CARDIOVASCULAR EVENTS FOLLOWING RENAL TRANSPLANTATION:

A SINGLE-CENTER COHORT STUDY

by

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A THESIS

Presented to the Department of Public Health and Preventive Medicine

And the Oregon Health & Science University

School of Medicine

in partial fulfillment of

the requirements for the degree of

Master of Public Health

June 2004

School of Medicine
Oregon Health & Science University

CERTIFICATE OF APPROVAL

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Acknowledgements

Without the help and encouragement of family, friends, and colleagues, this thesis would not have been possible. Foremost are the author's three outstanding mentors: Thomas Becker, Douglas J. Norman, and Motomi Mori. All three have contributed to this project through guidance, counsel, and insightful criticism. When the time came, they served as dedicated thesis committee members, improving this report through careful reading and comments. Credit also goes to Dr. Jonathan C. Prather for invaluable help with data collection, constructive criticism, and most helpful, he guided me with a unifying study design. Collectively their influences helped focus this research and guide it to completion.

A few individuals are due specific credits for their assistance. Dr. Ali J. Olyaei provided support with his enthusiasm, experience, and criticism about outcomes research in transplantation. Dr. Yugo Shibagaki and Ann Marie Rivinus for their help with data collection and constant encouragement during all phases of this project.

The author also wishes to express his deep gratitude to his wife, Cristina, and children: Camilla, Pedro, Melissa, and Isabella, for being his support system and cheering section during his master's studies.

The author would like to acknowledge the work of nurses, surgeons, and the entire transplant team at Oregon Health & Sciences University for their example of true dedication and commitment to patient care. The author is thankful to Dr. William M. Bennett and Dr. John M. Barry for their friendship and for the example of a lifelong commitment to advancement of transplantation.

The scope of this project would have been limited without partial funding provided by Fujisawa Healthcare, Inc. (Grant OGA ANEPH0052). The support of transplantation and outcomes research by this organization is appreciated.

Abstract

Background: Renal transplantation is the treatment of choice for individuals suffering from end-stage renal disease. Despite a survival advantage over renal dialysis, patients undergoing transplantation are at significantly increased risk for cardiovascular mortality as compared to the general population. As the acute care of patients with a cardiovascular event has contributed to the steady decline in cardiovascular death rates, studies focusing on non-fatal events are important to assess the burden of disease and to identify novel risk factors.

Methods: A cohort of 922 adult kidney-only recipients, whose transplants were performed at OHSU between January 1, 1993, and December 31, 1998, was used to analyze the associations among traditional and kidney-transplant specific risk factors and cardiovascular events following renal transplantation. Time to cardiac event, to cerebral vascular event, to peripheral vascular event, time to first cardiovascular event, and patient survival were the outcomes of interest. Traditional cardiovascular risk factors analyzed in this research were: systemic arterial hypertension, hypercholesterolemia, presence of diabetes mellitus prior to transplantation, obesity status, tobacco smoking history, gender, age, and history of cardiovascular events prior to transplantation. Renal transplant-specific risk factors were: time spent on renal dialysis prior to transplantation, modality of dialysis, presence of delayed onset of renal graft function (DGF), rejection episodes, serum levels of creatinine, previous cytomegalovirus (CMV) infection, type of organ donor, and immunosuppressive regimen. Univariate (Kaplan-Meier) and multivariable (Cox proportional hazard model) analyses were conducted.

Results: One hundred and seventy-six patients (19% of the entire cohort) experienced 201 cardio-vascular events during the observation period. One hundred and eleven patients (12%) experienced at least 1 cardiac event (65 myocardial infarcts, 18 coronary artery bypass surgeries, 16 angioplasties, and 12 new-onset angina). Forty-eight patients (5.2%) had at least 1 cerebral vascular event (39 cerebral vascular accidents, 6 transient ischemic attacks, and 3 endarterectomies). Forty-one patients (4.4%) had at least 1 peripheral vascular event (22 amputations, 17 revascularizations, 2 new-onset intermittent claudication). One hundred and ninety-two patients (21%) expired during the study period. The cause of death in 56 individuals was coded as cardiovascular (39 cardiac and 17 cerebral vascular deaths).

