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THE UNIVERSITY OF ALBERTA

MULTIVARIATE REGRESSION ANALYSIS OF A KIDNEY TRANSPLANT PROGRAM

by

© JOAQUIN MADRENAS

A THESIS

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Supervisor

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Date JAN 26/1988

DEDICATION

To Teresa,
because of her constant helping and love
that makes this thesis her achievement too;

to my parents,
because they worked to make it possible.

"We are fools to hope for relief
when only recovery can relieve him !
Search and hunt far and wide through the world
for every simple, every potion,
there is but one thing can help him -..."
(Parsifal, Act I)

ABSTRACT

The objective of this thesis is to test the goodness of fit of the Cox proportional hazards model for the analysis of a single-centre kidney transplant program, and the effect of cyclosporine use. We studied all of the renal transplants performed in the University of Alberta Hospital between January 1, 1967, and December 31, 1985 (426 patients).

Actuarial as well as multivariate analysis of this data showed two clear-cut periods according to the effect of year of transplant on graft and patient survival: 1967-1974, and 1975-1985. Due to changes in the values of the covariates studied, only patients transplanted in the second period were included in the multivariate analysis: 136 cadaveric allografts on azathioprine, 84 on cyclosporine, 43 living-related kidney transplants on azathioprine, and 24 on cyclosporine.

After establishing that type of donor and main immunosuppressive drug can be included in the model, and following a step-down procedure from the initially tested 14 covariates, we obtained the following set of significant variables to predict graft survival: main immunosuppressive drug ($p=0.001$), number of HLA A and B mismatches ($p<0.02$)(HLA DR antigens were not considered), highest percentage of reactive antibodies against panel cells ($p=0.009$), nephroangiosclerosis as primary renal disease ($p=0.04$), and type of donor ($p=0.01$) in the presence of an interaction term between type of donor and main

immunosuppressive drug ($p=0.04$). Pretransplant blood transfusions, cold ischemia time, and donor ABO blood group were initially significant but they dropped out in the step-down procedure.

The final predictor model of patient survival contained the following covariates: main immunosuppressive drug ($p=0.005$), number of HLA A and B mismatches ($p<0.05$), nephroangiosclerosis as primary renal disease ($p=0.03$), and age at transplant ($p=0.005$).

In our experience, there is a proportionality of risks between renal transplants on cyclosporine and those on azathioprine as well as between cadaveric and living-related transplants. In view of this, it is possible to perform multivariate analysis of renal transplants in single centre including type of donor and immunosuppressive regimen as covariates, and the presence of interaction between them. Cyclosporine use has significantly improved graft survival in cadaveric but not in living-related kidney transplants, and it has decreased the relevance of the risk factors analyzed.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ACTH:	Adrenocorticotrophic Hormone
ADCC:	Antibody-Dependent Cell-mediated Cytotoxicity
ALG:	Antilymphocyte Globulin
anti-HBc:	Antibodies against Hepatitis B-Core Antigen
ATG:	Antithymocyte Globulin
AZA:	Azathioprine
BT:	Blood Transfusions
CAD:	Cadaveric donor
CAPD:	Continuous Ambulatory Peritoneal Dialysis
CDC:	Complement-dependent Cytotoxicity
CsA:	Cyclosporine
DST:	Donor-specific Transfusions
ESRD:	End-Stage Renal Disease
F:	Female
HBsAg:	Hepatitis B Virus Surface Antigen
HD:	Hemodialysis
IPD:	Intermittent Peritoneal Dialysis
LRD:	Living-Related Donor
M:	Male
MLC:	Mixed Lymphocyte Culture
6-MP:	6-Mercaptopurine
NS:	Non significant

PRA:	Percentage of Reactive Antibodies
recp:	Recipients
rpmp:	Rate per Million of Population

I. INTRODUCTION

Despite the variety of renal diseases, progression of kidney damage common to all of them leads to a life threatening situation called end-stage renal disease(ESRD)(118). At this stage, kidneys have lost all their functions (endocrinologic, excretory, and regulatory). The time progression between the initial damage and ESRD is quite variable, ranging from days to years depending on the etiology of damage. Advances in the therapeutic field of kidney diseases have been more frequent in trying to substitute renal function than in trying to delay this progression. The methods now available to substitute renal function can be divided in two main types: dialysis, and kidney transplantation.

Dialysis therapies were introduced in the early 1960s (49). The basis of all the modalities of dialysis is blood clearance through a semipermeable membrane. Dialysis with extracorporeal devices which assure the interaction between patient's blood and an artificial dialytic membrane (hemodialysis) were the first used. Several modalities of hemodialysis have been further developed depending on the facilities that they require or on the dialysate solutions that they employ (49). Alternatively, trying to get a more natural approach for the treatment of ESRD, an *'in vivo'* membrane, peritoneum, was used (peritoneal dialysis, further developed as continuous ambulatory peritoneal dialysis(CAPD))(147). Both modalities guarantee the

maintenance of a good excretory function and they allow for the possibility of management of disorders of homeostasis by external interventions. Hemodialysis and CAPD still constitute the initial substitutive therapy for most patients with ESRD, providing them with a long life expectancy. However, they do not substitute endocrinologic functions of kidney. Moreover, they are also associated with their own pathology derived from the interaction blood-membrane itself, a phenomenon known as bioincompatibility (7). Finally, the quality of life achieved on dialysis is restricted by the periodicity that these therapies require (53).

With all this in mind, an alternative approach to the treatment of ESRD was considered, based on the substitution of the whole organ.

A. Historical overview of renal transplantation

The history of organ transplantation has two main periods, representing the two main problems in the development of this treatment. The first problem is the surgical technique for transplanting an organ conserving its whole function. After solving the transplantation problem, it becomes evident the importance of the second aspect: the immunologic phenomena triggered in the host by the presence of a foreign organ.

The first successful experimental kidney transplant was performed by Ullman in 1902 (204). At that time, the main

problem was surgical, that is, the implantation of the organ and its vascular supply (that instance was a dog kidney autotransplant to the vessels of the neck). In the next 10 years, more dog-to-dog kidney transplants were carried out by Carrel (23) and von Decastello (45). Jaboulay reported four years later the first human kidney transplants (89). Curiously, the organs transplanted were xenografts (from a pig and a goat). The experience was not hopeful (the organs were functioning for approximately one hour) and organ transplantation was temporarily forgotten up to 1950s, except for Voronoy who used a human organ for the first time in 1933 and performed six more transplants, all without success (73). In the early 1950s, 2 principal groups, in Paris (71) and Boston (79), renewed the interest in renal transplantation. Several kidney transplant allografts were performed with partial success, together with the first living-related (LRD) kidney transplant (73). Simultaneously, and in separate papers, Simonsen (168) and Dempster (46) described the pelvic position as preferable for renal transplant. It is interesting to note that most of these transplants were done without immunosuppression, and, by that time, dialysis was still not a regular treatment for patients with ESRD, making transplantation the last therapeutic resort (73).

Early and isolated studies by Murphy (up to 1914)(123) had suggested that the natural rejection response to foreign tissue, exerted by organs such as the spleen or the bone

marrow, could be attenuated by some external agents like radiation or benzol. In 1953, Simonsen (168) and Dempster (46) separately described for the first time that graft rejection was the event responsible for graft failure. The discovery of the major histocompatibility complex revealed that there was another aspect to consider in order to prolong life of the graft, that is, the need for control of the immmune response (43, 207, 208). The first method used for immunosuppression was irradiation (44, 72, 124). Concurrently, drugs were developed as immunosuppressive agents, specifically 6-mercaptopurine (6-MP), ACTH, and cortisone, and were generally used in association with radiation (72, 80, 81, 102, 163).

The first long-term survivor with 6-MP and intermittent prednisone was reported in 1962 (102). However, in 1961 azathioprine (AZA), a derivative of 6-MP, was shown experimentally to be more effective and less toxic (16). Azathioprine was available for clinical use in 1961 but the first long-term survivor was reported in 1963 (125). After this, immunosuppression with AZA and prednisone became the conventional therapy for kidney transplants (41, 82). Moreover, renal allografts (of cadaveric (CAD) or LRD origin) were used; there were only isolated attempts in using xenografts (73). By the mid 1960s, hemodialysis had become a regular maintenance therapy for ESRD (49). Also, the introduction of tissue typing techniques to select recipients (43, 207, 208) encouraged performance of more

renal transplants, and the study of new methods to prevent graft loss. In 1966, Kissmeyer-Nielsen recognized that a "positive lymphocytotoxic crossmatch" was responsible for hyperacute rejection (97), a discovery which lead to a remarkable decrease of early graft failures. In 1967, Dossetor *et al* suggested the possibility that pretransplant blood transfusions could improve graft survival (48). Nevertheless, the finding that preformed lymphocytotoxic antibodies could be deleterious to graft outcome (182), together with disadvantageous effects of hypersplenism, led to restriction of transfusions before transplantation (134, 135), many patients learning to live with hemoglobins below 5 g/dl. In 1972, the poor graft prognosis for non-transfused patients was reported (133) and confirmed by others. This led again to a more liberal pretransplant transfusion policy (136, 205).

During the 1970s, the only advance in the allograft therapy was antilymphocyte globulin (ALG) and its variants (antithymocyte globulin (ATG)), for use both in prophylaxis and in treatment of graft rejection (164, 166, 175, 180). Nevertheless, the results with ALG have not been uniform, principally because of inability to standardize the product, the critical assay being unknown at that time.

In the transplant immunology field, the discovery that DR-antigen mismatches influenced graft survival led to the introduction of HLA-DR matching in recipient selection, and claims for improved overall results (1, 65, 112, 119, 142,

194, 195).

Following advances in immunology in the 1970s, much effort was directed to monitoring immunologic events in relation to graft outcome, looking especially for those parameters which could be premonitory of graft rejection. Different techniques were developed, some using antibody assays (complement-dependent cytotoxicity (CDC), mixed lymphocyte culture (MLC) and its derivatives, erythrocyte antibody inhibition, endothelial-monocyte antibodies, antibody-dependent cell-mediated cytotoxicity (ADCC)). Systems were also developed to monitor donor-specific cell-mediated immunity (lymphocyte-mediated cytotoxicity, cell-mediated lympholysis, leukocyte migration test, leukocyte aggregation test); yet others were based on non-specific immunologic events (such as CD4/CD8 lymphocyte ratio, NK cell function, or circulating immunocomplexes)(213). Despite the relevance of the early diagnosis of graft rejection from a clinical point of view, none of these techniques has achieved a well established role in clinical transplantation. Mostly, they have been useful for understanding the pathophysiology of rejection, and for envisaging a future specific immunosuppression, with antigen-induced or antibody-induced specific unresponsiveness or through anti-idiotypic immunization.

In summary, the 1970s decade can be considered as the period in which kidney transplantation became a regular therapy for ESRD in most renal units. A high increase in the

number of renal transplants as well as in graft and patient survival was observed. Terasaki's group (183) recorded 15,594 kidney transplants with an overall 1-year graft survival of 47% for CAD kidney allografts, 68% for 1-haplotype-different parental kidney transplants, 70% for HLA-nonidentical sibling, and 85% for HLA-identical sibling transplants. Cadaveric donor was the most frequent source of kidneys, representing over two thirds of transplants.

The 1980s started with renewed enthusiasm for several reasons, the most important being the introduction of cyclosporine (CsA) as a new immunosuppressive drug (10, 17, 18). It has substantially increased graft and patient survival in CAD kidney transplants and it has reduced the need for adrenal glucocorticoids, sparing the corticoid-related complications. However, CsA has numerous side effects (34), nephrotoxicity being the most relevant (127). Conditioned by this, new techniques for histologic examination of the graft have been developed (fine-needle aspiration biopsy)(210, 212). Besides, CsA has questioned different factors related to renal transplantation: the need for a good HLA match (199), pretransplant blood transfusions (200), etc. Moreover, CsA has stimulated research for new immunosuppressive regimens to avoid its nephrotoxicity (167). The most popular are triple low-dose therapy with CsA, AZA, and prednisone(106), and switching from CsA to AZA three to six months after transplantation (58, 77, 120, 122, 177, 190); others still under evaluation include sequential

therapy with AZA, prednisone, and ALG, changing to CsA and prednisone few days after transplantation (172).

In relation to LRD transplants, prior to CsA, pretransplant donor-specific blood transfusions (DST) were shown to increase graft survival (154), specially in those receiving HLA-haploidentical transplants (88). However, there remains the problem of sensitized patients because of blood transfusions or previous transplants (86, 87) and this remains a challenge to the clinician.

The discovery of monoclonal antibodies has also been beneficial to clinical transplantation in several ways. Monoclonals have been used in treament of graft rejection (especially OKT3 (36) and OKT12 (96); and recently, against interleukin-2 binding site receptor (173)) as well as in histologic examination of grafts and in immunologic monitoring (37).

Another aspect that has been actively studied in the last 10 years has been the support of potential cadaveric donors. The demonstration that early function of graft was an important prognostic factor for its survival (21, 93, 158) led to study of possible ways of decreasing organ damage in the preagonal period, as well as to determine the best method for preservation, using such agents as thyroxin, insulin, and corticoids (130, 211). These studies may question again the preservation advantages of cold storage over machine perfusion of the excised organ (70).

In summary, kidney transplantation has become the preferred modality of therapy for ESRD. Transplantation immunology has emerged as a new field of study of the underlying processes that condition graft and patient survival. The application of the techniques of molecular biology to this field is just starting to open doors to a deeper knowledge of graft rejection (69), and, hopefully, will be decisive for improving graft survival.

Legal and ethical considerations are also important in the overall evaluation of kidney transplant programs (22) as, for example, in the use of living-unrelated donors (105). Further, the degree of rehabilitation of transplanted patients, measured by the employment status, has been shown to be higher than for patients on dialysis (91, 92, 174); also, renal transplantation has a better cost/benefit ratio than dialysis (150), or even other regular surgical procedures like resection of colo-rectal cancer (121). These 2 aspects dictate the importance of obtaining more kidneys as well as defining criteria for suitability for transplantation, in terms of patient well-being and health care economics.

B. The need for survival analysis of transplant patients

Since the creation of the Registry in Human Kidney Transplantation and Eurotransplant in early 1960s (4, 207), different national (6, 11, 170) and international (144, 185) groups have been created to perform periodic statistical

studies of transplant patients, and their results have had a tremendous impact on policy for organ transplantation. To compare patient survival, as between dialysis and renal transplantation, very elementary statistics such as actual or actuarial survival curves of grafts and patients are used. However, reasons for more sophisticated statistical analysis of transplant data derive from the fact that organ transplantation constitutes, among the different medical therapies, a clear prototype of biased treatment because it leads to selection of the best recipient candidate on the basis of information gathered under a biased policy. It is evident that there is need to establish clear prognostic factors which could determine less biased decisions (15). Here emerges a second principal reason for more sophisticated statistical surveys of transplant data: to determine prognostic factors which will allow for better understanding of transplant behaviour. This was started with survival tables, by considering one variable at a time. Soon the need was evident to evaluate sets of variables and their possible interactions. Initially, this was also done by univariate methods but, with increasing number of variables, it led to categories of very small size, so results became valueless (39). To overcome this problem, multivariate analysis of transplant data was proposed. This type of analysis also predicted graft and patient survival for different groups, following the rules of regression modeling and statistical inference. The proposal of multivariate

analysis of kidney transplant data by Bailey *et al* in 1977 (3), according to an approximation to the Cox proportional hazards model, was quickly adopted by Mickey *et al* (114), who used a logistic regression of transplant data to establish a predictor model, and by Barnes *et al* (5) using the model proposed by Bailey *et al*. Since then, other studies using multivariate methods have been performed (62, 64, 83, 93, 100, 115, 148, 149, 157, 159, 160, 161, 169, 174, 181, 189, 198, 209). Most of them have been applied to subgroups of transplanted patients [mainly CAD allografts on AZA (114, 115, 149, 157, 159, 160)], and for data collected from different centres, because of the need for large samples. However, a 'centre effect' soon became evident ('the centre where a graft is inserted influences its outcome'). Its significance remains uncertain as it is probably multifactorial, related to pretransplant factors such as time on dialysis or quality of dialysis as well as posttransplant events, such as quality of surgery or skill in the use of clinical immunosuppression (67). This aspect was solved by introduction of stratification by transplant centre (stratified proportional hazards regression)(63).

It is important to note that the lack of power and precision in identification of factor effects in single centres (because of the small sample size) could correspond to a lack of power and precision in identification of interactions between factors in multicentre studies (63). Another aspect to consider when evaluating multivariate

analysis of transplant data is the goodness of fit of the model (94). This has not always been tested, even though the constant proportionality seen in actuarial survival curves makes the goodnes of fit easy to accept. On the other hand some variations to the Cox model have been added for studying the influence of a set of covariates at specific periods of time (63). At least two predictors have been reported which use multivariate regression analysis (75, 114), but we are not aware of any which consider type of donor and the use of CsA based on single-centre long-term transplant data.

From a statistical point of view, multivariate analysis has become the preferred statistical approach to evaluate prognostic factors for renal transplantation. According to Gore (67), univariate analysis has at least four kinds of distortions. First, it is possible that some variables considered significant through univariate analysis, are in fact only significant through association with other covariates. Second, it is possible that univariate analysis exaggerate, underestimate or reverse the true effect of one covariate. Third, it is possible that different significant covariates in univariate analysis carry the same kind of information with regards to the outcome. Finally, univariate methods do not consider the possible interactions between covariates and the possibility of multiplicative effects when they are present. These reasons could explain some differences between univariate and multivariate results in

terms of predicted survival curves, even though there is, in general, a close agreement between the two methods.

There has been much research on methods for survival analysis in the last 10 years (13, 15, 39). There are now four main models for multivariate analysis of survival data (39): the exponential model, the Weibull model, the proportional hazards model, and the log-logistic model. All accept the presence of a constantly determined hazard, whose mathematical form changes according to the model. The exponential model assumes a constant risk for the terminal event, with time. The Weibull model assumes a monotone risk of graft failure, and the log-logistic represents risk as a non-monotone hazard accommodating different hazards for different times (accelerated failure time model). The assumption of a constant hazard is quite unlikely (67). Moreover, there is the possibility that prognostic factors could change with time, as has been demonstrated by Gore (67), requiring introduction of time-dependent covariates if analysis of the effect of the set of covariates at different time points is desired. Because of these facts, the Cox proportional hazards model has been the most frequently used (38). It does not assume a specific form for the base-line hazard and it also accommodates the possibility of time-dependent covariates.

Two more reasons justify the performance of statistical analysis of transplant data (15). One is the ability to use the statistical results for future adjusted survival

analysis, based on prognostic factors previously determined. The second is that statistical results can help us in designing new lines of research to explain unanticipated facts revealed in the analysis.

C. Objective

According to the Canadian Renal Failure Register (20), in 1985 there were 4,272 patients with ESRD following dialysis treatment in Canada. This represents 168.4 patients per million of population (rpmp). Of those patients, 65% were on hemodialysis, and 35% on different modalities of peritoneal dialysis. The corresponding figures for Alberta were: 345 patients on dialysis (146.9 rpmp) being 70% on hemodialysis and 30% on peritoneal dialysis. Moreover, 1,533 patients (60.5 rpmp) entered ESRD in Canada during 1985 (147 patients (62.6 rpmp) in Alberta), almost 15 rpmp more than in 1981. This increase was due, predominantly, to patients older than 65 (they constituted 28% of the new patients recorded). On the other hand, records show that there were 3,502 functioning kidney grafts in Canada in 1985 (138.1 rpmp), 306 were from Alberta (130.3 rpmp). During that year, 737 renal transplants were performed (29.1 rpmp) of which 65 were done in Alberta (27.7 rpmp). Eighty six percent of Canada wide kidneys came from the CAD source (with 78% of CAD kidney transplants in Alberta). These transplant figures represent an increase of about 53% between 1981 and 1985.

Despite the increase in numbers of renal transplants, the proportion of would-be recipients on waiting lists remains stable: 24% of all dialysis patients. Forty-five per cent of dialysis patients are considered medically not suitable for kidney transplantation, in part due to the higher rate of acceptance of older patients in dialysis programs. Remarkably, 7% of patients on dialysis do not want to be transplanted. Social and economical implications of these numbers should be kept in mind. They are also too low; if CAD kidneys were more plentiful, the proportion of dialysis patients deemed unsuitable would fall.

In Canada, then, and specially in Alberta, renal transplantation is not only the theoretically preferred therapy for ESRD but also is the substitutive therapy for almost 50% of patients with ESRD.

The goals of this thesis are justified by the need for full statistical analysis of transplant data, at the single centre level. Thus, it can be stated that the final objective of this work is to perform a statistical analysis of a kidney transplant program, in terms of graft and patient survival, using different techniques, especially a multivariate method (the Cox proportional hazards model). We also wish to test the possibility of including the regimen of immunosuppressive and the type of donor as covariates of this multivariate model. If the model, with these two covariates included, fits the data well it would be easier to analyze single-centre transplant experiences because it

would enable an increase in sample size.

The main advantage of this kind of study would be the lack of 'centre effect' and the possible derived interactions. Also included is an attempt to analyze, in a long-term follow-up population, the significance of several covariates as risk factors for graft and patient survival. Finally, a predictor model is developed for graft and patient survival according to our results. This could now be applied to predict the influence of different factors in separate future groups of patients with a view to establishment of 'a priori' high-risk patient groups for renal transplant.

II. MATERIAL AND METHODS

A. Patient Population

This study includes 426 kidney transplants performed between January 1, 1967, and December 31, 1985. Most of these patients were transplanted in the University of Alberta Hospital. However, some patients transplanted elsewhere were also included if transplant follow-up was done in our division from one month after transplantation. The sample included 361 (85 %) first kidney transplants, and 65 (15 %) regrafts (57 second transplants, 7 third transplants, and 1 fourth transplant). All the patients had a minimum follow-up period of one year.

For each patient, graft and patient survival were noted. Graft survival was considered as the elapsed time between kidney transplant and loss of function of the graft or death, even with a functioning graft. Patient survival was recorded as the time between renal transplantation and death, provided death occurred with a functioning transplant or within 12 months of return to dialysis. The date on which the study was closed for new follow-up was the day on which the statistical analysis was performed (April 20, 1987).

Variables studied were:

- sex of recipient: male or female,
- ABO blood group of donor and recipient: O, A, B, and AB,
- primary renal disease: especially diabetes mellitus

and nephroangiosclerosis,

- time (months) on dialysis before transplantation,
- dialysis treatment modality: home hemodialysis, hospital hemodialysis, self-care hemodialysis, intermittent peritoneal dialysis, and continuous ambulatory peritoneal dialysis (CAPD),
- presence of Hepatitis B virus surface antigen (HBsAg) and anti-core antibodies (anti-HBc) against this virus in recipient pre-transplant,
- pre-transplant social rehabilitation evaluated by the physician in charge of the patient: normal activities vs restricted life, and employment status (employed vs unemployed),
- number of pre-transplant blood transfusions received before transplantation,
- highest percentage of different individuals' lymphocytes killed by patient's serum lymphocytotoxic antibodies (PRA): if PRA was over 50 %, such a serum was deemed to have come from "hyper-responder",
- number of pregnancies before transplant,
- age at transplant,
- type of donor: CAD vs LRD,
- age of donor,
- mismatches for HLA A/B, C, and DR between donor and recipient (maximal: 4/4 for A and B),
- warm and cold ischemia times,

- main immunosuppressive drug (AZA vs CsA), and
- number of previous kidney transplants.

HLA antigens were recorded according to the nomenclature recomended in the last Histocompatibility Workshop (129). Patients without both antigens for a specific locus, were treated as missing values. Cells on which only one A and/or B locus antigen was detected were considered as homozygous for that locus (8). Any donor's antigen which was not present in the recipient was recorded as one mismatch.

Warm and cold ischemia times were drawn from the chart where they had been recorded by the surgeon in charge of the transplant operation. Warm ischemia time was defined as the time between clamping donor's renal vascular tree and extracorporeal reperfusion of the kidney. Cold ischemia time was determined as the period of time between donor's nephrectomy and the release of the arterial clamp on vascular anastomosis in the recipient.

The therapeutic regimens were considered on the basis of the main immunosuppressive drug, that is, AZA vs CsA. Azathioprine regimen consisted on AZA at 2.5 mg/Kg/d initially and dosage afterwards was adjusted according to white blood cell count, and prednisone at 1 mg/Kg/d, reducing gradually to 0.25 mg/kg/d every other day by three months. In the CsA regimen, the patient received CsA at 14 mg/Kg/d with subsequent regulation of dosage according to serum levels, and prednisone at 2 mg/Kg/alternate day

decreasing 5 mg every 3rd dose until 0.25 mg/Kg/alternate day. Rejection episodes in both groups were treated with i.v. methylprednisolone sodium succinate (Solumedrol) 1 g/d for 3-4 days. In some exceptional cases these two protocols were slightly modified, with addition of i.v. antilymphocyte globulin, graft irradiation or withdrawal of corticoids.

The kidney transplant protocol also included pretransplant blood transfusions. Before CAD kidney transplants, potential recipient received, independently of previous blood transfusions, prior to dialysis, 4 transfusions of packed red cells at different intervals. Before some LRD kidney transplants, DST were administered according to a protocol of 3 x 200 ml at two week intervals, with the third at approximately eight weeks prior to transplant. In both CAD and LRD groups there were some non-transfused patients.

Diagnosis of acute rejection episodes was made on the basis of clinical signs. They occur predominantly in the first three months after transplantation, being confirmed in some cases with graft biopsy. In patients treated with CsA, serum levels of CsA were determined to limit the risk of nephrotoxicity associated with persistent serum levels greater than 100 ng/ml. Chronic rejection was considered in cases in which declining renal function was observed during the first three months after transplantation without evidence of CsA nephrotoxicity, together with a compatible graft biopsy.

To avoid the effect of year of transplant on the results we used changing annual actuarial graft survival as well as multivariate analysis as an indicator for establishing two clear-cut different periods: 1967-74 and 1975-85 (p=0.007). Moreover, some variables have evolved from simple to more complex systems between these two periods, e.g. HLA profiles. Consequently, both periods have been further analyzed, separately.

B. Data management

Patient information concerned is stored in a computerized database (Stanford Public Information Retrieval System (SPIRES)) implemented in the University of Alberta computer network (84). In this file, patient data were introduced in two main types of values: text, and numeric data. The first step has been the translation of this data into a numeric rectangular matrix in order to process them with a statistical package. This has been performed using the formatting capability of SPIRES system (85). Formatting language permits codification and decodification of different kinds of values as well as some basic mathematical transformations. The constructed formatting program allows the user to obtain numerical matrices in a few seconds from non-numeric values in the database.

The statistical packages used in this thesis have been SPSS^{X} (version 2.1) for performing standard actuarial estimates, Gehan's test for comparison of survival curves,

and the Cox proportional hazards model (111). The logrank test was done using the SAS system for data analysis (462).

Accuracy of data in the database was evaluated by random comparison between values retrieved through the computer and those recorded in medical records. The index of error (number of errors over the total number of pieces of information evaluated) was around 0.7 %.

C. Statistical methods

Statistical analysis of survival data deals mainly with the time elapsed between a well-defined starting event and the occurrence of another well-defined terminal event (94). This time is known as waiting or survival time. Nevertheless, the true waiting time for some elements will not be known if, at the time the analysis is done, they have not presented the terminal event. Those cases are called censored cases because the analyst only knows that their survival time will be greater than their follow-up time (39). Two types of censoring can be defined (94): type I or 'time censoring', in which censored cases are those who did not present the terminal event before termination of the study, and type II or 'order statistic' censoring, in which censored cases are recorded as soon as certain order statistics are observed.

Survival time can be determined using different functions (13): the survivor function, the probability density function and the probability distribution function,

the conditional density, and the hazard function. All of them are closely related. Their mathematical expressions are outside the bounds of this thesis. The survivor function is the probability of surviving at least for a specific time, t. Both the distribution function (for discrete variables) and the density function (for continuous variables) can be considered as the probability of presenting the terminal event by time t (this would be the equivalent to 1 - survivor function). The conditional density is the probability density function given a previous survival. Finally, the hazard function or risk or force of mortality can de defined as the probability that an individual alive at time t will die in the next small unit of time. For our purposes, in relation to the proportional hazards model used in the multivariate analysis of this sample, the hazard function will be the one to consider. However, because of its relationship with the survivor function, it can easily be transformed into survival curves and *vice versa* .

According to the treatment of the hazard function, we can establish three principal classes of test for survival analysis (15): non-parametric, semiparametric, and parametric. Non-parametric tests are those which do not assume any specific distribution form of the hazard function. In contrast, parametric models are characterized by assigning specific mathematical functions to the hazard function. Finally, we can say that a model is semiparametric if it establishes an arbitrary base-line hazard but it does

not depend on the mathematical form of this hazard.

Univariate analysis

Univariate analysis is the initial approach to survival data. It considers one variable at a time to construct, on the basis of survival times, a survival curve for individuals for a given characteristic (39). The whole group can be split into several categories to give different survival curves which can then be compared in order to determine which categories have significantly different risks.

Several methods have been proposed for estimation of a survival curve. We have used in this thesis the standard actuarial estimate described by Berkson and Gage (9)(in the univariate analysis part), and the Product-Limit of Kaplan-Meier estimator (95) for survival times (in the comparison and test of goodness of fit of the Cox proportional hazards model). Both methods can be considered as nonparametric because they do not assume any specific distribution for the sample. Their main basis is the estimation of conditional probabilities of surviving intervals, estimated by the effective number of individuals exposed to risk (in actuarial methods) or by the fraction of those individuals at risk surviving each interval of time (in the Kaplan-Meier estimate).

One of the interesting aspects of univariate analysis of failure time data is to decide whether two categories

have significantly different behaviours with time. The basic approach could be to compare survival estimates of two survival curves at a given time, using a Chi-square test. However, this type of testing does not take into consideration the true evolution of groups with time, being totally arbitrary as to selection of time points for comparison as well as the censoring usually present in the sample (39).

To compare whole survival curves, a variety of tests has been developed in recent years. Most of them can be considered as modifications of the Mantel-Haehzel test or logrank test (110).

The logrank test is based on the ratio of the sum of differences between the observed and the expected numbers of terminal events for two categories at different intervals of time over the variance estimator of each category. This ratio is distributed approximately as Chi-squared with one degree of freedom. The logrank test has been shown to be the most used test for comparison of survival curves (39). The different methods that have been derived from the logrank test can be seen as generalizations of this test. Among them, we have used the Gehan's generalization of the Wilcoxon test (60) which is a weighted logrank test useful for comparison of survival curves from samples without too much censoring.

Univariate analysis of data was performed for both periods using the standard actuarial estimate and the

Gehan's generalization of the Wilcoxon test for comparison of the survival curves obtained. In those sets of comparisons with high censoring rate, Gehan's test was substituted by the logrank test.

Multivariate analysis

Description of the method

The main goal of multivariate analysis is to define a set of independent covariates (considering also their interactions) which are significant in predicting the result of a dependent covariate. In survival studies, the interest is in estimating the time until a terminal event occurs, and in establishing which covariates or prognostic factors are significantly involved in determining that time.

For the analysis of the Kidney Transplant Program, we have used the Cox proportional hazards model (38, 94). This method is a semiparametric multivariate analysis which deals with hazard functions (time-specific failure rates). It establishes an arbitrary base-line hazard (called $\lambda_0(t)$) for the studied population. A set of significant variables (z_1, z_2, z_3,....., z_n) which act according to their respective coefficients (β_1, β_2, β_3,.....,β_n), (equivalent to their 'relative weight' in the association between the covariate and the hazard of occurrence of the terminal event) over the common

base-line hazard. The result is the hazard of presenting a terminal event (this hazard is represented by $\lambda(t;z)$) for a specific individual of the series. All this can be stated in this formula:

$$\lambda(t;z) = \lambda_0(t) \times \exp \beta' i \, z i .$$

In a practical sense, the method determines the coefficients for each one of the covariates studied, and their significance. In fact, this is the significance of the estimated standard regression coefficient which is the coefficient divided by its standard deviation. If the level of significance is greater than 0.05, we can consider the covariate as not significant in predicting the hazard for the population, and the variable drops from the model. Since all of the remaining variables in the model have significant coefficients, i.e., all the coefficients have a p-value lower than 0.05, we have reached a good statistical model to predict the hazard function for that population.

The method also enables calculation of the relative risk associated with the presence of that characteristic. The risk of a terminal event for a specific group of individuals presenting one characteristic can be defined as the proportion of terminal events on a specific time among those surviving for that specific time. The relative risk for this group is the risk of that group divided by the risk of the reference group. This relative risk is also obtained

through the calculation of:

$\exp \beta' i z i$.

We define that a relative risk lower than 0.89 means a significant benefit and a relative risk higher than 1.20 means a significant risk.

It is important to point out some aspects of the model:

1. Negative coefficients will decrease the hazard function and, consequently, will increase survival.
2. There is an arbitrary reference level for each one of the hazard variables. As stated below, for example, the reference level for number of A/B mismatches is the hazard of patients with 4 mismatches; for transfused patients, the reference level is that of non-transfused patients; and so on.
3. From a clinical point of view, it is important to determine the significance of each variable's coefficient in the full model (with all the studied variables in) because, even though the coefficients can change when some variables are dropped, the full model represents the most real situation. It should be understood that those variables which drop out of the model are not significantly important for predicting outcome, from a statistical point of view.

The proportional hazards model assumes that there is a constant and proportional hazard relationship between different sets of covariates. Sometimes this assumption cannot be maintained. In those cases, there is the possibility of evaluating the data using different strata, that is, different categories for which there is no proportional hazard. The decision of including strata is based on graphic checking of predicted survival curves for each one of the categories of the covariate being tested for defining strata, looking for the constancy of difference between curves with time (curves proportionally equal).

The procedures in the application of this statistical model then involve the introduction of covariates which seemed to be significant for predicting outcomes in the univariate analysis, followed by a step-down procedure of dropping out those covariates which are not significant. This step can also be done in the forward sense, that is, a stepwise procedure with a new covariate introduced each time. Finally, after achieving a good predictor model, it is possible to test interaction terms between different covariates.

One of the exciting fields in the development of the Cox method is testing the appropriateness of that model for the data. The main way as well as the easiest is again the graphic checking between the survivor function predicted by the the Cox model and the survival

curve estimated by univariate analysis. A more sophisticated approach is plotting the cumulative hazard of residuals against the residuals, obtaining an straight line when the the Cox model fits the data.

Application of the Cox model to the University of Alberta Kidney Transplant Program

The Cox proportional hazards model was applied just to the patient group in the second period (1975-1985) because the number of patients in the first period was too small.

We initially tested a model containing 14 variables (those which seemed to be involved in transplantation outcome, after the actuarial analysis). The variables were categorized as follows:

- Immunosuppressive – 1: AZA, 2: CsA; reference level: none.
- Type of donor – 1: CAD, 2: LRD.
- A/B mismatches – 0 mismatches, 1 mismatch, 2 mismatches, 3 mismatches; reference level: 4 mismatches.
- sex – male; reference level: female.
- Percentage of different individuals' lymphocytes killed by a given serum's lymphocytotoxic antibodies (PRA) – > 50%; reference level: lower than 50 %.
- Primary renal disease – diabetic nephropathy,

nephroangiosclerosis; reference level: other diseases.

- Time on dialysis – less than two years, more than two years; reference level: no dialysis before transplantation.
- Pre-Transplant transfusions – transfused; reference level: non-transfused.
- Warm ischemia time – real time.
- Cold ischemia time – real time.
- Age at transplant – real value.
- Transplant number – 2nd transplant, 3rd or more; reference level: first transplant.
- Blood group of recipient – O, A, B; reference level: AB.
- Blood group of donor – O, A, B; reference level: AB.

III. RESULTS

A. Univariate analysis of the University of Alberta Kidney Transplant Program

The distribution of renal transplants according to the year in which they were performed and the source of the organ is represented in Figure 1.

PERIOD 1967 - 1974

This period can be considered as a 'learning period', during which renal transplant techniques and clinical skills became stable. Policies regarding kidney transplants were frequently changed. It is then difficult to determine what factors could be involved in graft and patient outcomes because of the small number of cases as well as the strong interaction which all of them have with the year of transplant, *per se*. As there were no relevant statistically significant differences for any factor analyzed, in this period, comment may only be made as to 'trends' (Plots of this period are done using thinner lines to represent this fact).

