mortality). As expected, angina was a powerful predictor of cardiac mortality (Relative risk 5.1).

2. Tests for non-proportionality

Following the completion of the analysis, the proportional hazards assumptions were tested. The analysis which follows indicates that the proportionality assumption was not met with regard to the variable 'hypertension' (which had been included even though the crude coefficient was not statistically significant). Plots of the log-minus-log survival function are shown in Figure 5, according to strata of the x-variates included in the model described in Table 1.4. The plots indicate that with the exception of hypertension (5A), the proportionality assumption is reasonable for all variables considered (5B-5E). (If the plots remain reasonably constantly separated over time, then the proportional hazards assumption holds; in contrast, if curves cross then the assumption is violated.) Plots of the hazard function are not available for time-dependent covariates; the BMDP 2L program instead offers a function to test the proportionality assumption. The function produced a coefficient whose z

statistic (-.8867) suggests that the proportionality assumption is not inappropriate with regard to the variable transplantation.

To accommodate the non-proportional hazard, the model in Table 1.4 was repeated in the form of a stratified analysis (by hypertension absent/present), whereby the survival function is estimated within each stratum and the likelihood maximised is the product of the individual stratum-specific likelihoods. The results are shown in Table 1.6. None of the estimates is substantially different from those in Table 1.4. Thus, although the variable 'hypertension' failed to meet the proportionality assumption, the conclusions were not substantially affected.

3. Components of Left Ventricular Mass Index

The estimation of left ventricular mass is based on measurement of both posterior wall thickness and left ventricular cavity dimension. In order to identify which component of left ventricular mass estimation was associated with an adverse outcome, the effect of each was examined in a limited survival model which included only measured posterior wall thickness and cavity dimension. The estimates thus obtained are adjusted for the other factor (Table 1.7). For both all-cause (one-sided p=.01) and cardiac (one-sided p=.04) mortality, an independent relationship between survival and wall thickness is evident, with patients in the uppermost quintile of the distribution manifesting a two-fold greater risk of death compared with those in the lowermost quintile. The independent estimates for cavity dilatation are not conventionally significant, but similar trends are observed.

4. Effects of wall thickness adjusting for impaired systolic function

A dilated left ventricular cavity at enddiastole may reflect increased venous return during diastole (true volume overload) or a raised left ventricular volume at endsystole (effective volume overload) with normal venous return. A raised volume at endsystole indicates systolic dysfunction, and is usually associated with clinically evident heart failure, radiologic cardiomegaly, or reduced left ventricular ejection fraction on ventriculography. It is thus meaningful to look at the effects of posterior wall thickening conditional on endsystolic dimension, as a guide to the clinical usefulness of measuring wall thickness once systolic function has already been quantitated. This analysis is shown in Table 1.8. An independent effect of wall thickening is evident after adjusting for endsystolic dimension.

5. Stepwise procedure

The Cox model survival analysis (Section C.1) was repeated using a stepwise (competing) regression program. The results are described in detail in Appendix 2. The effect of LVMI was similar to that seen in the main analysis.

D. Cohort studied late only

Cox model analysis: survival from the time of echocardiography

Only crude estimates were determined for this small population (Table 1.9). With the exception of angina, the point estimates of coefficients and relative risks were all similar to those in the cohort who were studied early, although two-tailed p-values exceeded .05. The estimated relative risk with LVMI in the uppermost quintile was 2.5. Since these 22 patients were selected for having survived to the time of echocardiography (median 366 days, range 103 to 898 days after starting dialysis), by definition, angina determined at entry

had been nonfatal, and it is not surprising that in these patients angina no longer appeared to confer any risk.

E. Discussion

This study is the first to examine the relationship between left ventricular hypertrophy and prognosis in end-stage renal disease in longitudinal fashion. The prognostic importance of LVH evident in the present study is consistent with findings in patients with hypertension (3), in apparently normal persons (5,6,7), and in trained athletes (59). Ventricular arrhythmias, probably reflecting subendocardial ischaemia due to abnormal vasodilator reserve (27,28) or structural changes in the coronary microcirculation (26) appear to be the most likely mechanism of increased risk for death, both unexpected and associated with intercurrent acute illness.

The effect of LVH appeared to be strong and persisted after adjustment for known important prognostic covariates. These included age, diabetes mellitus, coronary disease, and blood pressure.

Since coronary angiography was not part of our routine evaluation, we will necessarily have misclassified some patients. We chose to use angina rather than definite myocardial infarction as our marker for coronary disease in order to maximise sensitivity. Angina may occur in LVH without coronary artery disease, but the effect of this would be to reduce, rather than enhance, the relationship between hypertrophy and survival seen in the multivariate analysis. Given the reported high prevalence of coronary disease in patients with end-stage renal disease (15) it is likely that coronary artery disease is the most important factor in determining survival in these patients, and that hypertrophy magnifies the impact of associated coronary artery disease.

The importance of 'parallel' or 'concentric' hypertrophy manifesting as wall thickening (18, 19) versus hypertrophy presenting as cavity dilatation ('series' or 'eccentric') was evident when the models examining the components of left ventricular mass index were examined. Since there appears to be no plausible mechanism whereby coronary disease might lead to wall thickening without cavity enlargement, it is unlikely that unrecognised coronary artery disease was responsible for the apparent independent effect of wall thickening on survival.

Several limitations of this study must be recognised. Followup was complete for all patients deemed eligible, thus avoiding a potential bias in longitudinal followup studies of this type, and patients who were transferred elsewhere were followed as to survival status. Nevertheless, only 91 patients (77%) were studied by echocardiography at the initiation of dialysis. The findings in the remaining, however, support the importance of LVH in determining outcome. Since it has been suggested that hypertrophy tends to progress on dialysis (7), survival in patients studied for the first time late in the course of treatment was examined from the time of echocardiography, not the commencement of replacement therapy. The estimated relative risk associated with LVH in these patients was quantitatively similar to that in the 'early' population. Of the six patients who died before echocardiographic study, four had ECG-LVH. It is likely that these patients would have strengthened the association between LVH and death had they been included.

Because of the retrospective nature of this study and the paucity of autopsy data, the attending physician was asked to assign the mode of death. Although blinded to the precise nature of the study question, whether or not patients manifested LVH was known to the physician and might have influenced the assignment of cardiac or non-cardiac death. For this reason, all-cause

mortality was chosen as the primary endpoint of the study. However the findings for all-cause and cardiac mortality are similar and consonant with the hypothesis that LVH is an independent marker of risk in these patients.

Part 2. Factors associated with hypertrophy

A. Clinical characteristics

For this analysis, the population was studied in cross-sectional fashion at two points in patient time. The 'baseline' cross-section (N=87) related LVMI determined at or near the commencement of dialysis to variables measured at that point in time. The 'followup' cross-section (N=85) related LVMI measured after a variable period of replacement therapy to variables measured at that (later) time. 59 patients had paired studies and were common to both cross-sections. In these patients, the change in LVMI between paired studies was examined in relation to changes in the variables of interest.

The clinical characteristics of the three cross-sections are shown in Table 2.1. (These populations are not independent: the 59 patients in the 'paired' population are common to both 'baseline' and 'followup' cross-sections, and the values in the table are those at their 'baseline' evaluation). The prevalence of hypertension was high at both 'baseline' and 'followup', and in most other respects, the cross-sections were similar. The patients studied in paired fashion were not substantially different from other patients, aside from a slightly lower prevalence of definite myocardial infarction.

B. Linear regression analysis

1. Baseline cross-section (Table 2.2)

(Values are expressed as mean ± standard deviation)

Left ventricular mass index was higher in patients with a history of hypertension (125±37 vs 108±54 g/m^2, p=0.026) and in diabetics (132±56 vs 115±37 g/m^2, p=0.020). An inverse relationship (ß= -0.17 g/m^2/g/l) existed between LVMI and haemoglobin level, but this was not statistically significant (p=0.21). Aside from hypertensive or diabetic nephrosclerosis, underlying kidney disease was not associated with LVMI, nor was LVMI different in patients with prior 'definite' myocardial infarction. Neither age nor parathyroid hormone levels were significantly associated with LVMI.

2. Followup cross-section (Table 2.2)

A significant relationship existed between LVMI and systolic blood pressure, with an estimated regression coefficient of 0.62 g/m^2/mmHg (95% confidence limits, 0.23 to 1.0, Figure 6). There was no relationship with diastolic blood pressure. LVMI was higher (p=.11) in those with a history of hypertension (140±45 vs 124±64 g/m^2), (Table 2.2). In contrast to the relation in the baseline cross-section, LVMI was considerably higher across strata of haemoglobin level (161±36 g/m^2 in patients with Hb <80 g/L, 106±27 g/m^2 with Hb >110 g/L, p=.0002) (Figure 7). Mean LVMI was again higher in diabetics (151±80 vs 130±80 g/m^2, p=0.03) (Figure 8). Mean LVMI was 153±72 g/m^2 in those with definite prior myocardial infarction versus vs 131±46 in those without, and 157±44 versus 128±46 g/m^2 in patients with a history of angina. Again no relationship was found to parathyroid hormone.

Effects of treatment

LVMI was lower in 12 patients with a functioning transplant (112±58 vs 139±37 g/m^2, p=0.061). No data were available regarding either the presence or the size of an arteriovenous fistula. Since a fistula is an absolute requirement for haemo- but not peritoneal dialysis, differences in LVMI between patients treated by haemodialysis as opposed to peritoneal dialysis were sought. No treatment differences were seen. Since crossover occurred between treatment modes (approximately equal in both directions), the analysis was repeated with such patients excluded, and still no differences were evident.

In addition to fistula flow, another factor in haemodialysis is volume expansion (either longstanding or intermittent). The measure of hypertrophy used in this study (LVMI,g/m2), adjusts LVM for body surface area, which is calculated from height and weight. Consequently, any effects of volume expansion (with weight gain) would not be detected by this analysis.

Components of LV mass estimation

Since left ventricular mass is determined by both wall thickness and cavity dimension, the relationships between LVMI and X-variables of interest were investigated further, in an attempt to gain insights into the mechanisms by which these factors are associated with hypertrophy. These analyses are summarised in Table 2.3. Rank correlations are reported, and the 'associations' are not adjusted for the other variables.

Parameters reflecting coronary disease (definite myocardial infarction, angina, or coronary grafting) were correlated with cavity dilatation (one-sided p=.03), while hypertension was correlated with increased wall thickness. Anaemia was correlated with both posterior wall thickness and cavity dilatation. Surprisingly, diabetes was correlated with wall thickening rather than cavity

dilatation. In view of this, the diabetes/LVMI relationship was more closely examined to see if confounding by hypertension (a common accompaniment of diabetes both with and without renal failure) explained the apparent diabetes/hypertrophy relationship. The diagnosis of hypertension, rather than the level of blood pressure, was used for this analysis, which is shown in Table 2.4. The difference between Type I (hierarchical) and Type III (all terms adjusted) sums of squares indicates that some confounding by hypertension is present. The analysis using the level of blood pressure rather than the diagnosis of hypertension was similar (not shown in Table 2.4). Also not shown is the analysis including an interaction term which did not suggest modification of the effects of diabetes or hypertension by each other.

2.1. Logistic Regression

In this (a subsidiary) analysis, LVH was defined categorically (as LVMI>125 g/m^2) and the multiple logistic model fitted to the 'followup' data. These analyses are described in Appendix 3. The odds ratios against developing LVH were 5.0 and 3.3 to 1 for patients with serum haemoglobin values in the highest and middle strata, respectively, when compared with the lowest stratum. The same variables were examined as in the multiple linear regression analysis (section B.2). The observed effects of these variables were affected by the cutpoint chosen to define LVH (see Appendix 3).

3. Paired comparison

59 patients had a baseline study, performed prior to beginning dialysis, and a subsequent study, a median of 24.6 months (range 4 to 54 months) after the first. The overall mean difference in LVMI between first and last studies was statistically significant (+12 g/m^2, p=0.03) but the range of change was

highly variable (-70 to +147 g/m^2, median 3.5 g/m^2). The change in LVMI was inversely related to the change in haemoglobin level (ß= -0.44 g/m^2/g/l, p=0.03). LVMI decreased by 23.6±13 g/m^2 in 12 patients transplanted (p=0.078). This reduction was due to both reduced wall thickness and reduced cavity size. In contrast, LVMI increased in most patients not transplanted (Figure 9). The relationship between the change in LVMI and change in haemoglobin was only slightly diminished after adjusting for transplantation (ß= -0.39 g/m^2/g/l, p=0.07).

C. Discussion

No validation exercises were performed in this study, and numerous sources of (random) error could not be avoided. This is most pertinent to those factors which seem to be not related to survival nor the development of left ventricular hypertrophy, where the possibility of type II (beta) error must be considered.

The first source of error derives from both the method and performance of echocardiography for the estimation of left ventricular mass. Considerations regarding this and other important sources of error are dealt with in Appendix 4. It is likely that the error in LVMI estimation in this study is the same as in other studies of similar design.

This analysis was imperfect for estimating the effects of blood pressure, a most important determinant of LVH (see Appendix 4). Blood pressures measured during hospitalisation or at hospital visits may be poor markers for ambulatory blood pressure or blood pressure over the period during which hypertrophy develops. Furthermore, single readings may be misleading, and in some instances the temporal relationship between measurement of blood pressure and echocardiography was less than optimal. For these reasons, the weak

relationship between blood pressure and hypertrophy should not be taken to imply that blood pressure was not an important determinant in these patients.