Variables associated with cardiac events on multivariable analyses were: prior cardiovascular event combined with diabetes (RR 4.91, 95% CI 2.59 to 9.31, $p<0.001$), or not associated with diabetes (RR 4.77, 95% CI 2.55 to 8.93, $p<0.001$), diabetes (RR 4.29, 95% CI 2.48 to 7.41, $p<0.001$), a history of tobacco smoking (RR 3.61, 95% CI 2.30 to 5.67, $p<0.001$), obesity (RR 3.13, 95% CI 1.82 to 5.39, $p<0.001$) or overweight status at transplant (RR 1.68, 95% CI 1.02 to 2.76, $p=0.04$), multiple rejections (RR 2.05, 95% CI 1.16 to 3.62, $p=0.014$), and dialysis longer than 1 year (RR 1.94, 95% CI 1.21 to 3.11, $p=0.006$). BMI at transplantation was a significant independent variable associated with post-transplant cardiac events even if entered in the model as a continuous variable (RR 1.08, 95% CI 1.04 to 1.13, p value <0.001).

By multivariable analyses, variables associated with cerebral vascular events were: diabetes combined with peritoneal dialysis (RR 11.28, 95% CI 4.66 to 27.3, $p<0.001$), age older than 45 years at transplant (RR 6.11, 95% CI 2.76 to 13.52,

p<0.001), diabetes (RR 5.35, 95% CI 2.18 to 13.14, p<0.001), a serum creatinine level above 1.6 mg/dl at 3 months post-transplant (RR 3.33, 95% CI 1.65 to 6.71, p=0.001), prior cardiovascular event (RR 3.1, 95% CI 1.6 to 6.01, p=0.001), peritoneal dialysis in non-diabetic recipients (RR 3.03, 95% CI 1.1 to 8.36, p=0.03), and obesity at transplantation (RR 0.33, 95% CI 0.11 to 0.99, p=0.049).

Independent variables associated with peripheral vascular events were: diabetes (RR 8.48, 95% CI 3.97 to 18.1, p<0.001), history of tobacco smoking and prior CMV infection (RR 3.88, 95% CI 2.06 to 7.31, p<0.001), age older than 45 years at transplant (RR 2.31, 95% CI 1.14 to 4.66, p=0.019), prior cardiovascular event (RR 2.25, 95% CI 1.17 to 4.35, p=0.016), and peritoneal dialysis (RR 2.13, 95% CI 0.71 to 6.42, p=0.18).

By multivariable analyses, variables associated with a cardiovascular event post-transplant were: diabetes combined with prior cardiovascular event (RR 9.56, 95% CI 6.07 to 15.05, p<0.001), diabetes (RR 4.69, 95% CI 3.12 to 7.06, p<0.001), prior cardiovascular event (RR 4.58, 95% CI 2.84 to 7.38, p<0.001), history of tobacco smoking (RR 2.36, 95% CI 1.72 to 3.24, p<0.001), age older than 45 years at transplant (RR 2.07, 95% CI 1.47 to 2.93, p<0.001), prior CMV infection (RR 1.38, 95% CI 1.00 to 1.9, p=0.051), and dialysis longer than 1 year (RR 1.37, 95% CI 0.99 to 1.88, p=0.056).

Independent variables associated with patient death were: history of tobacco smoking and transplant from a deceased donor (RR 3.52, 95% CI 1.97 to 6.31, p<0.001), age older than 45 years at transplant (RR 1.81, 95% CI 1.25 to 2.63, p=0.002), diabetes pre-transplant (RR 1.76, 95% CI 1.24 to 2.51, p=0.002), pulse pressure greater than 58 mmHg at three months post-transplant (RR 1.64, 95% CI 1.05 to 2.55, p=0.029), prior cardiovascular event (RR 1.52, 95% CI 1.02 to 2.26, p=0.04), dialysis longer than 1 year

(RR 1.47, 95% CI 1.02 to 2.12, p=0.04), and hypercholesterolemia at transplantation (RR 0.7, 95% CI 0.5 to 1.00, p=0.05). Duration of dialysis prior to transplantation was also significant when entered in the model as a continuous variable (months). The adjusted relative risk for patient death was (1.07, 95% CI 1.02 – 1.11, p value = 0.004).

Conclusions: Traditional and renal transplant-specific risk factors are independently associated with cardiovascular events following transplantation. Renal transplant-specific risk factors appear to be outcome-specific rather than broadly associated with all outcomes studied. Some factors such as obesity status at transplantation appear to have opposite associations depending on the outcome studied. Interactions among traditional and novel risk factors are significant and deserve further analyses.

Introduction

End-Stage Renal Disease and Cardiovascular Disease

Due to its rehabilitation potential and cost-effectiveness, renal transplantation is the preferred modality of therapy available to individuals suffering from end-stage renal disease (ESRD). Most recently, a patient-survival advantage has been demonstrated with transplantation, as compared with dialysis, the other modality of treatment for ESRD (1).