During this period 100 kidney transplants were performed: 87 CAD and 13 LRD. General characteristics of these patients are shown in Table 1. Sixty seven per cent of recipients were between 15 and 45 years old; 57% of donors were also in the same age category (Figure 2). No patients with diabetic nephropathy as primary renal disease were

transplanted during this period. The immunosuppressive regimen, mainly on the basis of AZA and prednisone use, was considered uniform throughout. Graft survival, at 1 month, 1 year, and 5 years was 76%, 45%, and 26% for CAD allografts, and 69%, 31%, and 23% for LRD kidney transplants (Figure 3). Despite the poorer graft survival for LRD kidney recipients, patient survival was better for this group: 100%, 77%, and 46%, vs 93%, 66%, and 43%, at 1 month, 1 year, and 5 years (Figure 4). It is interesting to note that it was already established that the first 3-month period was associated with the highest risk for graft loss (morphology of survival curves are similar in both periods studied).

Even though there was no demonstrably significant benefit from HLA A and B matching on graft survival in CAD kidney recipients (Figure 5), HLA-identical LRD kidney recipients had better graft survival than haploidentical recipients (67% vs 25% at 1 yr; p=0.0745) (Figure 6). Good HLA A and B matching was also associated with better patient survival in LRD transplants, but not in CAD allografts (Table 2).

In terms of ABO blood groups, O group was the main type for donors, being used for O as well as for other ABO group recipients. Forty CAD O kidneys were used for 28 O recipients, 10 A recipients, and 2 AB recipients. No CAD AB kidney was transplanted. All the B group recipients were transplanted with B kidneys. Living-related transplants were performed mainly from O kidneys (8 cases), the rest being of

ABO A group (5 cases); 2 O kidneys were used for transplanting 2 A patients. No specific trend was observed for different ABO groups in terms of graft or patient survival (Tables 3,4).

Other immunologically-related parameters such as pretransplant blood transfusions,or previous transplants did not show any clear trend during this period (Tables 5 - 8). Pre-transplant pregnancies could not be evaluated because only 2 patients had had previous pregnancies.

Achievement of a good quality of life during pre-transplant dialysis, assessed by the clinician according to social and professional rehabilitation, showed a tendency towards better prognosis for graft and patient survival (Figures 7 - 10). There were 42 patients who were employed at the time of transplant: 37 received a CAD kidney and 5 a LRD kidney. The rest of patients did not have any regular job before transplant: 47 received a CAD allograft (56% of all CAD renal transplants) and 8 a LRD kidney (61.5%). Social rehabilitation rates achieved with dialysis were higher than those for professional rehabilitation. Eighty per cent (67 patients) of CAD kidney recipients and 92% (12) of LRD transplants were considered to have a normally active lives.

No modality of dialysis (home hemodialysis, hospital hemodialysis and intermittent peritoneal dialysis) was associated with higher survival rates (Table 9, 10). However, patients whose first renal replacement therapy was

kidney transplantation had better survival rates than those who were on dialysis before transplantation. For this latter group, those patients on dialysis less than 2 years had higher survival rates than those on dialysis more than 2 years (Figures 11, 12). Probably, this fact reflects the initial quality of dialysis, or physician bias in selecting those whose outcome would confer credit on a relatively new procedure.

None of the other factors studied showed any suggestive pattern during this period.

PERIOD 1975 - 1985

This period can be considered as the steady state of renal transplantation from a technical point of view, in contrast to the first period.

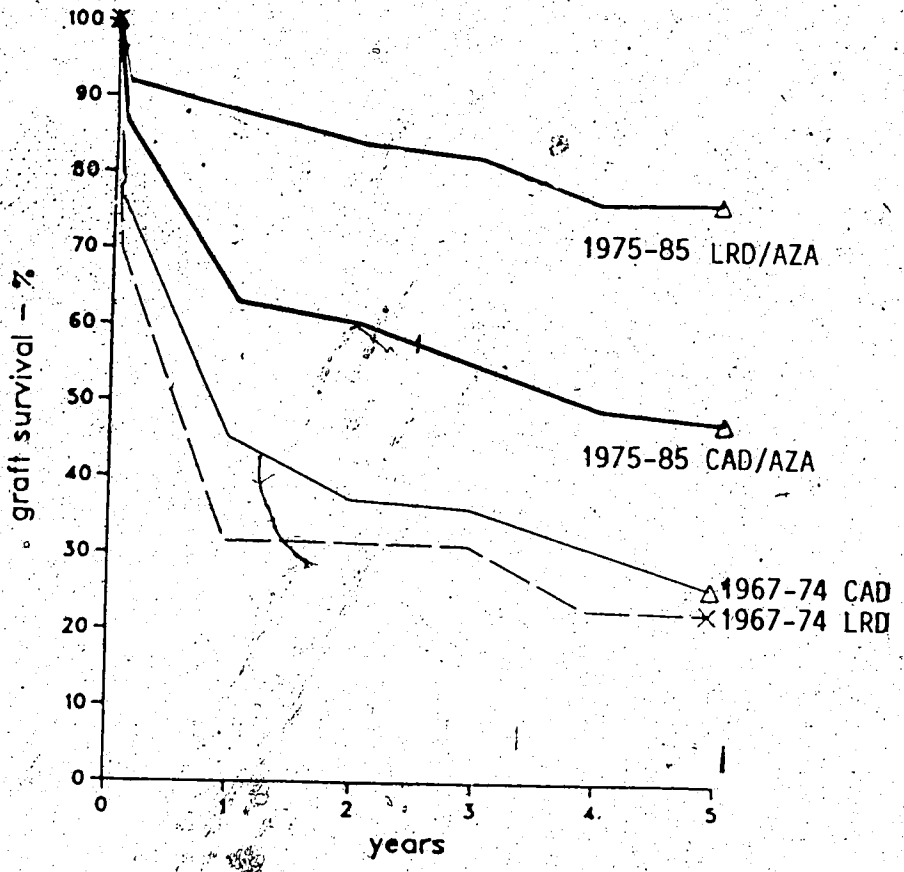
Two aspects deserve comment before presentation of the statistical analysis. First, there was a more or less uniform increase in the number of transplants/year, throughout these 11 years. Three hundred twenty six renal transplants were performed: 250 were with CAD kidneys and 76 with LRD kidneys. The second factor was the introduction of CsA as a new immunosuppressive drug as part of the Canadian Multicentre Trial Group protocol in 1981 (187). The general characteristics of patients transplanted during this period are shown in Tables 11, 12, and 13. Univariate and Multivariate analysis of data of these patients discarded an effect of year of transplant on graft and patient survival

either in AZA-treated or in CsA-treated transplants. The group of CAD kidneys recipients on CsA had significantly shorter warm and cold ischemia times, higher percentage of poorly matched (more than 2 mismatches) for HLA A and B antigens, more diabetic patients, and fewer non-transfused recipients than the CAD group on AZA.

Fifty-five percent of CAD donors were between 15 and 45 years old; for LRD donors, the most frequent age group was that of 31 to 45 years old. The percentages of recipient ages were quite similar to those observed during the first period. The percentage of CAD recipients older than 60 increased slightly as did the number of patients between 46 and 60 years old. Living-related recipients between 15 and 30 years old represented almost 53% of all LRD recipients (Figures 13, 14).

Both CAD and LRD kidney recipients transplanted during this period had significantly better graft and patient survival rates than those of the first period ($p < 0.001$ for both survival rates, for both types of recipients) (Figures 15 - 18). Graft survival at 1 month, 1 year, and 5 years was 85%, 61%, and 44% for CAD recipients on AZA, 94%, 83%, and 77% for CAD allografts on CsA, 92%, 88%, and 76% for LRD transplants on AZA, and 96%, 88%, and 79% for those LRD recipients on CsA. Graft and patient survival rates for those patients on AZA transplanted during this period were also significantly higher than those of patients transplanted during the first period ($p < 0.003$ for graft

survival in CAD kidney recipients, $p < 0.001$ for patient survival in that group; and $p < 0.001$ for both graft and patient survival in LRD kidney recipients)(see illustration below).



Cyclosporine improved significantly graft and patient survival rates in CAD kidney recipients ($p < 0.0001$ and $p < 0.0092$, respectively). The improvement achieved by using CsA in CAD transplants is, in our experience, 22% on graft survival at 1 year, and 33% at 5 years (this last figure should be considered cautiously because of the small number of patients on CsA with 5-year follow-up (8 patients)), with a mean of 19.7%. However, CsA did not improve significantly either graft or patient survival rates in LRD kidney

recipients even though this group was comparable to LRD kidney recipients on AZA in terms of sex, age at transplant, age of donor, time on dialysis, blood group of donor and recipient, number of pretransplant transfusions, number of non-transfused patients, number of sensitized patients, proportion of HLA identical vs haploidentical, and time of warm and cold ischemia (Tables 12 and 13).

The most common ABO blood group for CAD donors was group O for those cases whose recipients were on AZA (48%), and group A for those who were on CsA (39%). In the LRD group, O group was the most common for donors blood group. For recipients, A was the most common blood group for all the subgroups except for that of LRD kidney recipients on AZA. Recipients of the AB blood group were transplanted mainly with non-AB kidneys, especially with O kidneys (50%). At 1 year, graft survival was lower, but not significantly, for those B CAD recipients; the best graft survival rates were shown for A recipients (Tables 14, 15).

The effect of HLA matching on graft survival was shown in the group of patients on AZA but not in those on CsA. Good HLA-A and -B matching was associated with higher graft survival rates in CAD kidneys recipients on AZA ($p < 0.05$)(Figure 19). This effect was not shown in the CAD kidney recipients group on CsA ($p < 0.36$ between 0 and 4 mismatches; $p < 0.6622$ between 2 and 4 mismatches)(Figure 20). We found a significantly better patient survival for better HLA A and B match in AZA-treated patients ($p < 0.03$

for the difference in patient survival between the group totally matched vs the one with 4 mismatches)(Figure 21). This fact was not observed in the group of transplants on CsA (Figure 22).

To evaluate the possible effect of DR match on graft survival, we studied those patients transplanted between January 1/1981 and January 1/1986. We selected this subperiod because DR typing became constant or standardised after January 1/1981. A total of 138 patients received CAD kidneys in this subperiod: 50 were on AZA and 88 on CsA. In the AZA group, well DR matched (0 mismatches) patients had significantly better graft survival rate than less well matched recipients (1 or 2 mismatches) (100%, 75%, 75% vs 88%, 45% and 35% at 1 month, 1 year and 3 years, respectively; $p < 0.05$)(Figure .23). This fact was not observed in those patients on CsA (92%, 92%, 79% in zero-DR-mismatched patients vs 96%, 81%, and 80% for those with 1 or 2 DR-mismatches for the same three time periods; p NS)(Figure 24).

A significant negative effect ($p < 0.02$) on graft survival was shown for the PRA (less than 50% PRA vs. more than 50% PRA) on graft survival in CAD allografts. (In LRD, the number of patients with more than 50% of PRA was so small than comparisons were not possible). Studying separately these CAD allografts according to their immunosuppressive drug, the difference in graft survival between those with less than 50% of PRA and those with more

than 50% was significant ($p < 0.042$) for patients on AZA but not for those on CsA even though there was also an evident difference for this last group (Figure 25). No effect of the highest PRA on patient survival was detected (Table 16).

Patients transfused before renal transplantation showed higher graft survival rates than those non-transfused. This fact was observed in the AZA as well as in the CsA group. The difference was not statistically significant (Figures 26 - 29), presumably, in the case of CsA, because the non-transfused group was so small.

During this second period of 11 years, kidney transplantation was carried out on 29 diabetic patients with end-stage diabetic nephropathy, of whom 27 received CAD kidneys (12 were on AZA and 15 on CsA) and the other 2 received an LRD kidney (both on CsA). Even though there was no statistically significant difference, the 12 AZA-treated diabetic patients had a worse graft survival rate than non-diabetics (Figure 30), but the 15 CsA-treated did comparably as well as non-diabetics (Figures 31, 32). Patient survival was significantly worse for diabetic nephropathy vs other renal disease ($p < 0.050$) in the group of patients treated with AZA (Figure 33), but not in those on CsA (Figure 34).

We also studied the outcome for patients whose primary renal disease was nephroangiosclerosis (we tried to avoid inclusion of patients where this diagnosis was made by exclusion, only). Of 13 such patients: 12 received CAD

kidneys (9 were on AZA and 3 on CsA) and 1 received a LRD kidney (and was on CsA). In this group of patients, graft and patient survival rates were also lower than the observed for the overall group, especially for those 3 patients on CsA ($p < 0.0423$ for graft survival and $p < 0.001$ for patient survival)(Figures 30 - 34). Number were very small, again.

During this period, 7 HBsAG-positive patients were transplanted: all of them received CAD kidneys; 5 were on AZA and 2 on CsA. Moreover, 159 patients had determined anti-HBc, being 20 positive. Eighteen received CAD allografts: 15 were on AZA, and 3 on CsA. The other 2 received LRD kidneys and were on CsA. Even though it was not statistically significant, we detected worse graft survival rates for recipients who were positive for HBsAg (Table 17). Patient survival was not affected by the presence of that hepatitis virus B marker in blood (Table 18), Similar findings were obtained for the presence of antibodies against hepatitis B virus-core antigen, again without statistical significance (Tables 19 - 20).

Second transplants did not have a significantly worse prognosis when assessed by graft or by patient survival rates (Tables 21, 22).

No modality of dialysis showed a trend for better graft or patient survival (Tables 23, 24). Time on dialysis did not significantly determine graft survival. However, we detected a slight trend toward better patient survival inversely related to the time on dialysis (Tables 25, 26).

Social and professional rehabilitation were not significant determinants of graft and patient survival (Tables 27 - 30).

No particular significant trend was demonstrated for graft and patient survival according to the number of pregnancies before transplantation.

Plots of continuous variables (cold and warm ischemia times, age of donor and recipient) against graft and patient survival did not show any specific trend. They were not categorized for actuarial analysis but were entered directly into the multivariate study.

B. Multivariate analysis of the University of Alberta Kidney Transplant Program

From the initial number of patients transplanted during the second period, we had to exclude 39 because of the lack of information on some covariates studied. Thus, 287 patients were included in the analysis; their distribution according to type of donor and immunosuppressive drug is represented in Figure 36. Characteristics of these patients are shown in Tables 31 to 33.

The mean follow-up periods were 55 ± 48 months for patients on AZA, and 31 ± 18 months for those on CsA.

The initial models to be tested for graft and patient survival contained 14 covariates, those which seemed to be significant in the univariate analysis part: type of immunosuppressive drug, type of donor, number of mismatches for HLA A and B antigens, sex, highest percentage of

reactive PRA, pretransplant blood transfusions, time on dialysis before renal transplant, presence of diabetes and nephroangiosclerosis as primary renal diseases, cold and warm ischemia times, age at transplant, age of donors and number of previous transplants.

On these models we tested the adequacy of the Cox proportional hazards model for studying graft and patient survival, comparing the survivor function estimate obtained by the regression models with the Kaplan-Meier estimates of survival function. Both functions were very similar, meaning that the Cox model fitted the data well (Figure 37, 38). Moreover, we also tested the adequacy of introducing type of immunosuppressive drug and type of donor as covariates, instead of strata. For that verification, we used plots of the log survivor function for the subsets determined by type of immunosuppressive drug (AZA vs CsA), type of donor (CAD vs LRD), and type of immunonosuppressive drug plus type of donor (CAD on AZA, CAD on CsA, LRD on AZA, LRD on CsA), checking for the proportionality of hazards for each one of these subsets, that is, checking for lines which should be proportionally equal. Again the different subsets tested had proportional risks, allowing for the inclusion of these 2 covariates in the models. In fact, models without type of donor and immunosuppressive regimen as covariates fitted the data worse, as can be seen by comparison with the actuarial survival for the same categories (Figures 39, 40).

In the initial 'full model' for graft survival (model G1), seven covariates were statistically significant (Table 34): 3 of them had negative coefficients, which means that their presence decreases the risk of graft failure (type of immunosuppressive drug, lower number of HLA A and B mismatches, and pretransplant blood transfusions); the other 4 covariates were associated with positive coefficients increasing the risk of graft loss (PRA higher than 50%, nephroangiosclerosis as primary renal disease, increasing cold ischemia times, and donor B ABO blood group). The most significant benefit was obtained with the use of CsA (relative risk = 0.3879), the highest risk being an ABO B-kidney transplant (relative risk = 8.794). The increase of risk with increasing number of HLA A and B mismatches was not uniform, being more patent from 0 to 1 mismatch than from 2 to 3 mismatches. The risks associated with 1 and 2 A and B mismatches were similar. Even though they were not significant, transplant from a living-related donor, male as a recipient, more than 2 years on dialysis, shorter warm ischemia time, and first renal transplant were associated with lower risk of graft failure. Curiously, the presence of diabetes was not associated with higher risk for transplantation.

In the initial 'full model' for predicting patient survival (model P1) only 4 covariates were statistically significant (Table 35): 2 associated with decreasing risks for patient death (immunosuppressive drug, and lower number

of HLA A and B mismatches); the other 2 conditioned higher risk (nephroangiosclerosis as primary renal disease, and age at transplant). Presence of diabetes, PRA higher than 50%, increasing time on dialysis, and regrafting led to an increase of risk for patient death, even though they were not statistically significant.

After dropping the covariates which were not statistically significant, the predictor model obtained for graft survival (model G2) contained the following covariates (Table 36): type of immunosuppressive drug, number of HLA A and B mismatches, PRA, nephroangiosclerosis as primary renal disease, and cold ischemia time. The last three covariates were associated with a significant increase in graft failure. In this model, the most risky situation was the antecedent of nephroangiosclerosis as primary renal disease; the lowest risk of graft failure was for patients with no mismatches for HLA A and B antigens.

The final model for predicting patient survival (model P2) contained the 4 covariates which were statistically significant in the full model, with very slight variations in their coefficients as well as in their relative risk (Table 37). This final model fitted well the data (Figure 4.1).

We tested also the possible interactions between the main immunosuppressive drug and 4 covariates (type of donor, highest level of PRA greater than 50%, HLA A-B matching, and pretransplant blood transfusions) in both models. Only the

interaction term between type of immunosuppressive regimen and type of donor was significant in the predictor model for graft survival. In its presence this model was reduced to the effects of type of immunosuppressive drug, type of donor, interaction term between type of donor and type of immunosuppressive drug, number of HLA A and B mismatches, highest PRA, and nephroangiosclerosis as primary renal disease (model G3)(Table 38). According to this model G3 for predicting graft survival, the most substantial benefit is obtained with CsA use and the highest risk for graft failure is the antecedent of nephroangiosclerosis as primary renal disease. The interaction term had a positive coefficient with a high relative risk associated to it. The fitness of this model in relation to data is represented in Figure 42 comparing its graft survival estimate to that from Kaplan-Meier method.

No relevant changes in the coefficients for each one of the significant covariates were observed when each covariates was analyzed isolatelly using the Proportional Hazards Model. Moreover, the same final model (model G3) was obtained when the interaction term was already included in the initial model (model G1) and the step-down procedure was applied to it.

For the final predictor model of graft survival we calculated separately the relative risks associated with each one of the specific number of mismatches for loci A and B. The results showed an increasing risk from 0 mismatches

for loci A and B (r.r.= 1) to 4 mismatches for both loci (r.r.= 6). Nevertheless, this increase was not uniform, and, for example, the relative risk associated to 2 mismatches for locus B and 0 for locus A was much higher than that associated to 2 mismatches locus A and 0 for the B. It can be inferred from our results that locus B is probably more important than A in terms of graft survival; the presence of just 1 mismatch for locus B is enough to increase the risk for any other combination of HLA A mismatches. Relative risks associated with different combinations of mismatches are shown in Figure 43. Except for the coefficient of 1 B mismatch, all the others were significant at 0.01 level.

Cyclosporine use in CAD kidney recipients decreased the magnitude of risks for each one of the categories of HLA A and B mismatches (Figure 44).

IV. DISCUSSION

The analysis performed in this thesis presents evidence of a proportionality of risks in renal transplantation between CAD and LRD recipients, and even more evident, between different immunosuppressive regimens, after the introduction of CsA. This proportionality of risks is observed in relation to the same risk factors as those which are significant for patients on AZA. This fact suggests that discrepancies shown in different studies could be to due to different degrees of relevance for these factors. However, multivariate analysis has shown to be a powerful tool for discovering their significance in the presence of single-centre interactions.

According to these results, significant covariates for predicting transplant allograft outcome are: type of immunosuppressive regimen, type of donor, HLA A and B mismatches (DR were not considered in this study), highest PRA, and nephroangiosclerosis as primary renal disease. These are the covariates included in model G3, that with one interaction term. It reflects the known fact that LRD allografts have a better prognosis than CAD as well as our finding with regards to the lack of benefit of CsA use in LRD transplants. In fact, the benefit for LRD allografts using CsA is not higher than that obtained with AZA; however, it is higher than that of CAD transplants on CsA (for ethical significance of this increase see Conclusions section). Nevertheless, CsA use is the more beneficial

isolated factor for transplant outcome to the overall group.

Three covariates were dropped out in the step-down procedure: pretransplant blood transfusions, cold ischemia time, and donor's blood group. This fact could mean that these covariates could be useful considering the whole set of covariates but they do not add any statistically significant benefit for predicting kidney graft outcome after evaluation of the other covariates included in the final model. At the same time, they could represent the trends determined by the introduction of CsA in our centre.

In terms of patient survival, the set of significant covariates was: type of immunosuppressive regimen, number of mismatches for HLA A and B antigens (again, DR antigen were not considered in this analysis), presence of nephroangiosclerosis as primary renal disease, and age of recipient at transplant. Interaction terms tested for this model were not significant.

We will discuss the main points of interest of these results comparing them with those reported by other groups.

A. The effect of CsA use in renal transplantation

Introduction of CsA as the main immunosuppressive agent in renal transplantation is the most widely accepted factor of improvement of graft survival in CAD allografts. It has increased one-year graft survival between 7 and 35% in randomized prospective trials (19, 52, 78, 120, 152, 187; review: 201). It is interesting to note that centres with

previous high graft survival rates (80% or higher at one year) did not show any substantial benefit of its use (68, 128, 165, 178). In our centre, CsA is responsible for an improvement of 22% in one-year graft survival.

According to our results, CsA did not improve graft survival rate significantly in LRD kidney recipients. This surprising finding was suggested some years ago by Kovithavongs *et al.* (99). A recent multicentre study has shown the same trend (31, 155). In contrast, other centres evidenced improvement of graft survival in LRD recipients using CsA (2, 54-57, 104, 132). However, these studies are quite heterogeneous and the role of other factors such as DST or ALG could interfere with the interpretation of their results.

It is not clear why there is no improvement of results using CsA in LRD recipients. One possibility could be the need for very large numbers of patients to achieve significance for a small increase in graft survival when the survival rate using AZA was already so high. The number of cases (determined by the normal approximation to the binomial distribution for the 2-sample test for binomial proportions (153)) required in both groups to achieve a significant increase ($p<0.05$) of 4% is 257, and rapidly escalates for still smaller differences. Another possibility could be absence of significant CsA effect when patients receive DST before transplantation. According to our results, the positive effect of CsA would not be additive to

that of DST. In our sample, the proportion of patients non-transfused was greater in th[illegible] group; even though, this group presented the sa[illegible]graft survival as CsA patients. Then, there are probably other factors involved to explain these results. An additional explanation for the lack of beneficial effect of CsA on LRD transplants could be a deleterious role of CsA on longer term graft survival (127). However, it is well known that there is difficulty in the differential diagnosis between CsA nephrotoxicity and 'chronic rejection' (126). Some patients diagnosed as chronic rejection could be affected by progressive CsA nephrotoxicity. The deleterious effect of CsA is also reflected by the increase of creatinine levels with time, as it has been evidenced by previous reports from our centre (98, 99) and by others (19, 52, 92, 117, 132, 178).

Cyclosporine immunosuppression and rejection episodes

Another aspect to consider is the incidence of rejection episodes when CsA is the main immunosuppressive drug. There is a lower number of rejection episodes in patients treated with CsA, at least in those receiving CAD kidney transplants (76, 92, 128, 131, 132, 178); in LRD renal transplants, there is much more discrepancy (99, 113, 128). Nevertheless, a reduced incidence of rejection episodes has not always been significant elsewhere, probably because of other factors such as ALG in association with conventional therapy.

Cyclosporine use and patient survival

In terms of patient survival, CsA use has been associated with increased patient survival, even though the increase usually has not been statistically significant (54, 83, 178, 188). It is interesting to note that the reduced mortality observed with CsA is correlated with the age of recipient (201): the more significant increase in patient survival is recorded for recipients older than 59. The main cause of death is still cardiovascular; in fact, some studies have shown a higher incidence of vascular complications for CsA-treated patients in comparison with those on conventional therapy (117, 178, 187). The possible relationship between this fact and the ability of CsA to produce hypertension invites attention.

Cyclosporine immunosuppression and new trends in renal transplantation

The benefit of CsA may have eliminated lesser degrees of benefit previously conferred by such factors as the HLA matching effect and the need for pretransplant blood transfusions. At the same time, CsA has been associated with some specific trends in renal transplantation (32, 161). The differences observed between CAD kidney recipients on AZA and those on CsA in our sample reflect the trends reported by other authors. Except for the fewer non-transfused patients in the CsA group, the CsA group contains more poorly matched and more diabetic recipients, as well as

shorter warm and cold ischemia times (32, 161). These trends could be misleading when interpreting results by univariate analysis.

Even though CsA has significantly improved graft survival in CAD renal transplants, we have shown that a proportionality of risks still exists in relation to CAD transplants on AZA. In other words, patients on CsA are submitted to the same risk factors as those on AZA but in lower magnitude.

After CsA had been introduced, subsequent reports failed to show any benefit of HLA matching (4, 52, 54, 92, 117, 187). Studies which demonstrate the presence of a HLA matching effect, even with CsA, often show a greater range between poor and good HLA A, B, and DR match (24, 31, 33, 161). Sanfilippo *et al* (161) did not obtain any significanct benefit with CsA use in cases with 2 or more HLA A and B matched antigens. Overall, one-year graft survival is increased between 4-14% with CsA, and 18-22% by a good HLA A, B, and DR match. In our experience, the relative benefit associated with CsA use (0.1504) is only exceeded by the presence of a totally HLA A and B matched transplant. However, the difference in one-year graft survival between totally matched vs totally mismatched transplants was around 15% in contrast to the 22% graft survival improvement with CsA use.

The role of pretransplant blood transfusions in increasing graft survival rate in renal transplants on AZA

is well established (review: 26). As I will be discussed later, despite the initial reports that pretransplant blood transfusions were not beneficial in association with CsA (52, 54, 83, 95), later reports on larger numbers of patients have shown benefit (24, 137, 202). The effect of blood transfusions in CsA patients seems to be additive, that is, CsA and blood transfusions would act independently to increase graft survival (24, 33). The increase of graft survival with pretransplant transfusions is around 11% (33, 202). Due to the lack of a representative sample of non-transfused CsA-treated patients in our study, no conclusion can be drawn about that. In the specific setting of LRD transplants, our conclusion is that the CsA effect is not additive to the substantial benefit obtained with DST. The fact that CsA is strongly associated with greater number of non-transfused patients should alert us to a possibly lower graft survival rate than the one to be expected (32).

Cyclosporine Side Effects: Nephrotoxicity, Hypertension, Infections, Neoplasms

Cyclosporine is a drug with important side effects (34). Among them, nephrotoxicity is the most common and also the most harmful (107). Its overall incidence is quite variable (as high as 60% of all the CsA-treated patients during the first 6 months (54, 66, 92, 117, 127, 150, 178, 188, 189)). Most of the long-term trials have demonstrated the presence of higher serum creatinine levels in

CsA-treated transplant patients, especially in CAD kidney recipients, and mostly without evidence of chronic rejection (19, 52, 188). Three principal varieties of CsA-induced nephrotoxicity are (127): transient acute renal failure, protracted acute renal failure, and chronic nephropathy. The possibility of both transient or the protracted acute renal failure is important because the clinical situation improves with switching from CsA to conventional therapy with AZA. This is what happens to 14-34% of all CsA-treated CAD allografts (52, 187). However, some believe that CsA-induced chronic nephropathy will probably determine the long term use of CsA because it appears to be irreversible and progressive to ESRD (126, 127). The usual incidence for nephrotoxicity is about 15-30% of CsA-treated patients (19, 188, 189). Chronic CsA nephrotoxicity is also histologically quite difficult to differentiate from chronic rejection (126, 127). Kahan *et al* made an interesting observation that, in spite of the same incidence of nephrotoxicity for LRD and CAD renal transplants, serum creatinine levels at one year were progressively higher according to three sources of donor (HLA-identical vs HLA haplo-identical vs CAD renal transplants). This indicates the possibility of low-grade rejection episodes as partially responsible of the impaired renal function (92).

Cyclosporine-induced nephrotoxicity has led to the evaluation of alternative regimens by which to obtain the beneficial effects of CsA and yet avoid its side effects.

These strategies include : the use of CsA in conjunction with AZA and corticoids at lower doses (106), sequential therapy with AZA, ALG, and glucocorticoids, delaying the introduction of CsA until the graft functions (172), and switching from CsA to AZA 3 to 6 months after transplantation (58, 77, 120, 122, 177, 190). The date for switching has been established between 3 and 6 months after transplantation because CsA-induced renal injury up to this time is still reversible (58, 120, 127, 177). However, initial reports on switching to AZA showed an increased incidence of rejection episodes [28 to 83% of patients presented a rejection episode after switching (58, 103, 117, 151, 177, 206)]. Recent reports on conversion from CsA to AZA are more optimistic probably because of longer overlap periods between both therapies and/or increased dosage of glucocorticoids at the time of conversion (77, 122, 190). At this point, it is important to note that one of the advantages of CsA therapy is the overall sparing effect on glucocorticoids requirement (189). Initial European trials tried to avoid all use of prednisone but results were worse than those from America where regimens retained a small dose of corticoids in addition to CsA (17, [illegible], 52, 187).

Another important side effect of CsA is the induction of hypertension (34, 108, 191). The origin of this phenomenon is not clear. It seems to be independent of activation of the renin-angiotensin system. Cyclosporine may inhibit a prostacycline-stimulating factor of unknown

nature, which might lead to predominance of a thromboxane-induced vasoconstrictor (40). Incidence of hypertension varies between 60-80% (54, 66, 92, 117, 188), usually requiring drug therapy. Cyclosporine-induced hypertension may increase the incidence of cardiovascular complications after renal transplant. This aspect could be related to the worse graft and patient survival in our population of transplanted patients whose primary renal disease was nephroangiosclerosis. This point will be discussed more extensively later.

Important to consider is the reduction, even though not always significant, in the number and severity of infections observed in renal transplants on CsA (54, 92, 113, 128, 132, 178, 187, 193). This is seen specifically in relation to viral infections (54, 146, 178) but it is also showed for bacterial infections (117). However, not all the reports agree on that point (101). A surprising finding is the higher incidence of *pneumocystis carinii* pneumonia in CsA-treated transplant recipients compared to those on conventional immunosuppressive therapy (66, 92, 117).

Multicentre studies have failed to show a higher incidence of neoplasms (lymphoproliferative disorders) in patients on CsA in comparison with conventional immunosuppresion (52, 187, 201).

The Canadian Multicentre Transplant Study Group in its prospective trial on CsA in renal transplantation showed a significantly poorer graft survival for those patients who

had reanastomosis time longer than 45 minutes (187 - 189). This result was confirmed by the European Multicentre Trial (52) though it was not statistically significant (52). However, univariate and multivariate analysis of other CsA series have demonstrated that warm and cold ischemia times are significant covariates to predict graft survival (5, 62, 92, 198). It might be expected that renal vasoconstriction induced by CsA, the mechanism most frequently invoked to explain CsA-induced nephrotoxicity (127), would be more intensive in those with more evidence of ischemic damage. As will be discussed later, in our experience cold ischemia time is a significant prognostic factor for patients on AZA as well as on CsA.

Cyclosporine immunosuppression for high-risk renal transplant groups

In our centre, diabetes mellitus is not a significant risk factor for graft outcome, especially when immunosuppressed with CsA. Graft survival for CsA-treated patients is similar to that observed in non-diabetic patients. In fact, CsA is responsible for a 43% increase in one-year graft survival in diabetic patients, an improvement which is maintained at 2 years. Our results corroborate that this subgroup of allografts is that which has improved most dramatically with the use of CsA (35, 83, 117, 178), though similar improvement is noted for those whose primary renal disease was nephroangiosclerosis. However, the latter still

have a significantly poorer prognosis than the rest of population; this difference being more evident when we analyze CsA patients (25, 35). Different studies have shown that in spite of an improvement in graft survival in CsA-treated nephroangiosclerotic CAD recipients, they still have the poorest prognosis. Nevertheless, our findings strongly support the use of CsA in these 2 categories.

Another situation showing particular benefit with CsA is regrafting (30, 54, 59). Even though prognosis of regrafts is poorer than first transplant, CsA increases their survival in relation to conventional immunosuppression. We did not show a significantly worse graft survival for second transplants, and the number of third or more transplants was small. So, conclusions on the effect of CsA in this special setting are not significant.

Cyclosporine has been shown to be the immunosuppressive drug of choice in older patients (> 55 years)(92, 155, 188). This can be atributted its sparing effect on the amount of glucocorticoids, thereby avoiding their specially harmful side effects on this subgroup.

The role of CsA according to the HLA matching status and pretransplant blood transfusions will be discussed later. It is interesting to point out that after testing for interactions between the use of CsA and a) the number of mismatches for HLA A and B, b) pretransplant blood transfusions, c) PRA and d) type of donor, only the interaction with this last covariate was significant. We are

aware of only one study which tested interactions of CsA treatment with blood transfusions and HLA mismatches (198). In that study, none of the interactions were significant. From a statistical point of view it cannot be argued that there is special benefit from CsA for any of those situations.

Impact of CsA in the cost of renal transplantation

Cyclosporine is a costly drug, specially in comparison with conventional immunosuppression. The Canadian Transplant Study Group calculated a cost around $C 17.26 per diem during the first 90 days after transplant (around $ 1500 per 3 months). The cost decreases progressively (around $ 5,000 per year) and at 2 years is around $ 10.40 per diem (188). There is general agreement that CsA use is associated with a reduction in the number of readmissions after renal transplant as well as a decrease in the number of hospitalization days, and specifically in the length of the initial admission (54, 92). These events are in relation to the decrease in the incidence of rejection episodes and infections associated with a immunosuppressed patient. Nevertheless, the incidence of CsA-induced nephrotoxicity may become a limiting factor in most of the cost:benefit studies. The true knowledge of this side effect, especially its outcome and the possibility of its avoidance will help to increase both medical and financial benefits (150).

The increased rehabilitation rate with CsA (89%) over that achieved with conventional immunosuppression (65%)(91, 92) is as expected from the higher graft survival rate.

In our experience, CsA is the drug of first choice for CAD kidney transplantation, in association with low dose glucocorticoids, the latter drug being especially advisable in high risk groups. Cyclosporine-induced nephrotoxicity should lead to the evaluation of alternative regimens utilizing the benefits of CsA, but avoiding its side effects. Among them, switching from CsA to AZA 3 to 6 months after transplantation and/or 'triple low-dose' therapy with CsA/AZA/corticoids are the most promising.

The value of CsA is much less clear for LRD renal transplants. Despite the lack of agreement about a decreased number of rejection episodes with CsA, the mild increase in graft survival at 1 month makes us consider the merits of switching from CsA to AZA after 3 months or to 'triple low-dose' therapy (CsA/AZA/prednisone). This might avoid a possible incidence of late loss of grafts in LRD kidney recipients.

AZA should be considered the first choice drug in LRD kidney recipients, with or without previous treatement with DST.

B. The relevance of the type of donor in renal transplantation

Living-related kidney transplants have a well-established better graft survival than CAD allografts (2, 109, 184, 186) for multifactorial reasons (histocompatibility, minimal ischemia and controlled pre-operative immunologic preparation, etc.).

Cyclosporine has increased one year-graft survival of CAD renal transplants to almost the percentage previously obtained in LRD transplants (186). Nevertheless, HLA identical CsA-t[redacted]ecipients have still much better graft survival [redacted]ecipients (27, 28, 54, 92, 186). On the other hand, according to growing evidence, CsA has not increased graft survival in LRD renal transplants, specially those which are HLA-identical (155).