The most interesting finding, potentially amenable to correction, was the association between anaemia and hypertrophy. Not only cavity dimension, as previously reported (36), but also wall thickness was increased in anaemic patients. The mechanism whereby this may be is speculative but in the candidate's view, most plausible. It has previously been shown that anaemia increases cardiac output and cardiac work in renal failure (50), the consequence being that to maintain oxygen delivery, an effective volume overload is placed on the heart. The heart could meet this increased demand either by increasing heart rate or increasing stroke volume. Heart rate is the major determinant of myocardial oxygen demand (22) and is a most inefficient way to increase cardiac output in the longterm; however stroke volume can be increased relatively efficiently by increasing cavity dimension and utilising 'preload reserve' (60). However in order to maintain normal systolic wall stress (and maintain contractility), it is necessary for hypertrophy to develop.

In this study, in patients studied at baseline, the relationship between haemoglobin and left ventricular mass was not statistically significant. However, since some of these echocardiographic studies were performed several months pre-dialysis, in several patients contemporaneous haemoglobin measurements were not available. Haemoglobin levels measured closer to the commencement of dialysis were used, and as described in Appendix 4, haemoglobin fell as dialysis approached. In patients who could be studied in paired fashion, left ventricular mass increased as haemoglobin fell, and by the time of the 'followup' cross-section, the association between anaemia and LVH was clearly evident.

It remains possible that the 'effect' of anaemia suggested by the paired

comparison is confounded by some other factor. For more than half the patients, the 'baseline' study was performed prior to the initiation of dialysis, and falling haemoglobin was not the only factor changing at this time. In a limited analysis (data not presented) of 48 patients who had paired studies, the first being after the initiation of dialysis, the same relationship was seen.

Clearly the aetiology of left ventricular hypertrophy in patients with end-stage renal failure is multifactorial, and anaemia is only one factor involved. As mentioned, estimating the effect of blood pressure accurately is not possible from this study. Furthermore, no account was taken of the haemodynamic impact of the arteriovenous fistula, which should also act to produce eccentric LVH. However since a fistula is an absolute requirement for haemo- but not peritoneal dialysis, the effect of fistula flow on the development of hypertrophy was sought as treatment differences. No such differences were seen, whether those who received only one treatment or those who crossed over were examined. The possible contribution of fistula flow to the development of hypertrophy remains unanswered, since it is likely that some patients receiving peritoneal dialysis had a functioning fistula. Furthermore, patients might have been selected for peritoneal dialysis on account of haemodynamic factors (including LVH).

In those patients transplanted and studied in the paired comparison, LVMI decreased, suggesting that transplantation itself allows regression of hypertrophy. The possible mechanisms include reversal of the uraemic state, correction of the fluid overloaded state, reduced blood pressure, or perhaps reversal of anaemia. In a recent study (38, 39), regression of hypertrophy following transplantation was confirmed: in these patients all the above changes were achieved.

A surprising finding of these analyses was the apparent wall thickening

seen in diabetic patients. The a priori hypothesis regarding diabetes was that cavity dilatation would account for any increase in left ventricular mass observed. Although confounding by the diagnosis of hypertension did not account for all the variance in LVMI 'explained' by diabetes, it is possible that had blood pressure been more accurately recorded, no independent relationship between diabetes and hypertrophy would have been evident. This said, a plausible biologic mechanism can be speculated on whereby diabetes might produce concentric LVH in renal failure.

It has been reported that the risk of developing nephropathy in patients with insulin-dependent diabetes is greater in those with abnormalities of red cell sodium-lithium countertransport (61,62) or a parental history of hypertension (62). Similarly, in offspring of patients with essential hypertension, sodium-lithium countertransport is a better marker of predisposition to hypertension than measured blood pressure. Although the physiologic role of the sodium-lithium countertransport pump is not certain, it is thought to be closely related to the sodium-potassium pump, which is extremely active in the neonatal heart undergoing hypertrophy. Although the role of membrane pumps in cardiac hypertrophy in the adult with hypertension have not yet been studied, it may be that diabetic patients with renal failure are prone to develop hypertrophy by virtue of the same predisposition which led to their developing renal failure. While testing of this hypothesis may be worthwhile to further define the biologic mechanisms of hypertrophy, the degree of hypertrophy associated with diabetes in this study was at most modest, and of limited clinical importance.

No relationship was found between LVMI and parathyroid hormone (PTH), in contrast to reports in the literature, where a weak inverse relationship has been evident (36,49). The PTH assay used in this study has been validated

(54); however PTH levels increase with time on dialysis, and the timing between measurement of PTH and echocardiography was less than optimal in some patients. In those patients in whom measurements close in time were obtained, however, no relationship appeared to exist between PTH and left ventricular mass, nor was PTH measured at the time of the 'baseline' study related to LVMI at 'followup'. It must be noted that the alleged effects of hyperparathyroidism are to prevent hypertrophy and worsen anaemia, and any unrecognised effects of PTH in this study would reduce, rather than enhance, the apparent anaemia/hypertrophy relationship.

Finally, in addition to error, the study methods may have introduced bias. A single operator (the candidate) designed and conducted the study, including data abstraction. For variables such as blood pressure or haemoglobin, a maximum of 12 values per patient were abstracted. For patients with scant data, no selection took place; but for patients in whom several readings were available (such as patients admitted to hospital), values were selected: first by attention to the temporal relationship between the measurement and the date of echocardiography, or if a choice still existed, the mode of available readings. Electrocardiograms were abstracted from the medical record; where possible other data was abstracted before the ECG, but in some cases the selection of values of the explanatory variables might have been influenced by this knowledge. Fortunately, ECG-LVH had a low prevalence and such circumstances were rare.

6. FURTHER DIRECTION

Viewed in retrospect, there were many imperfections in the design of this study. The most influential were it's retrospective nature and the poor timing between echocardiography and the measurement of other variables, as well as the ad hoc data collection. This has limited the insights into pathophysiology which may have been possible.

The measure of hypertrophy used - left ventricular mass index - does not distinguish between concentric and eccentric types of hypertrophy, nor the 'adequacy' or 'appropriateness' of hypertrophy. The estimation of wall stress, on which such considerations are based, requires accurate, simultaneously measured blood pressure. If this were achieved (by advance design) then survival could be examined as a function of the patterns of hypertrophy.

To examine the factors associated with hypertrophy, a cross-sectional design is appropriate, but the inclusion of all available patients is inefficient. A 2-point design, studying only patients with substantial hypertrophy and those without, is convenient. Validated echocardiographic measurements, 24 hr recording of blood pressure, and measurement of fistula flow and blood volume could all be achieved and the timing of all measurements improved.

7. CONCLUSION & IMPLICATIONS

The finding that left ventricular mass index as measured by echocardiography was independently related to survival in this study suggests that it's measurement might be useful in predicting outcome in patients beginning therapy for end-stage renal failure. Every effort was made to ensure that the patients followed were representative of the usual spectrum of patients being evaluated for replacement therapy, and the finding may reasonably be generalised to prospective patients.

In the Framingham cohort, patients manifesting regression of LVH were found to have a better prognosis than those whose hypertrophy persisted (63). The results of this study suggest that regression of left ventricular hypertrophy might be considered as a potential goal of therapy in end-stage renal disease, although that regression of hypertrophy would improve the clinical outcome remains to be demonstrated.

In hypertension, regression of hypertrophy with the use of certain antihypertensive agents has been demonstrated. Their use in patients with end-stage renal disease might be expected to achieve similar gains. The finding that serum haemoglobin was related to left ventricular mass index in patients established on therapy, and that left ventricular mass rose as haemoglobin fell in patients studied in paired fashion, suggests that anaemia contributed to the pathogenesis of hypertrophy in these patients. Whether reversal of anaemia might achieve regression of hypertrophy has yet to be established.

The effect of Erythropoeitin

Over the past few years, advances in genetic engineering have led to the development of recombinant human Erythropoeitin, a hormone which stimulates the bone marrow and is deficient in end-stage renal failure. Initial studies in humans have shown efficacy in correcting the anaemia of end-stage renal failure with few side effects, but these do include hypertension in some patients (64,65). Limited data suggest improved peripheral haemodynamics (66) and some reduction in both cavity size and wall thickness (67), following maintenance of normal haemoglobin.

Over the past 18 months, a multicentre study has been in progress across Canada, evaluating the effect of r-HuEPO on quality of life in haemodialysis patients. The study is randomised, double-blind, dose-ranging and placebo-controlled and includes two strata of target haemoglobin: 90 to 115 g/L, and 115 to 135 g/L. Echocardiographic data has been collected at entry, at 2, 4 and 6 months of the trial, and following a further 6 months of open-label EPO treatment.

This study provides a unique opportunity to examine the impact of reversal of anaemia on left ventricular mass in patients treated by haemodialysis. Aside from it's occasional effect on blood pressure (which would be expected to promote hypertrophy), r-HuEPO has no important effects on the uraemic state other than correction of anaemia, in contrast to transplantation.

Since the double-blind component of the trial only continues for six months, and since in some patients titration of the r-HuEPO dose to achieve the target haemoglobin may take some months, analysis according to treatment group may fail to show any significant effect on regression of LVH with r-HuEPO. To examine the efficacy of r-HuEPO in reversing LVH, echocardiograms

at entry and following three months of achieved target haemoglobin will be compared. These will be read by two observers blinded to the order of the studies. This study is currently in process, with the candidate as participating investigator for the Canadian Multicentre Study Group.

8. APPENDICES

Appendix 1

Mode of Death assignment

With regard to the following patients who were under your care, please assign a mode of death according to the criteria below. You may consult the medical record if you wish.

S: Sudden (unexpected) death: Death occurring within 60 minutes of the onset of new symptoms, or having last been seen without them. An 'unexpected' death occurs only in a patient not confined to bed or hospital within 24 hrs of death, unless hospitalised for an elective reason.

H: Death in heart failure, refractory to dialysis or ultrafiltration, in a patient not critically ill by virtue of another (noncardiac) problem at the time.

I: Definite ischaemic heart event in a patient not critically ill by virtue of another (noncardiac) problem at the time.

N: Death by whatever mode in a patient critically ill with a noncardiac problem.

Classification (not included in request to attending physician)

Cardiac mortality: S,H,or I above

All-cause mortality: S,H,I and N

Appendix 2

Stepwise model

In multivariate modelling, the order of entry of variables can have major influence on the outcome of the analysis. Furthermore practical considerations of power and precision may limit the inclusion of any term. Thus a model may become 'too full' when terms displaying collinearity (perhaps even by chance) are entered, such that while the p-value for the overall model may be 'highly significant', none of the individual estimates achieves statistical significance. For this reason it has become commonplace to enter only either 1) those terms which are significantly associated with the outcome in the univariate analysis, or 2) those which add statistically significant improvement to the overall model when other variables are already entered. This latter approach is used in automated stepwise procedures: a variable enters only if it adds statistically significant information in an hierarchical fashion.

In the BMDP stepwise regression programs, as in other systems, the order of entry of variables into the model is not determined by biological, but rather mathematical considerations: two methods are available, based on either the maximum likelihood ratio (MLR) or the approximate asymptotic covariance estimate (ACE). The asymptotic covariance estimate is derived from the covariance matrix, and varies with the distribution of the independent variables (68). Since the distribution of the independent variables is determined by the study design, this estimate does not only reflect the strength of the biologic association, but includes the certainty with which the association is estimated, incorporating the information on which it is based. Similar considerations apply to the MLR. Thus stepwise models, while maximising precision, do so at the expense of biologic considerations, and variables which are important but poorly represented in the data perform poorly in models of this type. These models have the further drawback of being hierarchical, and a term already in the model may prevent another entering at all through collinearity.

The multivariate survival analysis of the cohort studied early (Section 5,Part 1,C.1) was repeated using a stepwise, automated model (p=0.1 to enter, 0.15 to remove). The results were as follows:

Summary of stepwise results:

Step	Variable entered	df	Log Likelihood	Improvement Chi-sq	p	Global Chi-sq	p
0			-131.914				
1	Age	1	-114.568	34.69	.000	33.53	.000
2	LVMI	2	-111.095	6.95	.008	40.08	.000
3	Transplant	3	-109.227	3.74	.053	43.15	.000

Next Step. Statistics to enter or remove variables

Variable	Chi-sq enter	Chi-sq remove	p value	Log likelihood
Age		24.81	.0000	-121.6300
LVMI		6.34	.0118	-112.3992
Hypertension	.81		.3680	-108.8221
Angina	2.58		.1080	-107.9355
Diabetes	2.15		.1429	-108.1544
Transplant		3.74	.0533	-111.0951

No term passed the remove or enter limits (.15, .10).

The adjusted coefficients and relative risks (based on comparison of upper and lowermost quintiles for continuous variables, as in Table 1.4) for the three-variable model selected by the stepwise program are thus:

	Coefficient	Relative Risk
Age	.0682	17.3
LVMI	.0132	3.0
Transplant	-1.6595	.19

These are similar to those in Table 1.4. However neither angina nor diabetes entered the stepwise model; as seen in Table 1.2, angina was a powerful univariate predictor of all cause mortality, but it's association with age and left ventricular mass determined that it could not enter in the hierarchical model. Similarly the crude relative risk with diabetes (Table 1.2) was 3.2; however the prevalence of diabetes was low (23%), the p-

value for the coefficient was only .032, and diabetes was associated with left ventricular mass: this term was also unable to enter.

The stepwise approach was also used to fit the data to a full model including all the terms included in Table 1.2. This approach ignores the problems of collinearity (such as exists between LVMI and endsystolic dimension, hypertension and blood pressure, or angina and 'definite' myocardial infarction).

Summary of stepwise results

Step	Variable entered	df	Log Likelihood	Improvement Chi-sq	p	Global Chi-sq	p
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Hypertension	.81		.3680	-108.8221
Angina	2.58		.1080	-107.9355
Diabetes	2.15		.1429	-108.1544
Transplant		3.74	.0533	-111.0951
Gender	.24		.6233	-109.1068
ESD	.09		.7634	-109.1821
Syst BP	.73		.3924	-108.8616
Definite MI	.04		.8495	-109.2094

No term passed the remove or enter limits (.15, .10).