In the current era of transplantation, death with a functioning organ is the main cause of graft failure. Similar to death rates among the general population, the main cause of mortality following renal transplantation is cardiovascular. However, for reasons not completely understood, patients suffering from chronic kidney disease are at increased risk for premature cardiovascular disease and mortality associated with cardiovascular events (2). Cardiovascular mortality is underestimated in transplant recipients because of incomplete ascertainment of cause of death in these patients. Furthermore, mortality due to cardiovascular disease has decreased significantly in the United States over the past decade, despite a steady increase in the overall incidence of cardiovascular disease in the same period, as attested by the rate of admission to hospitals due to acute coronary syndrome (3). This phenomenon can be explained by the improvements in acute care of individuals experiencing cardiovascular events. Such changes in the profiles of outcomes may result in the underestimation of the burden of cardiovascular disease, if one looks at mortality data as the only outcome of interest. Most of the data published in renal transplantation use mortality data as the main outcome.

Despite numerous national and international registry efforts initiated in the 1980's, the tracking and analysis of outcomes other than graft survival remain leading challenges for the transplant research community. While national registries such as the United Network for Organ Sharing (UNOS) Scientific Registry contain variables available at the time of transplant and track standard outcomes such as graft survival and cause of graft loss, they are not reliable sources for researching outcome variables such as nonfatal cardiovascular events. In addition, the United States Renal Disease System (USRDS) database has limited long-term follow-up data on transplant recipients due to Medicare reporting regulations being limited to three years following transplantation. Finally, most published researchers using large databases have failed to adjust their models for important pre-existing conditions, such as the history of a nonfatal cardiovascular event or tobacco smoking prior to transplantation.

Proposed Research

To explore the associations among traditional risk factors for cardiovascular disease and post renal transplant cardiovascular events a cohort of renal transplant recipients was used. Traditional cardiovascular risks factors analyzed in this research were: systemic arterial hypertension (systolic and diastolic blood pressure levels in the clinic), hypercholesterolemia (fasting total cholesterol levels), presence of diabetes mellitus prior to transplantation, obesity status (measured as body mass index), tobacco smoking history, gender, and age. In addition, a history of cardiovascular events prior to transplantation was recorded for each patient. This cohort provided the investigators the opportunity to research nontraditional cardiovascular risk factors such as: pulse pressure (the difference between systolic and diastolic pressures), time spent on renal dialysis

prior to transplantation, modality of renal dialysis (peritoneal or hemodialysis), presence of delayed onset of renal graft function, serum levels of creatinine (a surrogate marker of renal function), the impact of previous cytomegalovirus (CMV) infection, type of organ donor (living or deceased), and immunosuppressive regimen (type of primary calcineurin inhibitor agent).

Methods

Data Source

The Oregon Health & Science University (OHSU) database is one of the largest and most comprehensive renal transplant data sources in the United States. Detailed information pertaining to more than 3,300 renal transplants spanning longer than 4 decades has been collected in a prospective fashion. This database is the repository of all renal transplants performed in the state of Oregon up to 1998. The ethnicity and gender distribution in the study cohort is reflective of the end-stage renal disease demographics in the state of Oregon. The database is updated weekly and a Social Security Death Master File (SSDMF) search is conducted periodically using the entire database.

Patient Cohort

The cohort used in this research included all adult renal-only recipients, whose transplants were performed at OHSU between January 1, 1991 and December 31, 1998. This time period was chosen because the overall medical and surgical care, and the criteria for accepting patients for transplantation did not change significantly during this short period of time. In addition, the authors aimed for a minimal follow-up of five years

for the entire cohort. Such a period also provided a sample size large enough to include several explanatory variables in a multivariable model. Pediatric patients (i.e., patients younger than 18 years of age at the time of transplantation) were excluded because of the low incidence of cardiovascular disease in this population. Likewise, multi-organ recipients most often have other co-morbid conditions that could not be fully accounted for in the analytical phase of the study.

Outcomes Definitions

The outcomes of interest used in the study were: 1) Time to cardiac event, defined as: length of time between the date of transplant and the date of new onset angina pectoris, first acute myocardial infarct, coronary artery angioplasty, coronary artery bypass surgery, or cardiac death as coded in the death certificate. 2) Time to cerebral vascular event, defined by the length of time between date of transplant and date of first transient ischemic attack, cerebral vascular accident, carotid endarterectomy or angioplasty, or death due to a cerebral vascular accident. 3) Time to peripheral vascular event: time span between transplant date and date to new-onset intermittent claudication, first limb revascularization, or amputation. 4) In addition, a composite outcome named "time to first cardiovascular event" was defined as the length of time between the date of transplant and the date of any of the previous events that happened the earliest following transplantation; and 5) Time to patient death (called for the purpose of the study "patient survival time"). A cardiovascular event was considered fatal for the purpose of this study if the death date was recorded within 30 days of the cardiovascular event date. The date of last follow-up was defined as the date of last input in the database: either a clinic visit,

laboratory data, or death date. Patients that did not reached an outcome of interest were "censored" at the date of last follow-up.