Long-term graft loss induced by CsA may reinforce our contention that LRD renal transplants are best treated with AZA and low dose prednisone to achieve optimal long-term graft survival (32).

C. HLA - matching effect in renal transplantation

The discovery of the HLA complex as the major histocompatibility system in man (43, 139, 207, 208) started an immunological approach to kidney transplantation. The better graft survival rates in LRD than CAD transplants and the correlation with HLA haplotypes suggested the possibility of a direct effect of HLA matching on graft

survival (196). This led to different categories of risk for kidney transplantation according to the number of mismatches for those antigens. However, defining this effect for CAD allografts has been a problem from a statistical point of view, and large samples are necessary to achieve significance (115).

Several questions need to be answered to define the HLA-matching effect (64). First, we have to study the presence of an HLA-matching effect in 2 main settings: conventional immunosuppressive therapy and CsA regimens. Secondly, if there is an effect of HLA matching on graft survival then we have to determine which HLA antigens are involved, what kind of relationship exists between numbers of antigen mismatches and graft survival rates. Differences then need testing for linearity of this effect; testing the possibility of different effects for different antigens; the independence of these effects when they are combined in different mismatches patterns; and, finally, to explore the possibility of modifying this effect.

HLA-matching effect in LRD allografts

The effect of a good HLA-matching in LRD is clearly established for treatment with AZA and prednisone. Different studies demonstrated that graft survival was around 90 - 95% in HLA identical transplants, at one year. This figure decreased to 70 - 75% in those HLA haploidentical and to 55 - 65% in non-shared haplotypes transplants (27, 171, 179,

196). The difference in graft survival between the first two groups becomes more evident with time (with follow-up periods up to 10 years)(176, 179). This effect is so strong that it has been deemed unethical to use live donors sharing no haplotypes with the recipient, in most transplant units (196).

However, about 10% of HLA-identical allografts are rejected in the first year despite immunosuppression (27, 55, 56, 104, 109, 196). This probably means that, besides the HLA system, other histocompatibility factors like red cell antigens or some host defense factors could also play a role (196).

In LRD allografts, considered as a whole group, CsA has not significantly improved graft survival rate (27, 98, 155). Our centre's results corroborate this. However, Cecka (27) and Flechner *et al* (56, 57), considering the different HLA-matching subgroups, report a higher (but non significant) one-year graft survival rate for HLA-identical CsA-treated allografts vs HLA-mismatched patients. These results were not confirmed by Lundgren *et al*. (109), whose increase of graft survival between 0 and 1 DR mismatched recipients (95 vs 91%) at one year was not significant, but found a significant lower incidence of rejection episodes in well HLA-DR matched and in HLA-identical patients (90, 109, 132). Curiously in Lundgren's report (109), at 2 years, all the well matched subgroups separately gave better survival but it was not statistically significant. Several factors

could explain these discrepancies: the statistical factor, that big samples are required to confer significance for small differences; and that time (5-15 years) may have to pass before the HLA matching effect would become evident (179).

From studies reported in the literature it seems that, in LRD transplants treated with AZA and prednisolone, HLA matching has a clear effect (5, 27, 100, 148, 196, 197, 203, 209) but this effect cannot be well seen in more recent studies which are restricted to HLA-identical and one HLA-haplotype disparate allografts only. Within this limitation, CsA studies show no significant difference (27, 199).

HLA-matching effect in CAD allografts

In a large percentage of transplant units, HLA typing has been used as a clear-cut criterion for establishing policy for recipient selection and organ sharing. Nevertheless, this role for HLA-matching requires re-examination.

HLA-matching effect in non-CsA treated CAD allografts.

In the precyclosporine era, most multicentre studies showed benefit from good HLA matching for graft survival of CAD allografts (50, 100, 116, 143, 148, 157, 159 - 161, 192, 197). This effect becomes evident one year after transplantation and the effect increases with time (140, 176, 179, 197). The difference in graft

survival between the best and the worst match, considering A and B antigens only, is about 10% at one year, increasing to 17% at five years. In our experience (Figure 19), the difference observed between these 2 groups in terms of graft survival was 13% at one year (71% for 0 A and B mismatches vs 58% for 4 A and B mismatches; p=0.05) increasing remarkably at five years (71% vs 25%). As in other reports (14, 27, 42, 158-160), we found that graft survival rate is similar for 1 and 2 A and B mismatches (45% at five years), decreasing for 3 and 4 mismatches (39% and 25% at five years, [illegible]vely).

Several reasons might explain the groupings in 1 and 2, and 3 and 4 mismatches. First, some patients only had 1 of 2 antigens identified for a locus; these patients were considered homozygous for that antigen (8). Second, it could mean that 2 B mismatches are more harmful than 2 A mismatches (27). DR antigens were not introduced fully into recipient selection rate in 1980 (1, 112, 142, 194, 195) and even techniques were not standardized until 1981 (65, 119). However, DR mismatches in relation to graft survival has illustrated several characteristics of the HLA-matching effect (42, 65, 119, 138). It appears that each individual antigen does not contribute equally to this effect. Equal contribution is attributed to B and DR antigen (33, 42, 64, 138, 197, 199), but for some authors there is a

grading effect between A, B, and DR antigens on non-CsA treated patients, with DR mismatches contributing more powerfully than B mismatches which, in turn, are more powerful than A mismatches (12, 61, 62, 119). Restricted polymorphism of the DR antigens will be advantageous for achieving a good match (197). Despite the small sample in our data, DR mismatching showed a significant difference between good matching (0 mm) and poor matching (1 or 2 mm) (Figure 23). We also showed that graft survival is not significantly different between 1 or 2 DR mm. This suggests that DR is so immunogenic that 1 DR antigen is enough to trigger a major rejection response.

It is also evident that there is an overall linear decrease of graft survival with increasing numbers of mismatches, considering either A and B mismatches, A B and DR mismatches, or B and DR mismatches. However, recent studies (33, 64) have demonstrated that this apparently simple linear relationship is quite complex. Our results, though lacking DR antigens, are relatively similar to the United Kingdom Transplant Service report (64), which shows a) a beneficial effect of HLA matching in those patients with 0 mismatches for A. B and DR antigens; b) a significant increase of risk for grafts with 1 mismatch either for A or B antigens, which is much lower than that observed for 1 DR mismatch or 2 or more A B and DR mismatches; and c) a mild but

significant increase of risk from 2 to 6 A B and DR mismatches. We suggest that the most beneficial HLA A and B combination is that with no mismatches for those antigens. The presence of 1 or more A and B mismatches is associated with significantly higher risks for graft survival. Interestingly, successively greater degrees of A and B mismatch (i.e. 2, 3 or 4) show less and less increments in risk as compared to the increment due to 1 mismatch (Figures 43, 44). As will be discussed later, the relevance of a good HLA A and B match is more evident in CAD allografts treated with AZA than in those treated with CsA.

Except for very unusual situations (29), no additional benefit is reported from a good HLA C matching in the presence of A B and DR matching (27, 171); our data support this for C in relation to just A and B matching.

Some specific situations with conventional immunosuppression show greater benefit from HLA A and B matching. HLA-sensitized patients show 10% decrease in graft survival at one year and 27% at 2 years in comparison with non-sensitized (14). For regrafts, the 85% graft survival for zero A, B and DR mismatched transplants falls to 42% when all 6 A B and DR antigens are mismatched (70% for zero A and B mismatches vs 51% for 4 A and B mismatches)(141). For regrafts, a further factor may be sensitization to kidney-specific (non-HLA)

antigens. Our multivariate analysis results showed no significant increase of risk for regrafts, especially in poorly matched patients. Several reports also show an additive effect of good HLA matching on non transfused patients, achieving in some cases, similar graft survival rates to transfused ones (119, 195).

Ten year follow-up of CAD transplants (mostly on AZA) shows that HLA A and B matching is the most important factor for long-term graft survival (176, 179). There are no 10 year follow-up studies on DR antigens, as yet. However, this fact should be borne in mind when recommending broad changes in transplant policy.

HLA-matching effect in CsA-treated CAD allografts.

A really powerful new immunosuppressive drug might eliminate previously established, relatively weaker selection criteria such as HLA matching or pre-transplant blood transfusions, as well as reducing generalized immunosuppressive side-effects such as infections or neoplasms. The introduction of CsA into clinical management experience in the early 1980s (17, 18) coincided with a clear improvement of HLA typing techniques, especially those related with DR antigens (1, 112, 142, 194, 195). It is now established that good graft survival rates (around 80 - 87% at one year) can be achieved independently of the possible influence of HLA matching (64). Thus, there is reduced emphasis on

looking for a good HLA match because this leads to reduced likelihood of using an organ locally, though most believe in greater use of HLA matching for highly sensitized patients or regrafts, even when CsA is used.

Initial studies of CsA-treated CAD allografts reported a significant increase in graft survival of HLA mismatched categories so that they reached the level of survival previously achieved by totally HLA-matched AZA-treated CAD allografts. This suggests that there might be no additional benefit of HLA A B and DR matching on CsA-treated graft survival (47, 52, 54, 92, 109, 145, 181, 187). Some exceptional studies showed even a detrimental effect of good HLA matching on CAD transplants on CsA (74). Our results, using univariate methods, show the same trend as the majority of early reports: no statistically significant difference between patients well matched and poorly matched for A and B, or DR antigens (117). However, our multivariate analysis which took into account the number of previous transplants and previous sensitization, shows a significant benefit, for patients on CsA, of zero HLA A and B mismatching. The presence of 1 or more A and B mismatches was associated with significant increases in graft survival risk. Despite the statistical significance of these findings, they are less relevant than with AZA therapy. Similar results have now been reported showing some benefit from HLA matching with

CsA-treated patients (11, 12, 24, 27, 33, 51, 63, 64, 93, 138, 161, 174, 199, 209), even though some of them have only shown significance when DR antigens are included (33, 138). In short-term studies, HLA-matching has been shown to have an even stronger effect than CsA (26% of improvement with a good HLA match on CsA-treated patients over 12% of increase in graft survival by using CsA)(24, 31, 33).

According to the literature (33, 64, 161), the most substantial benefit is obtained in cases with no mismatches for A B and DR antigens. When many thousands of kidney allografts are considered, the increase of risk for graft survival between [illegible] and more than 2 mismatches is no longer significant. From data in Figures 43, and 44, we, too, can conclude that priority should be given to cases with zero mismatches for A, B and DR antigens, or at most 1 mismatch for A or B antigens with no DR mismatches. Patients with 2, or more than 2, mismatches for A, B and DR antigens all have quite similar risk (even though a significant increase at 0.05 level was found by the United Kingdom Transplant Service (64), its relevance to CsA-treated patients can be considered very mild). In our data, some combinations of 2 A and B mismatches overlap in risk with that observed in 1 A and B mismatched patients, suggesting that those combinations could have some priority in recipient selection. However, this should be

interpretated with caution because of the small numbers.

As described for AZA-treated CAD allografts, sensitized patients (either male or female) of first CAD transplant on CsA also obtain benefit from good HLA matching (in this situation the correlation can be established considering A and B, B and DR, and A B and DR antigens)(27). Cecka *et al* (27) considered those with more than 20% of cytotoxic antibodies to be 'sensitized'. That particular group of patients showed a 5% decrease in graft survival for each HLA A and B mismatch from 0 to 3. In our sample, patients with a PRA >20% were 23% of all CsA-treated patients. Interestingly, the effect of good matching on sensitized patients receiving a first transplant was not observed in regrafts (30).

An unexpected finding has been the significant effect of HLA DR, B-DR, and A-B matching found on graft survival of first CAD allografts in non sensitized female but not male recipients (28, 30). This is also shown in regrafts (30). These findings lead to speculate on the possibility of different immunogenicity of kidneys according to sex of donor as well as different effects controlled with CsA in males but not in females. Despite the short-term follow-up of these results, if they are confirmed, we can postulate the lack of relevant benefit of HLA matching in CAD kidney transplants involving non sensitized male recipients

(28). Nevertheless, it is suitable to wait for long term studies to get a true idea of HLA matching effect on CsA-treated patients as it has been demonstrated in long follow-up of AZA-treated CAD allografts (170).

HLA matching effect on renal transplant patient survival

Few reports on patient survival after renal transplantation include comparison with different degrees of HLA mismatching. Our results (Figure 21 and 22) show an influence of good HLA A and B match on patient survival, probably due to more agressive immunosuppressive therapy required to avoid rejection in those who are poorly matched. Even though not significant, the North Italia Transplant group reported better patient survival for well matched patients (170), also. Another report achieved significance for this difference in patients on AZA, but patients on CsA were not studied (186).

D. The effect of cytotoxic antibodies and pretransplant blood transfusions on renal transplant outcome

Initially, cytotoxic antibodies were thought to have a deleterious role on graft survival (182). These antibodies arise from prior exposure to antigens in previous blood transfusions, pregnancies, or transplants(86, 87). Exposure to antigens is not always deleterious. However, in some cases, this exposure is responsible for sensitization leading to a high risk of hyperacute rejection. Avoidance of

this by the need to await a negative pre-transplant lymphocytotoxic crossmatch seriously restricts opportunity for the sensitized patient.

The overall percentage of sensitized patients is quite variable. Among transplanted patients, almost 90% of males and 75% of females have less than 10% of cytotoxic antibodies (87). The rest of patients constitutes a pool of high risk patients.

The percentage of antibodies considered to be a significant level to increase risk for transplantation is arbitrary. Nevertheless, univariate survival studies of first-cadaver kidney transplants have demonstrated that graft survival is not significantly different between patients with less than 10% and those with 10 - 50% of cytotoxic antibodies (86, 87), provided all meet the criterion of a negative pre-transplant lymphocytotoxic crossmatch. On the other hand, for those with >50% PRA (current or remote), even when meeting the criterion of a negative crossmatch, graft survival is less (87). The immunologic reason for this is not known. For these reasons, we chose the value of 50% for dividing the whole sample in two subgroups.

The frequency of sensitized patients according to a highest PRA greater than 50% was 13% of all transplanted patients in our centre.

Our results confirm that a highest PRA greater than 50% constitutes a risk factor for renal transplantation (twice

as much risk as that for patients with less than 50%). This is particularly evident in patients on AZA (5, 100, 160). However, the risk is still high for patients on CsA, even though the difference did not reach statistical significance in actuarial survival (61, 62, 149, 169, 198). A surprising fact, reported in the literature, is the discrepancy between results obtained in CsA-treated patients by univariate and multivariate methods in relation to graft survival and highest PRA (198, 209). Univariate methods yielded no significant difference in graft survival for patients with increasing highest PRA, but multivariate predictions showed a gradual decrease according to greater highest PRA. The interpretation may relate to small sample size.

The effect of the highest PRA becomes more evident in regrafting and in poorly matched patients (87). Also, the incidence of kidneys with no function for one month increased with level of sensitization (8% if PRA were <50%, 15% if it was >75%), suggesting that preformed cytotoxic antibodies or antibodies to other antigen systems are responsible (87).

As would be expected, PRA does not lead to worse patient survival.

Under these circumstances, pretransplant blood transfusions were not expected to show benefit for graft survival. Their enhancing effect on graft survival was first reported by Dossetor *et al* in 1967 (48). At that time, blood was used to prime dialysis machines and all patients

received many units of blood (20-200 units). Despite this, not only was sensitization infrequent, but those who had had over 100 transfusions had better graft survival. Some years later, after an intense policy of restriction of blood transfusion in dialysis, poorer graft survival was reported for the non-transfused patients (133, 136, 205). This led, again, to a liberal policy for pretransplant blood transfusions.

The mechanisms by which blood transfusions act are not well established (202). At least, four theories have been proposed (26): selection of nonresponders (as those not able to produce cytotoxic antibodies) for renal transplantation, induction of tolerance, altered host immunologic competence due to induction of supressor cells, and production of varying subclasses of antibodies such as antiidiotypic antibodies to HLA, T3, interleukin-2 receptors or gamma-interferon receptor antigens. Lack of knowledge about the mechanisms of benefit from blood transfusions has led to empiric policies with regards to the amount of blood required, or the blood product responsible.

Our study shows a beneficial effect of blood transfusions on graft survival independently of the type of immunosuppressive regimen. While admitting benefit of transfusions on AZA-treated transplants (26), some groups reported that CsA-treated patients did not show any benefit from pretransplant transfusions (52, 54, 181, 209). Recent large sample reports (188, 202), however, still show a

strong transfusion effect even for CsA-treated patients. The effect of pretransplant blood transfusions seems to be independent of those of HLA matching and CsA usage, with a magnitude of 1[illegible]% of graft survival improvement at one year (33). Multivariate analyses usually corroborate this finding (161, 169, 174, 200).

E. Diabetes and nephroangiosclerosis: two high-risk renal transplant recipient groups

Diabetes mellitus and hypertension are two systemic diseases which not infrequently culminate in ESRD. In fact, the acceptance onto dialysis of diabetic patients with end-stage diabetic nephropathy has increased in the last five years from 7.9 new patients rpmp in 1981 to 12.3 rpmp in 1985 (20). This fact is probably due, in part, to better management of other complications, previously responsible for deaths of these patients, but principally, to improved techniques for dialysis for this group. No diabetic patients were transplanted in the first UAH period studied (1967-74), but were 9% of all transplanted patients during the second period. Nephroangiosclerosis was the primary renal disease of 8% of transplanted patients in the first period, and the percentage decreased to 4% for the second period, probably due to better medical control of hypertension.

Early experience with diabetic patients showed that graft survival achieved in this group of patients was significantly lower than that obtained for the rest of the

transplant population (121). This may be attributed to the cardiovascular complications of diabetes and greater difficulty in management of these patients on dialysis. For diabetic patients on AZA, transplanted during 1975 and 1985, only 75% of patients and 50% of grafts survived at one year. Thereafter, patient survival decreased rapidly, probably due to reasons other than transplantation. These percentages are not different from those reported by other groups [one-year patient survival of 85% and one-year CAD graft survival of 56%; aproximately 10% lower than the rest of the transplant population (25, 35, 121)]. Cyclosporine use has increased both survival rates making renal transplantation a good alternative treatment for diabetics on ESRD (35, 66, 178). It is interesting to note that most of multivariate analyses still show significantly higher risk for diabetic patients in terms of graft and patient survival, but more recent studies show lower significance (83, 100, 148, 160, 161, 174, 209), and Tiwari and Mickey did not find any significance at all for this covariate (198).

Nephroangiosclerosis as primary renal disease has not received as much attention as diabetes mellitus. However, the multisystem complications of that disease constitute a limitating factor for renal transplantation. Recent statistics report one-year graft survival of 58% for CAD allografts recipients on AZA, being only lower than the survival for patients with diabetes or systemic lupus erythematosus (35). Cyclosporine also has increased graft

survival for this group of patients but still remains as the lowest, except for systemic lupus erythematosus patients. In our study, nephroangiosclerosis is a risk factor for graft and patient survival. This finding has also been partially illustrated by other studies (25, 100). It is also important to remark that CsA has increased graft survival for these patients but CsA-induced hypertension should be evaluated further in order to determine possible long-term harmful effects.

F. The effect of warm and cold ischemia times on graft survival.

The increasing interest in donor characteristics and organ preservation has proved the importance of both warm and cold ischemia times on graft survival (93). The time in which these covariates affect allograft survival and the mechahism through which it is performed is not totally clear (21, 156). Most of the studies agree that shorter warm ischemia time is an important prognostic factor for improved early function, limiting the length of the acute tubular necrosis after transplant and improving the creatinine level at 1 month (5, 62, 198). In contrast, cold ischemia time seems to be a significant factor impacting on long-term graft survival (10 years)(174, 179). However, Kahan *et al* (93) have claimed that cold ischemia time determines also the incidence of posttransplant acute tubular necrosis. As early graft function is the most important predictor for

graft survival (Halloran P.: personal comunication), both times become impressively relevant. The fact that warm ischemia time was not a significant predictor covariate in contrast to cold ischemia time could be explained by the differences in those times between patients on AZA and those on CsA as well as the long-term follow-up of most of the patients. Accuracy of the data may also be a problem.

G. Donor ABO blood group

A surprising and unexpected result has been the deleterious role of donor ABO B group on graft survival. At least one multivariate analysis has reported similar results (198). The explanation of this is not clear. One report suggested different susceptibilities to infections for different ABO groups (28), another an influence of erythrocytic antigenic systems (186).

V. CONCLUSION

According to the results obtained, we can conclude that:

1. The year of transplant was a significant covariate during the time between 1967 and 1974, this effect disappearing after 1975. Thus, two clear-cut periods can be established in the University of Alberta Kidney Transplant Program: 1967-1974, and 1975-1985.
2. There is marked improvement in AZA results (CAD and LRD transplants) between these two time periods.
3. There is a proportionality of risks between renal transplants on AZA vs those on CsA as well as between recipients of CAD allografts and LRD allografts, in the second time period. This fact allows for the inclusion of these two variables as covariates in multivariate regression models.
4. In the second period, CsA use has significantly increased graft survival for CAD renal transplants (22%); this effect was not seen in LRD transplants.
5. Living-related transplants on CsA showed a 5% increase in one-year graft survival with respect to CAD allografts on CsA; this result could be argued to justify LRD transplants on children (who require a kidney transplant as soon as possible) but not in adults.
6. In our experience, and without evaluating HLA DR antigens, transplant of a zero HLA A and B mismatched

kidney represents a substantial benefit for graft survival. The risk of graft failure increases markedly with 1 or more mismatches but the relevance of this increase is much lower in patients on CsA.

7. Nephroangiosclerosis as primary renal disease, and a PRA greater than 50% are two significant factors for graft failure.

8. Pretransplant blood transfusions, shorter cold ischemia times, and non-B ABO donor group showed to be associated with a significant benefit but their predictive value is not significant probably due to their strong correlation with the use of CsA.

9. The presence of an interaction term between type of immunosuppressive drug and type of donor was significant in the final predictor model for graft survival; interaction terms between type of immunosuppressive regimen and number of HLA A and B mismatches, pretransplant blood transfusions, or highest PRA were not significant.

10. The final predictor model for patient survival contained the following covariates: main immunosuppressive drug, number of HLA A and B mismatches, nephroangiosclerosis as primary renal disease, and age at transplant; none of the interaction terms reported above were significant in this final model.

TABLES

		CAD(N=87)	LRD(N=13)
Age of recipient(yr.)		35.5±14.1	22.8±10.3
Sex (M/F)		57/30	9/4
Diabetic patients		0	0
Nephroangiosclerosis		8	0
HLA A and B mismatches:			
	0	10	9
	1	13	0
	2	42	4
	3	20	0
	4	2	0
Recipient blood group:			
	0	28	6
	A	45	7
	B	12	0
	AB	3	0
Donor blood group:			
	0	40	8
	A	35	5
	B	12	0
	AB	0	0
Cold ischemia time(min.)		1026±998	11±18
Warm ischemia time(min.)		11±16	0.15±0.50
Age of donor(yr.)		30.7±14.6	40.9±12.5
No. of pretransplant transf.:			
	0	5	3
	1-5	17	2
	>5	24	4
	Unknown	41	4
Dialysis therapy:			
	CAPD	1	0
	Home HD	3	2
	Hosp. HD	69	7
	IPD	11	3
Time on dialysis:			
	Never	3	1
	<2 yr.	72	10
	>2 yr.	12	2
Previous transplants:			
	0	72	12
	1	12	1
	2	2	0
	3	1	0

Table 1.- Descriptive statistics of patients transplanted in the first period (1967-1974). Values are given in absolute numbers, mean, and standart deviation.

HLA A/B MM(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
0 (10)	90	60	40	40	40	40
1 (13)	92	69	54	54	54	46
2 (42)	90	59	50	45	40	38
3 (20)	100	80	55	55	55	55
4 (2)	100	50	50	50	50	50
LRD recp.						
HLA ident. (9)	100	100	100	100	100	100
HLA haplo. (4)	100	75	50	25	0	0

Table 2.- Actuarial patient survival rates for CAD and LRD recipients during the first period (1967-1974) according to the number of mismatches for HLA A and B antigens (haplo. = haplo-identical; ident. = identical; MM = mismatches; recp. = recipients).

Recp. ABO groups(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
O (28)	82	43	36	36	36	32
A (45)	73	42	36	33	29	22
B (12)	75	58	42	42	25	25
AB (3)	50	50	50	50	50	50
LRD recp.						
O (6)	67	17	17	17	17	17
A (7)	71	43	43	43	29	29

Table 3.- Actuarial graft survival rate for CAD and LRD transplants performed during the first period (1967-1974) according to recipient ABO blood groups.

Recp. ABO groups(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
O (28)	93	61	50	50	50	46
A (45)	96	62	47	44	40	38
B (12)	92	92	58	58	50	50
AB (3)	50	50	50	50	50	50
LRD recp.						
O (6)	100	67	67	50	50	50
A (7)	100	86	71	71	43	43

Table 4.- Actuarial patient survival rates for CAD and LRD transplants performed during the first period (1967-1974) according to recipient ABO blood groups.

Blood transf.(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
Non-Transfused(5)	80	60	60	60	40	40
Transfused(41)	82	53	53	47	41	41
LRD recp.						
Non-Transfused(3)	67	33	33	33	33	33
Transfused(6)	50	50	50	50	50	50

Table 5.- Actuarial graft survival rate for CAD and LRD transplants performed in the first period (1967-1974) according to the pre-transplant blood transfusion status.

Blood Transf.(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
Non-Transfused(5)	100	80	80	80	60	60
Transfused(41)	94	88	82	76	76	76
LRD recp.						
Non-Transfused(3)	100	67	67	33	33	33
Transfused(6)	100	100	50	50	50	50

Table 6.- Actuarial patient survival rates for CAD and LRD transplants performed during the first period (1967-1974) according to their pre-transplant blood transfusion status.

Previous transplants(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
0 (72)	81	46	36	35	29	25
1 (12)	58	50	50	50	50	42
2 (2)	0	--	--	--	--	-
3 (1)	100	0	--	--	--	-
LRD recp.						
0 (12)	67	33	33	33	25	25
1(1)	100	0	--	--	--	-

Table 7.- Actuarial graft survival rate according to previous renal transplants for CAD and LRD renal retransplants performed in the first period (1967-1974).

Previous transplants(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
0 (72)	96	67	53	50	46	43
1 (12)	75	75	50	50	50	50
2 (2)	100	0	--	--	--	--
3 (1)	100	0	--	--	--	--
LRD recp.						
0 (12)	100	75	67	58	42	42
1 (1)	100	100	100	100	100	100

Table 8.- Actuarial patient survival rates according to previous renal transplants for CAD and LRD renal retransplants performed in the first period (1967-1974).

Dialysis modality(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
CAPD (1)	100	100	100	0	--	-
Home HD (17)	67	33	33	33	33	33
Hospital HD (69)	74	42	35	35	29	23
IPD (11)	82	36	27	27	27	27
LRD recp.						
Home HD (2)	100	100	100	100	50	50
Hospital HD (7)	71	14	14	14	14	14
IPD (3)	33	0	--	--	--	-

Table 9.- Actuarial graft survival rates according to modality of dialysis previous to transplant for CAD and LRD renal transplants performed during the first period (1967-1974). (CAPD = continuous ambulatory peritoneal dialysis; HD = hemodialysis; IPD = intermittent pritoneal dialysis).

Dialysis modality(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
CAPD (1)	100	100	100	0	--	-
Home HD (3)	100	33	33	33	33	33
Hospital HD (69)	94	67	50	48	44	41
IPD (11)	91	54	45	45	45	45
LRD recp.						
Home HD (2)	100	100	100	100	50	50
Hospital HD (7)	100	86	86	71	57	57
IPD (3)	100	33	0	--	--	-

Table 10.- Actuarial patient survival rates according to modality of dialysis previous to transplant for CAD and LRD renal transplants performed during the first period (1967-1974). (CAPD = continuous ambulatory peritoneal dialysis; HD = hemodialysis; IPD = intermittent pritoneal dialysis).

	CAD(N=250)		
	AZA(N=161)		CsA(N=89)
Age of recipient(yr.)	38.2±14.3		39.7±13.5
Sex (M/F)	112/49		56/33
Diabetic patients	12	*	15
Nephroangiosclerosis	9		3
HLA A and B mismatches:			
0	7	**	3
1	27		7
2	82		38
3	33		37
4	12		4
Recipient blood group:			
0	49		27
A	85		34
B	16		19
AB	11		9
Donor blood group:			
0	78		31
A	68		35
B	10		19
AB	5		4
Cold ischemia time(min.)	1516±748	***	1280±411
Warm ischemia time(min.)	6.5±13.7	*	3.8±2.4
Age of donor(yr.)	28.2±13.6		30.9±13.6
No. of pretransplant transf.:			
0	47	***	4
1-5	63		35
>5	42		49
Unknown	9		1
Dialysis therapy:			
CAPD	22		25
Home HD	63		33
Hosp. HD	66		28
Time on dialysis:			
Never	10		3
<2 yr.	110		54
>2 yr.	41		32
Previous transplants:			
0	133		73
1	25		15
2	3		1

Table 11.- Descriptive statistics of CAD allografts transplanted in the second period (1975-1985). Values are given in absolute numbers, mean, and standart deviation. (* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$).

	LRD(N=76)	
	AZA(N=50)	CsA(N=26)
Age of recipient(yr.)	24.6±11.0	29.0±11.1
Sex (M/F)	28/22	17/9
Diabetic patients	0	2
Nephroangiosclerosis	0	1
HLA A and B mismatches:		
Ident.	27	16
Haplo.	23	10
Recipient blood group:		
0	32	10
A	11	12
B	4	4
AB	3	0
Donor blood group:		
0	35	13
A	10	10
B	4	3
AB	1	0
Cold ischemia time(min.)	34.5±157.1	115.8±338.6
Warm ischemia time(min.)	0.24±1.2	0.4±1.1
Age of donor(yr.)	36.6±12.3	36.0±9.5
No. of pretransplant transf.:		
0	11	2
1-5	22	11
>5	14	13
Unknown	3	0
Dialysis therapy:		
CAPD	5	6
Home HD	6	2
Hosp. HD	32	13
IPD	1	0
Time on dialysis:		
Never	5	3
<2 yr.	37	20
>2 yr.	8	3
Previous transplants:		
0	47	24
1	3	1
2	0	1

Table 12.- Descriptive statistics of LRD kidney recipients in the second period (1975-1985). Values are given in absolute numbers, mean, and standart deviation.

Highest PRA		<50 %	>50 %
CAD recp.	on AZA	137	19
	on CsA	74	13
LRD recp.	on AZA	39	7
	on CsA	25	1

Table 13.- Distribution of renal transplant recipients of second period (1975-1985) according to their highest percentage of reactive antibodies against panel cells.

Recp. ABO groups(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
O (49)	77	59	55	51	47	42
A (85)	91	67	63	59	47	44
B (16)	94	44	44	44	44	44
AB (11)	67	45	45	45	45	45
on CsA						
O (27)	100	93	88	88	74	74
A (34)	88	79	79	79	79	79
B (19)	100	74	68	68	68	68
AB (9)	89	89	89	89	89	89
LRD recp.						
on AZA						
O (32)	91	84	78	75	69	69
A (11)	91	91	91	91	82	82
B (4)	100	100	100	100	100	100
AB (3)	100	100	100	100	100	100
on CsA						
O (10)	90	90	79	65	65	65
A (12)	100	92	92	92	92	92
B (4)	100	75	75	75	75	-

Table 14.- Actuarial graft survival rates for renal transplants performed in the second period (1975-1985) according the recipient ABO group.

Recp. ABO groups(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
O (49)	96	92	92	92	90	85
A (85)	100	94	88	83	77	70
B (16)	100	81	81	81	81	81
AB (11)	100	91	91	91	91	91
on CsA						
O (27)	100	100	100	100	100	100
A (34)	100	97	97	97	97	97
B (19)	100	93	93	93	93	93
AB (9)	100	100	100	100	100	100
LRD recp.						
on AZA						
O (32)	97	97	94	94	94	94
A (11)	91	91	91	91	91	91
B (4)	100	100	100	100	100	100
AB (3)	100	100	100	100	100	100
on CsA						
O (10)	100	90	90	90	90	90
A (12)	100	100	100	100	100	100
B (4)	100	100	100	100	100	-

Table 15.- Actuarial patient survival rates for renal transplants performed in the second period (1975-1985) according the recipient ABO group.

Highest PRA(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
<50 % (137)	98	92	89	87	83	78
> 50 % (19)	100	89	84	79	74	67
on CsA						
<50 % (74)	100	100	98	98	98	98
> 50 % (13)	100	92	92	92	92	-

Table 16.- Actuarial patient survival rates for renal transplants performed during the second period (1975-1985) according to their PRA.

HBsAg NEGATIVE(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA (144)	84	59	55	50	44	42
on CsA (76)	95	83	81	81	78	78
LRD recp.						
on AZA (43)	91	86	81	79	74	74
on CsA (22)	95	86	82	76	76	76
HBsAg POSITIVE						
CAD recp.						
on AZA (5)	80	20	20	20	20	20
on CsA (2)	100	50	50	--	--	-

Table 17.- Actuarial graft survival rates for renal transplants performed in the second period (1975-1985) according to their status for HBsAg.

HBsAg NEGATIVE(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA (144)	99	91	87	85	81	76
on CsA (76)	100	99	97	97	97	97
LRD recp.						
on AZA (43)	95	95	93	93	93	93
on CsA (22)	100	95	95	95	95	95
HBsAg POSITIVE						
CAD recp.						
on AZA (5)	100	100	100	100	100	100
on CsA (2)	100	100	100	--	--	-

Table 18.- Actuarial patient survival rates for renal transplants performed in the second period (1975-1985) according to their status for HBsAg.

Anti-HBc NEGATIVE(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA (58)	84	53	48	43	36	34
on CsA (59)	93	80	78	78	73	73
LRD recp.						
on AZA (10)	94	83	83	83	72	72
on CsA (12)	92	92	83	75	75	75
Anti-HBc POSITIVE(N)						
CAD recp.						
on AZA (15)	87	27	20	7	7	7
on CsA (3)	100	67	67	--	--	-
LRD recp.						
on CsA (2)	100	0	--	--	--	-

Table 19.- Actuarial graft survival rates for renal transplants performed in the second period (1975-1985) according to their status for antibodies against core of hepatitis B virus (anti-HBc).

Anti-HBc NEGATIVE(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA (58)	100	95	91	91	91	91
on CsA (59)	100	98	96	96	96	96
LRD recp.						
on AZA (10)	100	100	100	100	100	100
on CsA (12)	100	92	92	92	92	92
Anti-HBc POSITIVE(N)						
CAD recp.						
on AZA (15)	100	93	93	93	93	93
on CsA (3)	100	100	100	--	--	-
LRD recp.						
on CsA (2)	100	100	100	--	--	-

Table 20.- Actuarial patient survival rates for renal transplants performed in the second period (1975-1985) according to their status for antibodies against core of hepatitis B virus (anti-HBc).

No.of Prev. transp.(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
0 (133)	85	62	60	55	49	46
1 (25)	84	52	44	39	30	30
2 (3)	100	67	67	33	33	33
on CsA						
0 (73)	96	85	82	82	82	82
1 (15)	93	80	80	80	48	
2 (1)	0					
LRD recp.						
on AZA						
0 (47)	91	87	83	81	74	74
1 (3)	100	100	100	100	100	100
on CsA						
0 (24)	96	87	83	78	78	78
1 (1)	100	100	100	100		
2 (1)	100	100	100	100	100	

Table 21.- Actuarial graft survival rates for renal retransplants performed during the second period (1975-1985) according to the number of previous transplants.

No.of Prev. transp.(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
0 (133)	98	91	89	87	82	78
1 (25)	100	96	88	84	84	72
2 (3)	100	100	100	67	67	67
on CsA						
0 (73)	100	99	97	97	97	97
1 (15)	100	100	100	100	100	
2 (1)	100	100	100			
LRD recp.						
on AZA						
0 (47)	96	96	94	94	94	94
1 (3)	100	100	100	100	100	100
on CsA						
0 (24)	100	96	96	96	96	96
1 (1)	100	100	100	100		
2 (1)	100	100	100	100	100	

Table 22.- Actuarial patient survival rates for renal retransplants performed during the second period (1975-1985) according to the number of previous transplants.