The fitted model is the same as the reduced model above.

Superficially, these analyses might be taken to indicate that prior definite myocardial infarction or diabetes are unimportant to outcome. This is clearly not the case; rather, in this population, the marginal information they provided was not statistically significant, reflecting either collinearity or poor representation in the data.

Appendix 3

Comparing multiple linear and logistic models

For this exercise, the followup cross-section was used to study the QUALITATIVE importance of the four X-variates of interest (Hypertension, Diabetes, Haemoglobin, Angina) to the development of left ventricular hypertrophy, when examined in two ways:

1. With LVMI as a continuous variable, by the method of multiple linear regression.
2. With LVMI categorised across the median, as LVH present/absent, and then the relationship to X-variates examined by the method of multiple logistic regression.

Multiple linear regression

A non-hierarchical model was examined (Type III SS / SAS Proc GLM).

Terms were entered according to their a priori credibility, not the results of the univariate analysis. In this and the logistic regression analysis which follows, X-variates were stratified.

Y-variate = LVMI (continuous)

X-variates = Diabetes 0/1
High BP 0/1 (across the median, 148 mmHg)
Myocardial Infarction 0/1
Haemoglobin 0/1/2 (<80, 80-110, >110 g/L)

ANOVA

Source	df	SS	F	p
Model	4	40937	8.28	.0001
Error	78	96432		
Total	82	137370		
R- square	.298			

Estimation

Variable	Coeff	SE	t	p
Diabetes	12.79	9.21	1.39	.169
High BP	18.97	7.82	2.42	.017
Hb	-25.33	6.50	-3.90	.0002
MI	20.24	10.6	1.91	.0604

Conclusions based on multiple linear regression

These are considered in depth in Section 5, Part 2.C. Briefly, haemoglobin stratum and hypertension appear to exert the most substantial effects. Neither the effects of myocardial infarction nor diabetes are significant at the .05 level (2-tailed).

Logistic Regression

On Stratification for categorical data analysis....

Choosing cutoff values is widely held to be an a priori consideration. 'Upper limits of normal' from controls or the literature are the most cited reference points. This is not always the most efficient way to stratify the data, if trends within the population are of interest. Separating the data according to **quantiles** is convenient, efficient, and 'a posteriori' only in the sense that the precise values are not known before. In this analysis LVMI was stratified across the median (131 g/m^2). This corresponds to 98th centile for normals (3).

Y-variate = LVMI > 131 (median) = LVH 1

< 131 = LVH 0

X-variates = Diabetes = 0/1

High BP (across the median, 148 mmHg) = 0/1

Myocardial Infarction = 0/1

Haemoglobin 0/1/2 (<80, 80-110, >110 g/L)

Full Model: All variables of interest are included

Variable	Coeff	SE	Odds Ratio	95 % CI Lower	Upper
Diabetes	1.3800	.6405	4.0	1.1	13.9
High BP	1.2317	.6039	3.4	1.0	11.2
Haemoglobin					
80-110 g/L	-1.1505	.5823	.31	.1	1.0
> 110 g/L	-1.6168	.9418	.20	.03	1.3
MI	2.4110	.8653	11.1	2.0	60.7

Conclusions based on logistic regression

Diabetes is an independent risk factor for LVH (Adjusted odds ratio 4.0, 95 % CI 1.1 to 12.0).

High Blood Pressure is an independent risk factor for LVH (Adjusted odds ratio 3.4, 95% CI 1.0 to 11.2).

Haemoglobin stratum exerts an independent 'protective' effect : Odds ratios against are 5:1 and 3.3:1 for those in the highest and middle strata, respectively.

Definite MI is very strongly associated with LVH (adjusted odds ratio 11.1). Criteria for MI were very specific : lesser criteria should lead to a lesser measure of association.

Comparing Models

IN QUANTITATIVE TERMS, the two models are not comparable. The coefficients have entirely different meaning: the multiple linear model deals with differences in mean LVMI, the logistic model with the odds of developing hypertrophy.

IN QUALITATIVE TERMS, the two methods of analysis may lead to different conclusions.

The multiple linear regression model accords most of the explained variance to anaemia (haemoglobin) and hypertension. Confounding of the diabetes/hypertrophy relationship is suggested, and the coefficient for diabetes does not achieve statistical significance. Myocardial infarction barely achieves statistical significance, and the

estimated effect is an increase in LVMI of only 20 g/m^2.

The multiple logistic model attributes the greatest risk (ten-fold) to myocardial infarction and independent risk to diabetes, of considerable magnitude. Both haemoglobin and hypertension perform as they did in the linear model.

THE DIFFERENCES are not accounted for by the underlying distributions of independent variates, since the same stratification was used for both models. Definition of the outcome variable (LVH) was most important, with establishing a dichotomy for a continuous variable quite arbitrary. In this case, redefining LVH as greater than the 75th centile of LVMI (data not presented) failed to show any effect of diabetes (as would be expected from Fig. 5, since diabetes was associated with mild, not severe, hypertrophy). Stratification across the median included most diabetic patients in the LVH group. The stratification of blood pressure was similarly arbitrary, and different estimates of effect were obtained with differing stratification.

Not only do the main effects appear to be different between when using linear or logistic models, but confounding of the diabetes/hypertrophy relationship by blood pressure was evident under the linear, but not the logistic, model. Since defining the outcome variate as present/absent inherently involves a loss of power, the logistic model is disadvantaged when the data are few as in this study. The criteria for modification are also different, and statistical interaction under additive and multiplicative models have different biologic meaning (69). This study lacked the precision to properly study modification.

Appendix 4

Sources of error

1. Echocardiographic estimation of left ventricular mass (LVM)

Methodologic considerations:

To derive LVM, the external and internal volumes of the LV are first calculated, which requires geometric assumptions regarding the shape of the ventricle, and also assumes uniform wall thickness. Whatever error results from the measurement of LV wall and cavity dimensions is cubed when volumes are calculated. The difference between these volumes is multiplied by the specific gravity of cardiac muscle (34), which may not be appropriate in patients with ESRD (70).

Reporting performance

The literature on reproducibility and other indicators of performance of echocardiography is sparse, and what is published is of limited value. This is largely on account of the inappropriate reporting of agreement by means of a product-moment correlation coefficient (71). The minimum for evaluating agreement is that the difference between repeated measurements be reported. The most useful parameters with regard to agreement are the mean and standard deviation of the differences between measures. These can be expressed as the coefficient of variation of the difference. No study evaluating performance in echocardiography has reported this measure. The standard deviation or coefficient of variation of the data itself (rather than the difference between repeated measures) reflects the spread of the data, a design feature. Most studies evaluating agreement in echocardiography have reported these parameters.

One study (72) reported the relative difference between studies in subjects studied at two examinations on the same day, and determined an average difference of 5% for LV diastolic dimension and 10% for posterior wall thickness. Other studies (73,74,75) have partitioned error by means of analysis of variance, and suggest that the variance attributable to repeated measurement of the same study (inter- and intraobserver) is approximately equal to the difference between studies, and that copy

quality accounts for more variance than either of the above. These studies suggest that differences of up to 20% for wall thickness and 10% for cavity dimension are within the range of measurement and temporal variability. These errors are then cubed in the calculation of LVMI.

Timing of dialysis

Changes in LV diastolic dimension of up to 15% have been reported following dialysis with fluid removal (76). Changes in wall thickness were not reported.

Comparison with other studies

No validation exercises were performed in this study. In order to evaluate whether measurement error is likely to have been greater than in similar studies in renal failure, the coefficient of variation of the data is contrasted with that in other studies. It must be remembered that this parameter is not invariant against design, but if selection criteria are similar it may be a proxy for performance error.

The coefficient of variation (mean/s.d.) for LVMI in this study was .29. The two studies of patients with renal failure which included determination of LVMI are those of London et al and Himelman et al (38, 39). The former examined haemodialysis patients without apparent heart disease, while the latter retrospectively evaluated 50 transplant recipients studied at the time of transplantation. The coefficients of variation for LVMI in those studies was .27 and .25, respectively.

2. Blood Pressure

Single measurements of blood pressure relate poorly to mean 24-hr blood pressure as determined by continuous monitoring (43). No continuous blood pressure data are available for patients with ESRD, and the volume shifts with dialysis compound the use of pre- and post-dialysis pressures as a measure of 'usual' blood pressure; furthermore suboptimal timing between measurement of blood pressure and echocardiography would fail to account for volume-dependent hypertension. In this study, the coefficients of variation for systolic and diastolic blood pressure were .14 and .13, respectively. In the study by Himelman et al (38, 39) they were .13 and .11, and in the

study by London et al (36), in which blood pressure measurement was standardised, .13 and .12.

3. Haemoglobin

In this study a relationship between serum haemoglobin and time to starting dialysis was seen, with haemoglobin .027 g/L higher for each day further removed from dialysis (t=2.97,p=.004). The timing between measurement of haemoglobin and LVMI was poor in several patients who had echocardiography some months before starting dialysis, but in whom only haemoglobin measured at the start of dialysis was available. This weakens the relationship between LVMI and haemoglobin in the 'baseline' cross-section (Section 5, Part 2, B.1).

9. BIBLIOGRAPHY

1. Kidney Foundation of Canada. Canadian Renal Failure Registry, December 1986.

2. Lindner A, Charra B, Sherrard D, Scribner B. Accelerated atherosclerosis in prolonged maintenance haemodialysis. N Engl J Med. 1974;290:697-701.

3. Casale P, Devereux R, Milner M et al. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Int Med. 1986;105:173-8.

4. Frohlich E. Left Ventricular Hypertrophy as a risk factor. Cardiol Clinics. 1986;4:137-45.

5. Kannel WB, Abbott R. A prognostic comparison of asymptomatic left ventricular hypertrophy and unrecognised myocardial infarction: The Framingham study. Am Heart Jnl. 1986;111: 391-7.

6. Levy D, Garrison RJ, Savage D, Kannel WB, Castelli WP. Left ventricular mass predicts coronary disease events independent of the standard risk factors. Circulation 1987; 76 (IV):435.

7. Anderson K. Sudden death, hypertension and hypertrophy. Jnl Cardiovasc Pharmacol. 1984;6 (Supp.3) S498-503.

8. Eisenberg M, Prichard S, Barre P, Patton R, Hutchinson T, Sniderman A. Left ventricular hypertrophy in end-stage renal disease on peritoneal dialysis. Am Jnl Cardiol. 1987;60:418-9.

9. Bergeron P. Orientation générale pour le traitement de l'insufficience rénale terminale au Québec. Conception des programmes, planification des services de santé, Québec 1975.

10. Hutchinson TA, Michaud L, Thomas DC. Comparing survival of patients on dialysis and after renal transplantation: the effect of the method of statistical analysis on results. ASAIO 1985; 8(1):18-21.

11. Hutchinson TA, Thomas DC, Lemieux JC, Harvey CE. Prognostically controlled comparison of dialysis and renal transplantation. Kidney Internat 1984; 26:44-51.

12. Hutchinson TA, Thomas DC, MacGibbon B. Predicting survival in adults with end-stage renal disease: an age equivalence index. Ann Int Med 1982; 96(4):417-423.

13. Burke JF, Francos GC, Moore LL et al. Accelerated atherosclerosis in chronic dialysis patients- another look. Nephron 1978; 21:181-5.

14. Parfrey PS, Harnett JD, Gault HM, Barre P & Guttman RD. Low-output left ventricular failure in end-stage renal disease. Am J Nephrol 1987; 7:184-191.

15. Sniderman A, Cianflone K, Kwiterovich PO, Hutchinson T, Barre P & Prichard S. Hyperapobetalipoproteinemia: the major dyslipoproteinemia in patients with chronic renal failure treated with chronic ambulatory peritoneal dialysis. Atherosclerosis 1987; 65:257-264.

16. Ikram H, Lynn KL, Bailey RR, Little PJ. Cardiovascular changes in chronic haemodialysis patients. Kidney Internat 1983; 24:371-6.

17. Moriarty TF. The Law of LaPlace. It's limitations as a relation for diastolic pressure, volume, or wall stress of the left ventricle. Circulation Research 1980; 46: 321-31.

18. Levy D, Anderson KM, Savage D, Kannel WB, Christiansen JC & Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. Ann Int Med 1988; 108:7-13.

19. Grossman W, Jones D & McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. Jnl Clin Invest 1975; 56:56-64.

20. Grossman W. Cardiac Hypertrophy: useful adaptation or pathologic process? Amer Jnl Med. 1980;69:576-84.

21. Gaasch WH, Carroll JD, Levine HJ & Criscitiello MG. Chronic aortic regurgitation: prognostic value of left ventricular end-systolic dimension and enddiastolic radius/thickness ratio. Jnl Am Coll Cardiol 1983; 1:775-82.

22. Gaasch WH, Zile MR, Hoshino PK, Apstein CS & Blaustein AS. Stress-shortening relations and myocardial blood flow in compensated and failing canine hearts with pressure-overload hypertrophy. Circulation 1989; 79:872-883.

23. Strauer BE. Myocardial oxygen consumption in chronic heart disease: role of wall stress, hypertrophy and coronary reserve. Am Jnl Cardiol 1979; 44:730-40

24. Ford LE. Heart Size. Circulation Research 1976; 39:297-303.

25. Gaasch WH. Left ventricular radius to wall thickness ratio. Am Jnl Cardiol 1979; 43:1189-94.

26. Tanaka M, Fujiwara H, Onodera T et al. Quantitative analysis of narrowings of intramyocardial small arteries in normal hearts, hypertensive hearts, and hearts with hypertrophic cardiomyopathy. Circulation. 1987;75:1130-9.