Independent Variables

Demographic data extracted from the database were as follows: Gender, race, height (meters), weight (kilograms), cytomegalovirus immunity status (measured as protective immunoglobulin G titers), and age (years) at transplantation. In addition, presence of diabetes mellitus prior to transplantation (even if not coded as the cause of ESRD), type of donor (deceased or living), presence of delayed onset of renal graft function (DGF), presence of a cardiovascular event preceding transplantation, number of rejection episodes, serum creatinine level (milligrams per deciliters), systolic and diastolic blood pressure (millimeters of mercury), and fasting total cholesterol levels (milligrams per deciliters) at transplantation and at three and twelve months post-transplant. Data on the number of anti-hypertensive and cholesterol-lowering agents were available as well. In addition, number of months of renal replacement therapy and modality of dialysis (hemodialysis or peritoneal) prior to transplantation were obtained.

Body mass index (BMI) was calculated by the formula: weight in kilograms divided by the square of the height in meters. Analyses were conducted using BMI both as a continuous variable as well as a categorical variable, defined as: low to normal (lower than or equal to 25 kg/m^2), overweight (greater than 25 and lower than 30 kg/m^2), and obese (greater than or equal to 30 kg/m^2). Systolic, diastolic, and pulse pressures were analyzed both as continuous variables and as categorical variables (tertiles). Systemic hypertension was defined by either a systolic blood pressure greater than 140 mmHg, a diastolic blood pressure greater than 90 mmHg, or the use of an

antihypertensive drug. Pulse pressure was calculated by subtracting the diastolic from the systolic blood pressure. A fasting total cholesterol level greater than 200 mg/dl, or the use of a lipid-lowering drug defined hypercholesterolemia, for the purpose of this study. Time on dialysis, measured in months, was used as a continuous variable, as well as categorical variables: No dialysis, dialysis less than one year, dialysis for one to two years, and dialysis for longer than two years. Categories of modality of dialysis were: hemodialysis, peritoneal dialysis, or both therapies prior to transplantation. Delayed onset of renal graft function was defined as the need for dialysis within the first week following transplantation. The immunosuppressive drugs used after transplantation were grouped according to the type of calcineurin inhibitor used as the primary immunosuppressive agent: Cyclosporin A or tacrolimus.

Statistical Methods

Continuous variables were categorized in tertiles or in cut-off levels chosen by the author and his investigators based on biological significance or previous publications. Time to the cardiac event following transplantation was used as one of the primary outcomes (event-free survival). In addition, times to cerebral, peripheral, first cardiovascular (composite) event, and patient survival were also outcomes of interest. With the exception of the patient survival analysis, patients were censored at the date of death if their demise was not associated with a cardiovascular event, or at the date of the last follow-up data.

Event-free survival curves were constructed using the product-limit method (Kaplan-Meier). Differences among survival curves were estimated by the log-rank test. Multivariable analyses were accomplished by fitting a Cox proportional hazards model

using variables with a p-value of 0.2 or lower in the univariate analyses, and variables considered by the author to be of biological significance. Log [-log (survival time)] versus log (survival time) plots were used to validate the proportionality of hazard increments assumption. To test the assumption of multiplicative risks of the multivariable model two-way interactions were screened by testing permutations among all variables of clinical or statistical significance. The authors analyzed the significance of a cluster of independent variables using the likelihood ratio test. To build a reduced model, the authors removed single variables from the complete model, and the ratio of the likelihoods of the reduced model to the complete model was calculated on a stepwise fashion (backward LR method). The best-reduced model was found once no further variables could be removed from the model. Multivariable analyses excluded patients with missing values, which resulted in smaller cohorts. For the purposes of the study, patients were censored if an event (outcome) occurred before the predetermined observation time for variables like rejection episodes, levels of pulse pressure, or creatinine levels at 3 months post-transplant. A two-tailed p value of 0.05 or lower was considered statistically significant.

SPSS for windows (SPSS® Inc., Chicago, IL) version 11.5 was used in the analyses.