Dial. Therapy(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
CAPD (22)	100	50	50	44	44	35
Home HD (63)	82	57	55	50	45	43
Hosp HD (66)	85	68	62	54	46	43
on CsA						
CAPD (25)	9[illegible]	80	80	80	80	
Home HD (33)	[illegible]	82	82	82	72	72
Hosp HD (28)	96	89	85	85	85	85
LRD recp.						
on AZA						
CAPD (5)	75	75	75	75	75	75
Home HD (6)	83	83	83	83	83	83
Hosp HD (32)	97	91	84	81	78	78
on CsA						
CAPD (6)	83	83	83	83	83	83
Home HD (2)	100	100	100	100	100	100
Hosp HD (13)	100	85	77	67	67	67

Table 23.- Actuarial graft survival rates for renal transplants performed during the second period (1975-1985) according to their modality of dialysis before renal transplant. (CAPD: continuous ambulatory peritoneal dialysis; HD: hemodialysis; Hosp: Hospital).

Dial. Therapy(N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
CAPD (22)	100	94	94	94	94	94
Home HD (63)	98	92	88	85	78	70
Hosp HD (66)	98	92	88	86	85	80
on CsA						
CAPD (25)	100	96	96	96	96	
Home HD (33)	100	100	96	96	96	96
Hosp HD (28)	100	100	100	100	100	100
LRD recp.						
on AZA						
CAPD (5)	100	100	100	100	100	100
Home HD (6)	83	83	83	83	83	83
Hosp HD (32)	97	97	94	94	94	94
on CsA						
CAPD (6)	100	83	83	83	83	83
Home HD (2)	100	100	100	100	100	100
Hosp HD (13)	100	100	100	100	100	100

Table 24.- Actuarial patient survival rates for renal transplants performed during the second period (1975-1985) according to their modality of dialysis before renal transplant. (CAPD: continuous ambulatory peritoneal dialysis; HD: hemodialysis; Hosp: Hospital).

Time on dial.(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
Never (10)	100	75	75	75	62	62
<2 yr. (110)	84	58	54	47	46	41
>2 yr. (41)	83	63	63	58	48	43
on CsA						
Never (3)	67	67	33	0		
<2 yr. (54)	96	85	85	85	85	85
>2 yr. (32)	94	81	81	78	66	66
LRD recp.						
on AZA						
Never (5)	100	100	100	100	100	100
<2 yr. (37)	89	83	78	75	69	69
>2 yr. (8)	100	100	100	100	100	100
on CsA						
Never (3)	100	100	100	100	100	100
<2 yr. (20)	95	84	79	72	72	72
>2 yr. (3)	100	100	100	100	100	

Table 25.- Actuarial graft survival rates for renal transplants performed during the second period (1975-1985) according to time on dialysis before renal transplant. (CAPD: continuous ambulatory peritoneal dialysis; HD: hemodialysis; Hosp: Hospital).

Time on dial. (N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
Never (10)	100	100	100	100	100	100
<2 yr. (110)	98	93	88	85	83	78
>2 yr. (41)	100	88	88	85	77	69
on CsA						
Never (3)	100	100	100	100		
<2 yr. (54)	100	100	100	100	100	100
>2 yr. (32)	100	97	93	93	93	93
LRD recp.						
on AZA						
Never (5)	100	100	100	100	100	100
<2 yr. (37)	94	94	92	92	92	92
>2 yr. (8)	100	100	100	100	100	100
on CsA						
Never (3)	100	100	100	100	100	100
<2 yr. (20)	100	95	95	95	95	95
>2 yr. (3)	100	100	100	100	100	

Table 26.- Actuarial patient survival rates for renal transplants performed during the second period (1975-1985) according to time on dialysis before renal transplant. (CAPD: continuous ambulatory peritoneal dialysis; HD: hemodialysis; Hosp: Hospital).

Prof. status(N)	Graft survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
Unemp.(68)	88	68	63	56	47	43
Employed (77)	80	57	54	51	47	44
on CsA						
Unemp.(18)	100	89	83	83	73	73
Employed (25)	88	80	80	80	80	80
LRD recp.						
on AZA						
Unemp.(33)	100	94	88	85	82	82
Employed (12)	75	75	75	75	75	75
on CsA						
Unemp.(6)	100	100	83	65	65	65
Employed (1)	100	100	100	100	100	

Table 27.- Actuarial graft survival rates for renal transplants performed during the second period (1975-1985) according to professional status before renal transplant.

Prof. status (N)	Patient survival (%)					
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
Unemp.(68)	98	90	88	84	82	76
Employed (77)	99	92	90	88	82	77
on CsA						
Unemp.(18)	100	100	94	94	94	94
Employed (25)	100	100	100	100	100	100
LRD recp.						
on AZA						
Unemp.(33)	100	100	97	97	97	97
Employed (12)	83	83	83	83	83	83
on CsA						
Unemp.(6)	100	100	100	100	100	100
Employed (1)	100	100	100	100	100	

Table 28.- Actuarial patient survival rates for renal transplants performed during the second period (1975-1985) according to professional status before renal transplant.

	Life activ.(N)	Graft survival (%)				
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
Restric.(9)	78	68	67	56	44	44
Normal (135)	84	61	58	52	46	43
on CsA						
Restric.(6)	100	100	82	82	82	82
Normal (37)	92	81	81	81	75	75
LRD recp.						
on AZA						
Restric.(3)	100	100	100	100	100	100
Normal (41)	93	88	83	80	78	78
on CsA						
Restric.(1)	100	100	100	0	--	-
Normal (6)	100	100	83	83	83	83

Table 29.- Actuarial graft survival rates for renal transplants performed during the second period (1975-1985) according to their social rehabilitation.(Restric.: restricted activities).

	Life activ.(N)	Patient survival (%)				
CAD recp.	1 m	1 yr	2 yr	3 yr	4 yr	5 yr
on AZA						
Restric.(9)	100	67	67	56	56	56
Normal (135)	98	93	90	88	83	78
on CsA						
Restric.(6)	100	100	100	100	100	100
Normal (37)	100	100	97	97	97	97
LRD recp.						
on AZA						
Restric.(3)	100	100	100	100	100	100
Normal (41)	95	95	93	93	93	93
on CsA						
Restric.(1)	100	100	100	100	100	-
Normal (6)	100	100	100	100	100	100

Table 30.- Actuarial patient survival rates for renal transplants performed during the second period (1975-1985) according to their social rehabilitation.(Restric.: restricted activities).

	CAD(N=220)		
	AZA(N=136)		CsA(N=84)
Age of recipient(yr.)	40.4±12.4		39.9±12.5
Sex (M/F)	92/44		53/31
Diabetic patients	12	**	15
Nephroangiosclerosis	7		3
HLA A and B mismatches:			
0	5		3
1	24		6
2	71		37
3	27		34
4	9		4
Recipient blood group:			
0	36		25
A	77		31
B	12		19
AB	11		9
Donor blood group:			
0	60		30
A	62		32
B	9		18
AB	5		4
Cold ischemia time(min.)	1570±707	***	1267±405
Warm ischemia time(min.)	9.7±13.7	*	4.5±4.5
Age of donor(yr.)	29.0±12.9		31.0±13.2
No. of pretransplant transf.:			
0	41	***	2
1-5	61		35
>5	34		47
Dialysis therapy:			
CAPD	14		23
Home HD	57		32
Hosp. HD	56		26
Time on dialysis:			
Never	9		3
<2 yr.	98		49
>2 yr.	35		32
Previous transplants:			
0	117		71
1	16		12
2	3		1

Table 31.- Descriptive statistics of those CAD allografts transplanted in the second period (1975-1985) and included in the multivariate analysis. Values are given in absolute numbers, mean, and standart deviation. (* = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$).

		LRD(N=67)	
		AZA(N=43)	CsA(N=24)
Age of recipient(yr.)		25.4±11.5	28.3±11.6
Sex (M/F)		25/18	15/9
Diabetic patients		0	1
Nephroangiosclerosis		0	1
HLA A and B mismatches:			
	Ident.	25	15
	Haplo.	18	9
Recipient blood group:			
	0	27	9
	A	10	11
	B	4	2
	AB	2	0
Donor blood group:			
	0	30	12
	A	9	9
	B	4	3
	AB	0	0
Cold ischemia time(min.)		88.2±160.1	94.5±320.2
Warm ischemia time(min.)		0.27±1.2	0.2±0.8
Age of donor(yr.)		36.3±12.6	36.2±9.5
No. of pretransplant transf.:			
	0	9	2
	1-5	22	11
	>5	12	11
Dialysis therapy:			
	CAPD	3	6
	Home HD	6	2
	Hosp. HD	28	13
	IPD	1	0
Time on dialysis:			
	Never	4	3
	<2 yr.	31	18
	>2 yr.	8	3
Previous transplants:			
	0	41	22
	1	2	1
	2	0	1

Table 32.- Descriptive statistics of those LRD kidney recipients in the second period (1975-1985) included in the multivariate analysis. Values are given in absolute numbers, mean, and standart deviation.

Highest PRA		<50 %	>50 %
CAD	AZA	120	16
	CsA	72	12
LRD	AZA	36	7
	CsA	23	1

Table 33.- Distribution of renal transplant recipients of second period (1975-1985) included in multivariate analysis according to their highest percentage of reactive antibodies against panel cells.

VARIABLE	COEFFICENT	P-VALUE	RELATIVE RISK
Immunosuppressor	-0.9471	0.0040(***)	0.3879
Type of Donor	-0.0805	0.8444	0.9226
Male	-0.1697	0.4061	0.8439
0 A-B mismatches	-1.977	0.0[illegible](***)	0.1385
1 A-B mismatch	-0.9248	0.03[illegible](*)	0.3966
2 A-B mismatches	-0.9246	0.0246(*)	0.3967
3 A-B mismatches	-0.4670	0.2715	0.6269
> 50 % of PRA	0.7395	0.0127(*)	2.095
Diabetic nephropathy	-0.0068	0.9855	0.9931
Nephroangiosclerosis	0.8725	0.0262(*)	2.393
< 2 years on dialysis	0.9852	0.1280	2.678
> 2 years on dialysis	0.6311	0.3479	1.880
Pre-trans BT	-0.6075	0.0181(*)	0.5447
Warm ischemia time	0.0023	0.4982	exp 0.0023x
Cold ischemia time	0.0003	0.0118(*)	exp 0.0003x
Age	-0.0080	0.3392	0.9919
Recipient			
Second transplant	0.1648	0.5510	1.179
> 3 transplants	0.4735	0.4165	1.606
Recipient O ABO-group	-0.3011	0.5889	0.7400
Recipient A ABO-group	-0.3796	0.4722	0.6842
Recipient B ABO-group	-1.097	0.1321	0.3339
Donor O ABO-group	0.9874	0.2182	2.684
Donor A ABO-group	0.6011	0.4425	1.824
Donor B ABO-group	2.174	0.0199(*)	8.794

Table 34.- Regression coefficients, their significance, and their relative risks for the full predictor model of graft survival (*: p<0.05; **: p<0.01; ***: p<0.001).

VARIABLE	COEFFICENT	P-VALUE	RELATIVE RISK
Immunosuppressor	-1.66	0.0010(***)	0.19
Type of Donor	0.5118	0.4441	1.6686
Male	-0.1088	0.7387	0.8969
0 A-B mismatches	-1.722	0.0468(*)	0.1787
1 A-B mismatch	-0.5260	0.3613	0.5910
2 A-B mismatches	-0.9426	0.0704	0.3896
3 A-B mismatches	-0.6810	0.2429	0.5061
> 50 % of PRA	0.3679	0.3730	1.445
Diabetic nephropathy	1.016	0.0570	2.761
Nephroangiosclerosis	1.179	0.0245(*)	3.253
< 2 years on dialysis	0.4524	0.6773	1.572
> 2 years on dialysis	0.8239	0.4579	2.279
Pre-trans BT	-0.2948	0.3827	0.7447
Warm ischemia time	0.0035	0.4818	exp 0.0035x
Cold ischemia time	0.0003	0.0853	exp 0.0003x
Age	0.0335	0.0165	1.034
Recipient			
Second transplant	0.2320	0.5826	1.261
> 3 transplants	1.378	0.0941	3.968
Recipient O ABO-group	-0.1345	0.8762	0.8742
Recipient A ABO-group	0.7360	0.3569	2.087
Recipient B ABO-group	-0.9765	0.5309	0.3766
Donor O ABO-group	0.2981	0.8180	1.347
Donor A ABO-group	-0.3780	0.7699	0.6852
Donor B ABO-group	1.910	0.3081	6.753

Table 35.- Regression coefficients, their significance, and their relative risks for the full predictor model of patient survival (*: p<0.05; **: p<0.01; ***: p<0.001).

VARIABLE	COEFFICENT	P-VALUE	RELATIVE RISK
Immunosuppressor	-0.9920	0.0001(***)	0.3708
0 A-B mismatches	-1.741	0.0006(***)	0.1753
1 A-B mismatch	-0.9049	0.0284(*)	0.4046
2 A-B mismatches	-0.8959	0.0146(*)	0.4082
3 A-B mismatches	-0.5661	0.1459	0.5678
> 50 % of PRA	0.6820	0.0086(**)	1.978
Nephroangiosclerosis	0.7315	0.0509(*)	2.078
Cold ischemia time	0.0003	0.0159(*)	exp 0.0003x

Table 36.- Regression coefficients, their significance, and their relative risk in the final predictor model for graft survival without interaction terms (*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$).

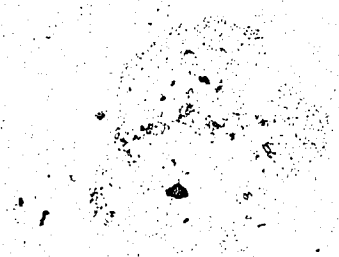
VARIABLE	COEFFICENT	P-VALUE	RELATIVE RISK
Immunosuppressor	-1.714	0.005(**)	0.1802
0 A-B mismatches	-1.633	0.0360(*)	0.1954
1 A-B mismatch	-0.9848	0.0568	0.3735
2 A-B mismatches	-1.343	0.0036(**)	0.2611
3 A-B mismatches	-1.044	0.0423(*)	0.3519
Nephroangiosclerosis	1.037	0.0353(*)	2.820
Age at transplant	0.032	0.0049(**)	1.033

Table 37.- Regression coefficients, their significance, and their relative risk in the final predictor model for patient survival (*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$).

VARIABLE	COEFFICENT	P-VALUE	RELATIVE RISK
Immunosuppressor	-2.592	0.0015(**)	0.07488
Type of donor	-2.078	0.0165(*)	0.1252
Interact. IS-Typ.donor	1.343	0.0402(*)	3.830
0 A-B mismatches	-1.733	0.0012(**)	0.1767
1 A-B mismatch	-0.9216	0.0259(*)	0.3979
2 A-B mismatches	-0.9556	0.0092(**)	0.3846
3 A-B mismatches	-0.6149	0.1142	0.5407
> 50 % of PRA	0.6808	0.0088(**)	1.975
Nephroangiosclerosis	0.7648	0.0413(*)	2.149

Table 38.- Regression coefficients, their significance, and their relative risks in the final model for predicting graft survival ((*: p<0.05; **: p<0.01; ***: p<0.001); Interac. IS-Type of donor: interaction term between type of donor and main immunosuppressive drug).

FIGURES



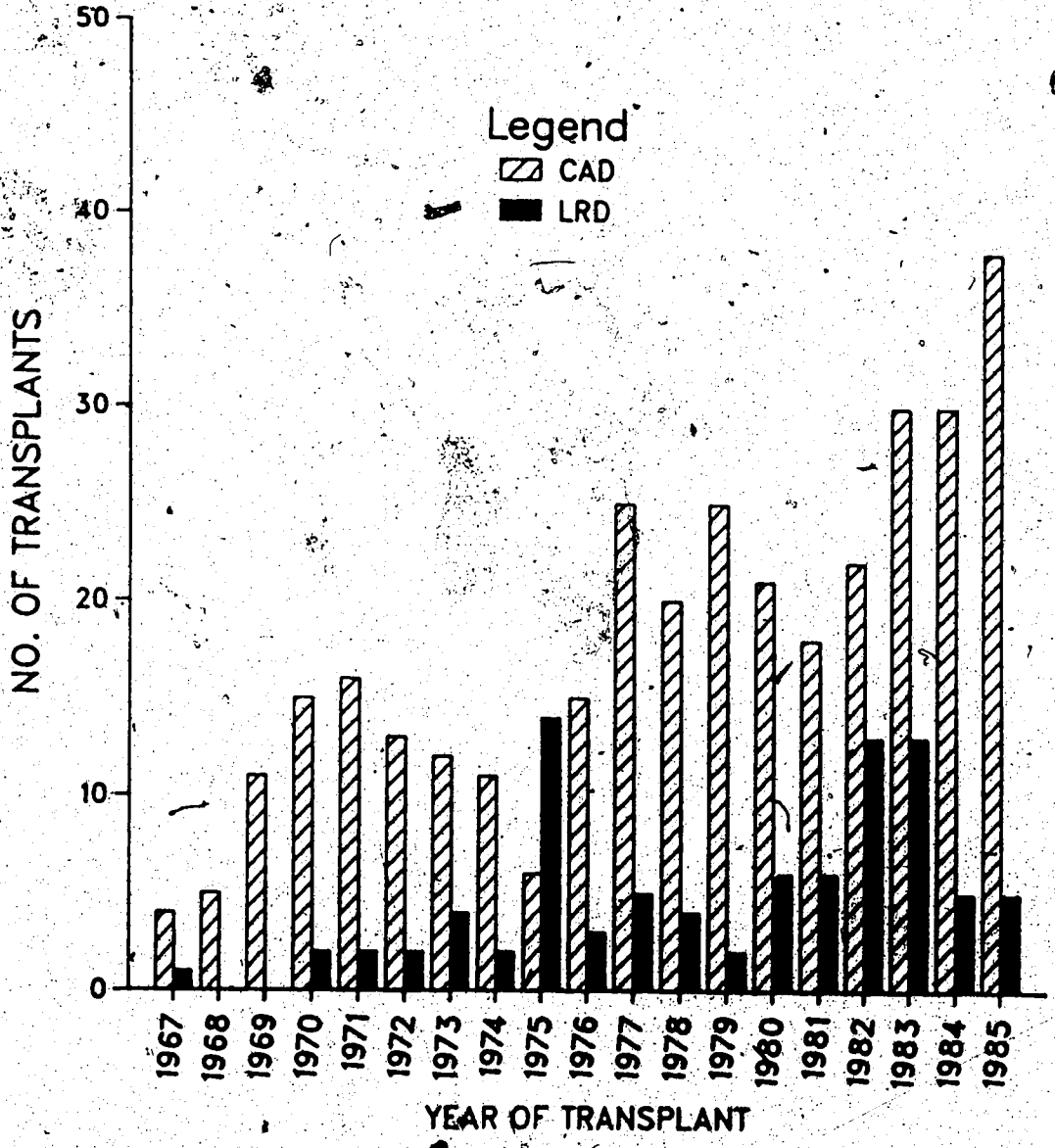


Figure 1.- Number of CAD and LRD renal transplants performed in the University of Alberta Hospital according to the year of transplant.

2.

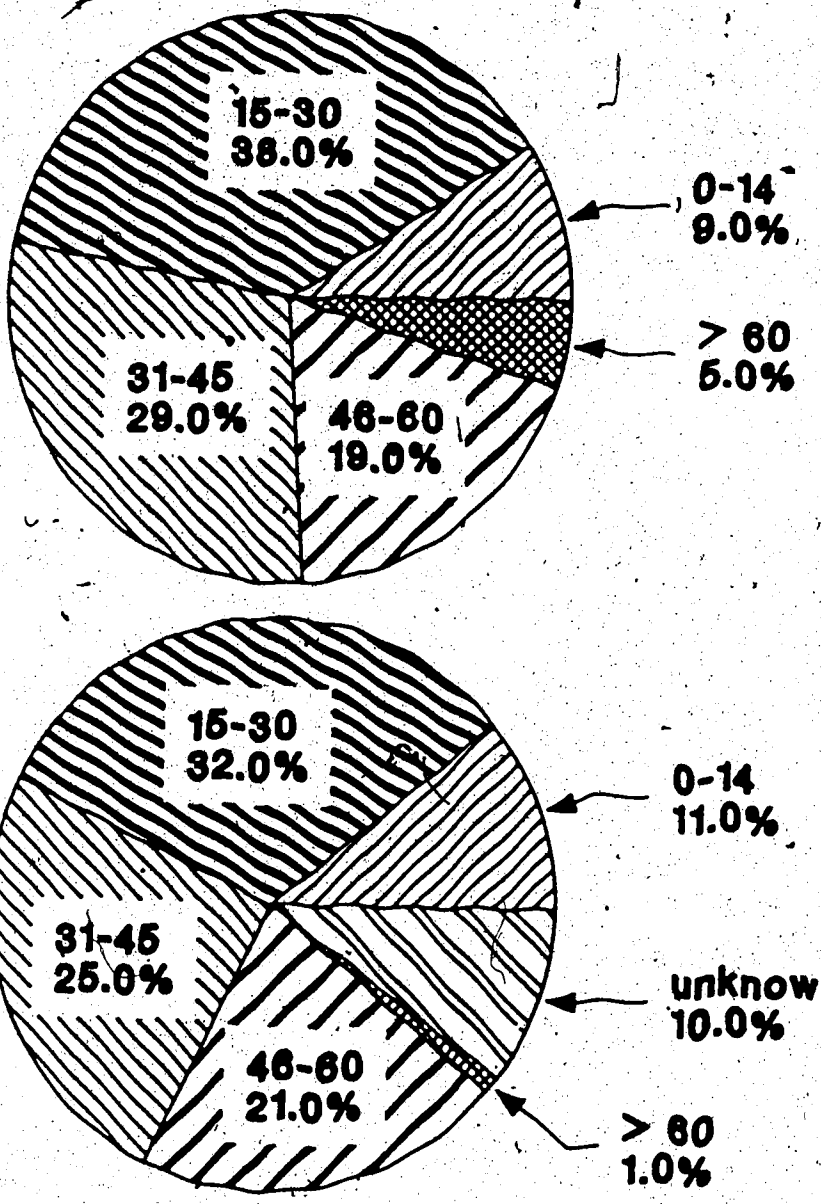


Figure 2.- Percentages of recipients (upper) and donors (lower) ages for renal transplants performed during the first period (1967-1974).

3.

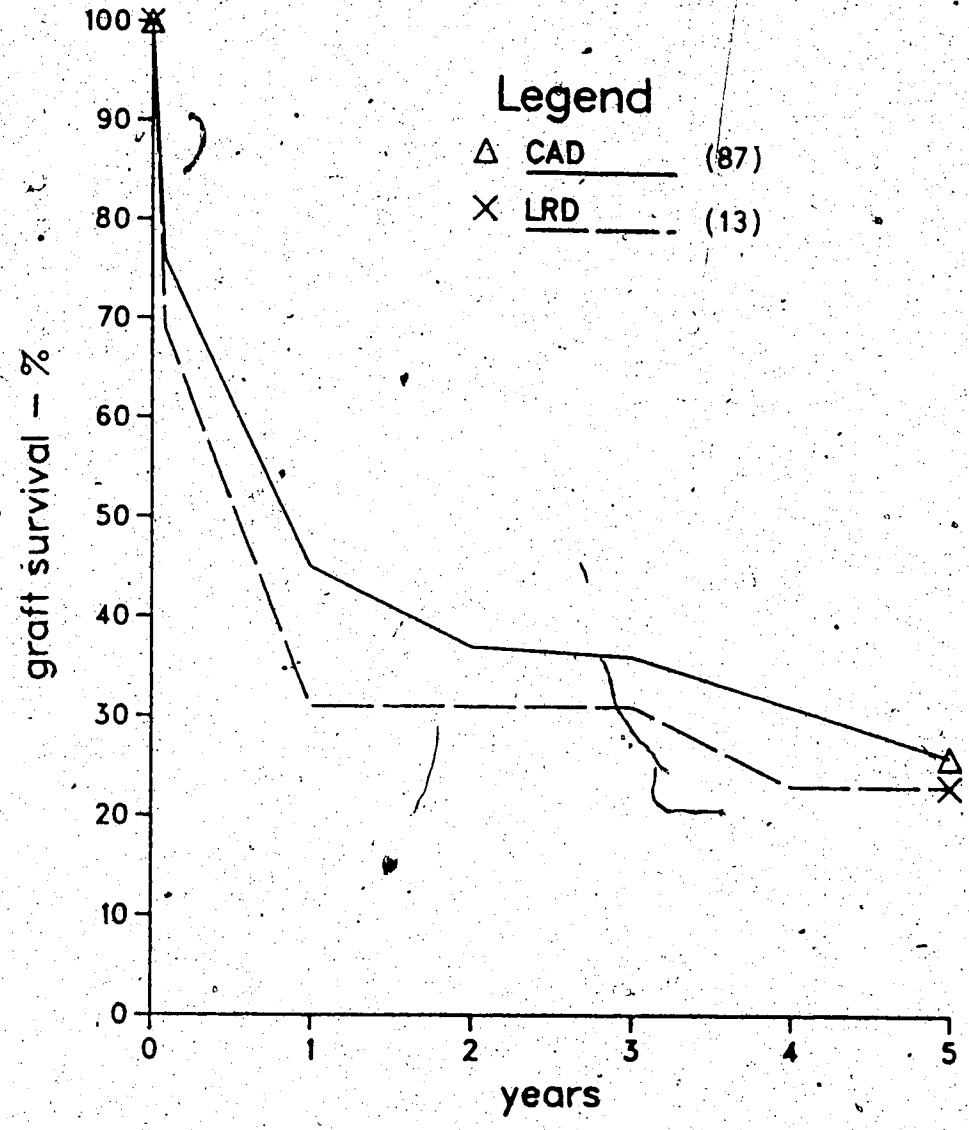


Figure 3.- Actuarial graft survival for CAD and LRD recipients in the first period (1967-1974).

4.

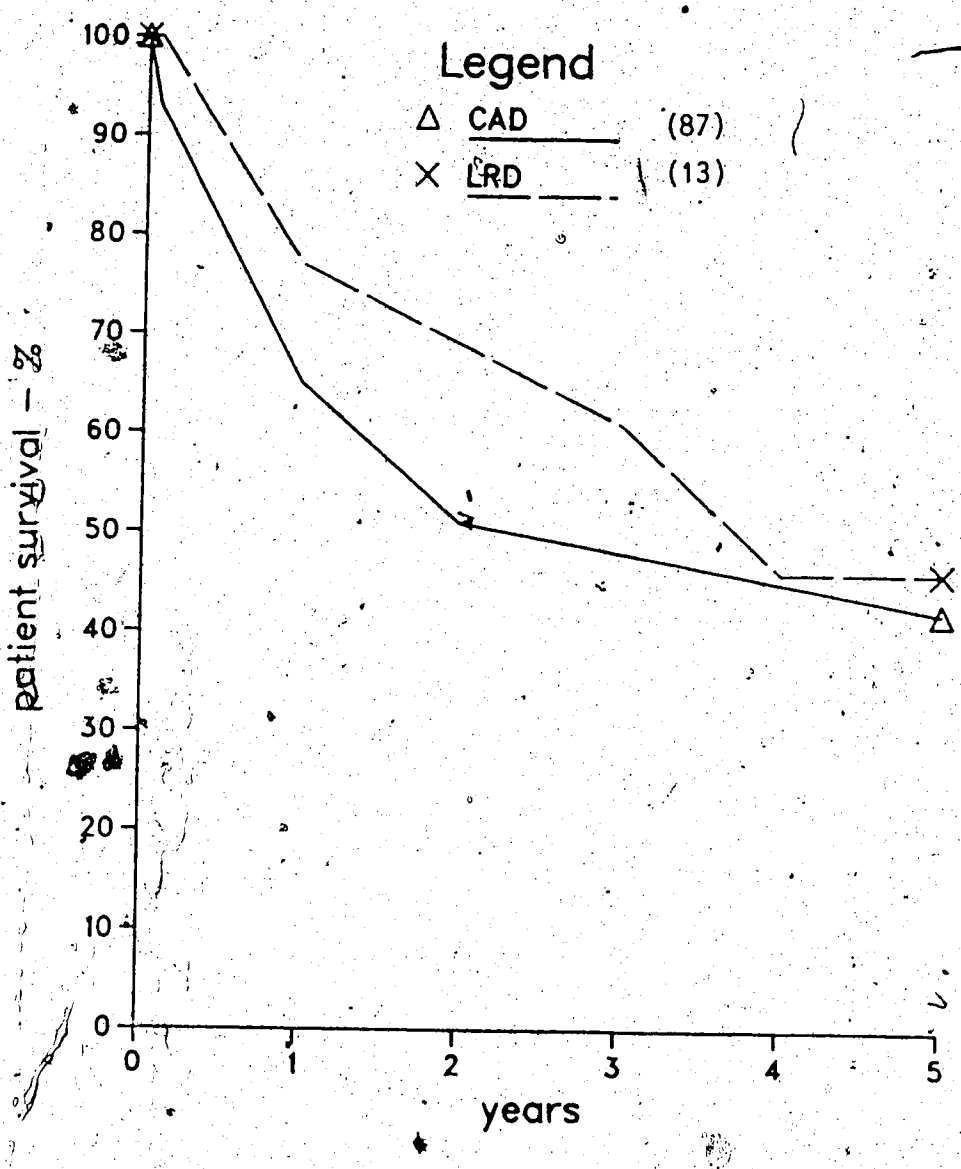


Figure 4.- Actuarial patient survival for CAD and LRD recipients in the first period (1967-1974).

5.

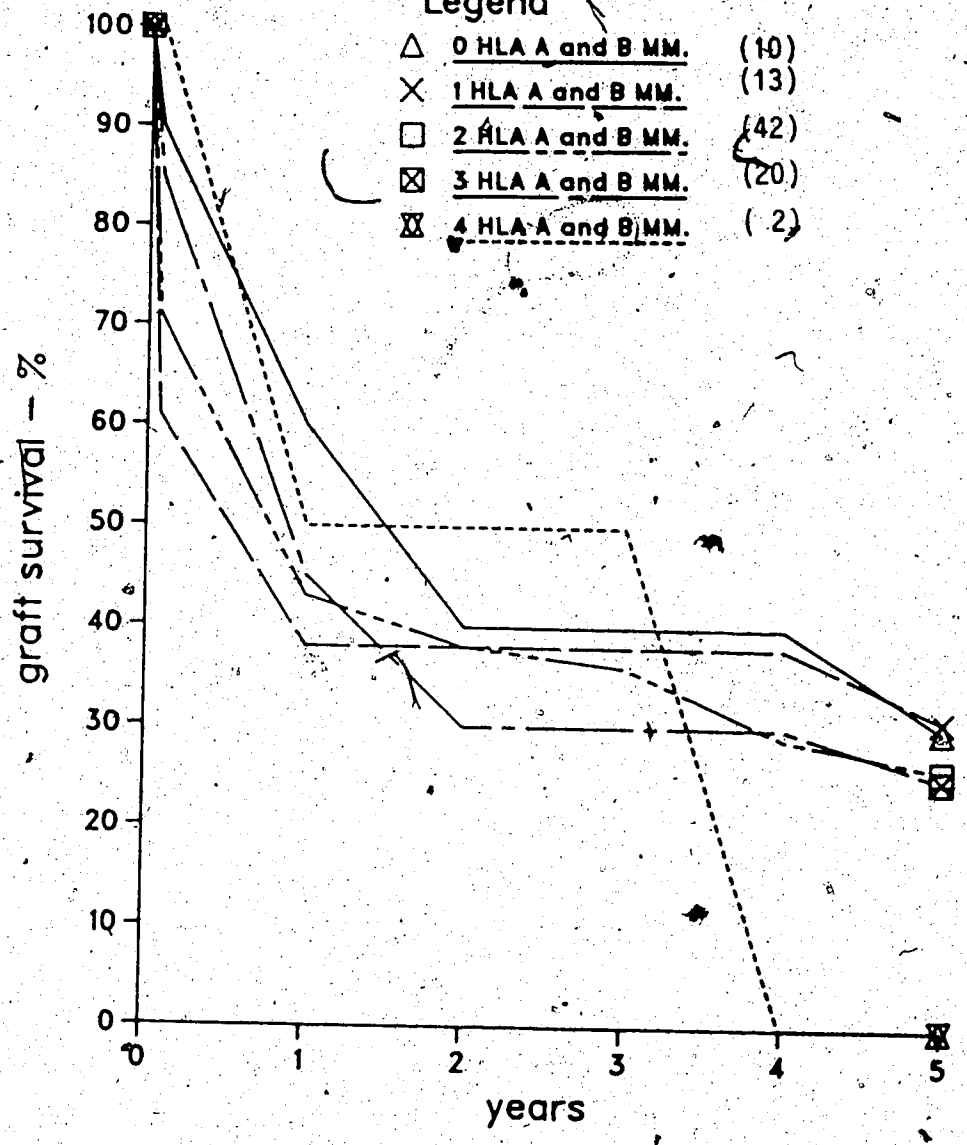


Figure 5.- Actuarial graft survival rates for CAD recipients in the first period (1967-1974) according to the number of HLA A and B mismatches.

6.

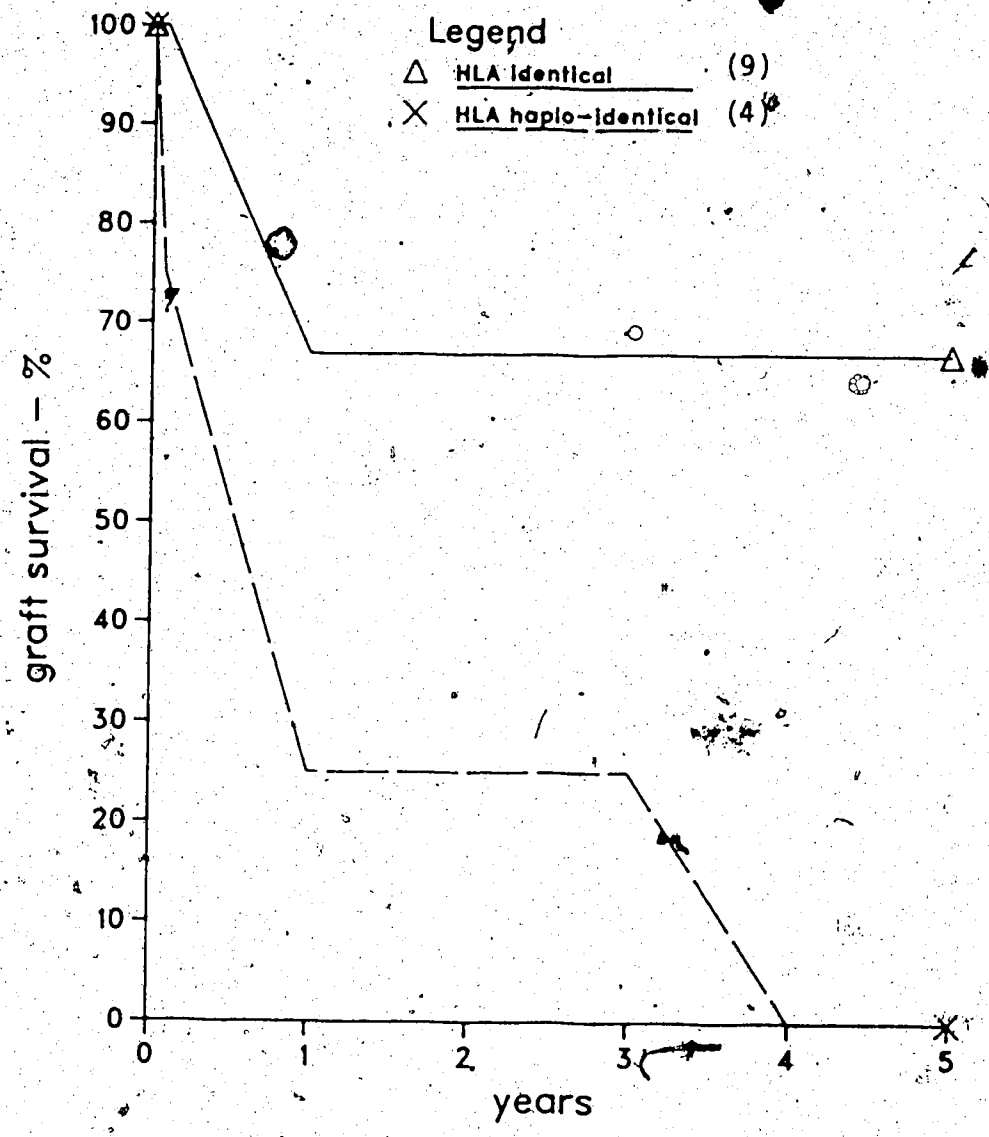


Figure 6.- Actuarial graft survival for HLA identical vs HLA haplo-identical kidney recipients in the first period (1967-1974).