27. Cannon R, Schenke W, Maron B et al. Differences in coronary flow and myocardial metabolism at rest and during pacing between patients with obstructive and patients with nonobstructive cardiomyopathy. Jnl Am Coll Cardiol. 1987;10: 53-65.

28. Marcus M, Doty D, Hiratzka L, Wright C, Eastham C. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. N Engl J Med. 1982;307:1362-6.

29. Wicker P & Tarazi RC. Coronary blood flow in left ventricular hypertrophy: a review of experimental data. Eur Heart Jnl 1982; 3(Supp A): 111-8.

30. McLenachan JM, Henderson E, Morris K, Dargie H. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. N Engl J Med. 1987;317:787-831.

31. Aronow W, Epstein S, Schwartz K, Koenigsberg M. Correlation of complex ventricular arrhythmias detected by ambulatory ECG monitoring with echocardiographic left ventricular hypertrophy in persons older than 62 years in a long-term health care facility. Am Jnl Cardiol. 1987;60:731-3.

32. Tarazi RC. Regression of left ventricular hypertrophy: partial answers for persistent questions. Jnl Am Coll Cardiol 1984; 3(5):1349-51.

33. Reichek N, Devereux RB. Left ventricular hypertrophy: relationship of anatomic, echocardiographic and electrocardiographic findings. Circulation 1981; 63: 1391-8.

34. Devereux R, Reichek N. Echocardiographic determination of Left Ventricular Mass in man: anatomic validation of the method. Circulation. 1977;55:613-8.

35. Devereux RB, Alonso DR, Lutas EM et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am Jnl Cardiol 1986; 57:450-8.

36. London G, Fabiani F, Marchais S, et al. Uremic cardiomyopathy: an inadequate LV hypertrophy. Kidney Internat 1987; 31: 973-980.

37. Parfrey PS, Harnett JD, Griffiths SM, Gault MH & Barre PE. COngestive heart failure in dialysis patients. Arch Int Med 1988; 148:1519-25.

38. Rostand SG, Sanders C, Kirk KA, Rutsky EA & Fraser RG. Myocardial calcification and cardiac dysfunction in chronic renal failure. Am J Med 1988; 85:651-7.

39. Himelman RB, Landzberg JS, Simonson JS et al. Cardiac consequences of renal transplantation: changes in left ventricular morphology and function. Jnl Am Coll Cardiol 1988; 12:915-923.

40. Frohlich ED & Tarazi RC. Is arterial pressure the sole factor responsible for hypertensive cardiac hypertrophy? Am Jnl Cardiol 1979; 44:959-63.

41. Devereux RB, Drayer JI, Chien S et al. Whole blood viscosity as a determinant of cardiac hypertrophy in systemic hypertension. Am Jnl Cardiol 1984;54:592-5.

42. Greenland S, Schlesselman JJ, Criqui M. The fallacy of employing standardised regression coefficients and correlations as measures of effect. Am Jnl Epidemiol 1986; 123:203-8.

43. Rowlands DB, Ireland MA, Stallard T, et al. Assessment of LV mass and it's response to antihypertensive treatment. Lancet 27 Feb 1982: 467-470.

44. Panidis IP, Kotler MN, Ren J-F et al. development and regression of left ventricular hypertrophy. Jnl Am Coll Cardiol 1984; 3: 1309-20.

45. Dodge HT & Baxley WA. Left ventricular volume and mass and their significance in heart disease. Am Jnl Cardiol 1969; 23:528-37.

46. Field BJ, Baxley WA, Russell RO et al. Left ventricular function and hypertrophy in cardiomyopathy with depressed ejection fraction. Circulation 1973; 47:1022.

47. Prosser D & Parsons V. The case for a specific uraemic myocardiopathy. Nephron 1975; 15:4-7.

48. Rubler S, Dlugash J, Yuceoglu Y et al. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am Jnl Cardiol 1972; 30:595-602.

49. London G, de Vernejoul M, Fabiani F, et al. Secondary hyperparathyroidism and cardiac hypertrophy in haemodialysis patients. Kidney Internat 1987; 32: 900-907.

50. Capelli J, Kasparian H. Cardiac work demands and LV function in end-stage renal disease. Ann Int Med 1977; 86: 261-267.

51. Neff M, Kim K, Persoff M, Onesti G, Swartz C. Hemodynamics of uremic anemia. Circulation 1971; 43: 876-883.

52. Hung J, Harris PJ, Uren RF et al. Uremic cardiomyopathy - effect of hemodialysis on left ventricular function in end-stage renal disease. N Engl J Med 1980; 302:547-51.

53. Feigenbaum, H. Echocardiography. Philadelphia: Lee & Febiger, 1986, p. 117.

54. Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial results: I. reduction in the incidence of coronary heart disease. JAMA. 1984;251:351-64.

55. Mitchell J, Goltzman D. Examination of circulating PTH in pseudohypoparathyroidism. Jnl Clin Endoc & Metabol 1985; 61(2): 328-334.

56. Mantel N, Byar DP. Evaluation of response-time data involving transient states: an illustration using heart transplant data. Jnl Am Stat Assoc. 1974:69:81-6.

57. Miettinen O. Estimability and estimation in case-referent studies. Am Jnl Epidemiol. 1975; 103:226-35.

58. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation. 1987;76:44-51.

59. Huston TP, Puffer JC, Rodney WM. The athletic heart syndrome. N Engl J Med. 1986;313:24-32.

60. Ross J. Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. Prog Cardiovasc Dis 1976; 18(4):255-64.

61. Mangili R, Bending JJ, Scott G et al. Increased sodium-lithium countertransport activity in red cells of patients with insulin-dependent diabetes and nephropathy. N Engl J Med 1988; 318:146-50.

62. Krolewski AS, Canessa M, Warram JH et al. Predisposition to hypertension and susceptibility to renal disease in insulin-dependent diabetes mellitus. N Engl J Med 1988; 318:140-5.

63. Kannel WB, D'Agostino RB, Levy D et al. Prognostic significance of regression of left ventricular hypertrophy. Circulation 1988; 78(II):89.

64. Eschbach JW, Egrie J, Downing M, Browne K, Adamson J. Correction of the anemia of endstage renal disease by recombinant human erythropoeitin. N Engl J Med. 1987:316 (2): 73-8.

65. Winearls CG, Oliver D, Pippard M, Reid C, Downing M, Cotes P. Effect of human erythropoeitin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet. 1986;8517:1175-7.

66. Nonnast-Daniel B, Creutzig A, Kuhn K et al. Effect of treatment with recombinant human erythropoeitin on peripheral haemodynamics and oxygenation. Contrib Nephrol 1988; 66:185-94.

67. Grutzmacher P, Scheuermann E, Low I et al. Correction of renal anaemia by recombinant human erythropoeitin: effects on myocardial function. Contrib Nephrol 1988; 66:176-84.

68. Mosteller F. Association and estimation in contingency tables. Jnl Am Stat Assoc 1968; 63:1-28.

69. Koopman JS. Interaction between discrete causes. Am Jnl Epidemiol 1981; 113:716-24.

70. Mall G, Rambausek M, Neumeister A et al. Myocardial interstitial fibrosis in experimental uremia: implications for cardiac compliance. Kidney Internat 1988; 33:804-11.

71. Bland JM & Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; i:307-10.

72. Pietro D, Voelkel G, Ray B & Parisi A. Reproducibility of echocardiography. A study evaluating the variability of serial echocardiographic measurements. Chest 1981; 79:29-32.

73. Felner JM, Blumenstein BA, Schlant RC et al. Sources of variability in echocardiographic measurements. Am Jnl Cardiol 1980; 45:995-1004.

74. Lapido GOA, Dunn FG, Pringle TH et al. Serial measurements of left ventricular dimensions by echocardiography. Br Heart Jnl 1980; 44:284-9.

75. Clark RD, Korcuska K & Cohn K. Serial echocardiographic evaluation of left ventricular function in valvular disease, including reproducibility guidelines for serial studies. Circulation 1980; 62:564-75.

76. Nixon JV, Mitchell JH, McPhaul JJ & Henrich WL. Effect of haemodialysis on left ventricular function. Dissociation of changes in filling volume and in contractile state. Jnl Clin Invest 1983; 71:377-84.

10. TABLES

Part 1. Survival analysis

Table 1.1 Clinical Characteristics

(Continuous values are expressed as mean/SD)

	Cohort studied:		
	Early	Late	No echo
No. patients	91	22	6
Age Mean	55/15	58/16	62/14
Range	20-87	24-83	47-82
Sex M/F	55/36	15/7	3/3
(% Male)	60	68	50
Kidney Disease*			
Glomerulonephritis	25 (27%)	5 (18%)	1
Diabetes	21 (23%)	5 (18%)	1
Nephrosclerosis	15 (16%)	5 (22%)	1
Pyelonephritis	13 (14%)	6 (22%)	1
Other	17	1	2
Definite MI	10 (11%)	1 (4%)	1
Angina	27 (30%)	5 (23%)	2
Hypertension	67 (73%)	15 (68%)	4
Systolic BP (mmHg)	152/24	145/24	149/25
Diastolic BP (mmHg)	86/11	85/14	78/20
Urea (mmol/L)	35/14	31/20	43/8
Haemoglobin (g/L)	90/25	85/18	83/5
Transplanted during follow-up	18 (20%)	2 (9%)	0

Table 1.1 (Continued)

	Cohort studied: Early	Late	No echo
Time to echocardiography			
Median (days)	-60	366	
Range	-903 to 60	103 to 898	
Echocardiography			
LVMI (g/m^2)	121/32	135/40	
Range	65-198	80-259	
LV End-Systole (mm)	34/7	34/8	
Range	20-60	22-50	
LV End-diastole (mm)	51/7	51/8	
Range	35-72	40-70	
LV Posterior Wall (mm)	11.4/1	12.2/1	
Range	9-15	10-15	
ECG LVH	20 (22%)	8 (36%)	4
Followup (days) from:			
Starting dialysis			
Median	576	985	17
Range	2-1839	416-1669	8-55
Echocardiography			
Median	642	585	
Range	18-2437	6-1391	

* Nephrosclerosis includes hypertension but not diabetes; Pyelonephritis includes analgesic nephropathy.

LVMI = left ventricular mass index

LV = left ventricle

ECG LVH = electrocardiographic left ventricular hypertrophy

Table 1.2 Crude Associations: All-cause mortality

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR#	95% C.I. Lower	Upper
Age (yrs)	.0785	.0148	5.29	<.0002	1.0817	26.6	7.9	89.6
Male Sex	.1049	.3617	.29	.77	1.11	1.1	0.8	1.4
LVMI	.0156	.0049	3.16	.0026	1.0157	3.7	1.6	8.3
ESD (mm)	.0664	.0374	1.78	.14	1.0687	2.6	0.9	7.4
Syst BP	.0094	.0071	1.32	.36	1.0094	1.8	0.8	4.3
H/Tension	.4569	.4884	.94	.68	1.58	1.6	0.6	4.3
Angina	1.5820	.3531	4.48	<.0002	4.86	4.9	2.4	9.8
MI	1.1616	.5089	2.28	.0320	3.19	3.2	1.6	6.5
Diabetes	.8400	.3440	2.45	.0234	2.32	2.3	1.2	4.5
Tplant	-2.53	1.029	-2.46	.0036	.08	.08	0.01	0.6

* LVMI = Left Ventricular Mass Index (g/m^2)
ESD = End-systolic dimension
Syst BP = systolic blood pressure (mmHg)
H/Tension = Hypertension
MI = definite myocardial infarction
Tplant = Transplant

+ p values are two-sided

RR = Relative Risk. For continuous variables, estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

C.I. = confidence interval

Table 1.3 Crude Associations: Cardiac mortality

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR'	95% C.I. Lower	Upper
Age (yrs)	.0653	.0187	3.50	.0004	1.0675	15.3	3.3	70.5
Male Sex	.2730	.4946	.55	.28	1.31	1.3	0.6	3.3
LVMI	.0157	.0067	2.33	.0354	1.0158	3.7	1.2	11.1
ESD (mm)	.0960	.0474	2.02	.0808	1.1007	3.8	1.1	13.9
Syst BP	.0075	.0096	.78	.86	1.0075	1.6	0.5	5.2
H/Tension	1.6272	1.0303	1.58	.158	5.089	5.1	0.7	38.4
Diabetes	1.2753	.4762	2.68	.0084	3.579	3.6	1.4	9.2
Angina	2.2167	.5039	4.40	<.0002	9.177	9.2	3.4	24.7
MI	1.7170	.6106	2.81	.0032	5.57	5.6	1.9	16.3
Tplant	**							

* LVMI = Left Ventricular Mass Index (g/m^2)
ESD = End-systolic dimension
Syst BP = systolic blood pressure (mmHg)
MI = definite myocardial infarction
H/Tension = Hypertension
Tplant = Transplant

+ p values are two-sided

' RR = Relative Risk. For continuous variables, estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

C.I. = confidence interval

** No transplanted patient suffered a cardiac death. The coefficient is thus inestimable.

Table 1.4 Adjusted Associations : All-cause mortality

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR#	95% C.I. Lower	Upper
Age	.0594	.0165	3.61	.0002	1.0612	12.0	3.1	46.4
LVMI	.0126	.0051	2.48	.0132	1.0127	2.9	1.3	6.7
H/Tension	.2512	.5069	.50	.6170	1.286	1.3	0.5	3.7
Angina	.6958	.3723	1.77	.0768	2.005	2.0	0.9	4.3
Diabetes	.5672	.3624	1.57	.1164	1.763	1.8	0.9	3.8
Transplant	-1.3317	1.0764	-1.24	.2150	.264	0.3	0.03	2.2

* LVMI = Left Ventricular Mass Index (g/m^2)
H/Tension = Hypertension

+ p values are two-sided

RR = Relative Risk. For continuous variables, estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

C.I. = confidence interval

Table 1.5 Adjusted Associations: Cardiac mortality

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR•	95% C.I. Lower	Upper
Age	.0417	.0201	2.07	.0384	1.0425	5.7	0.8	29.9
LVMI	.0119	.0068	1.76	.0784	1.0119	2.7	0.9	8.2
H/Tension	1.3243	1.0480	1.26	.2076	3.7594	3.8	0.5	30.2
Angina	1.6223	.5529	2.93	.0034	5.0649	5.1	1.7	15.2
Diabetes	.9827	.4993	1.96	.0488	2.6716	2.7	1.0	7.3

* LVMI = Left Ventricular Mass Index (g/m^2)
H/Tension = Hypertension

+ p values are two-sided

• RR = Relative Risk. For continuous variables, estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

C.I. = confidence interval

Table 1.6 Adjusted associations: Stratified analysis

All-cause mortality: stratified analysis according to the presence/absence of Hypertension.
Compare with Table 1.4.