Results

Overview of Events

Between January 1, 1991, and December 31, 1998, 950 transplants were performed on 922 patients at OHSU (26 patients received 2 and 1 patient 3 transplants during the observation period). **Table 1** shows the demographics of the entire cohort. Seven hundred and ninety one patients underwent their first transplant, 111 patients underwent their second, 13 patients their third, 6 patients their fourth, and 1 patient his fifth transplant during the study period. Because so few patients underwent 2 or more transplants the investigators chose to aggregate these transplants under a single category named "re-transplant".

During the study period, 176 patients (19.1% of the entire cohort) experienced 201 cardiovascular events. One hundred and eleven (12% of the entire cohort) patients experienced at least 1 cardiac event (65 myocardial infarcts, 18 coronary artery bypasses, 16 angioplasties, and 12 new-onset angina pectoris), 48 patients (5.2% of the cohort) at least one cerebral vascular event (39 cerebral vascular accidents, 6 transient ischemic attacks, and 3 carotid endarterectomies), and 41 patients (4.4% of the cohort) at least 1 peripheral vascular event (22 amputations, 17 revascularization procedures, and 2 new-onset claudications). One hundred and ninety-two patients (20.8% of the entire cohort) expired during the study period; 56 (29.1%) of the total deaths were due to cardiovascular events (39 cardiac and 17 cerebral vascular deaths). The cause of death for 53 patients (27.6% of total deaths) was coded as "unknown" in the database. Of the 139 patients with known causes of death, 56 (40.3%) were due to cardiovascular events.

Cardiac Events

The univariate analysis results for the time to cardiac event outcome are shown in **Table 2**. Transplantation after 1995, age at transplantation older than 45 years, male gender, recipients of a deceased donor organ, patients that experienced DGF, patients with a history of diabetes, tobacco smoking, or have experienced a cardiovascular event prior to transplantation were at higher risk for a cardiac event post-transplant. In addition, obese individuals, and those that experienced dialysis longer than 1 year prior to transplantation, also experienced more cardiac events. Because the event-free survival were similar between the sub-cohort of patients not yet on dialysis and the patients which had undergone dialysis for less than 1 year, the author decided to merge the two cohorts under the category: "dialysis less than 1 year". Likewise, the outcomes for the subgroup of patients who had undergone dialysis for "1 to 2 years" and the cohort of patients on dialysis for "longer than 2 years" were similar. Thus the category "dialysis longer than 1 year" was created. These two sub-cohorts were used throughout the analyses. Traditional cardiovascular risk factors like hypercholesterolemia and hypertension (with the exception of pulse pressure) were not significant in the univariate analyses. Re-transplantation status, prior CMV infection, presence of rejection, serum creatinine levels, type of calcineurin inhibitor, and modality of dialysis did not reach statistical significance.

From all the potential two-way interactions, only the history of diabetes and cardiovascular prior to transplantation was statistically significant. **Figure 1** shows the relative risks (RR) for post-transplant cardiac events for recipients with different permutations of pre-transplant diabetes mellitus (DM) and cardiovascular disease (CVD).

Based on these findings, three categorical variables ("dummy variables") were created: diabetes and prior cardiovascular event, cardiovascular event without diabetes, and diabetes without prior cardiovascular event. These variables were included in the multivariable model. **Table 3** shows the results of the multivariable analysis. In a model including all significant variables (complete model), prior cardiac event (with or without diabetes), diabetes, history of tobacco smoking, obesity at transplantation, and dialysis longer than 1 year were significant independent variables associated with cardiac events following renal transplantation. **Table 4** shows the best-reduced model. The only variables that significantly contributed to the fit of the model were: prior cardiovascular event, diabetes, history of tobacco smoking, obesity at transplantation, dialysis longer than 1 year, and overweight status at transplantation.

Table 5 shows the reduced model when the "rejection episodes at 3 months" variable was added to the model. The category "multiple rejections" was an independent variable associated with cardiac events occurring after 3 months post-transplant (RR 2.05, 95% CI 1.16 to 3.62, p= 0.014); however, a single rejection was not (RR 1.43, 95%CI 0.85 to 2.42, p= 0.18). The other variables listed in Table 4 were still significant.

BMI at transplantation was also significant when entered in the model as a continuous variable. The adjusted relative risk for cardiac event post-transplant was 1.08 (or a 8% increase) by each unit increased in the BMI (95% confidence interval of RR 1.04 – 1.13, p value <0.001).