7.

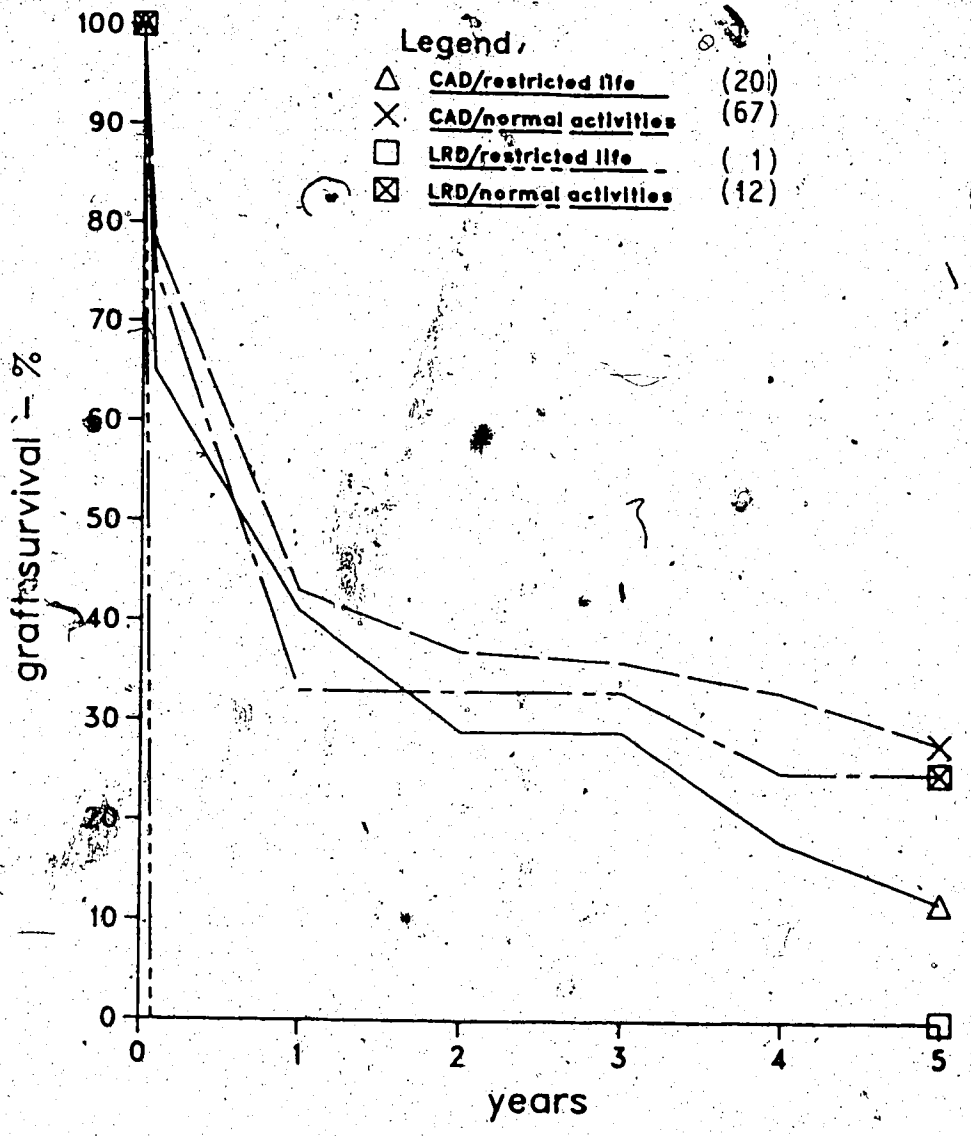


Figure 7.- Actuarial graft survival for CAD and LRD recipients in the first period (1967-1974) according to their life activity.

8.

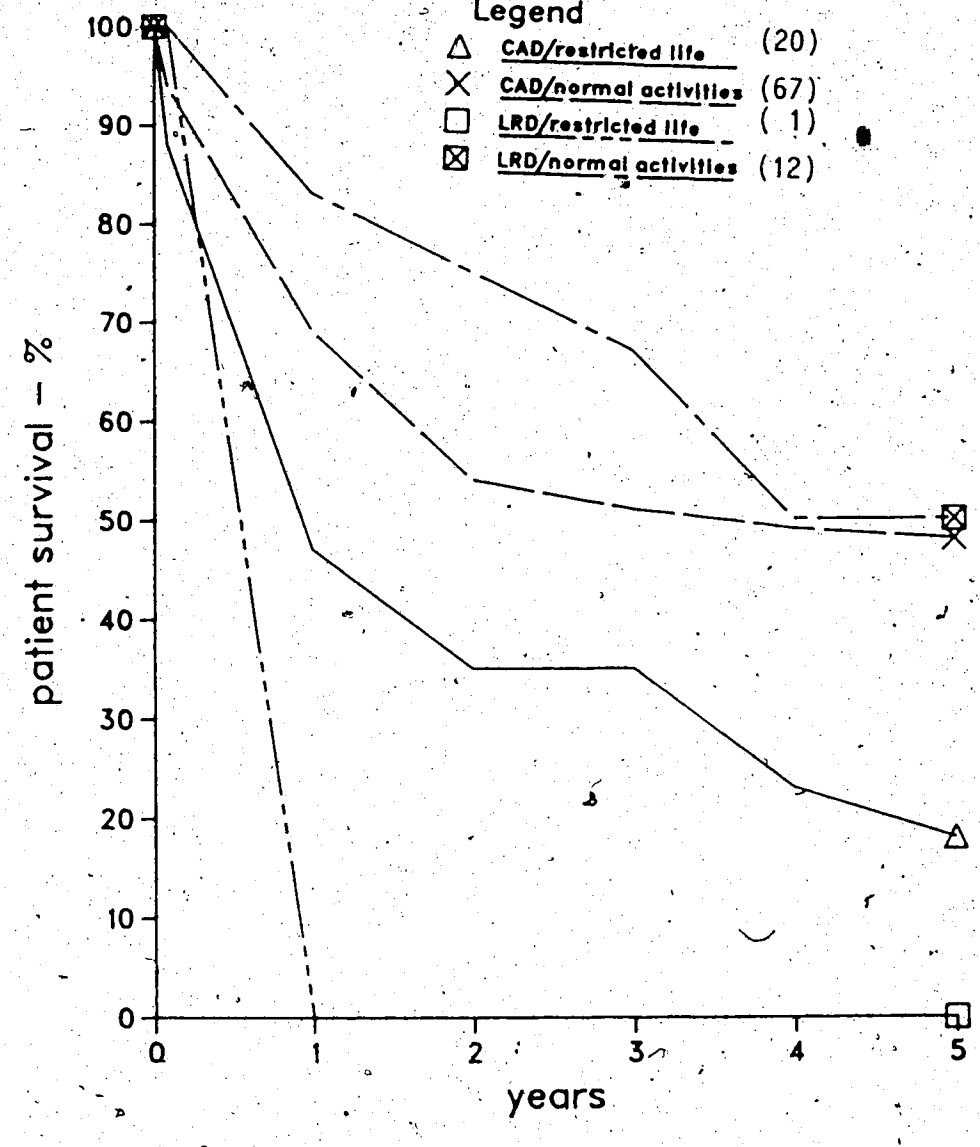


Figure 8.- Actuarial patient survival for CAD and LRD recipients in the first period (1967-1974) according to their life activity.

9.

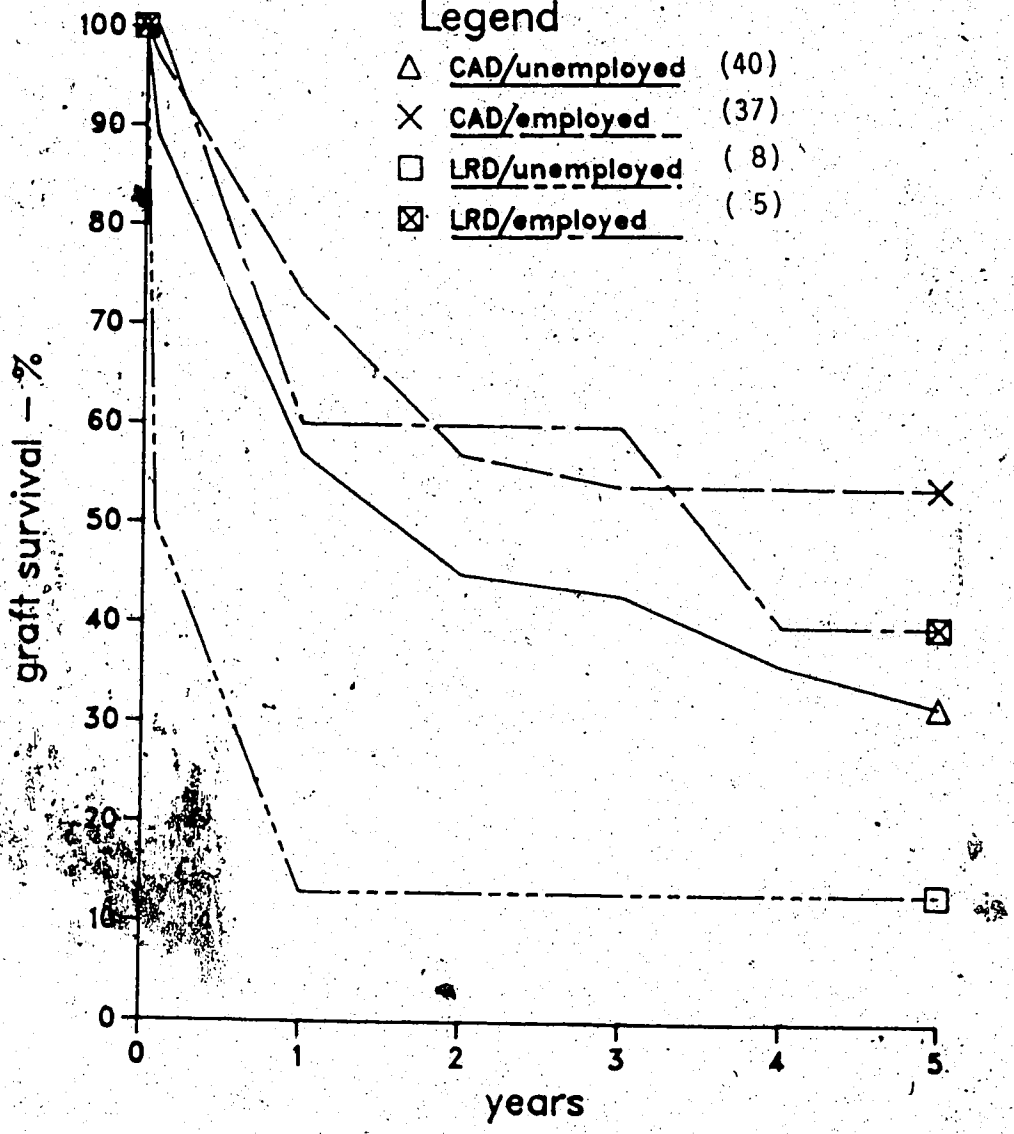


Figure 9.- Actuarial graft survival for CAD and LRD recipients in the first period (1967-1974) according to their professional status before transplant.

10.

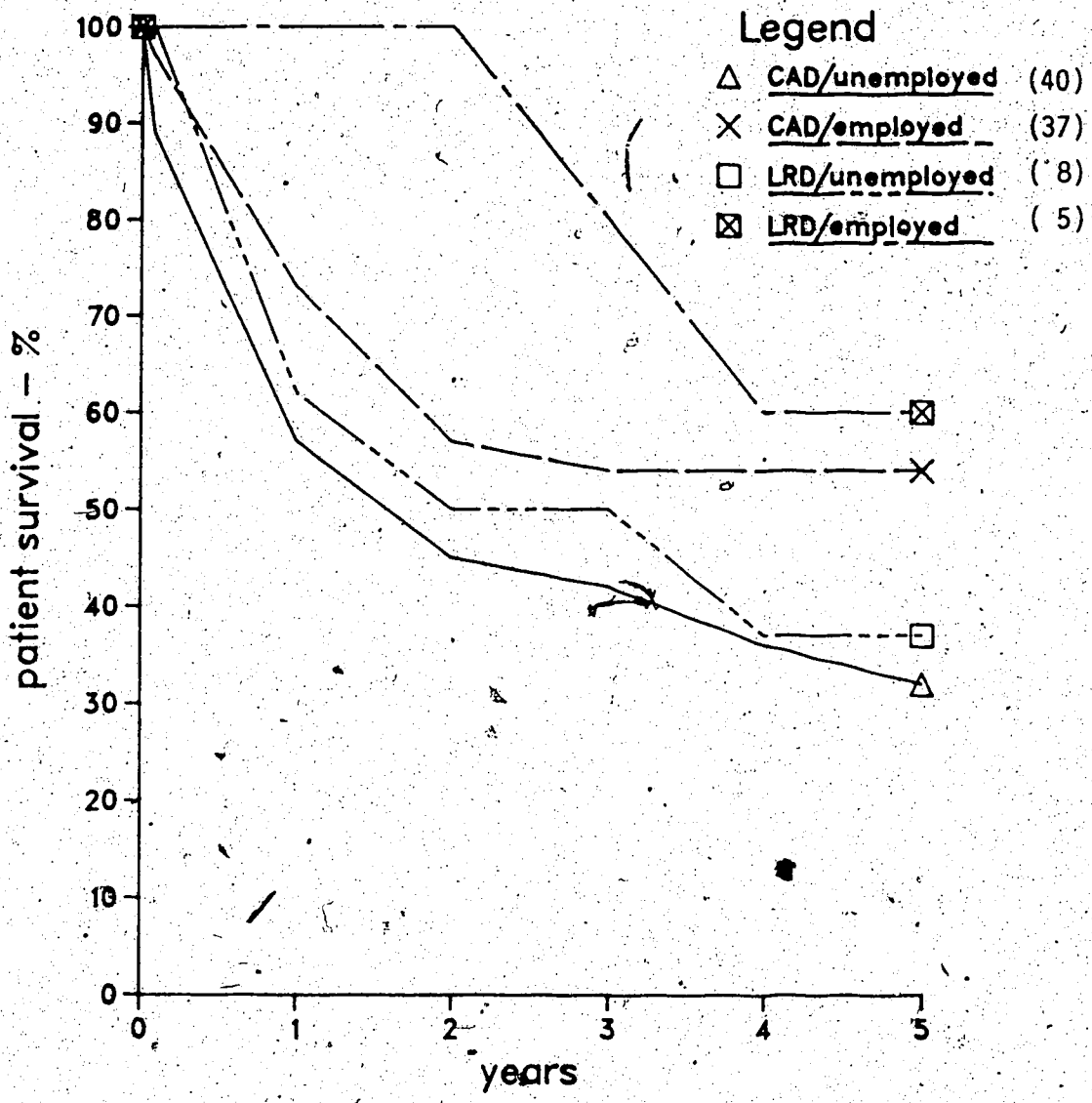


Figure 10.- Actuarial patient survival for CAD and LRD recipients in the first period (1967-1974) according to their professional status before transplant.

11.

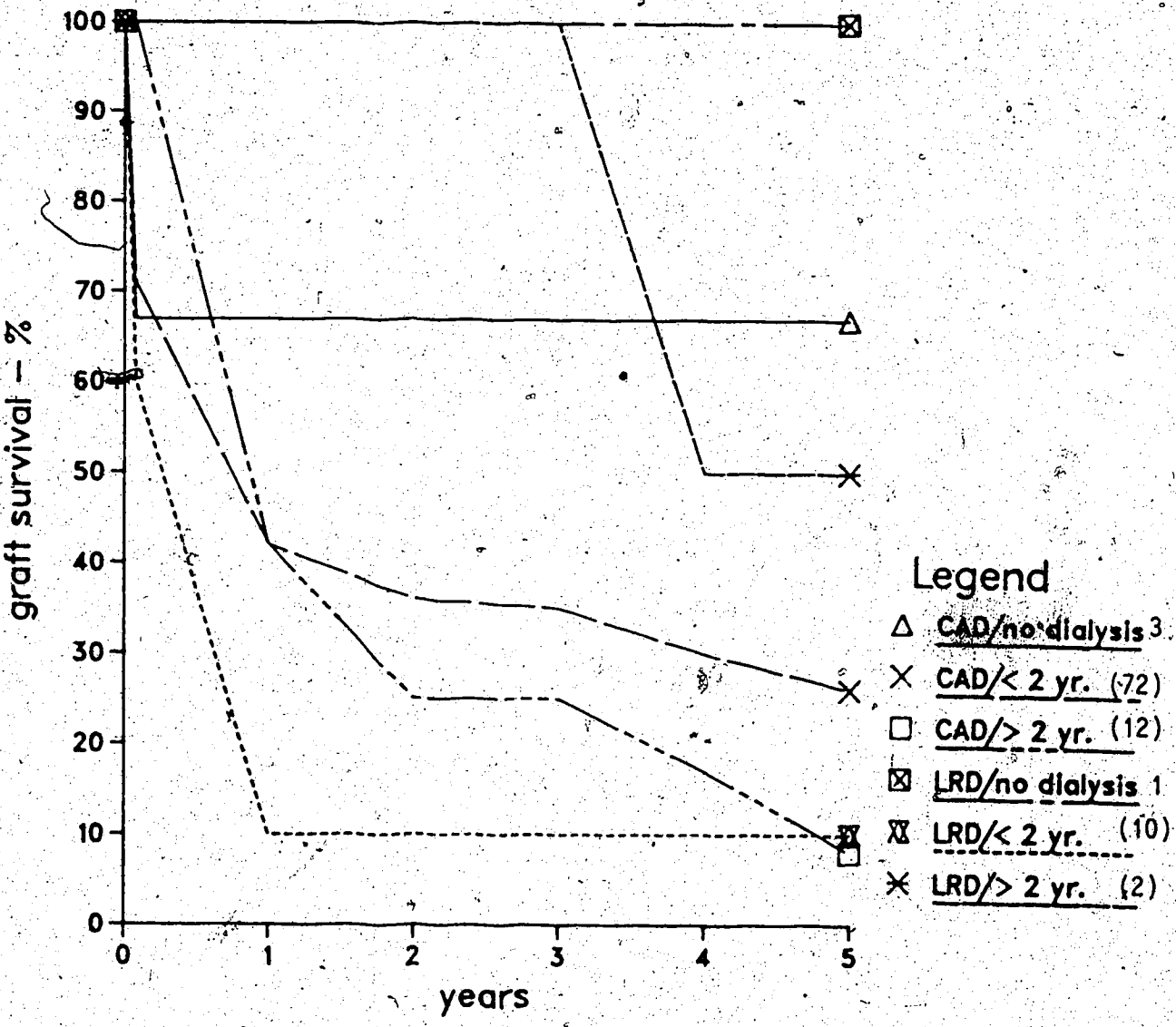


Figure 11.- Actuarial graft survival for CAD and LRD recipients in the first period (1967-1974) according to the time on dialysis before transplant.

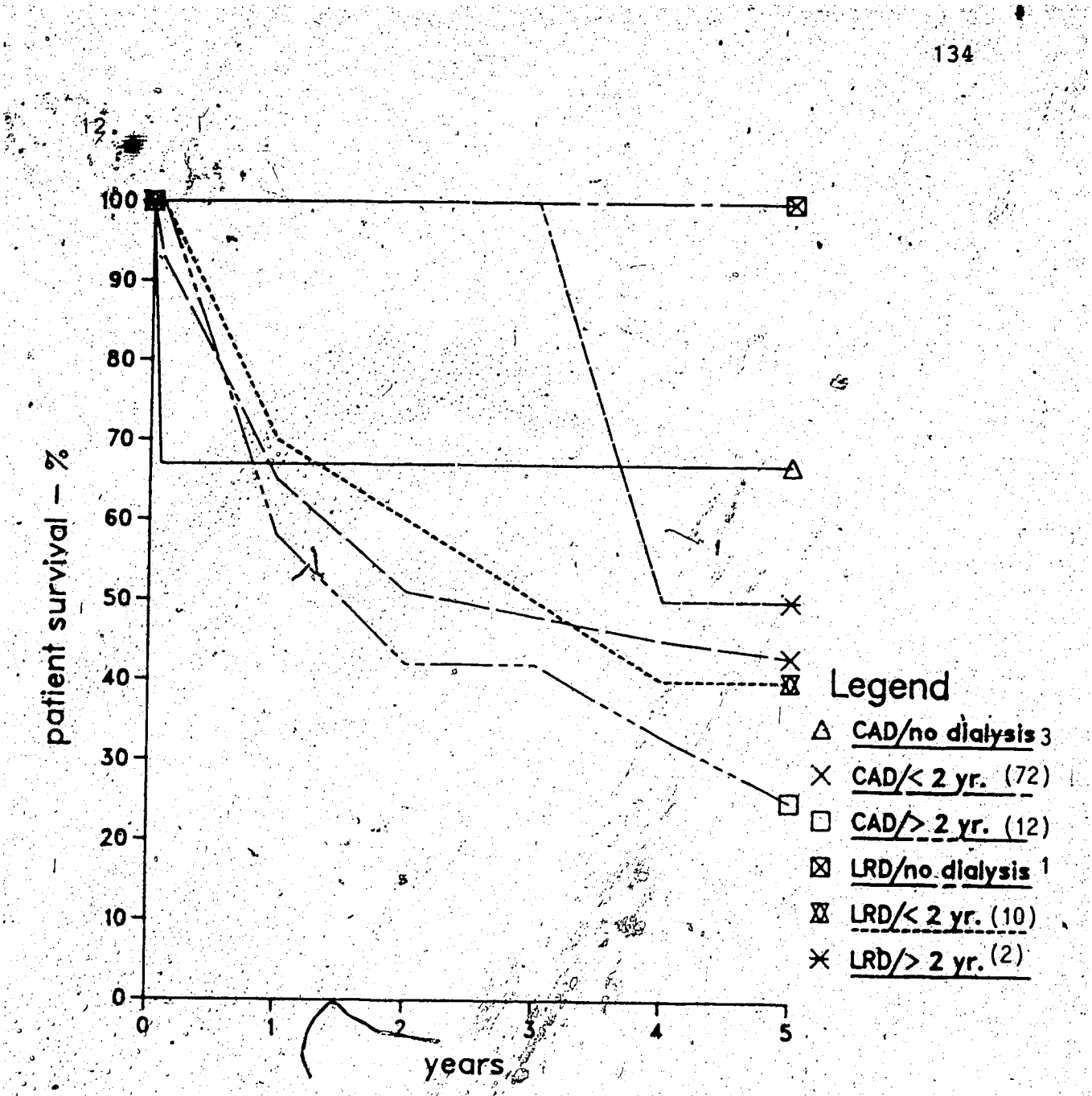


Figure 12.- Actuarial patient survival for CAD and LRD recipients in the first period (1967-1974) according to the time on dialysis before transplant.

13.

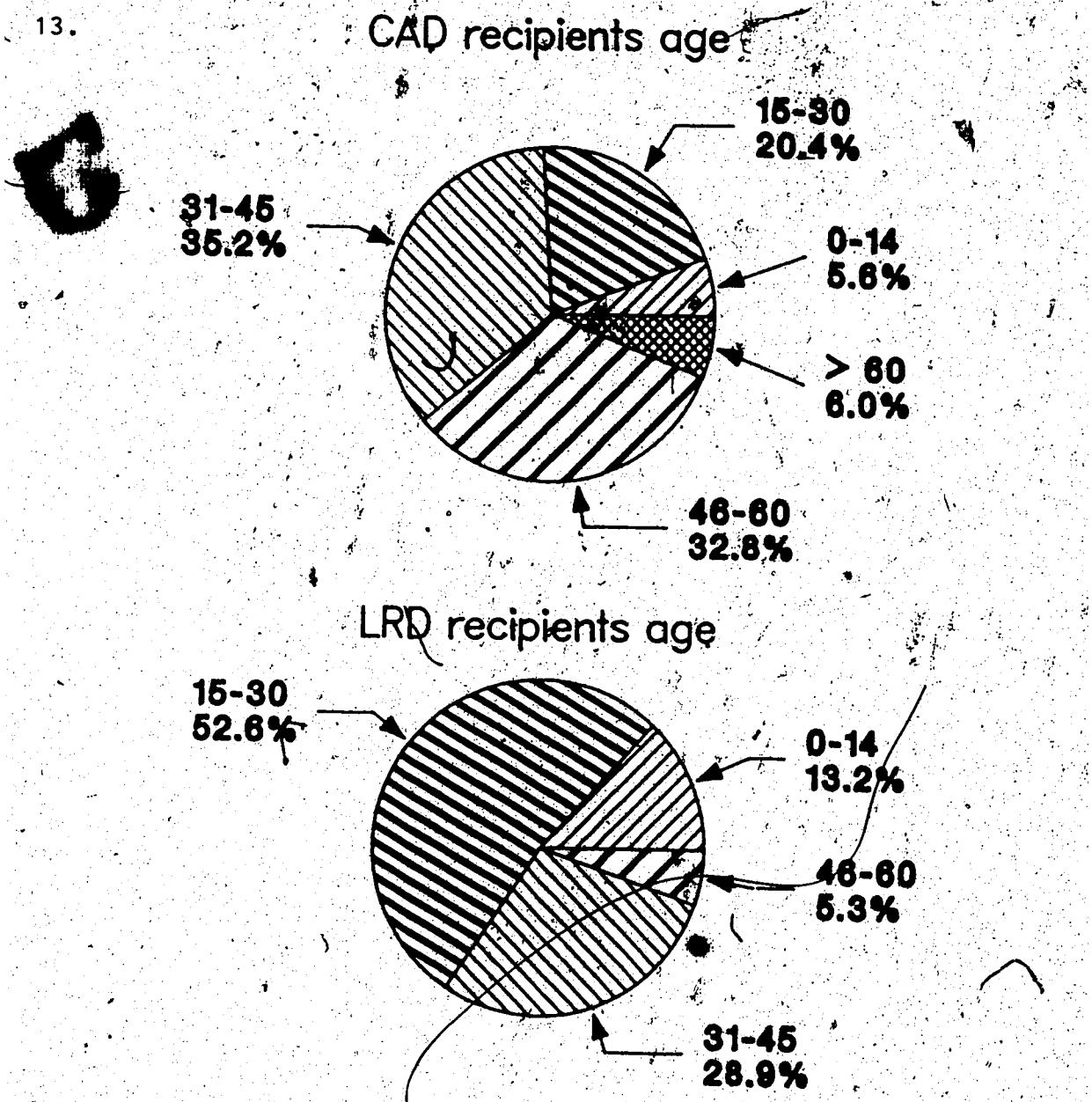


Figure 13.- Percentage of age groups for CAD and LRD recipients in the second period (1975-1985).

14.

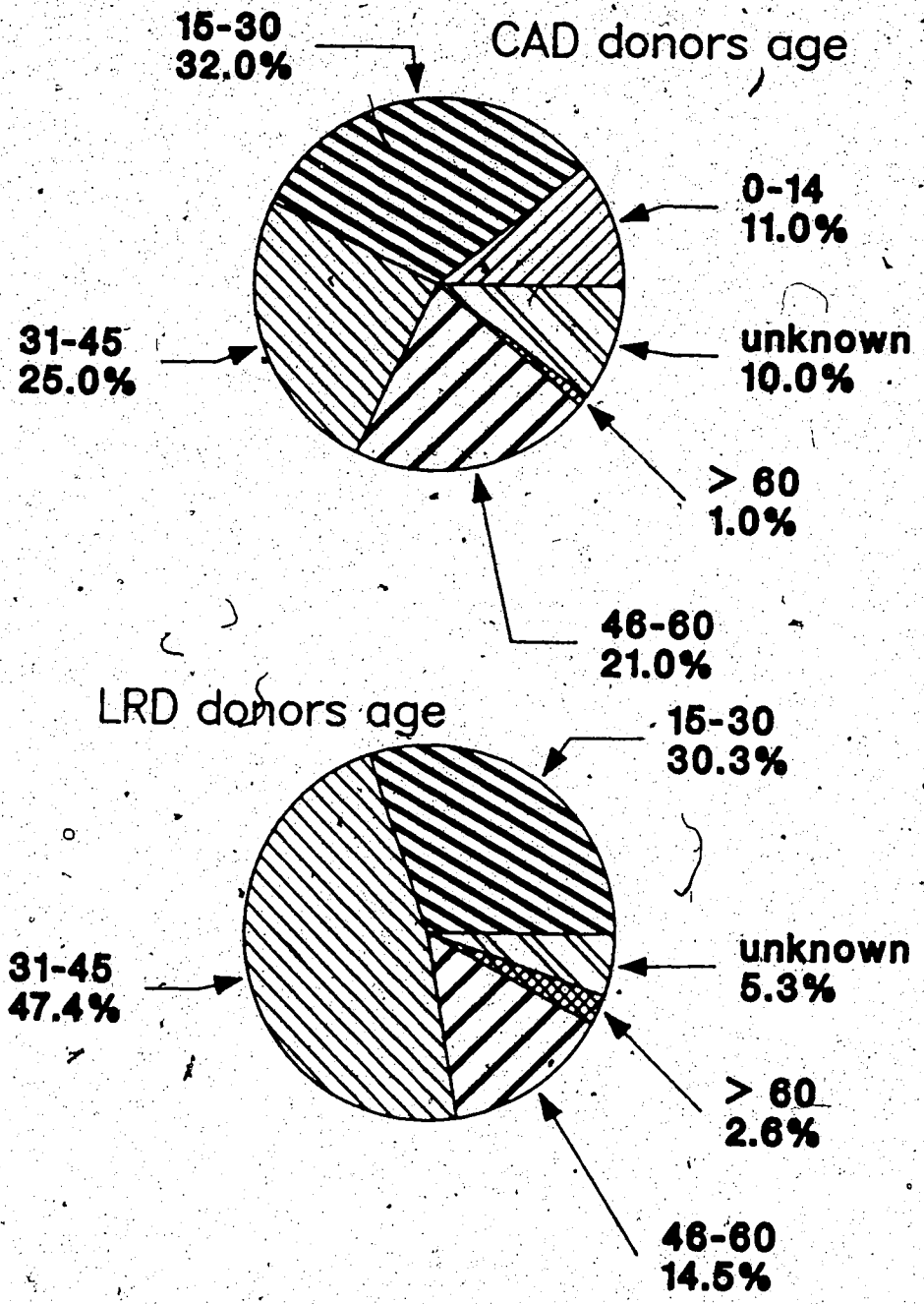


Figure 14.- Percentage of age groups for CAD and LRD donors in the second period (1975-1985).

15.

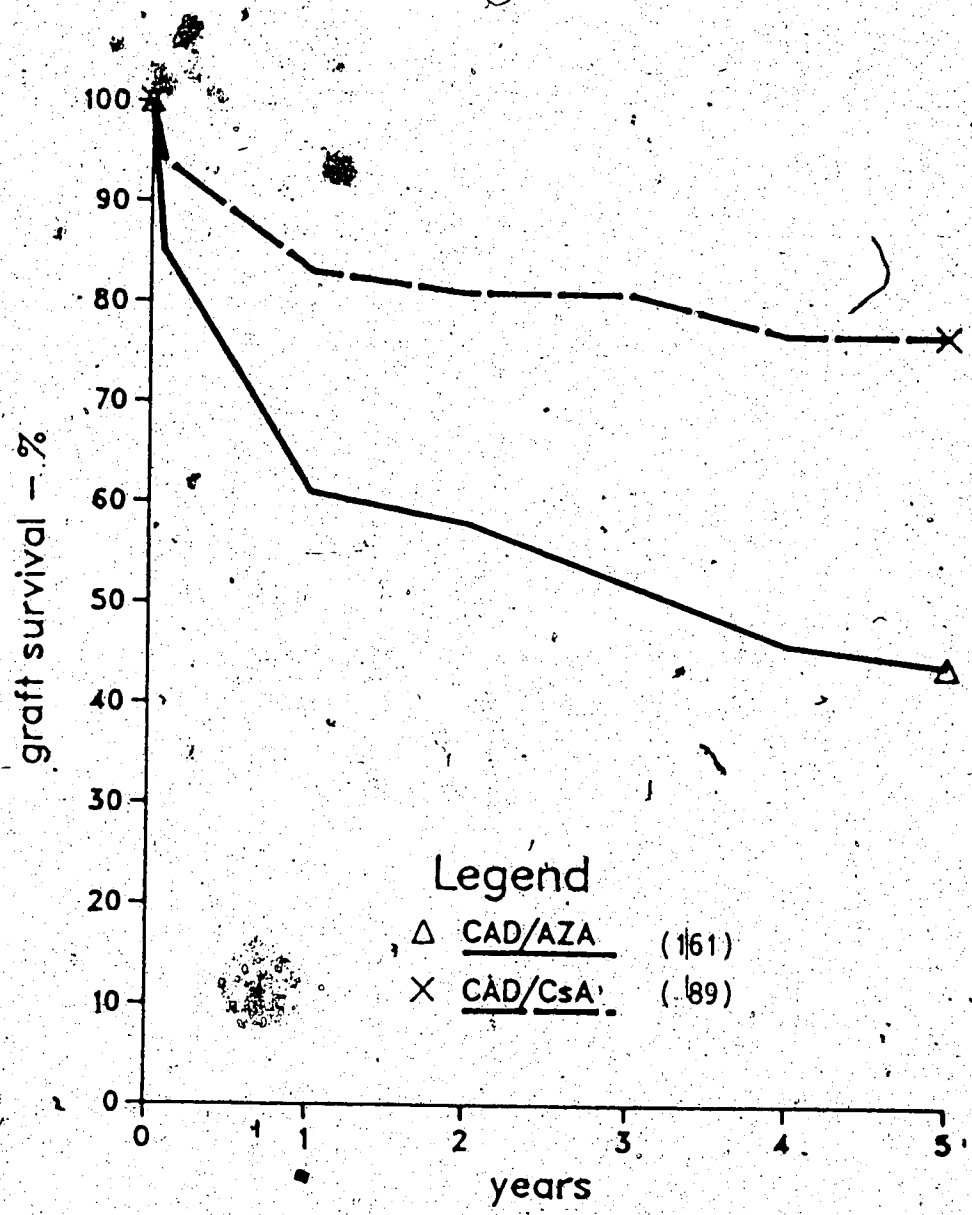


Figure 15.- Actuarial graft survival for CAD renal recipients on CsA vs those on AZA during the second period (1975-1985)($p<0.001$).

16.