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR#
Age	.0589	.0165	3.57	.0004	1.0607	12.4
LVMI	.0130	.0051	2.54	.009	1.0131	3.0
Angina	.6857	.3950	1.74	.08	1.9852	2.0
Diabetes	.4809	.3690	1.30	.20	1.6176	1.6
Transplant	-1.3230	1.0879	-1.22	.24	.2663	.27

* LVMI = Left Ventricular Mass Index (g/m^2)

+ p values are two-sided

For continuous variables, Relative Risk estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

Table 1.7 Components of LVMI: Adjusted associations

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR'	95% C.I. Lower	Upper
All-cause mortality								
PW thckness	.2581	.1162	2.22	.0272	1.2944	2.2	1.1	4.4
LV Diastole	.0328	.0227	1.44	.1499	1.0333	1.8	0.8	4.0
Cardiac mortality								
PW thckness	.2770	.1573	1.76	.0784	1.3192	2.3	0.9	5.8
LV Diastole	.0301	.0305	.98	.3270	1.0305	1.7	0.6	4.9

* PW thckness = posterior wall thickness

LV = left ventricle

+ p values are two-sided

' RR = Relative Risk. Estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

C.I. = confidence interval

Table 1.8 Wall thickness and endsystolic dimension: Adjusted associations

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR#	95% C.I. Lower	Upper
<u>All-cause mortality</u>								
PW thckness	.3203	.1193	2.69	.0072	1.3775	2.6	1.3	5.2
LV Systole	.0842	.0374	2.25	.0244	1.0878	2.1	1.1	4.0
<u>Cardiac mortality</u>								
PW thckness	.3660	.1646	2.22	.0264	1.4419	3.0	1.1	7.9
LV Systole	.1158	.0480	2.41	.0160	1.2228	6.0	1.4	25.7

* PW thckness = posterior wall thickness

LV = left ventricle

+ p values are two-sided

RR = Relative Risk. Estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

C.I. = confidence interval

Table 1.9 Patients studied late only (Survival from the time of echocardiography)

Crude Associations: All-cause mortality

Variable*	Coeff.	S.E.	z	p+	e^{coeff}	RR#
Age	.0570	.0360	1.58	.11	1.0586	11.0
LVMI	.0117	.0097	1.24	.21	1.0118	2.5
Syst BP	.0109	.0164	.66	.48	1.0110	2.0
Angina	-.6241	1.1203	-.56	.55	.5357	0.5
Diabetes	1.2731	.9326	1.37	.16	3.5720	3.6

* LVMI = Left Ventricular Mass Index (g/m^2)

Syst BP = Systolic blood pressure (mmHg)

+ p values are two-sided

RR = Relative Risk. Estimates are based on comparison of top and bottom quintiles (Q5 vs Q1).

C.I. = confidence interval

Part 2. Factors associated with hypertrophy

Table 2.1 Clinical Characteristics

(Continuous variables are mean / s.d.)

	Patients studied:		
	Baseline	Followup	Paired*
Number	87	85	59
Males (%)	52 (59%)	54 (63%)	36 (61%)
Age	54/17	54/14	53/17
Prior hypertension	63 (72%)	65 (76%)	42 (71%)
Mean systolic BP	152/23	150/21	153/17
Mean diastolic BP	86/11	85/10	87/11
Definite MI	9 (11%)	14 (17%)	4 (7%)
Diabetes	28 (32%)	20 (24%)	15 (25%)
Haemoglobin (g/L)	90/25	97/27	90/16
Urea nitrogen (mmol/L)	35/14	36/23	32/12
Serum calcium (mmol/L)	2.06/0.30	2.24/0.25	2.21/0.24
Serum phosphate (mmol/L)	1.92/0.60	1.81/0.40	1.74/0.45
PTH (mgeq/L)	176/149	196/154	186/154
LVMI (g/m^2)	121/28	135/36	119/28

* 59 patients are common to baseline and followup cross-sections. Values referred to in these patients are those at the baseline evaluation.

BP = blood pressure

MI = myocardial infarction

PTH = Parathyroid Hormone

TABLE 2.2 Left Ventricular Mass Index (g/m^2) according to selected variables: Unadjusted effects

	Baseline	Followup
Hypertension	125/37	140/45
No hypertension	108/54	124/64
p	.026	.11
Haemoglobin		
<80 g/L	118/74	161/36
80-110 g/L	125/54	129/35
>110 g/L	110/65	106/27
p	.208	.0002
Diabetics	132/56	151/80
Non-diabetics	115/37	130/80
p	.020	.030
Definite MI	120/74	153/72
No definite MI	121/28	131/46
p	.95	.06
Angina	123/65	157/44
No angina	120/36	128/46
p	.69	.005
Sex: male	119/36	135/45
female	124/46	135/55
p	.47	.96
Age: <44	116/54	134/42
44-65	118/46	134/43
>65	129/44	139/37
p	.17	.86
Parathyroid hormone:		
<60 mgeq/L	121/45	134/64
60-290 mgeq/L	121/28	133/60
>290 mgeq/L	118/36	140/82
p	.39	.83

Note: Values are mean / s.d. All p values refer to comparisons within cross-sections.

Table 2.3 Rank correlations with components of LVMI*

(Followup cross-section)

Variable	Spearman's Coefficient	t	p
Associated with PW thickness:			
Systolic BP	.289	2.83	.004
Diabetes	.334	3.70	.0002
Haemoglobin	-.313	2.92	.0036
Transplantation	-.210	1.86	.062
Associated with LV cavity dimension:			
Systolic BP	.216	2.01	.044
Angina**	.195	1.86	.062
Haemoglobin	-.201	1.93	.053

* Associations are not adjusted for other factors.

p Values are 2-sided.

** Angina includes patients with prior definite myocardial infarction or coronary artery grafting.

BP = Blood Pressure

PW = Posterior Wall

LV = Left Ventricle

Table 2.4 Adjusted estimates: Diabetes/Hypertension

ANOVA

Source	df	Type I SS*	F	p
Diabetes	1	7074	4.78	.0329
Hypertension	1	13017	8.79	.0040
		Type III SS*		
Diabetes	1	5376	3.63	.0602
Hypertension	1	13017	8.79	.0040

* SAS regression procedures derive hierarchical ('Type I') and adjusted ('Type III') sums of squares. Type I sums of squares are derived after the x-variates ahead in the list have been examined; that is, these are conditional on preceding x-variates only. Type III sums of squares are conditional on all other x-variates. The difference in diabetes sums of squares indicates some confounding by hypertension.

11. FIGURES

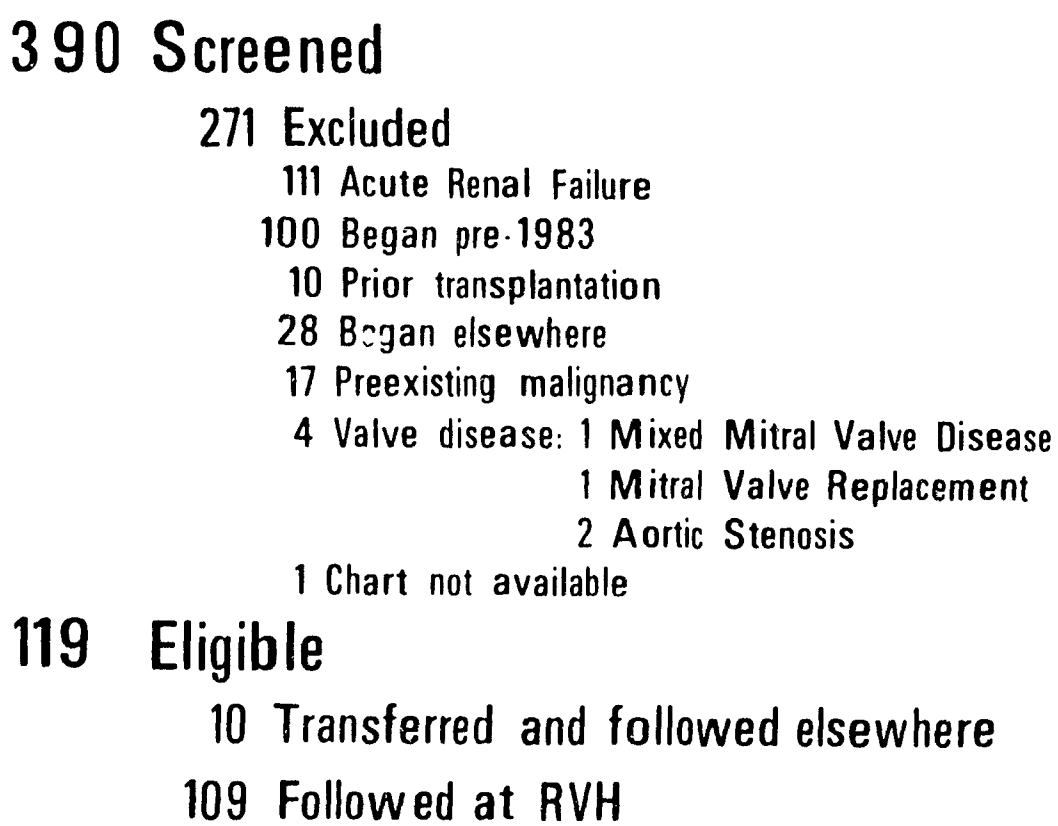

Figure 1. Patients screened for inclusion in the study. The 119 patients eligible as an 'inception' cohort are the subjects of study.

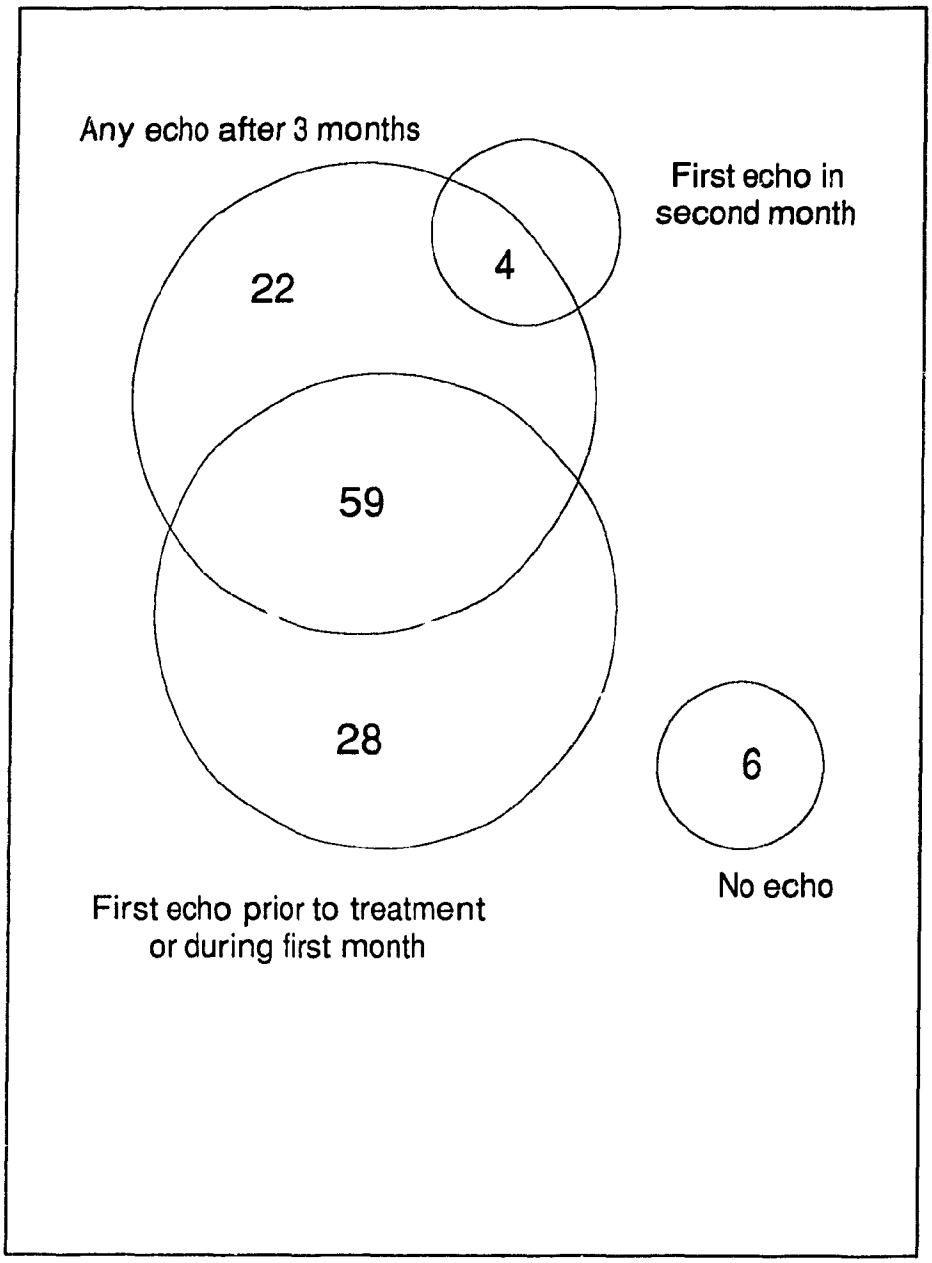

Figure 2a. Breakdown of 119 patients according to timing of echocardiography and the initiation of treatment. The composition of the sub-populations is shown on the next page.