Cerebral Vascular Events

Table 6 shows the explanatory variables associated with cerebral vascular events in the univariate analyses. Age at transplantation (older than 45 years), a history of

diabetes, prior cardiovascular event, prior peritoneal dialysis, a deceased-donor transplant, and prior CMV infection were significantly associated with cerebral vascular events post-transplant. In addition, absence of hypercholesterolemia and an elevated pulse pressure at 3 months post-transplant were statistically significant.

Figure 2 shows the two-way interaction between peritoneal dialysis and diabetes mellitus. Based on these results, three categorical variables were created: diabetes and peritoneal dialysis, diabetes and no peritoneal dialysis, and peritoneal dialysis without diabetes. These variables were included in the multivariable model. **Table 7** shows the multivariable analysis results. The complete model indicates that diabetic patients receiving peritoneal dialysis were at higher risk for development of a cerebral vascular event. Diabetes, age greater than 45 years, prior cardiovascular event, and peritoneal dialysis were significantly associated with cerebral vascular events post-transplant. Interestingly, obesity status had a significant inverse association with cerebral vascular events post-transplant. **Table 8** shows that the presence of hypertension at the time of transplantation and all the other variables shown to be significant in the complete model also contributed to the fit of the best-reduced model.

Table 9 shows the reduced model when creatinine levels and pulse pressure at 3 months post-transplant were added to the model. The higher tertile of serum creatinine level (level greater than 1.6 mg/dl) at 3 months post-transplant was found to have a significant association with cerebral vascular events occurring after 3 months post-transplant. Levels of pulse pressure at 3 months post-transplant did not contributed to the fit of the model.

Peripheral Vascular Events

Table 10 shows the explanatory variables associated with peripheral vascular events by univariate analysis. Age at transplantation (older than 45 years), a history of diabetes, prior tobacco smoking, previous cardiovascular event, and prior peritoneal dialysis (as compared to hemodialysis) were significantly associated with cerebral vascular events post-transplant. In addition, male gender almost reached statistical significance. The only potential two-way interaction found by screening the significant variables was between prior CMV infection and a history of tobacco smoking.

Figure 3 shows the interaction between prior CMV infection and history of tobacco smoking. Based on these results, three categorical variables were created: prior CMV infection and history of tobacco smoking, prior CMV infection and no history of tobacco smoking, and history of tobacco smoking without prior CMV infection. These variables were included in the multivariable model.

Table 11 shows the complete multivariable model. The variables significantly associated with peripheral vascular events following transplantation were: diabetes mellitus prior to transplantation, prior CMV infection and history of tobacco smoking, age older than 45 years at transplantation, and prior cardiovascular event. **Table 12** shows the variables contributing to the fitting of the best-reduced model. Despite not being significant as an independent predictor for peripheral vascular event post-transplant, peritoneal dialysis contributed to the fit of the model. Pulse pressure level at 3 months was not found to be significantly associated with peripheral vascular events post-transplant on a multivariable model.

First Cardiovascular Events

The results of the univariate analyses pertaining to the associations among exploratory variables and the first cardiovascular event following transplantation are shown on **Table 13**. Age of recipients (older than 45 years), history of diabetes mellitus, tobacco smoking, and cardio-vascular event prior to transplantation were associated with increased incidence of cardiovascular events post-transplant. In addition, male gender, deceased donor, obesity status at transplant, hypercholesterolemia, dialysis longer than 1 year, highest tertile of pulse pressure, and prior peritoneal dialysis were significantly associated with a cardiovascular event following renal transplantation.

Figure 4 illustrates the interaction between diabetes mellitus and a history of cardiovascular event prior to transplantation. Based on these results, three categorical variables were created: diabetes and history of cardiac event, diabetes and no history of cardiovascular event, and history of cardiovascular event without diabetes. These variables were included in the multivariable model.

Table 14 shows the results of the multivariable analysis (complete model). A history of diabetes mellitus and prior cardiovascular event, diabetes (without prior cardiovascular event), history of cardiovascular event (without diabetes), prior tobacco smoking, and age greater than 45 years were the variables associated with cardiovascular events post-transplant. In addition, prior CMV infection almost reached statistical significance. **Table 15** demonstrates that all the significant variables in the complete model, prior CMV infection, and dialysis longer than 1 year prior to transplantation significantly contributed to the fitting of the best-reduced model.

Patient Survival

Table 16 shows the univariate analysis results. Independent variables associated with patient death following renal transplantation were: age greater than 45 years, a deceased donor, delayed onset of graft function, history of diabetes, tobacco smoking, prior cardiovascular events, elevated pulse pressure at transplantation and at 3 months post-transplant, and duration of dialysis longer than 1 year were significant. In addition, repeated rejections within the first 3 months post-transplant almost reached statistical significance.