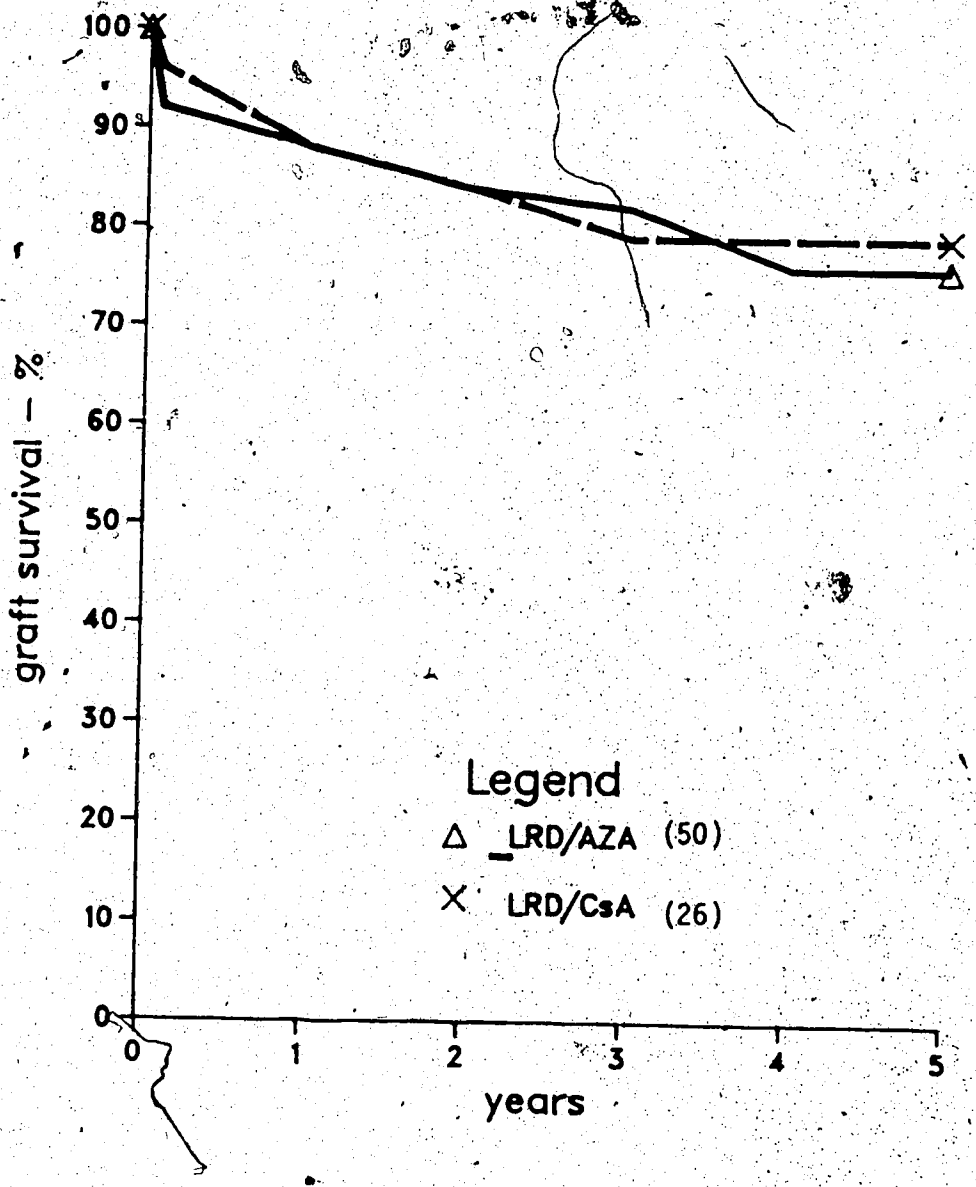


Figure 16.- Actuarial graft survival for LRD renal recipients on CsA vs those on AZA during the second period (1975-1985)(p NS).

17.

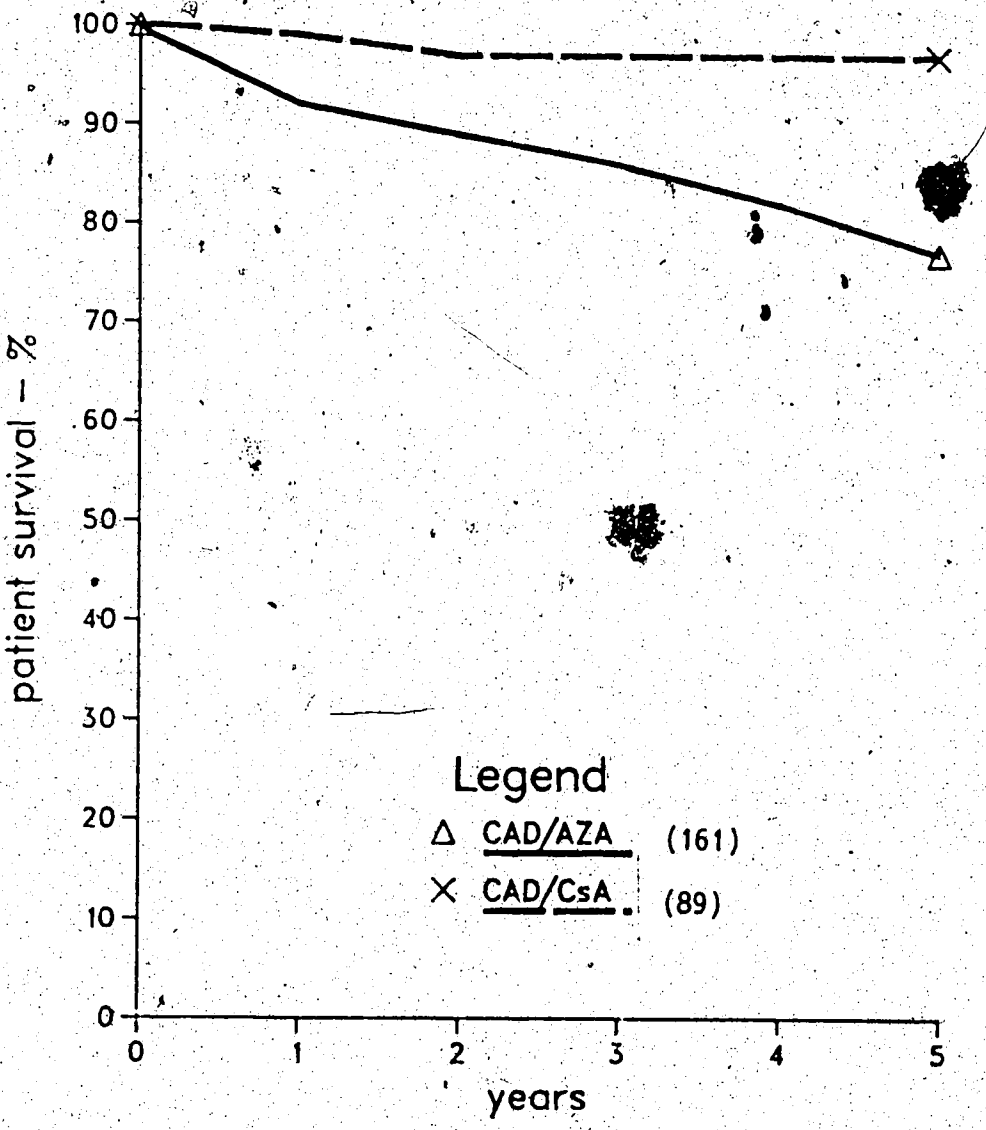


Figure 17.- Actuarial patient survival for CAD renal recipients on CsA vs those on AZA during the second period (1975-1985) ($p<0.001$).

18.

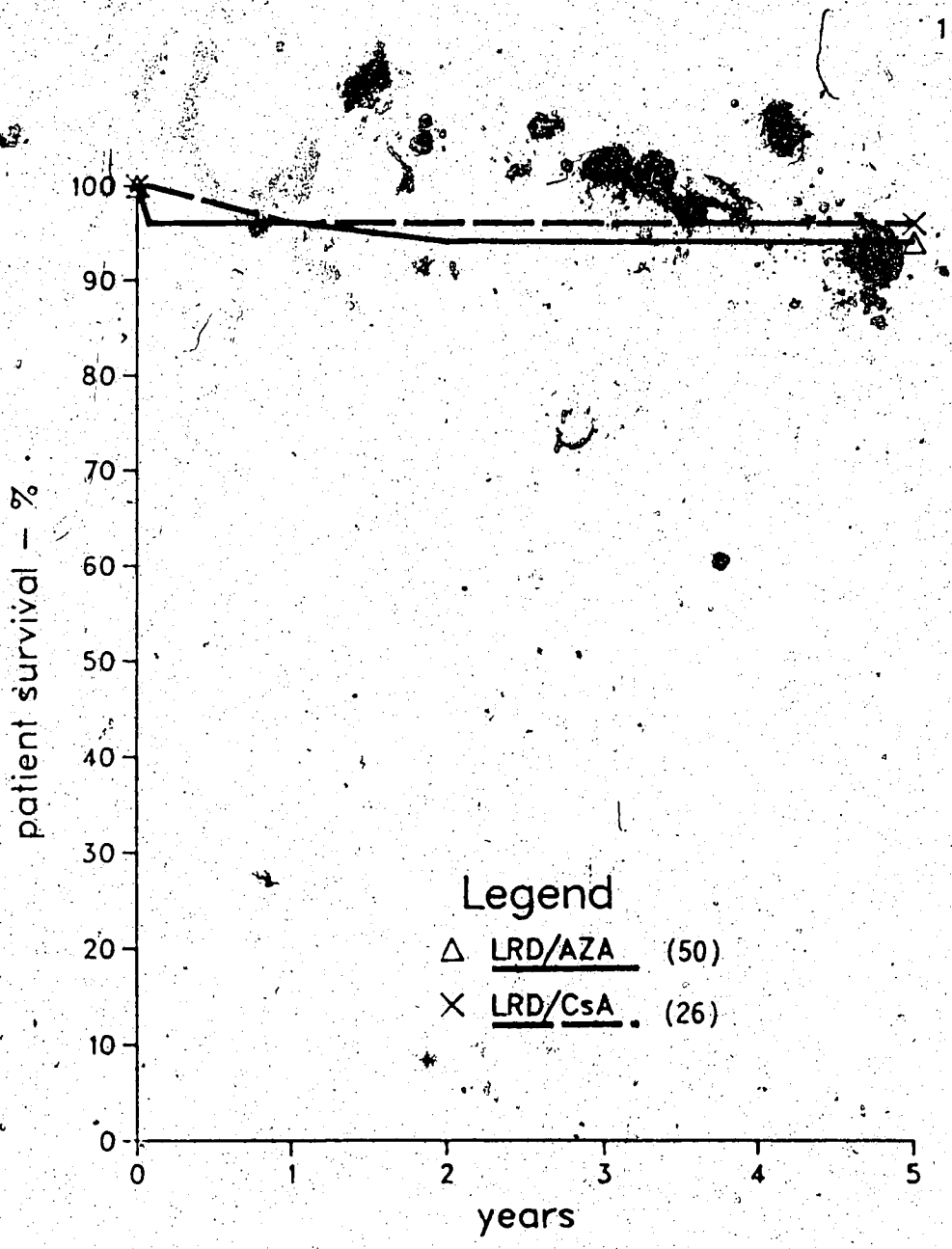


Figure 18.- Actuarial patient survival for LRD renal recipients on CsA vs those on AZA during the second period (1975-1985) (p NS).

19.

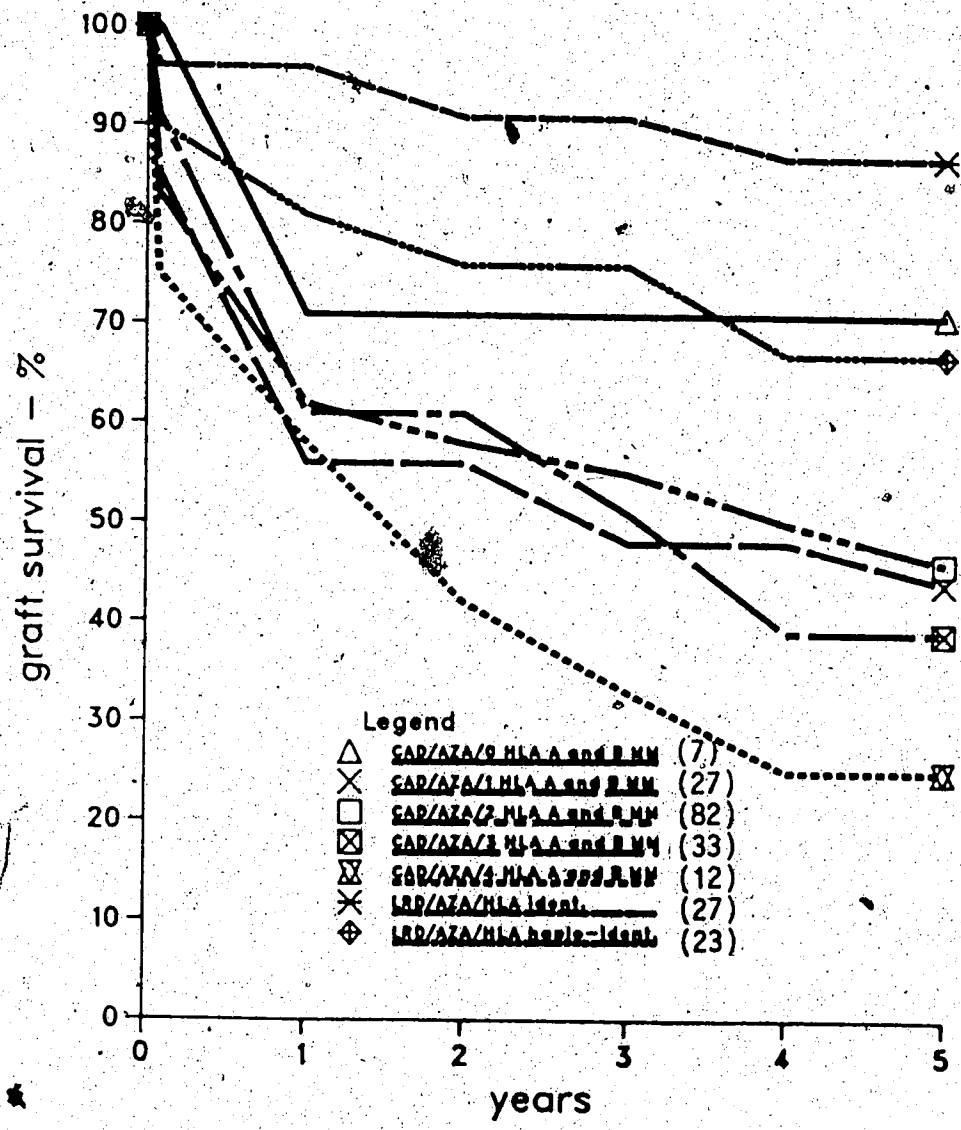


Figure 19.- Actuarial graft survival for renal transplants on AZA during the second period (1975-1985) according to the number of mismatches for HLA A and B antigens (p = 0.05 between 0 and 4 mismatches).

20.

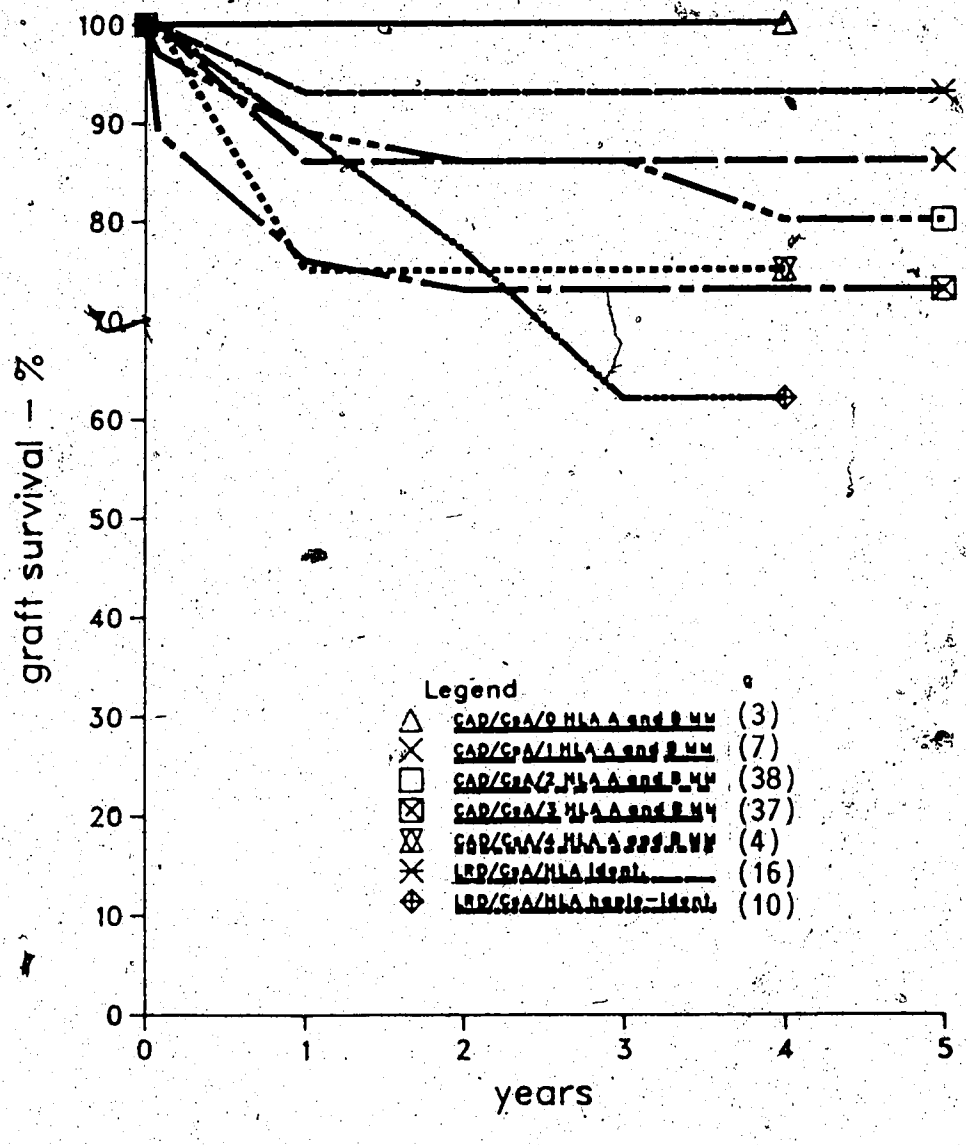


Figure 20.- Actuarial graft survival for renal transplants on CsA during the second period (1975-1985) according to the number of mismatches for HLA A and B antigens (p NS).

21.

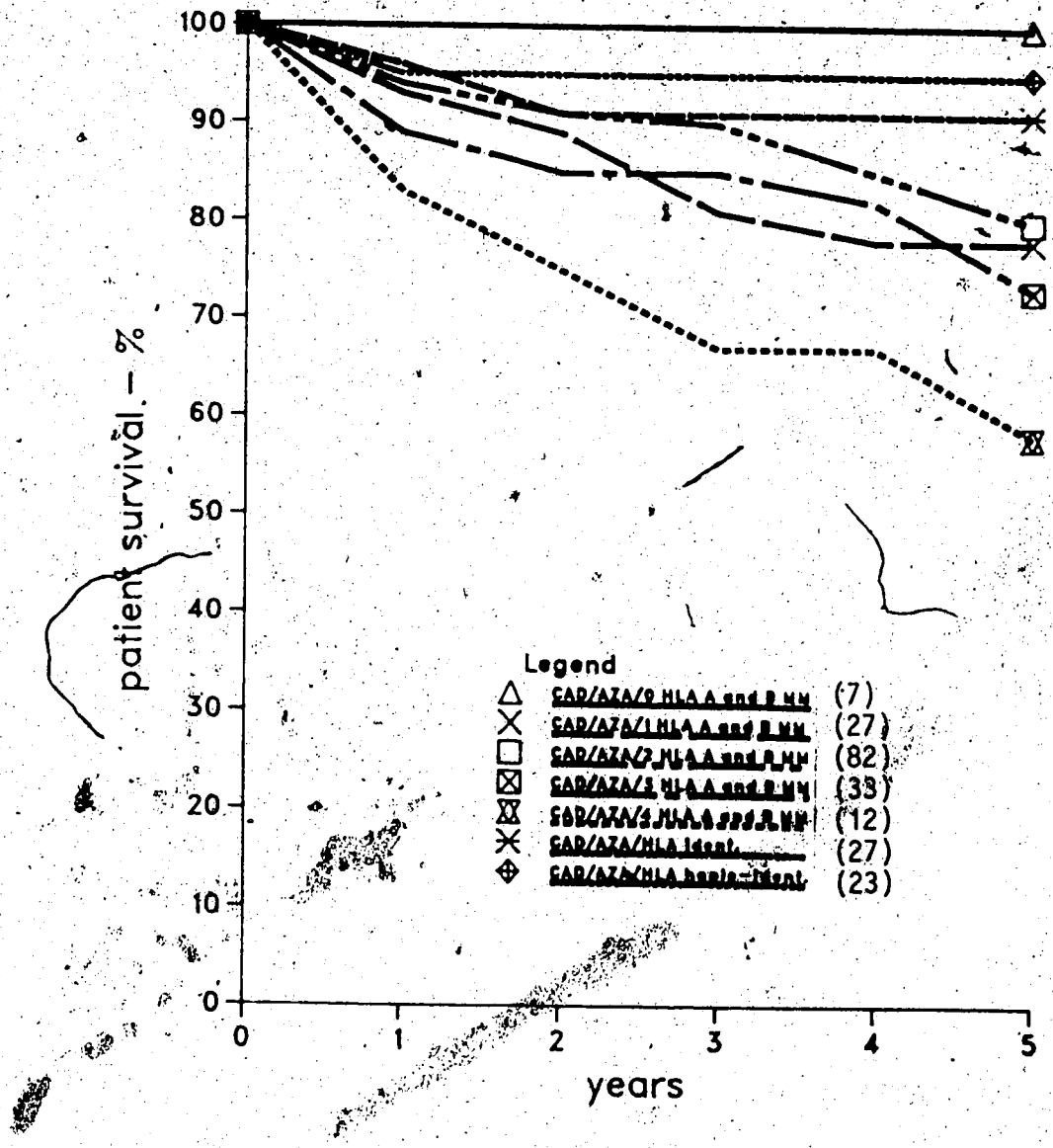


Figure 21.- Actuarial patient survival for renal transplants on AZA during the second period (1975-1985) according to the number of mismatches for HLA A and B antigens ($p<0.05$ between 0 and 4 mismatches).

22.

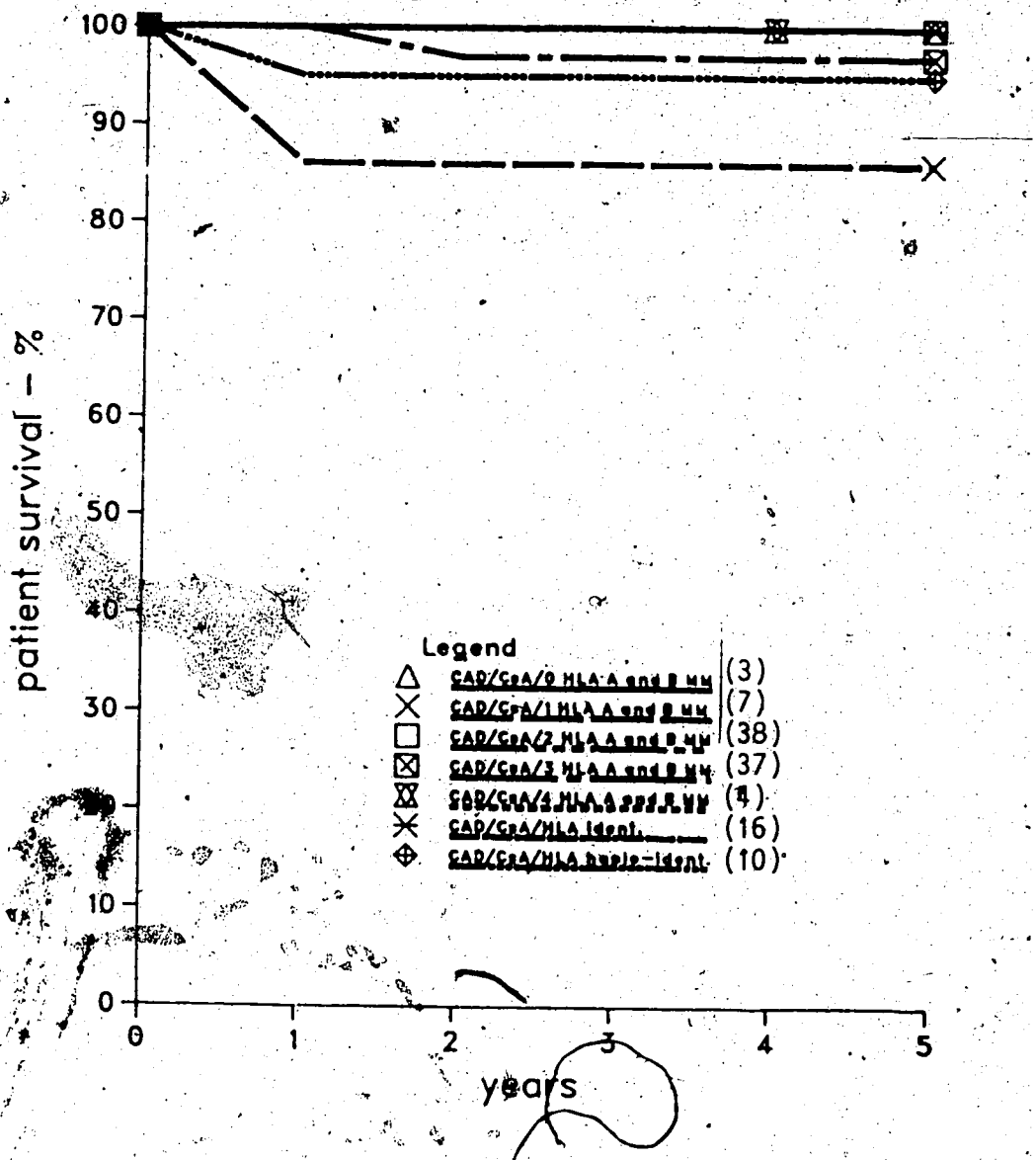


Figure 22.- Actuarial patient survival for renal transplants on CsA during the second period (1975-1985) according to the number of mismatches for HLA A and B antigens (p NS).

23.

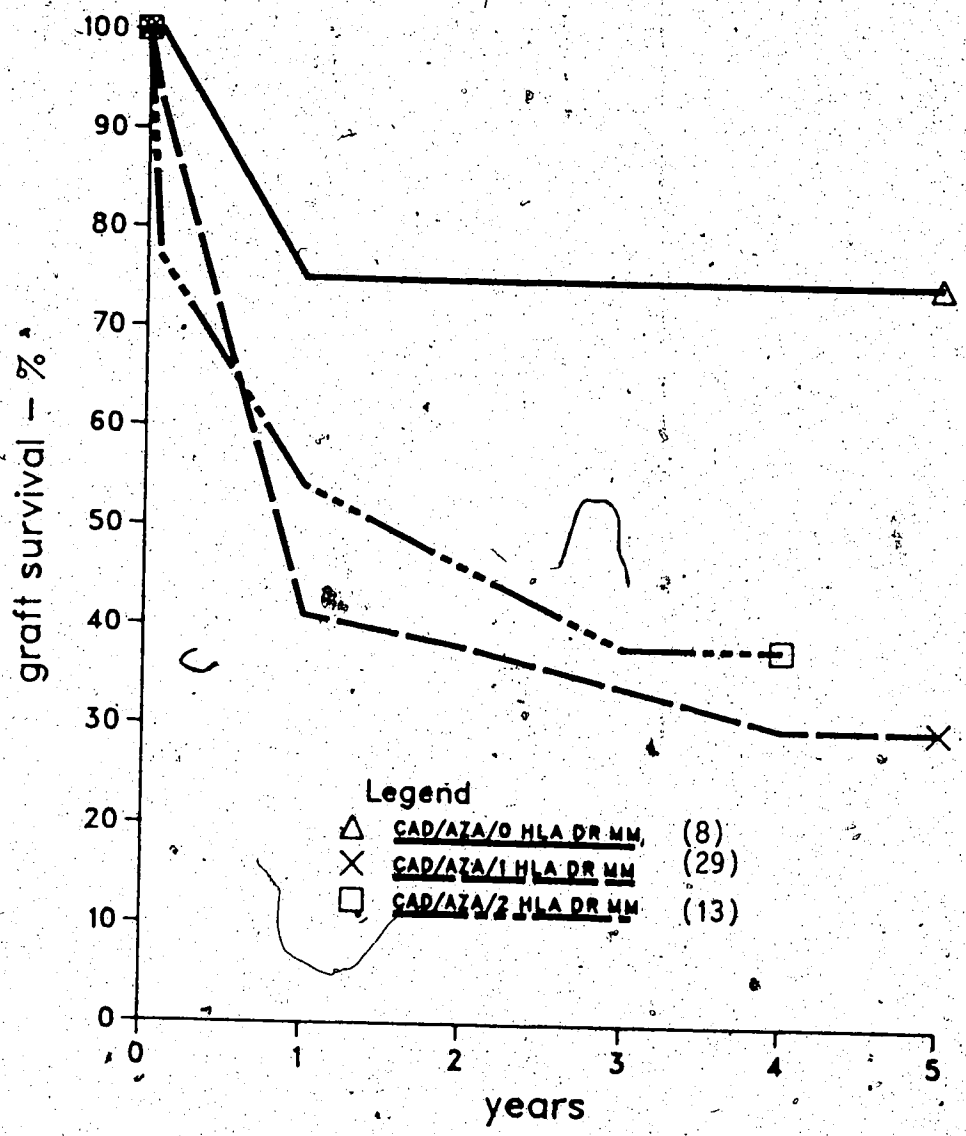


Figure 23.- Actuarial graft survival for CAD renal transplants on AZA during the second period (1975-1985) according to HLA DR mismatches ($P<0.05$ between 0 and 1 or 2 mismatches).

24.

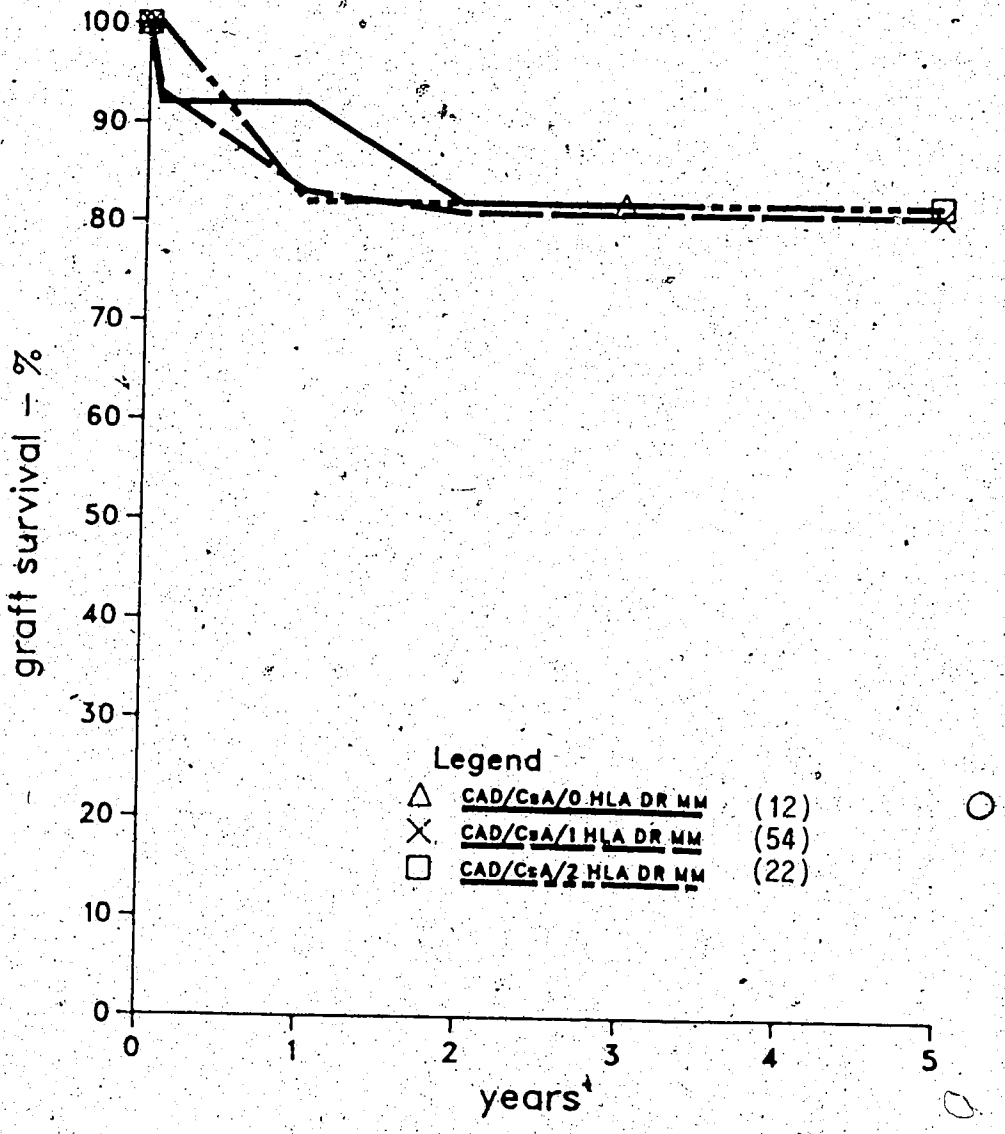


Figure 24.- Actuarial graft survival for CAD renal transplants on CsA during the second period (1975-1985) according to HLA DR mismatches (P NS).

25.

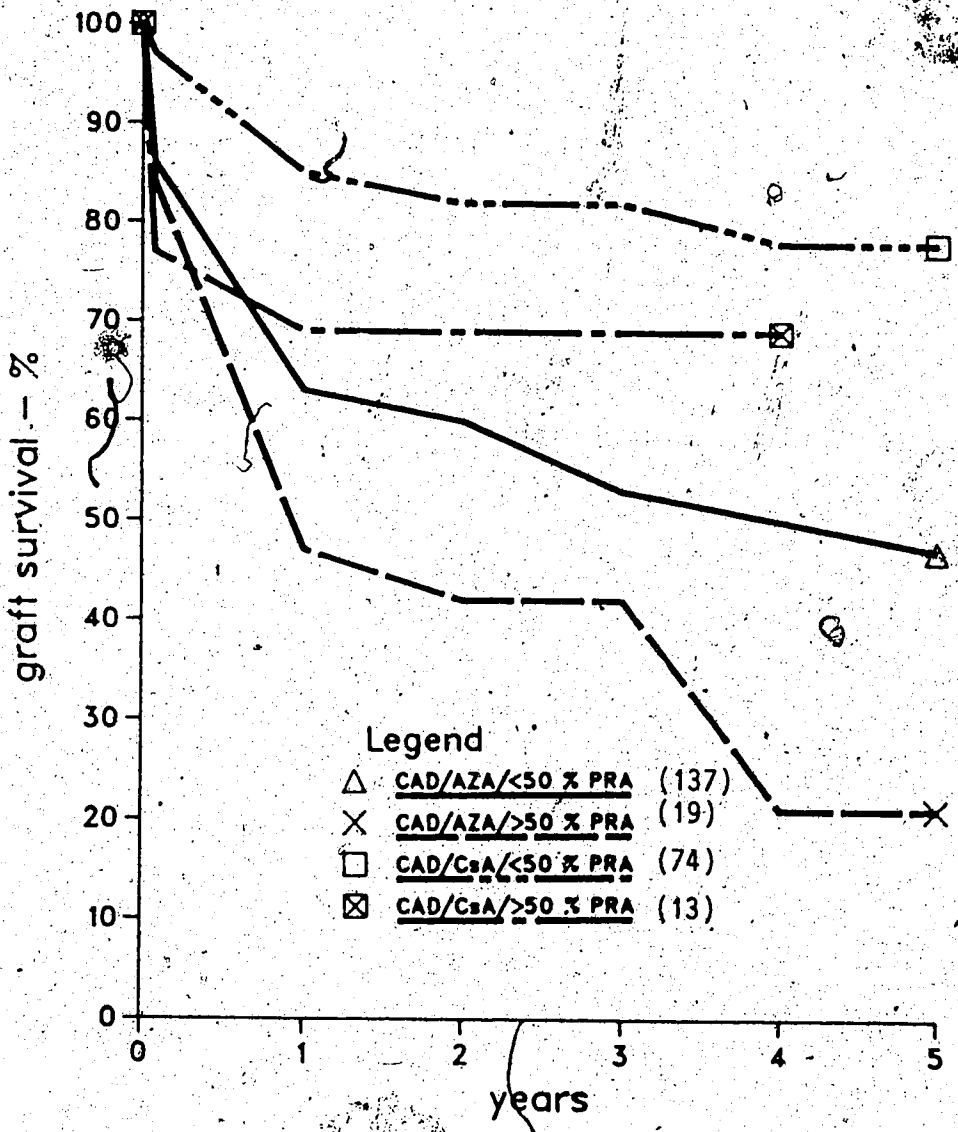


Figure 25.- Actuarial graft survival for CAD renal transplants during the second period (1975-1985) according to the their PRA and the immunosuppressive drug (p = 0.042 between those on AZA with more than 50 % and those with less than 50 %).

26.