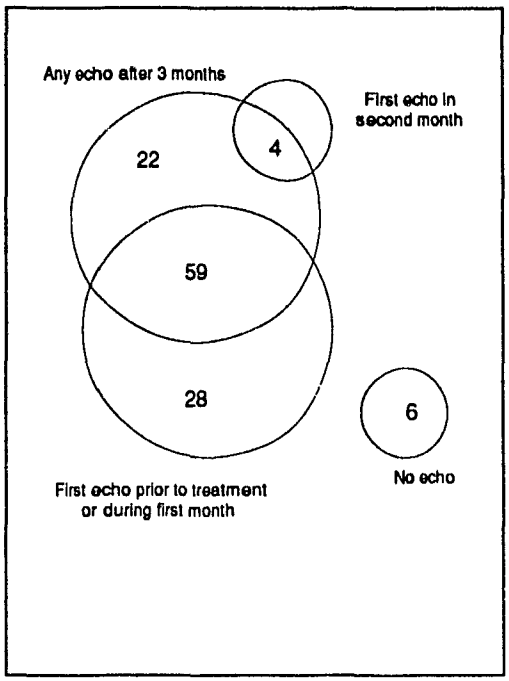

Figure 2b. Composition of subpopulations used for the various analyses.

Part 1: Hypertrophy and survival

Early cohort: 59 + 28 + 4	91 patients
Late cohort : 22	22 patients
No echo : 6	6 patients

Part 2: Factors associated with hypertrophy

Baseline : 59 + 28	87 patients
Follow-up : 59 + 22 + 4	85 patients
Paired : 59	59 patients

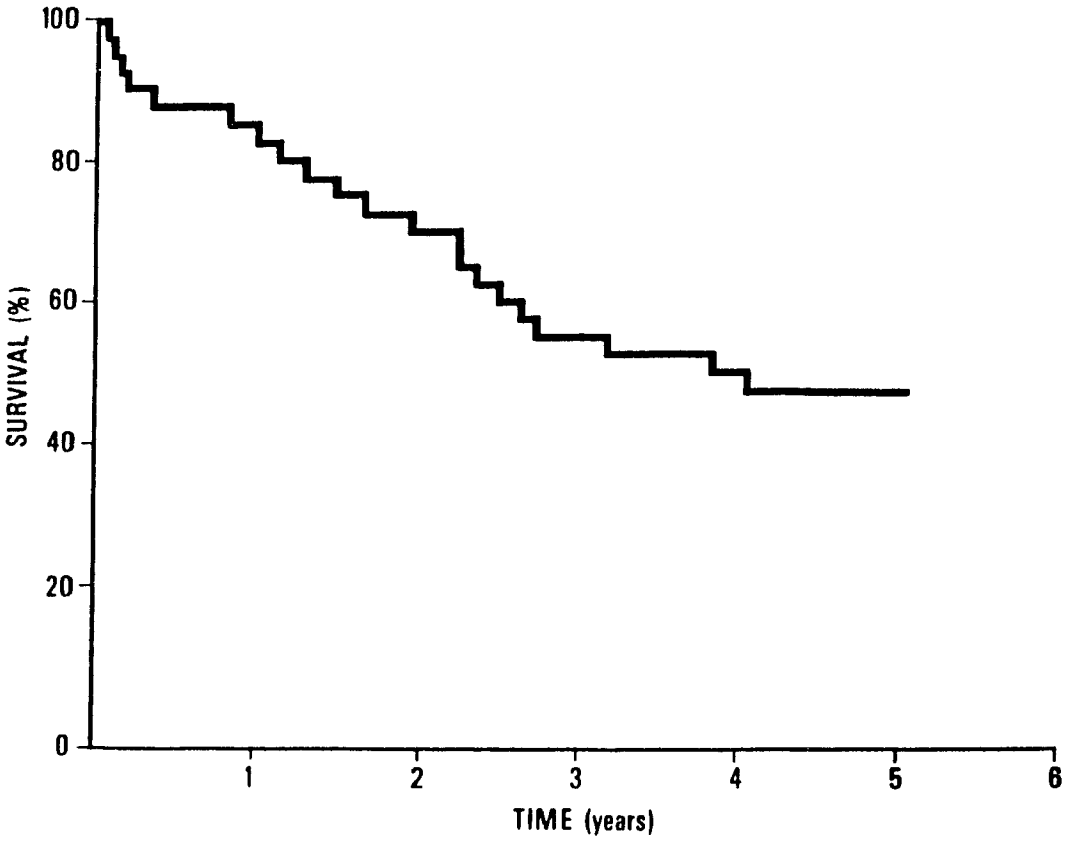

Figure 3. Actuarial survival of overall study population (N=119). Survival is similar to that reported in the Canadian Renal Failure Registry (1).

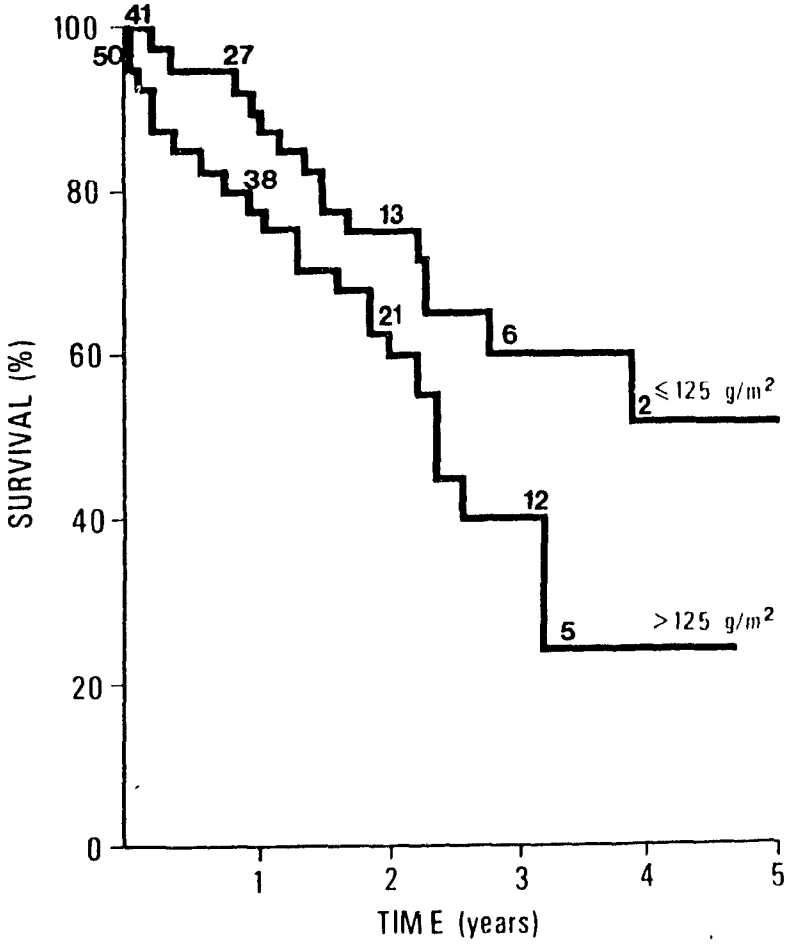

Figure 4. Actuarial survival according to left ventricular mass index greater or less than 125 g/m^2. This cutpoint is the upper 95th centile for normals reported by the authors who described the method used to estimate left ventricular mass (3).

Figure 5. Log-minus-log plots of the survival function according to strata of explanatory variables follow on the next 5 pages.

In all plots, the Y-axis is the log minus log survival function; the X-axis is time. If the curves remain reasonably constantly separated over time, then hazards are reasonably proportional. If curves cross, the proportionality assumption is violated.

A. Hypertension

B. Coronary artery disease

C. LVMI > 125 g/m^2

D. Age > 55 yrs

E. Diabetes

The variable Hypertension (Figure 5 A) violated the proportionality assumption. Hazards related to the other variables are reasonably proportional.

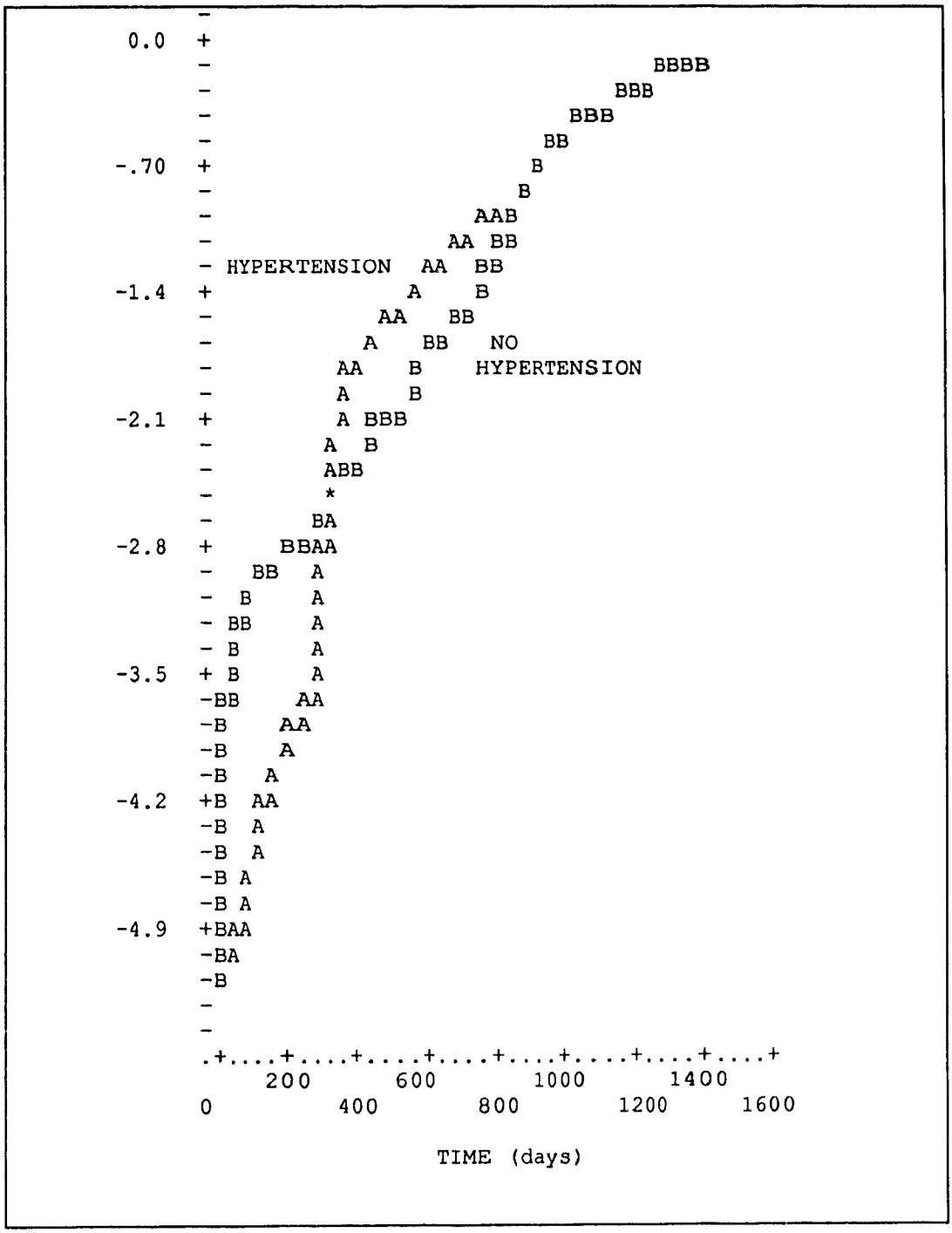

Figure 5 A. Hypertension. The proportionality assumption is violated.