Figure 5 shows the interaction between history of tobacco smoking and type of kidney donor (deceased versus living). Based on these results, three categorical variables were created: history of tobacco smoking and deceased donor, history of tobacco smoking and living donor transplant, and deceased donor without history of tobacco smoking. These variables were included in the multivariable model.

Table 17 shows the results of the multivariable analysis when all variables were included (complete model). History of tobacco smoking and deceased donor, diabetes mellitus, age older than 45 years at transplantation, prior cardiovascular event, and delayed graft function were independent risk factors for mortality following renal transplantation. Dialysis longer than 1 year prior to transplantation almost reached statistical significance. **Table 18** depicts the best-reduced model: a history of tobacco smoking in recipients of a deceased-donor transplant, diabetes mellitus, age older than 45 years at transplantation, dialysis longer than 1 year, previous cardiovascular events, and delayed onset of graft function were the variables contributing to the fit of the model.

Table 19 shows the best-reduced model when 3 month post-transplant variables were added to the model. The higher tertile of pulse pressure (greater than 58 mmHg) at 3 months was found to have a significant association with increased risk of death occurring after 3 months post-transplant. Number of rejections and tertiles of creatinine levels at 3 months post-transplant did not contributed to the fit of the model.

Duration of dialysis prior to transplantation was also significant when entered in the model as a continuous variable. The adjusted relative risk for patient's death was 1.07, or 0.7% increase per each month increase in dialysis duration (95% confidence interval of RR 1.02 – 1.11, p value = 0.004).

Discussion

Cardiovascular Mortality in Patients with Chronic Kidney Disease

Population–based studies in the United States (4;5) and abroad (6) have shown that cardiovascular mortality increases in patients with chronic kidney disease. Mortality from cardiovascular disease is 10 to 20 times higher among individuals treated with dialysis, as compared to general population (2). According to the national registry data (USRDS), the incidence of cardiovascular disease in kidney transplant patients is nearly twice that of the general population (7). Even young transplant recipients (ages between 35 to 45 years) experienced an increase of almost 10-fold in cardiovascular disease-related mortality (2). Reducing deaths from cardiovascular disease in persons with chronic kidney failure is described as one of the Healthy People 2010 objectives (8).

Risk Factors After Renal Transplantation

Risk factors associated with the increased incidence of ischemic cardiovascular disease after renal transplantation appear to be different than those described in large population-based studies like the Framingham Heart Study (9). The present cohort study analyzed the relationships among traditional and kidney transplant-specific risk factors for cardiovascular disease and cardiovascular outcomes. The author and his investigators have chosen to study events in separate categories according to organ(s) affected: cardiac, cerebral vascular, and peripheral vascular. In addition we used a composite outcome as time to first cardiovascular event and patient survival as secondary outcomes of interest.

Diabetes Mellitus

Diabetes mellitus is a major risk factor for cardiovascular mortality in the general population. Diabetic individuals with chronic kidney disease not yet requiring dialysis may experience an increased risk for calcification of coronaries and other arteries, a corollary of atherosclerotic disease (10). Analyses of most of large data sets may have underestimated the contribution of diabetes mellitus to cardiovascular events following transplantation because the investigators might have missed the presence of diabetes prior to transplantation, as it was not the cause of renal disease coded in the national registry data (11). The presence of diabetes mellitus prior to transplantation was a strong cardiovascular risk factor in a single-center cross-sectional study (9). Our cohort study demonstrated a strong association between pre-transplant diabetes and all the outcomes studied. Furthermore, interactions between diabetes and other variables such as: prior cardiovascular events and peritoneal dialysis were described. The analysis of our data did not allow a more refined analysis of as variable such as: duration of disease, presence of secondary complications (besides renal failure), and details on effectiveness of the control of hyperglycemia before transplantation were lacking in the database.

Tobacco Use

In our cohort, similar to the general population, tobacco smoking was one of the strongest risk factors for cardiovascular events and mortality (12). This could be explained by the cumulative impact of tobacco smoking prior to transplantation yet more specific data in terms of intensity or duration of exposure to tobacco are lacking in the database. In a report including only individuals undergoing dialysis therapy, it was found that the incidence of congestive heart failure, peripheral vascular events, and mortality was increased in individuals currently smoking tobacco, yet no difference was found in

the incidence of such events between former smokers and lifelong nonsmokers (13). Cigarette use has been associated with ischemic events following renal transplantation in a single center cross-sectional study (9). An explanation for these findings is that despite efforts to strongly discourage smoking post-transplant, a proportion of patients would eventually start using tobacco. One could speculate that individuals with history of tobacco smoking prior to transplantation would be more likely (as compared to those without prior exposure) to smoke following transplantation. It is not our practice to check nicotine levels post-transplant; therefore, tobacco smoking post-transplant could not have been fully recognized. Due to incomplete data collection, the use of tobacco has not been fully accounted for as a risk factor for cardiovascular events post-transplantation in previous publications (11). Interactions between tobacco smoking and other factors such as prior CMV infection or transplantation using a deceased donor organ are intriguing and deserve further studies.