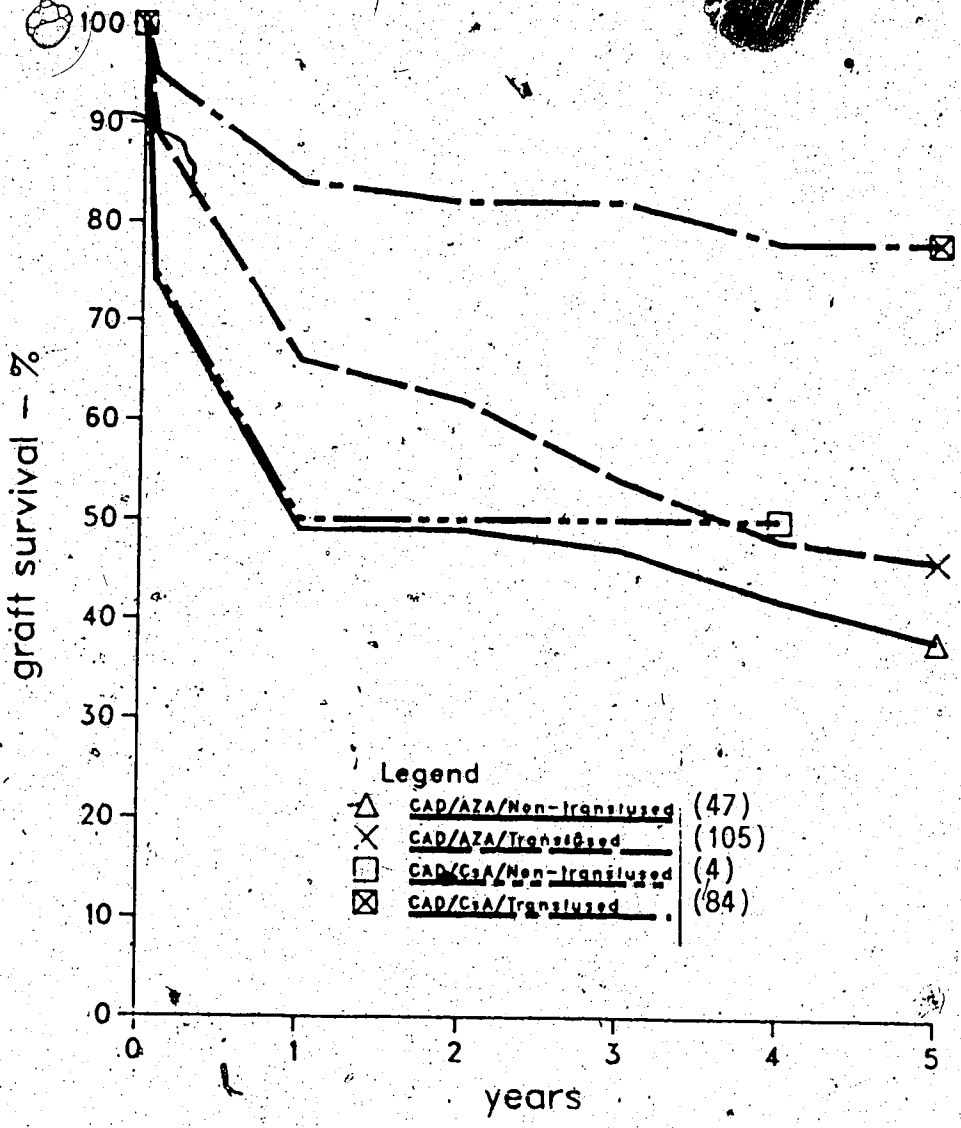


Figure 26.- Actuarial graft survival for CAD renal transplants during the second period (1975-1985) according to their pretransplant blood transfusion status (p NS between groups).

27.

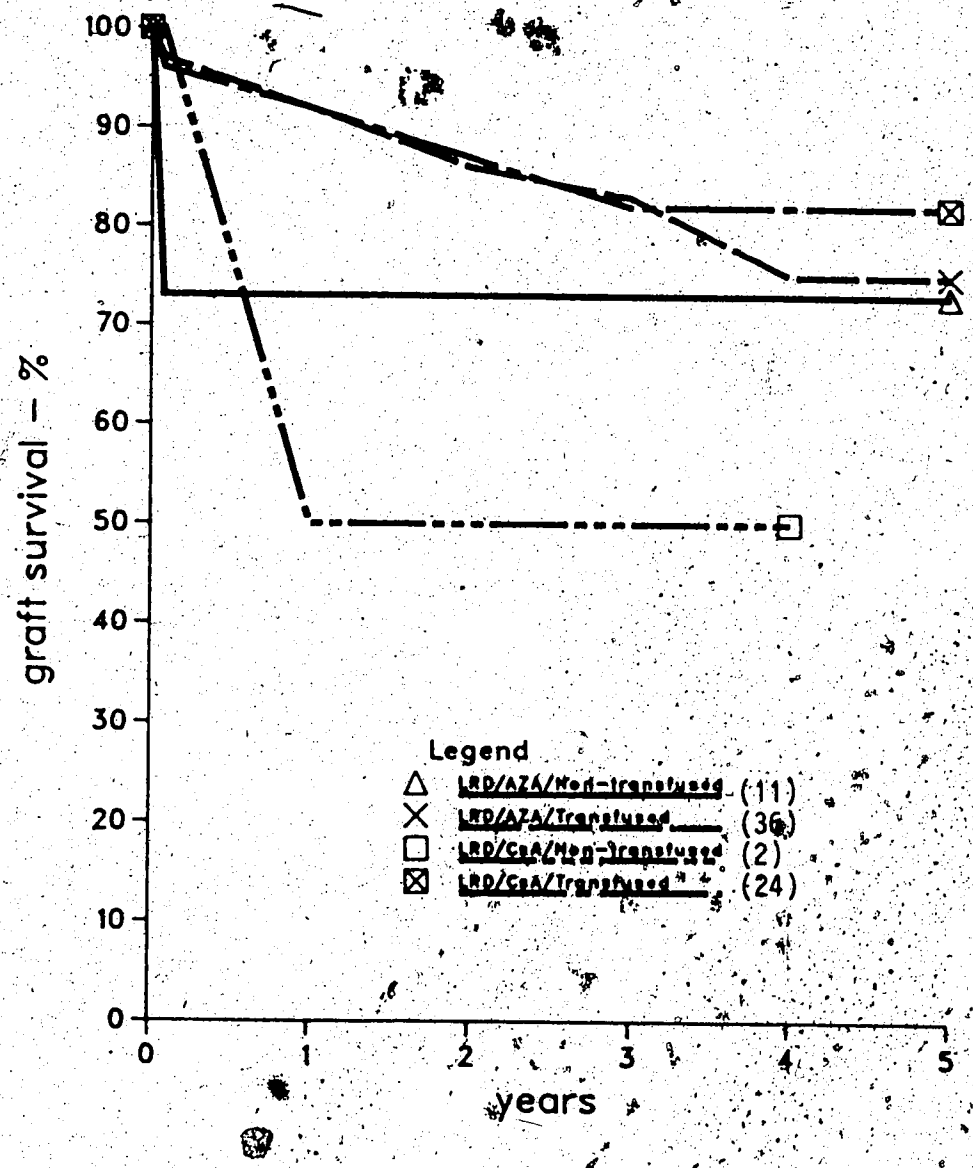


Figure 27. Actuarial graft survival for LRD renal transplants during the second period (1975-1985) according to their pretransplant blood transfusion status (p NS between groups).

28.

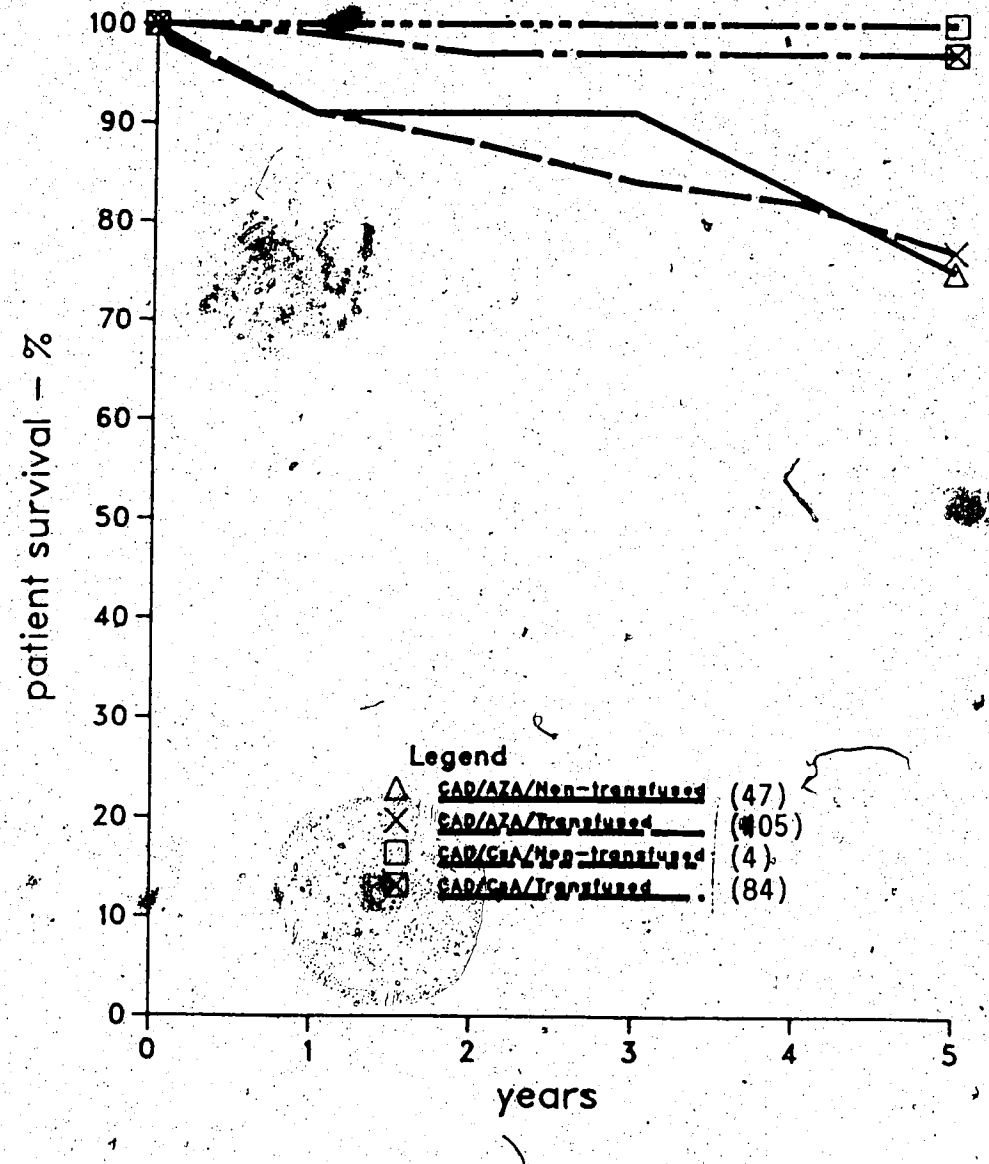


Figure 28.- Actuarial patient survival for CAD renal transplants during the second period (1975-1985) according to their pretransplant blood transfusion status (p NS between groups).

29.

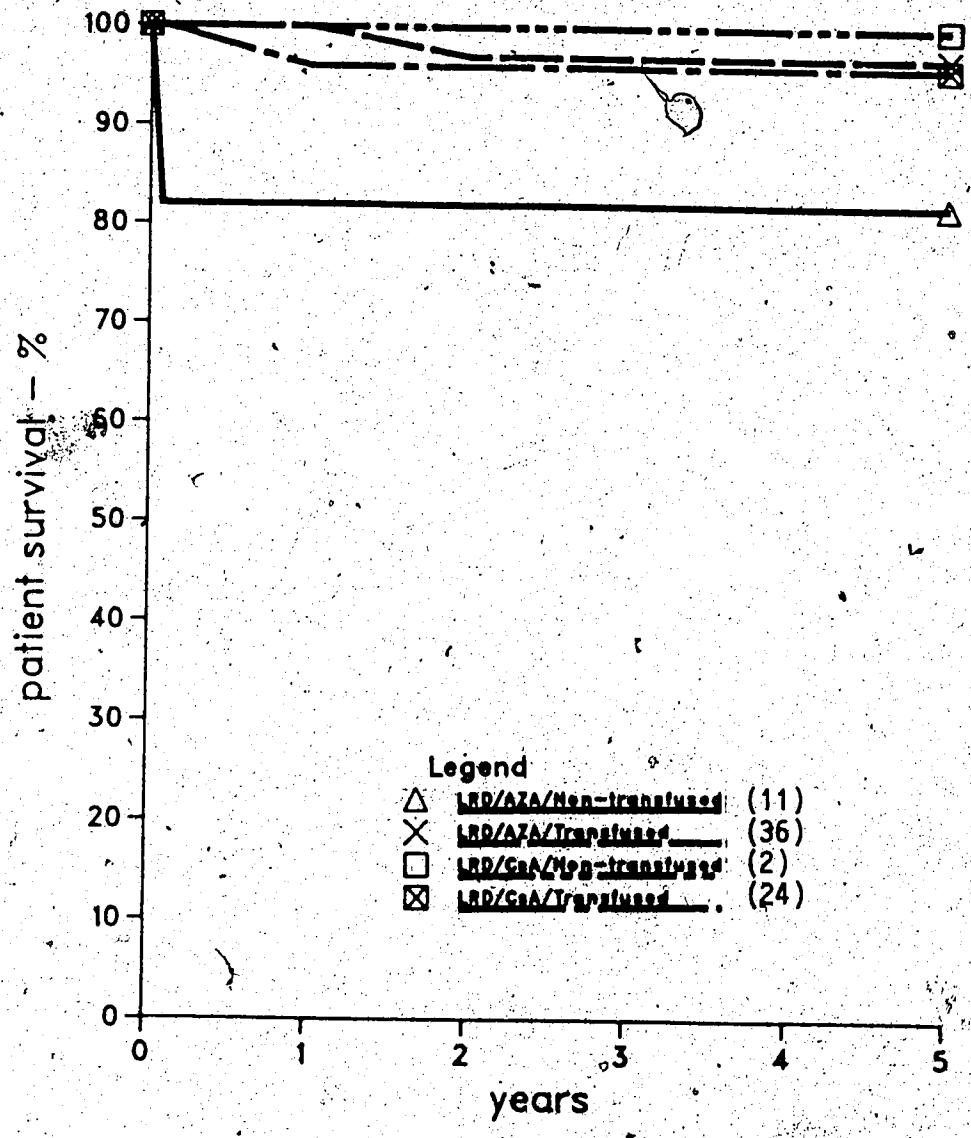


Figure 29.- Actuarial patient survival for LRD renal transplants during the second period (1975-1985) according to their pretransplant blood transfusion status (p. NS between groups).

30.

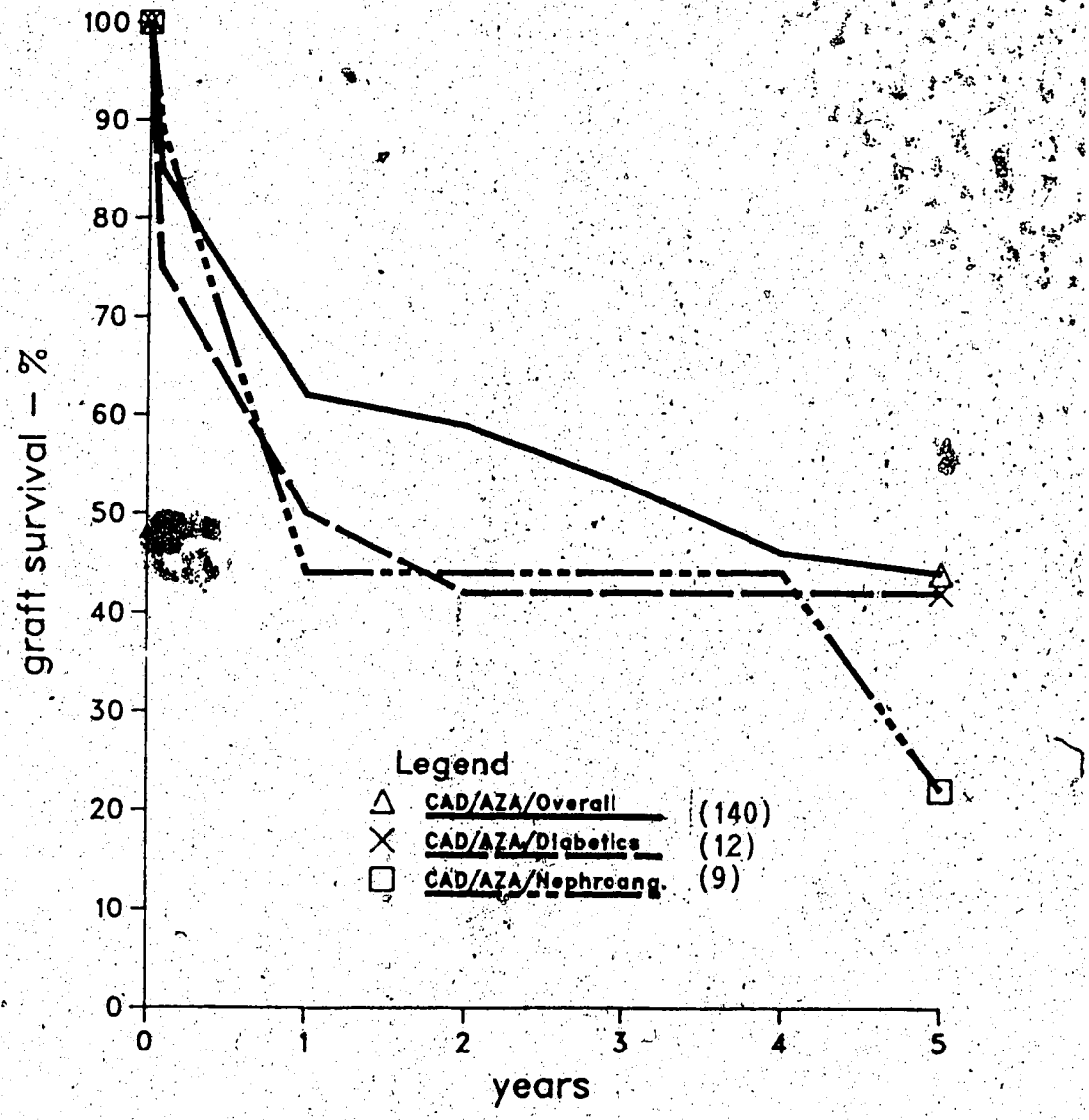


Figure 30.- Actuarial graft survival for diabetic and nephroangiosclerotic CAD renal transplants on AZA during the second period (1975-1985) compared to the overall population (p NS).

31.

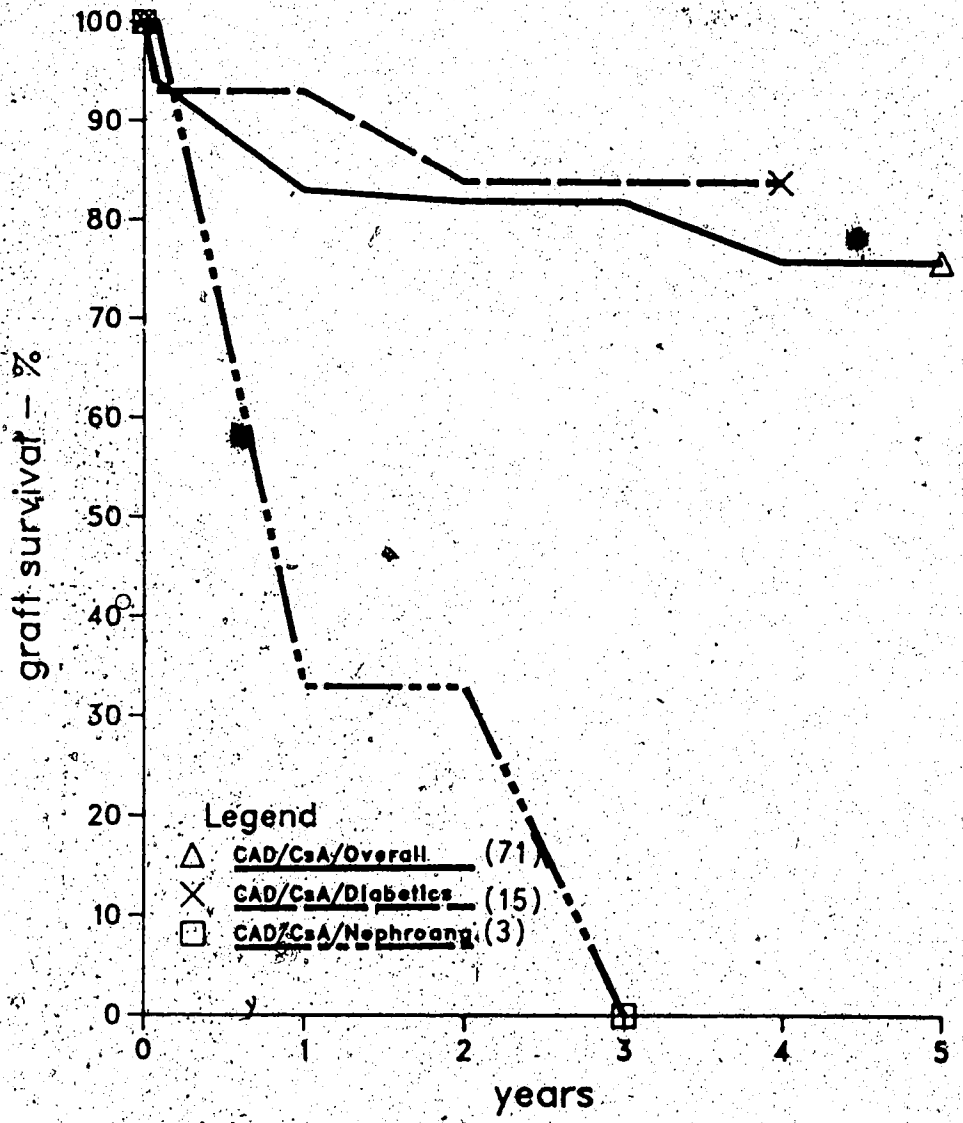


Figure 31.- Actuarial graft survival for diabetic and nephroangiosclerotic CAD renal transplants on CsA during the second period (1975-1985) compared to the overall population ($p = 0.0423$ for nephroangiosclerotic patients vs overall population).

32.

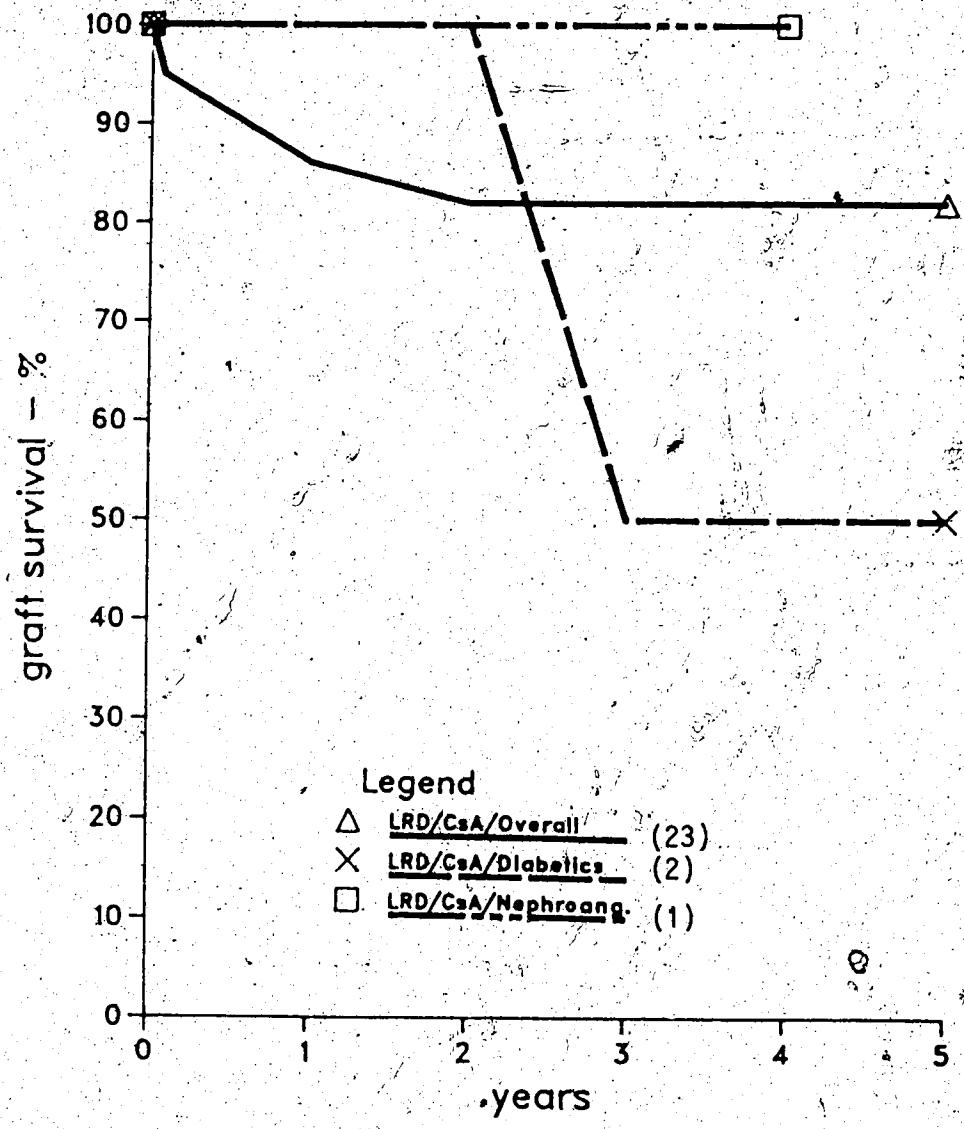


Figure 32.- Actuarial graft survival for diabetic and nephroangiosclerotic LRD renal transplants on CsA during the second period (1975-1985) compared to the overall population (p NS).

33.

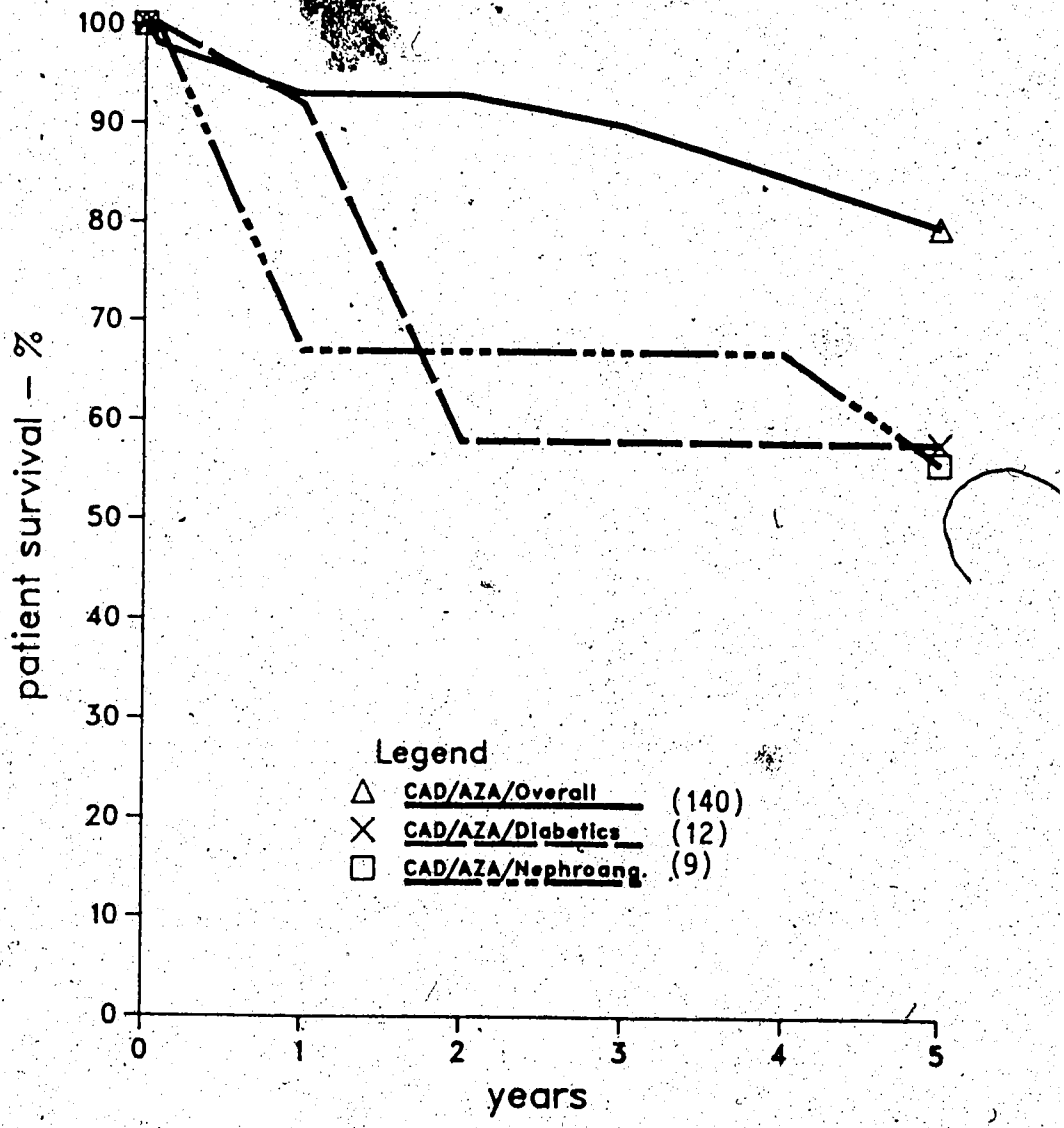


Figure 33.- Actuarial patient survival for diabetic and nephroangiosclerotic CAD renal transplants on AZA during the second period (1975-1985) compared to the overall population ($p = 0.05$ for diabetic vs overall population; $p = 0.001$ for nephroangiosclerosis vs overall population).

34.

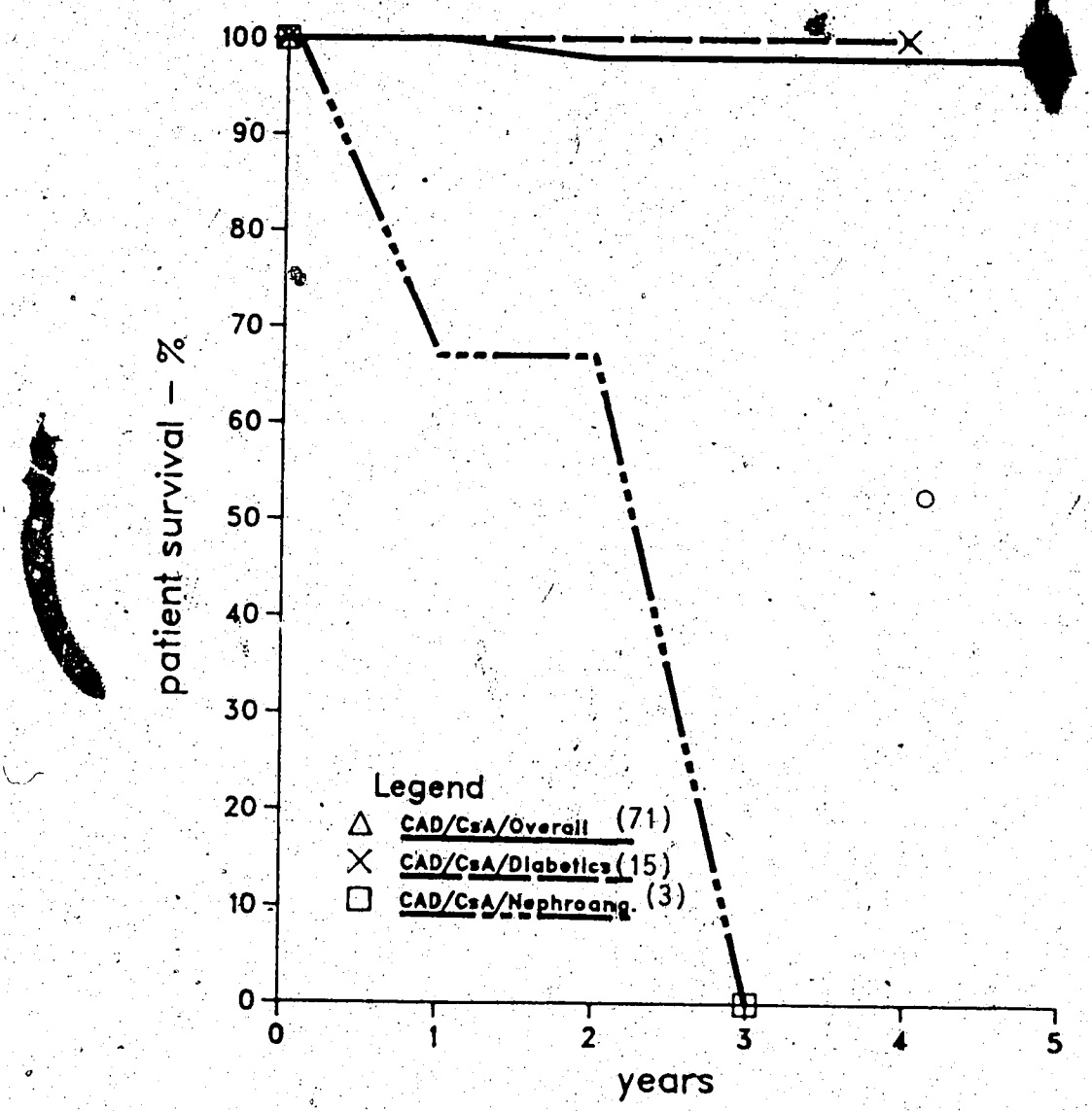


Figure 34.- Actuarial graft survival for diabetic and nephroangiosclerotic CAD renal transplants on CsA during the second period (1975-1985) compared to the overall population (p = 0.001 for nephroangiosclerotic patients vs overall population).

35.

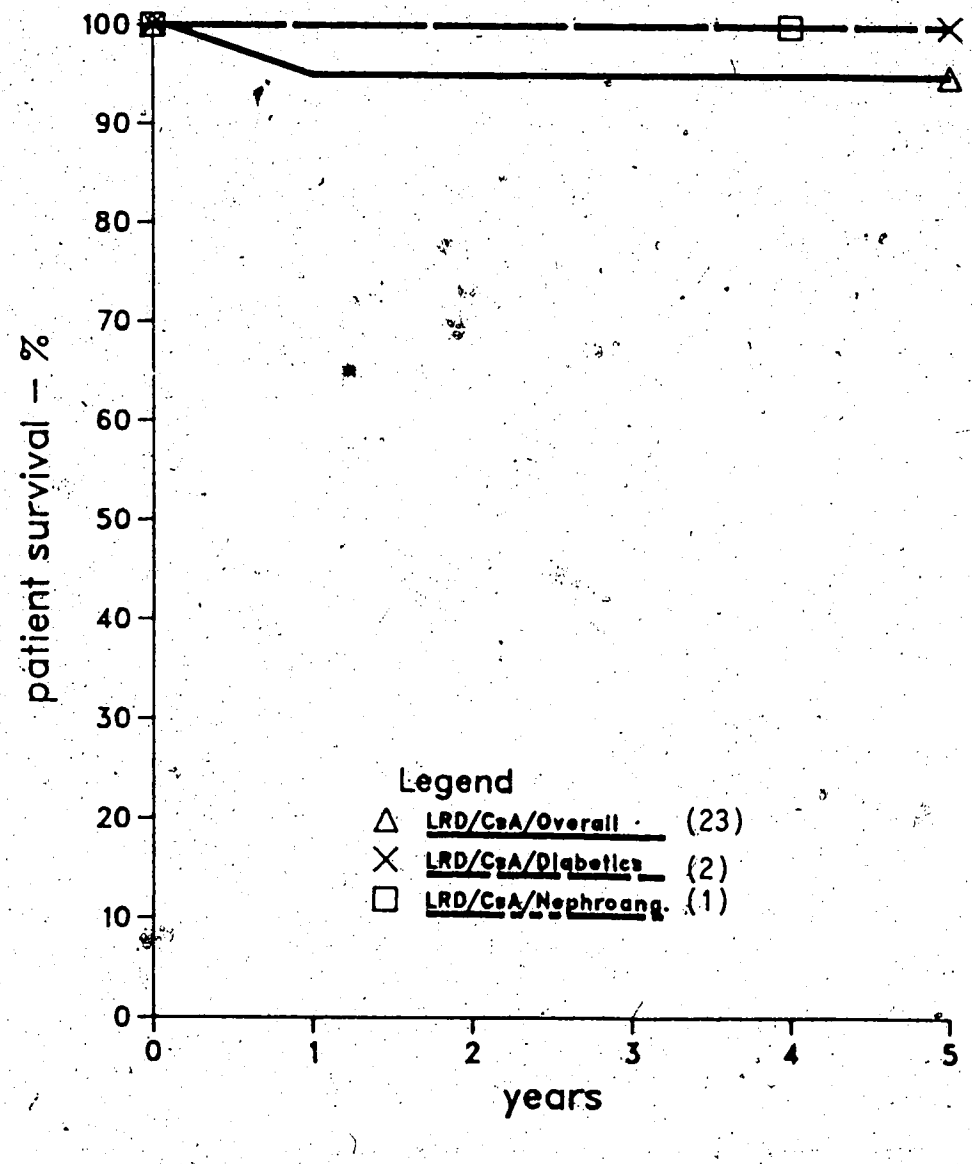


Figure 35.- Actuarial patient survival for diabetic and nephroangiosclerotic LRD renal transplants on CsA during the second period (1975-1985) compared to the overall population (p NS).