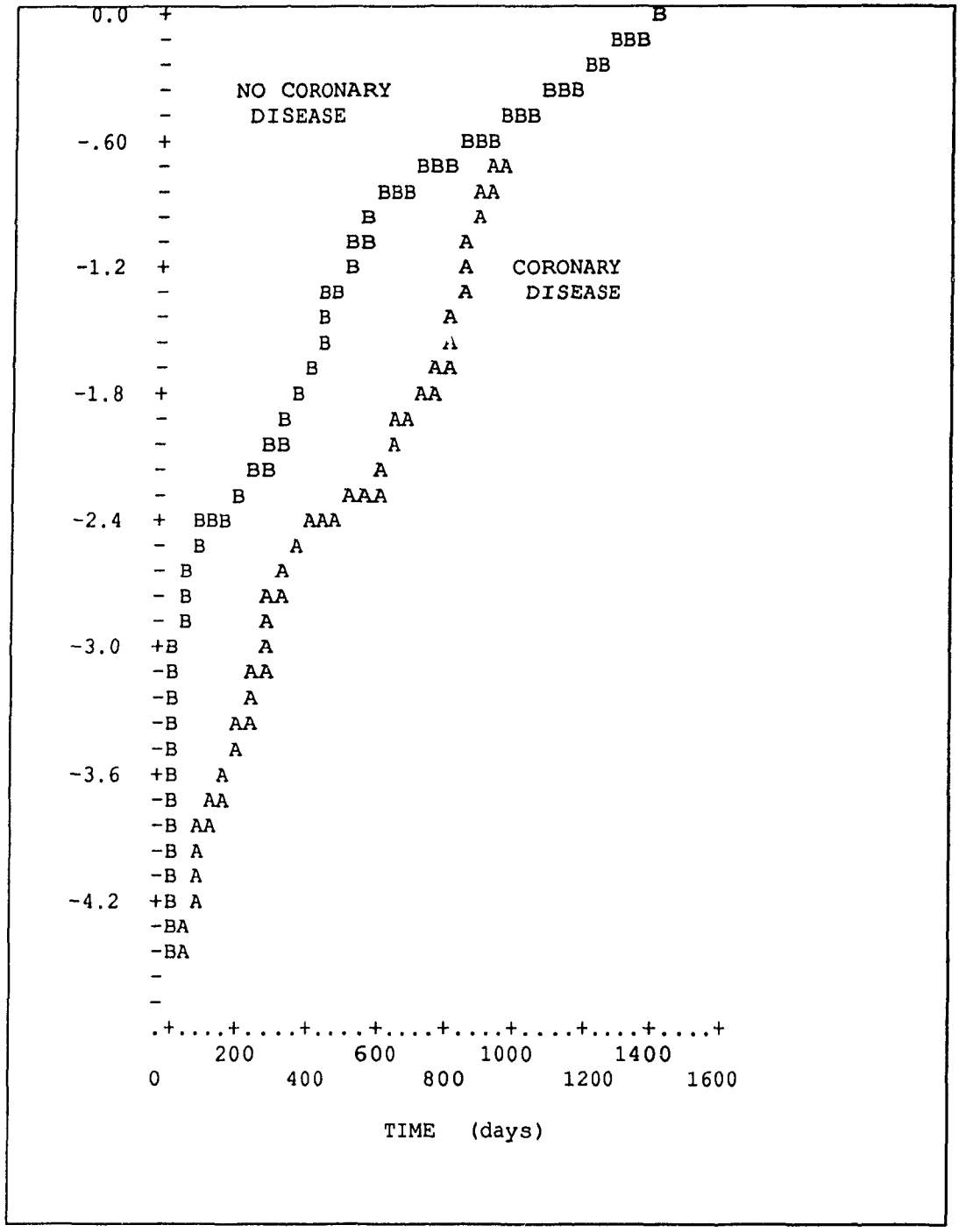

Figure 5 B. Coronary artery disease

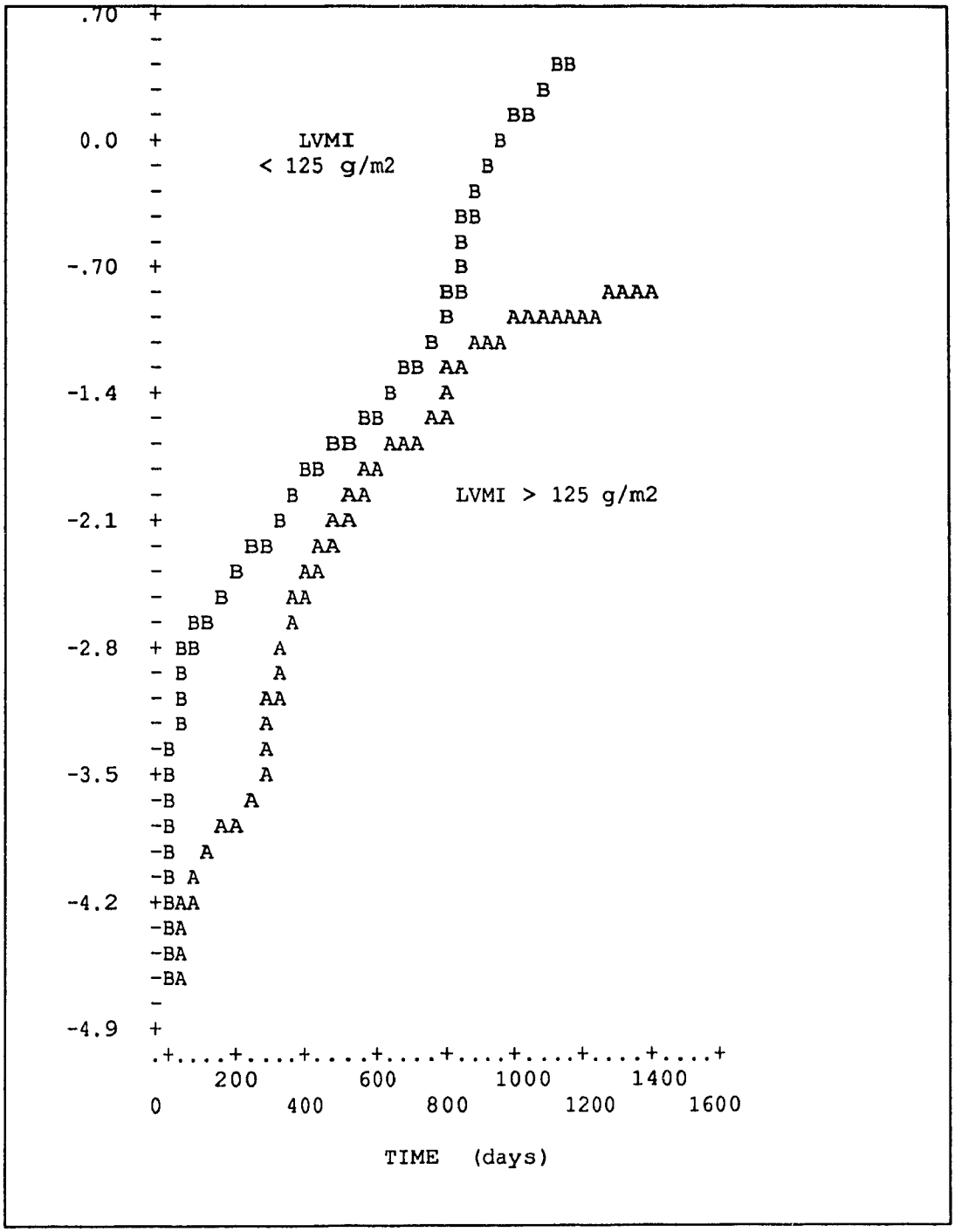

Figure 5 C. Left ventricular hypertrophy (defined as LVMI > 125 g/m²)

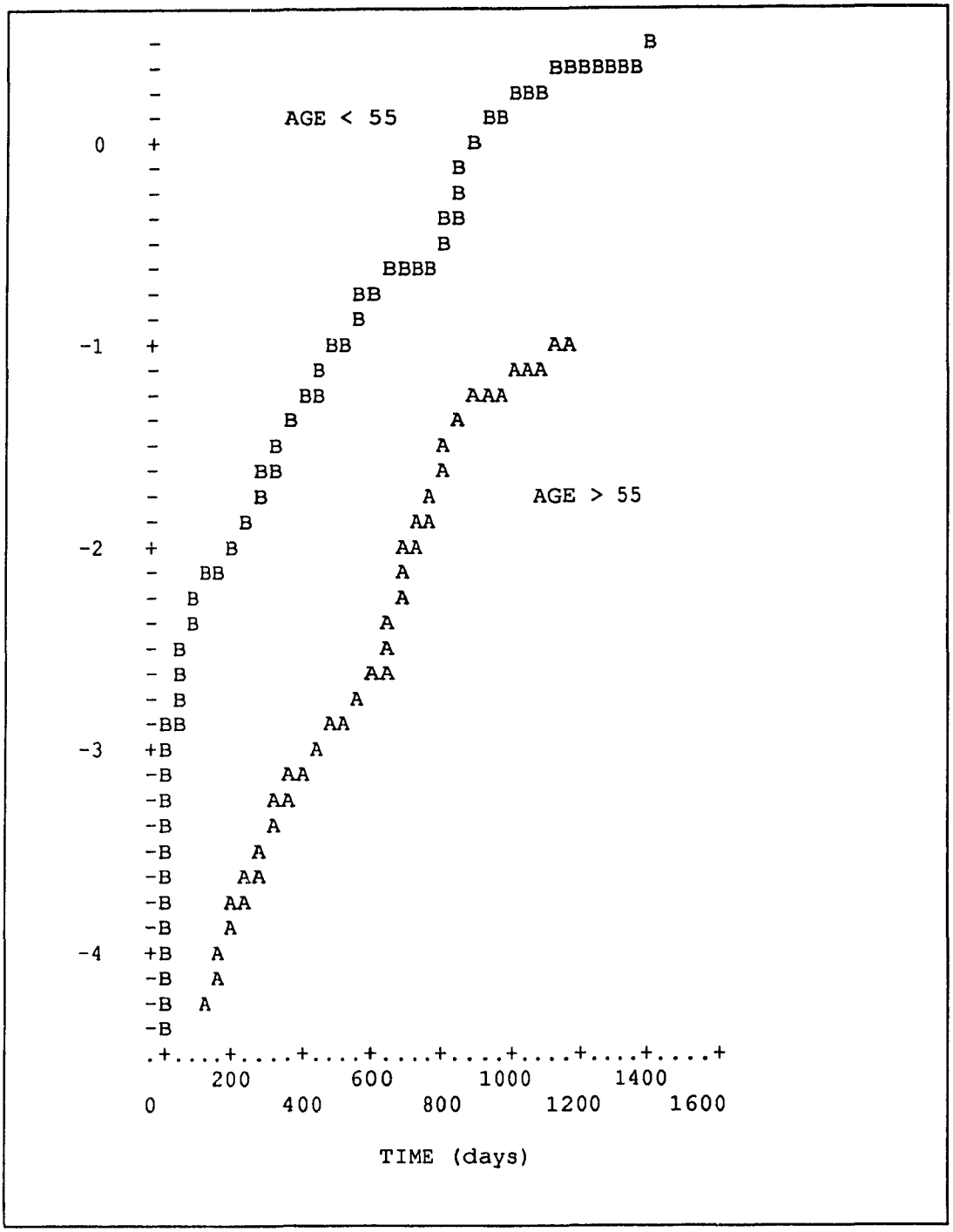

Figure 5 D. Age (greater than or less than 55 yrs)