36.

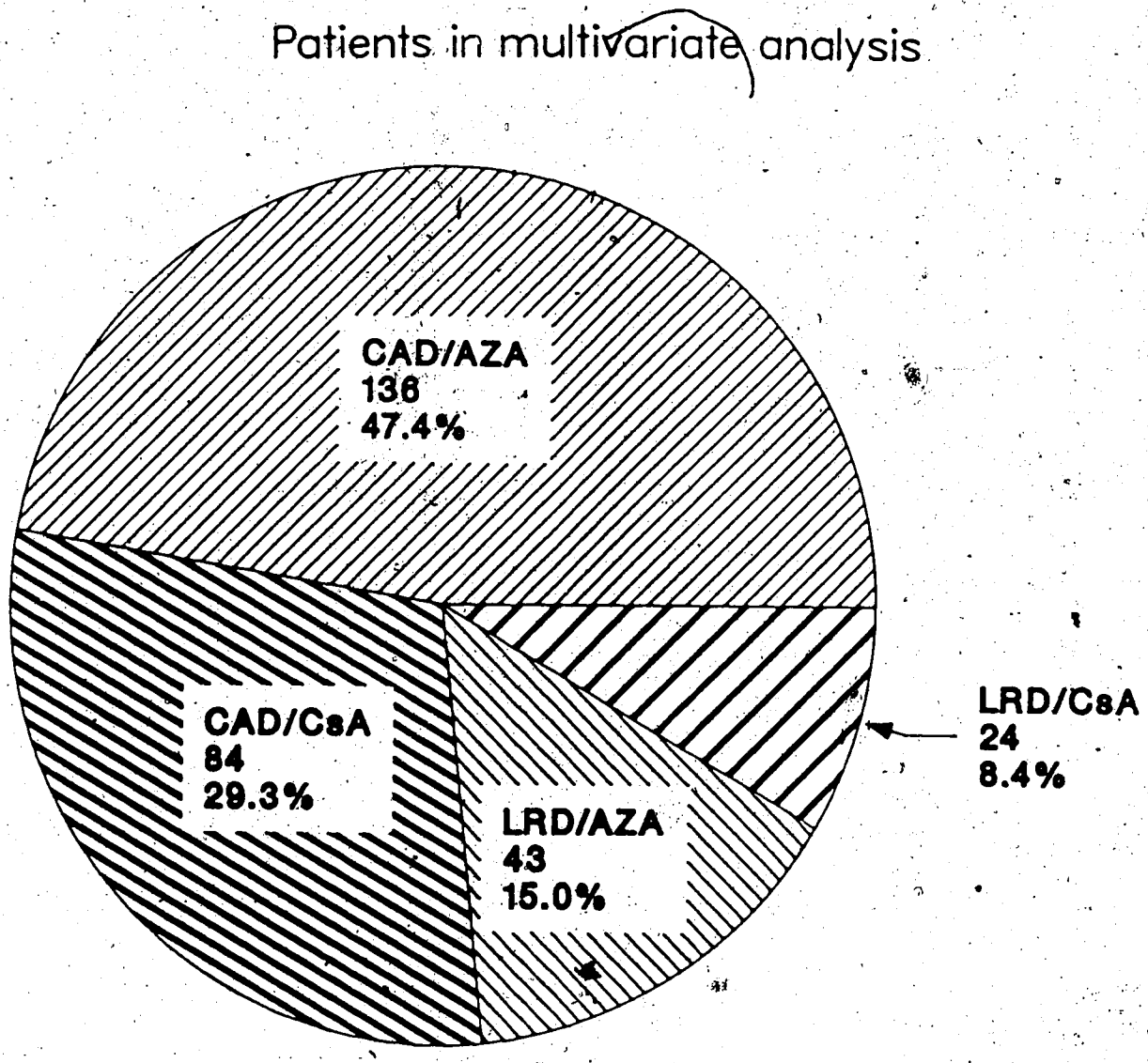


Figure 36.- Distribution of patients included in the multivariate analysis according to their type of donor and main immunosuppressive drug.

37.

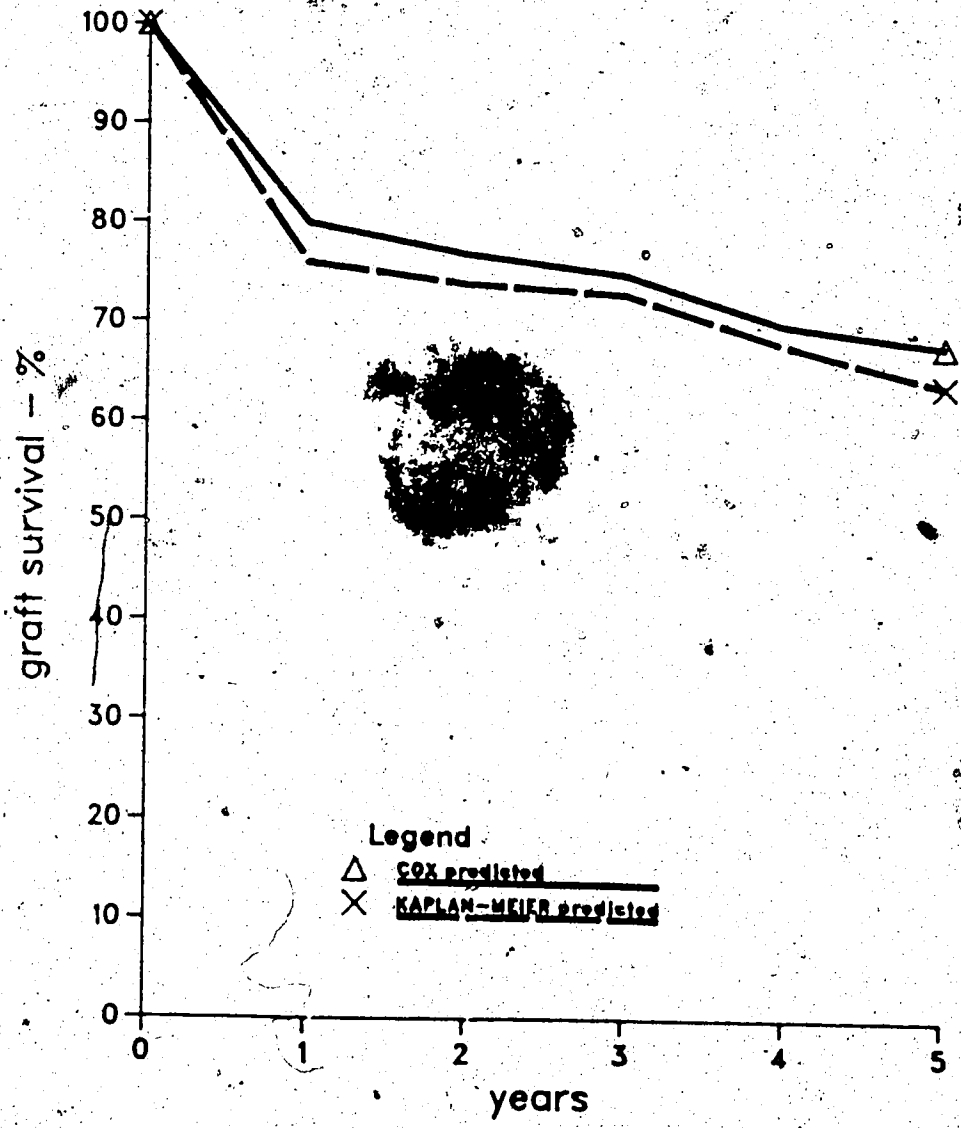


Figure 37.- Comparison of graft survivals obtained by Kaplan-Meier estimate and Cox model.

38.

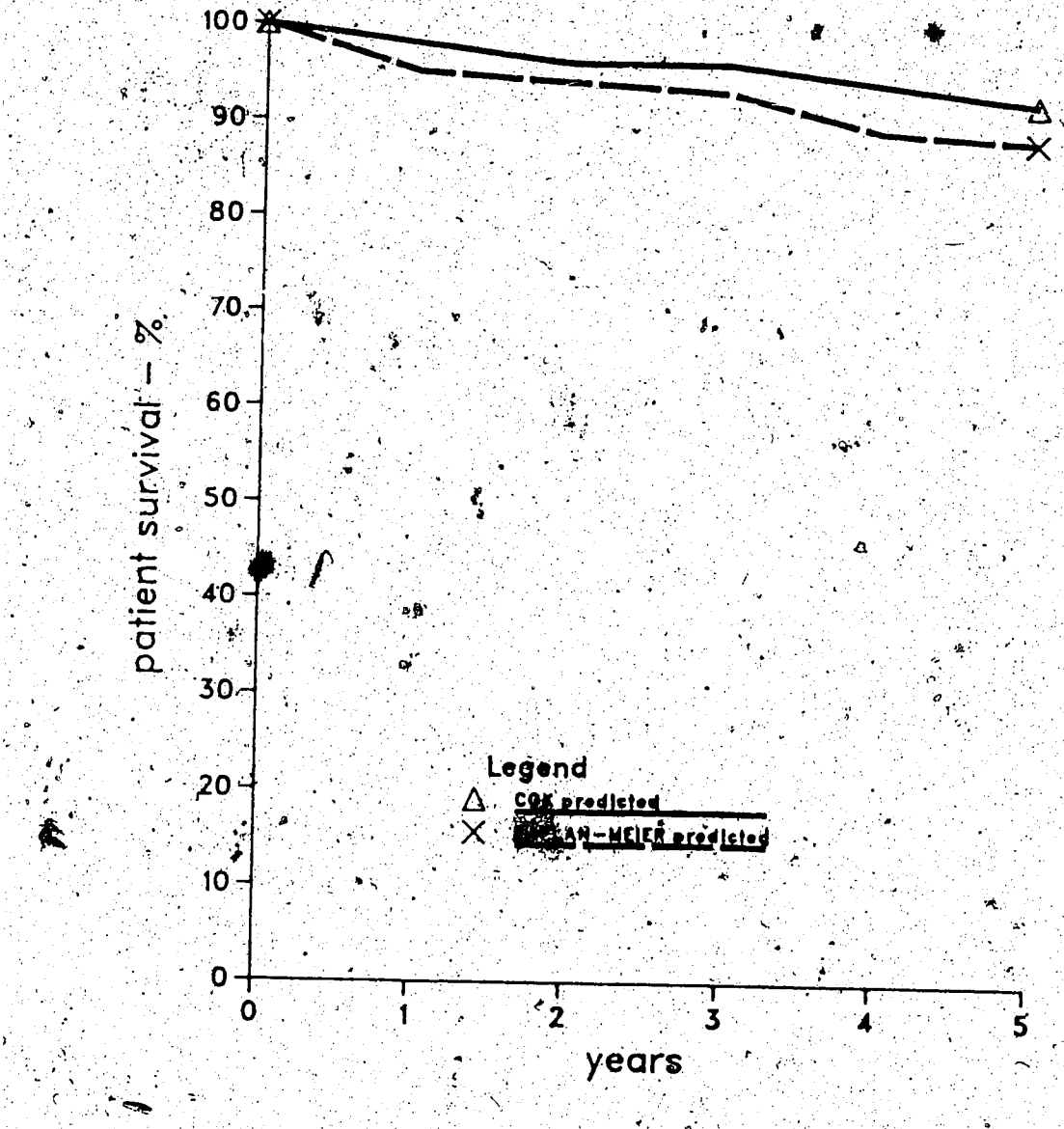


Figure 38.- Comparison of patient survivals obtained by Kaplan-Meier estimate and Cox model.

39.

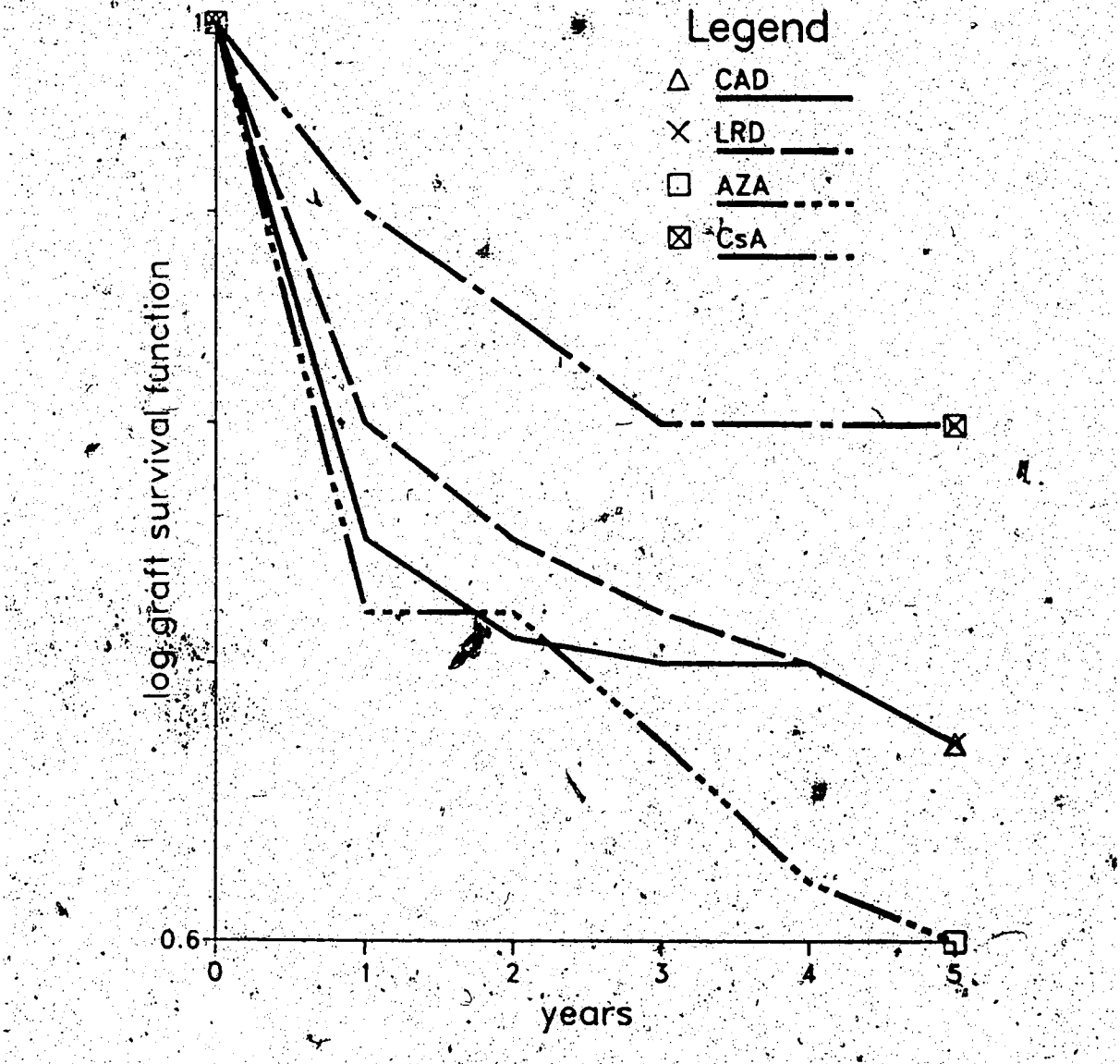


Figure 39.- Test for proportionality of risks between CAD and LRD recipients and between AZA and CsA tretated patients.

40.

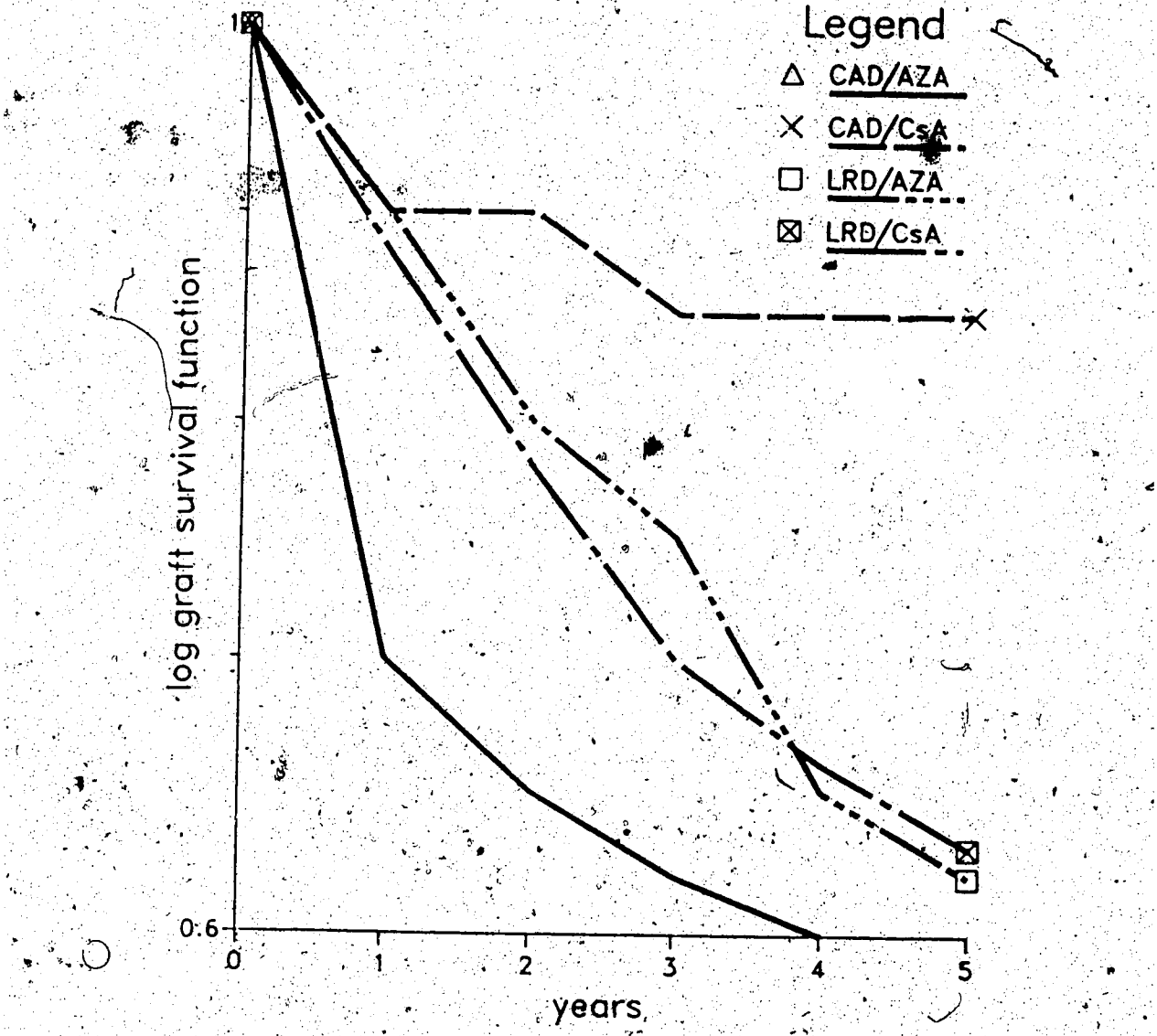


Figure 40.- Test for proportionality of risks between the 4 possible combinations of renal transplants according to type of donor and main immunosuppressive drug.

41.

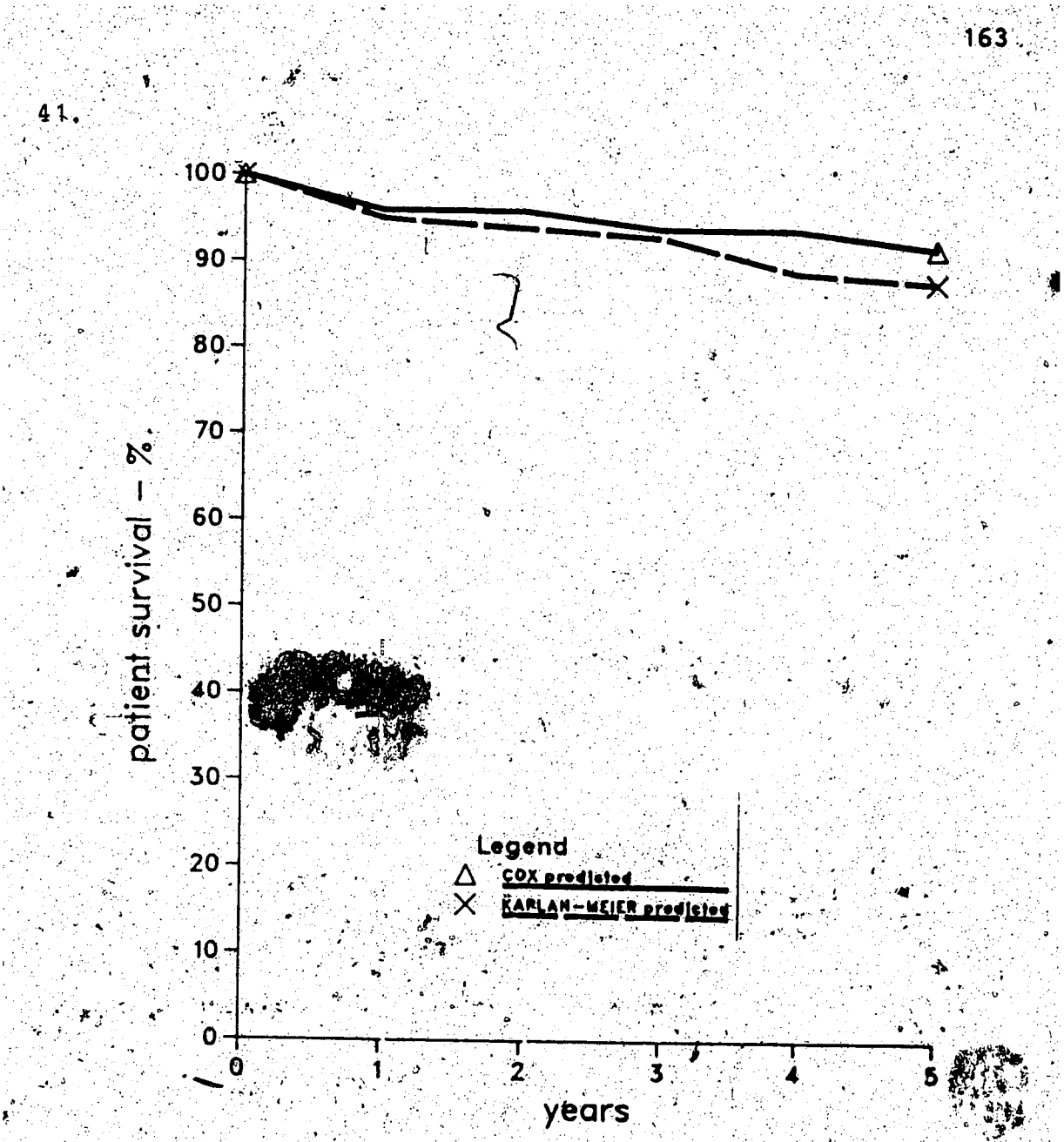


Figure 41.- Comparison of patient survivals obtained by Kaplan-Meier estimate and the final regression model.

42.

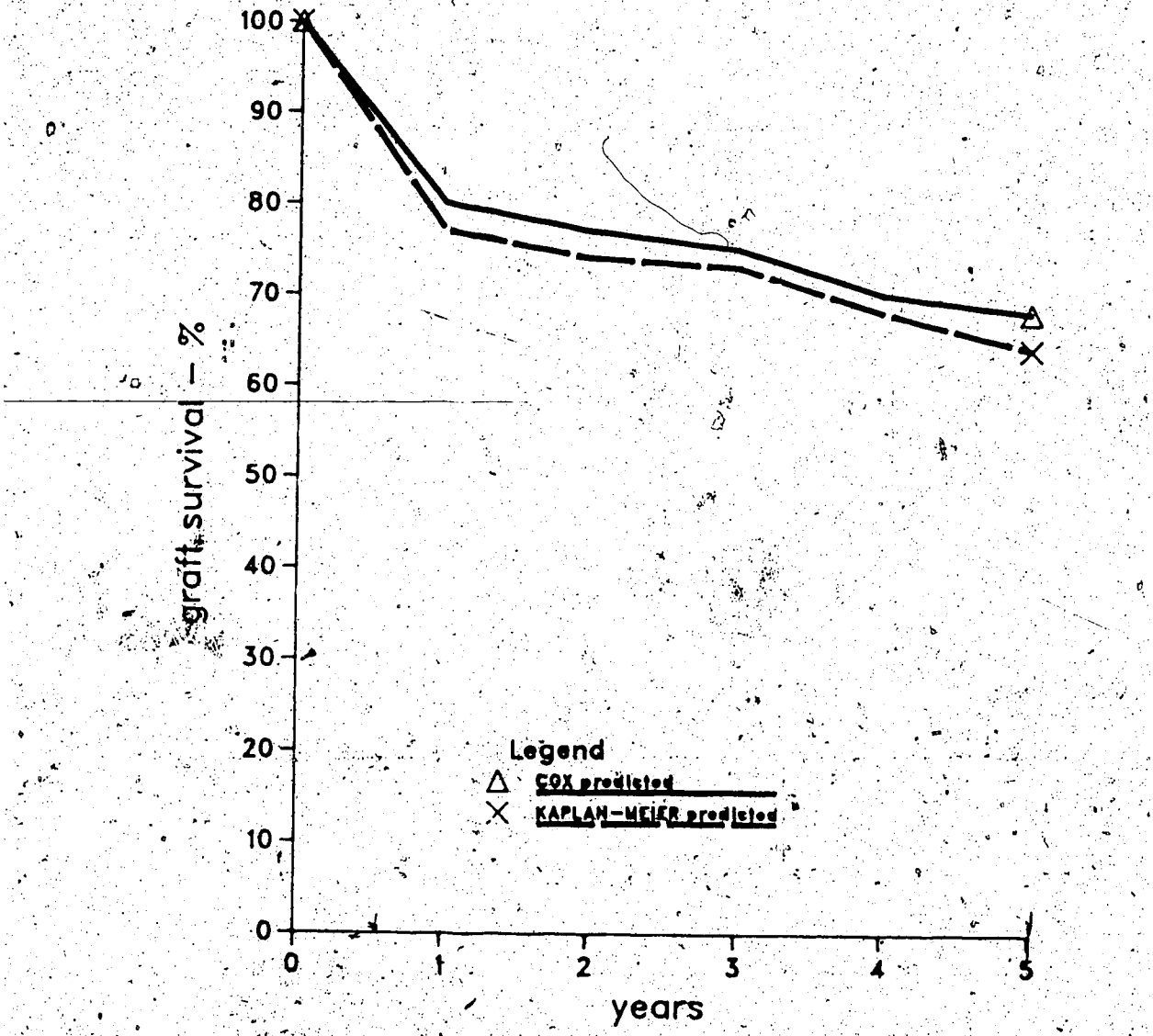


Figure 42.- Comparison of graft survivals obtained by Kaplan-Meier estimate and the final regression model.

43.

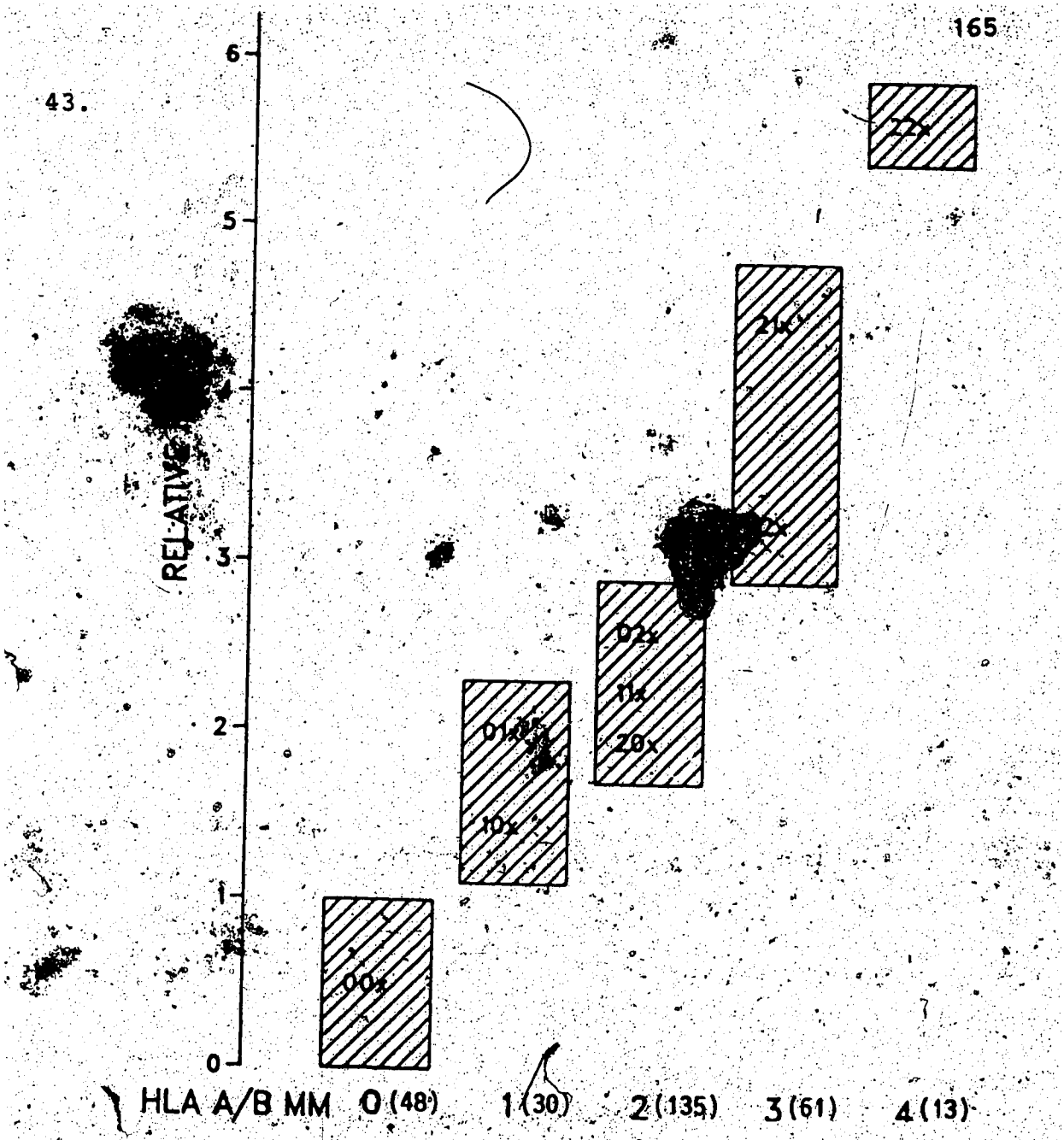


Figure 43. - Relative risks associated with different combinations of HLA A and B mismatches grouped according to the total number of HLA A and B mismatches. Shaded areas represent range of relative risk for each category. [(N) = number of patients in each category].

44.

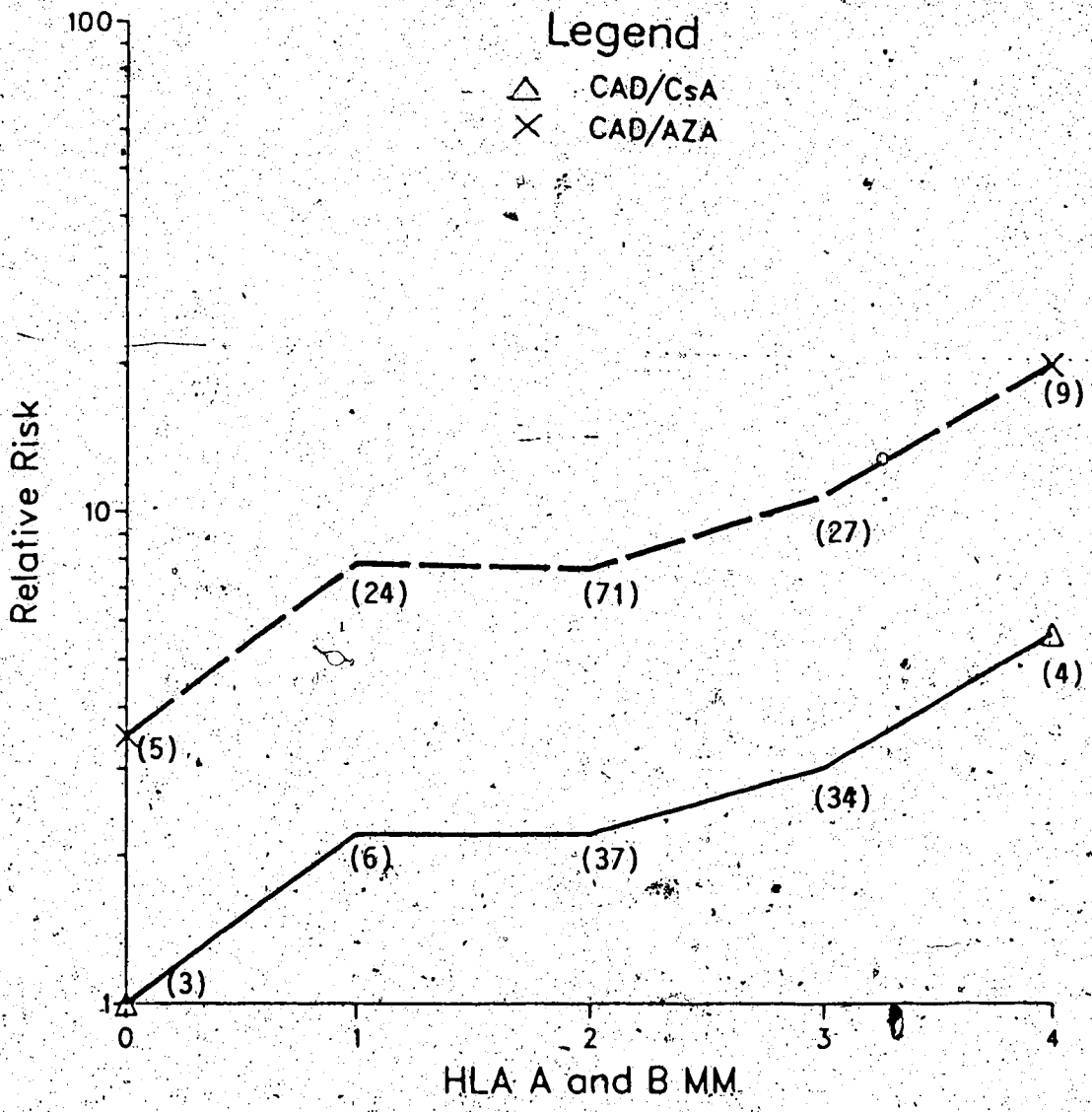


Figure 44.- Proportionality of risks between CAD renal recipients on AZA and those on CsA according to the number of HLA A and B mismatches. The magnitude of the increase of risk in AZA-treated transplants is much more relevant (y axis is on logarithmic scale). [(N) = number of patients in each category].

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