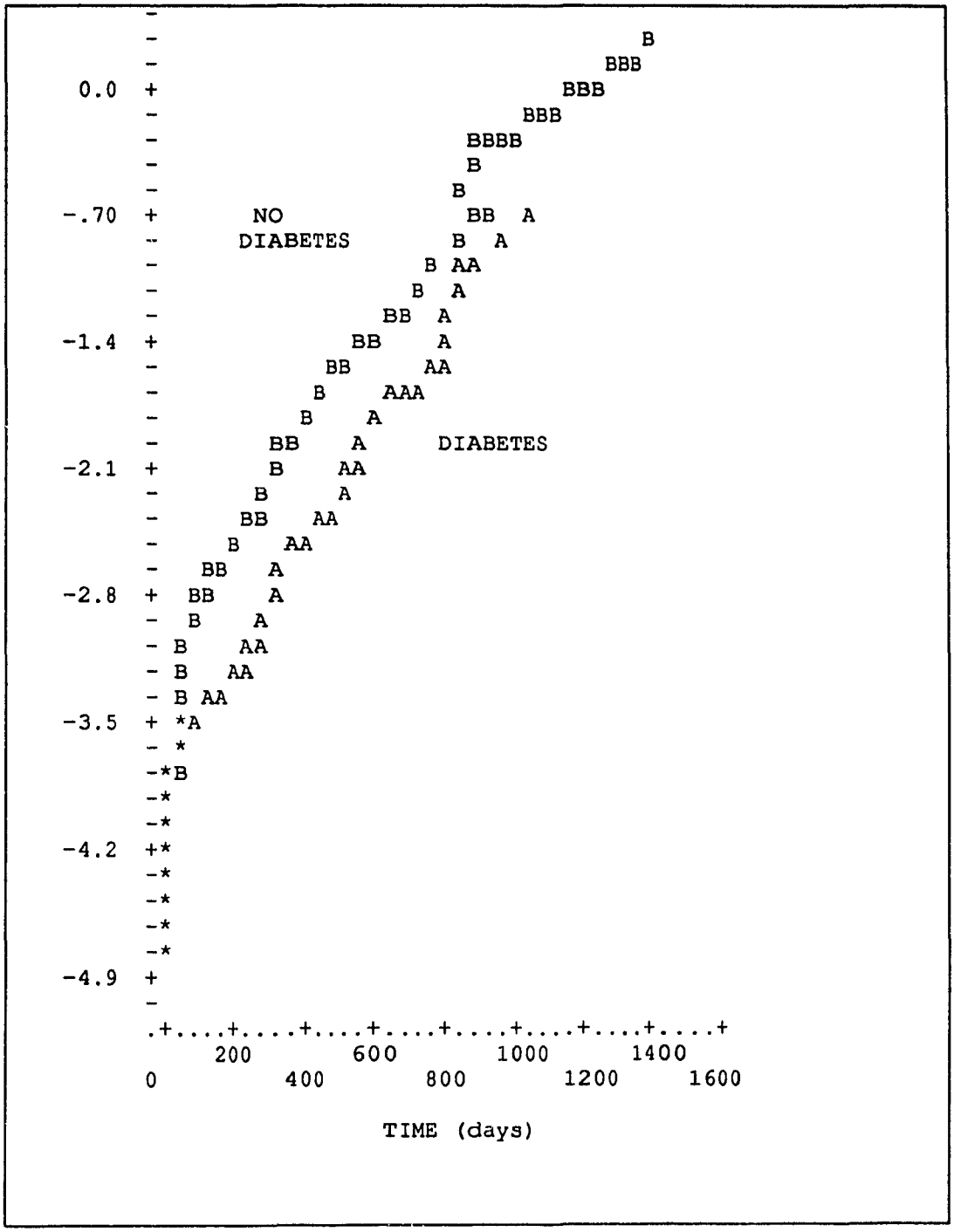

Figure 5 E. Diabetes

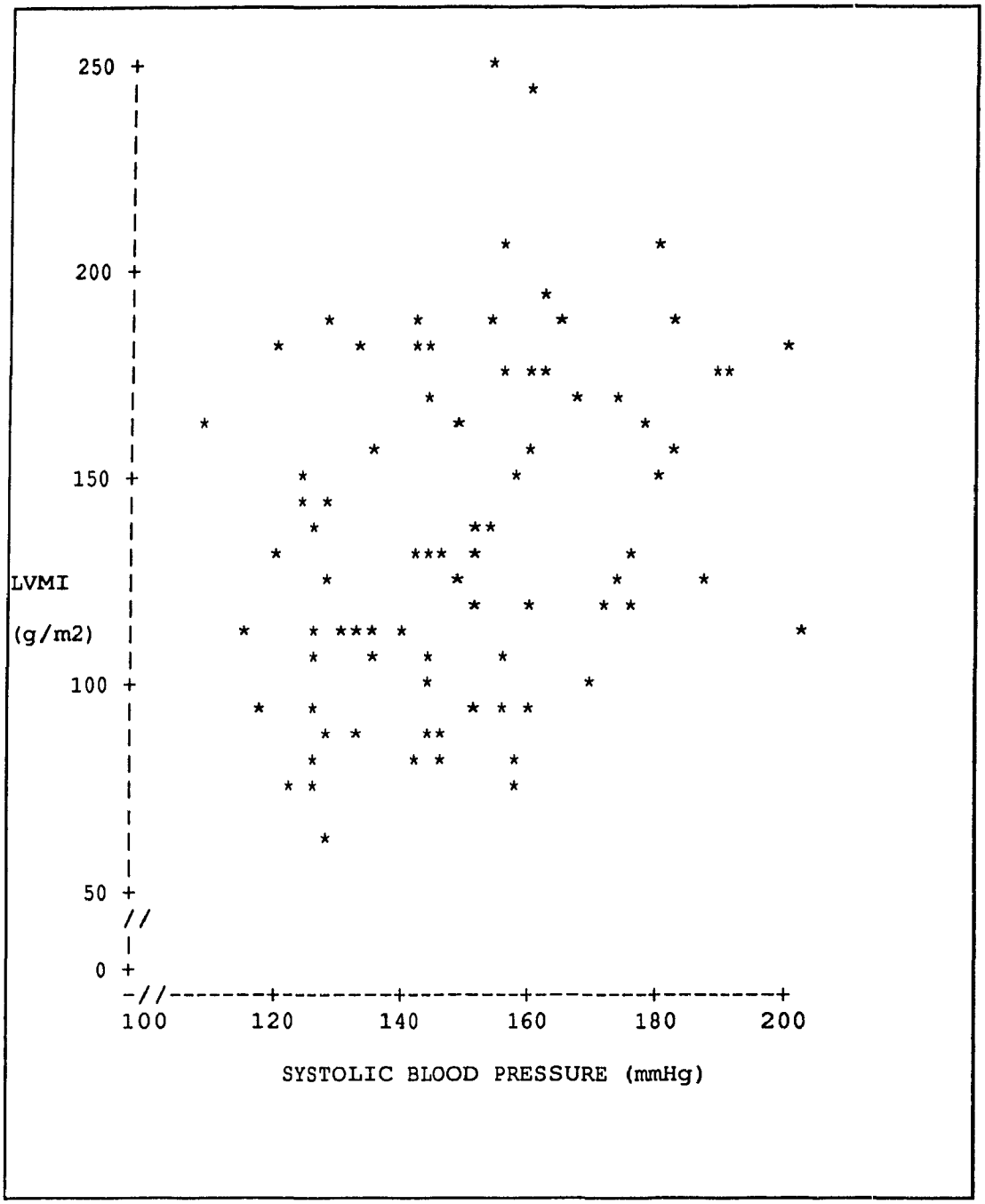

Figure 6. Left ventricular mass index (g/m^2) plotted against systolic blood pressure (mmHg).

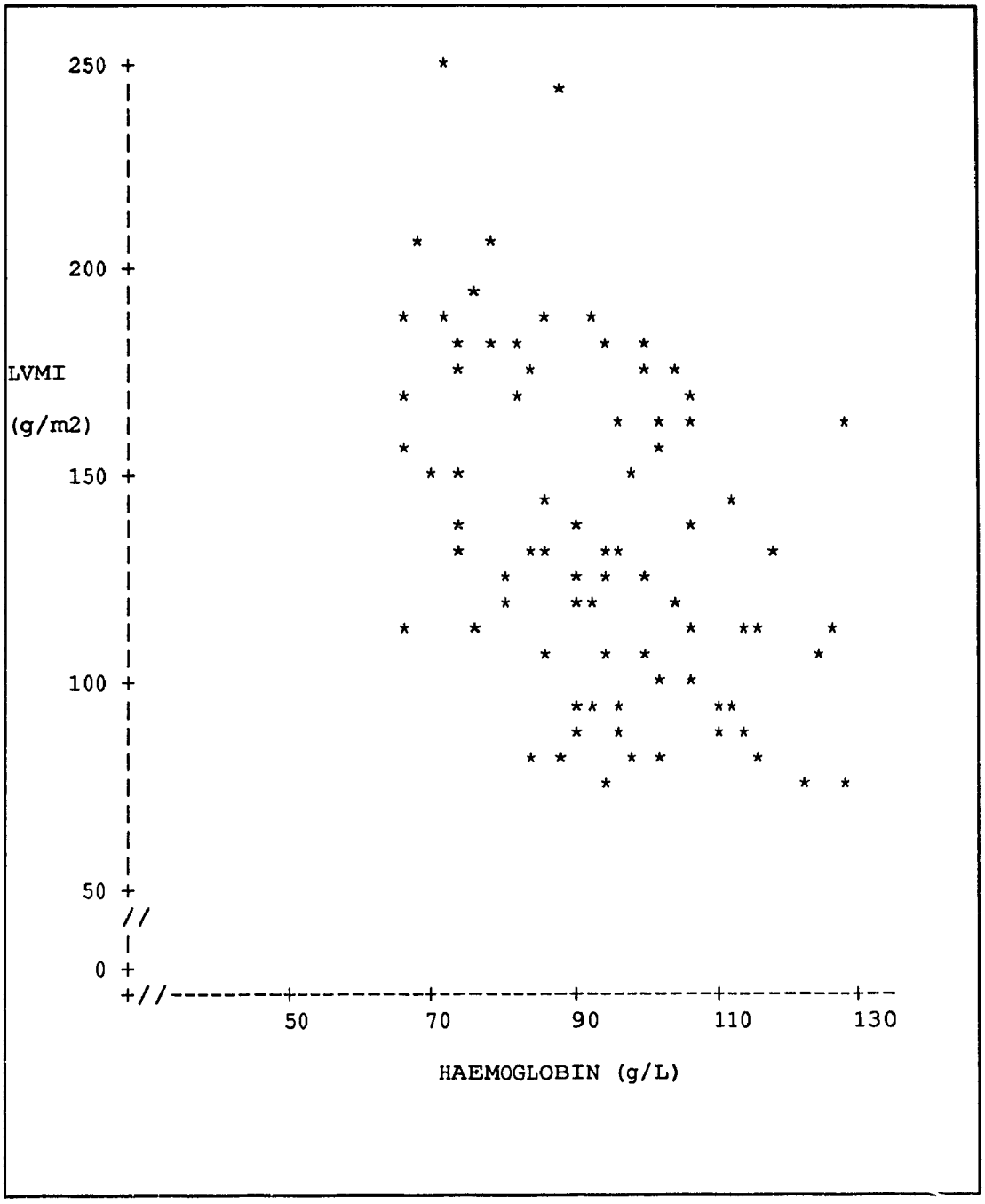

Figure 7. Left ventricular mass index (g/m^2) plotted against serum haemoglobin (g/L).

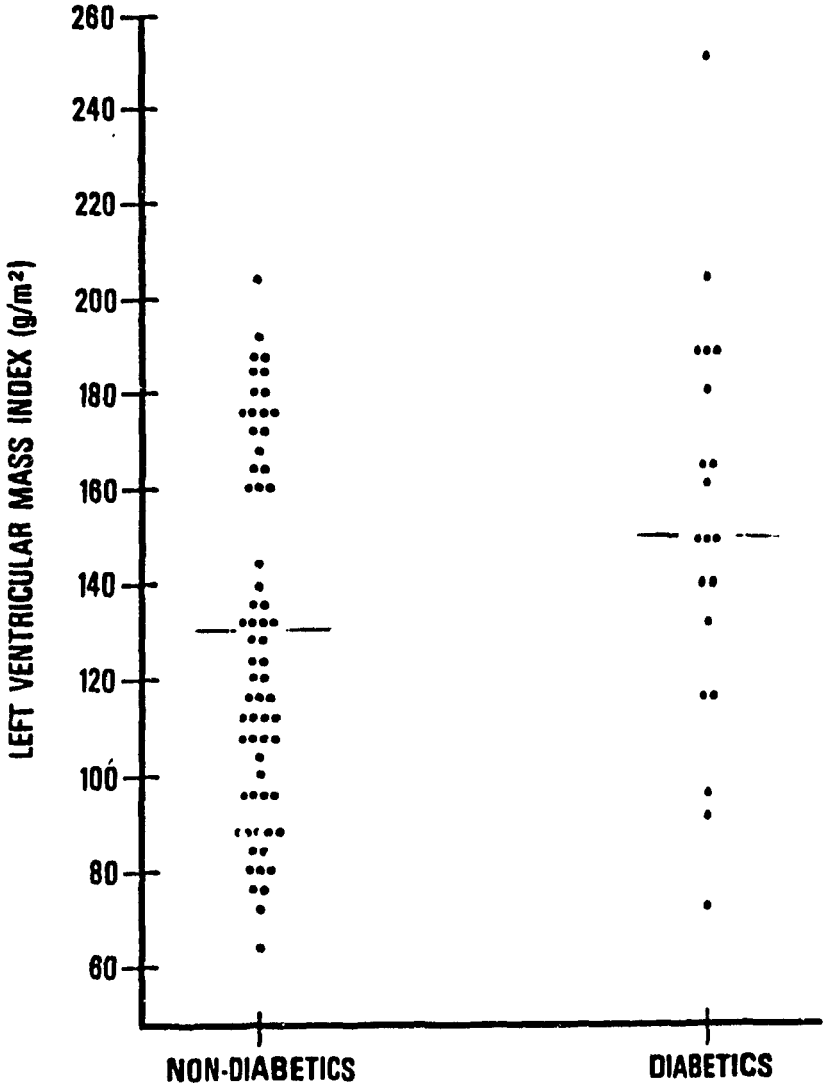

Figure 8. Left ventricular mass index (g/m^2) in diabetics and non-diabetics.

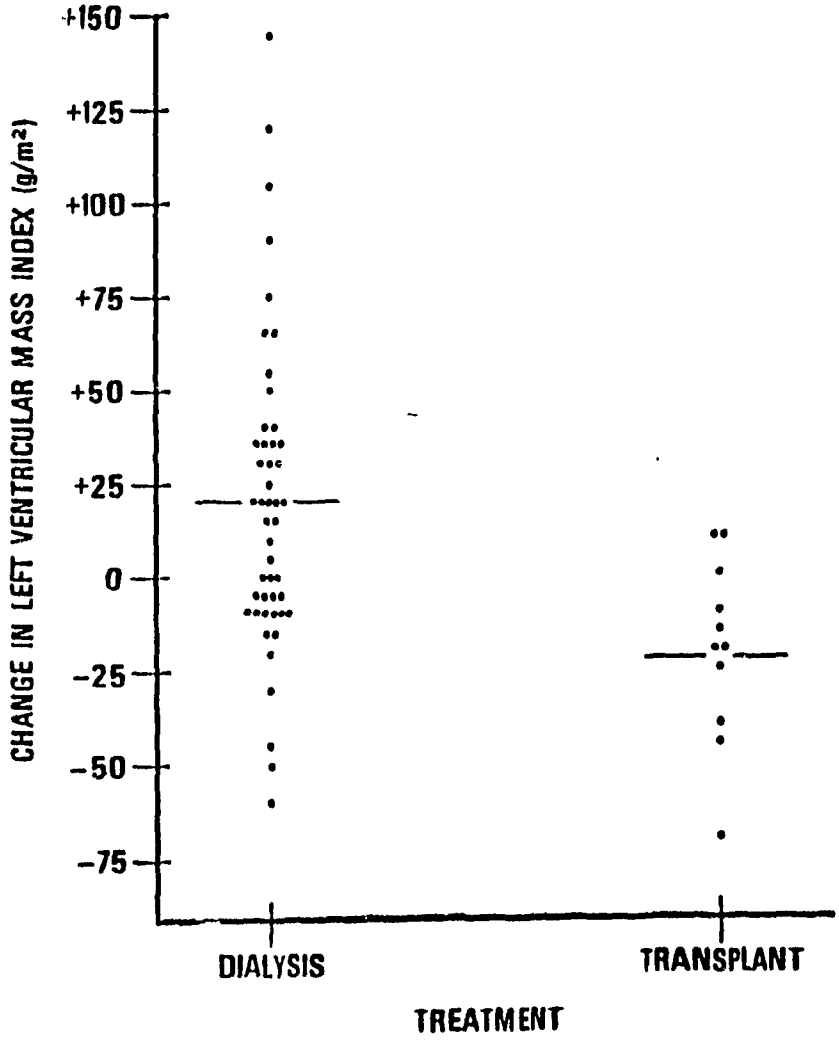

Figure 9. Change in left ventricular mass index (g/m^2) according to treatment modality at the time of followup echocardiographic study.