Obesity

Associations between obesity at transplantation (BMI greater than 30kg/m^2) and congestive heart failure (11) and cardiovascular mortality (14) have been described previously. However, an association between elevated BMI and ischemic heart disease has not. In the present cohort study obesity was associated with cardiac events with a suggestion of a dose-response phenomenon. Interestingly, the same data suggest that obesity might have a negative association with cerebral vascular events. One could speculate that a competing risks phenomenon could have played a role in such association. In other words: if a large number of obese individuals would die from other

causes soon after transplantation a lower proportion of such subjects would continue to be at risk for cerebral vascular events later on. However, the authors do not believe this would be a likely explanation, as no associations between obesity and death either on univariate or multivariable analyses were found (one year patient survival was 98%, 95%, and 96%, for normal, overweight, and obese status, respectively). The authors do not dismiss a potential association between obesity and peripheral vascular events or death following transplantation and it is possible that the observation period was indeed too short to accrue enough events.

Prior Cardiovascular Events

This report has also found that the history of a cardiovascular event occurring prior to transplantation was an important risk factor for cardiovascular events following renal transplantation. Data from the national registry (USRDS) demonstrated that the proportion of individuals with co-morbid cardiovascular disease at the time of a deceased-donor transplant has increased from about 40 percent in 1995 to 50 percent in 2001 (15), probably reflecting changes in patients' acceptance criteria for transplantation in more recent years. Interestingly, this important factor has not been accounted for in previously published studies addressing post-transplant cardiovascular events. Our study suggests that future research in the field of cardiovascular disease following transplantation must consider this variable in their design and analyses.

Hypertension and Hypercholesterolemia

Traditional risk factors for cardiovascular disease like hypertension and hypercholesterolemia have not been strongly associated with ischemic events in patients undergoing chronic dialysis therapy (16). Kasiske et al., (9) in a single-center

observational study have shown that hypertension and high cholesterol levels were associated with post-transplant ischemic events. However, patients with pre-existing cardiovascular disease or who experienced cardiovascular events within the first year post transplanted were excluded from their cohort. This exclusion criterion might have selected a cohort of patients with either absent or less advanced ischemic cardiovascular disease. This population is remarkably different than our cohort, which makes difficult to draw comparisons between the studies results. Low total cholesterol levels have been associated with poor survival on dialysis and might reflect poor nutritional status.

Renal Dysfunction

Evidence that even small degrees of renal dysfunction may be an independent predictor of future cardiovascular disease can be found in a large community-based study published 15 years ago (17). In the Framingham Heart Study a trend towards an association between minor renal dysfunction and future cardiovascular morbidity and mortality was described (4). Data on more than 6000 participants of the National Health and Nutrition Examination Survey II (NHANES II) have revealed an association between mild to moderate renal insufficiency and increased cardiovascular mortality, which was independent from other classical risk factors such as diabetes mellitus, smoking, or dyslipidemia (18). This observation has been confirmed in large prospective trials such as the HOT (19) and the HOPE (20) trials. A publication using the national transplant registry has found a positive significant association between decreased renal function at 1 year following transplantation and hospitalizations due to acute coronary syndromes or congestive heart failure (11). In their report the cohort of patients with the lowest quartile of estimated GFR (i.e., lower than 44.9ml/min per $1.73m^3$) experienced significantly

higher rate of cardiac events. Due to study design, patients experiencing cardiovascular events within the first year following transplantation were excluded from the analyses. The current study looked at cardiovascular events occurring at anytime following renal transplantation; the level of serum creatinine at 3 months post-transplant was associated with cerebral vascular events, but not with the other outcomes studied. An association between chronic mild renal dysfunction, measured as elevated serum creatinine levels, and cerebral vascular events has been described in a middle-aged, community-based population study (21). This association was stronger when renal dysfunction was accompanied by anemia. The researchers were not able to retrieve hemoglobin levels from the OHSU transplant database.

Duration of Dialysis

In a recent cohort study (16) an association between dialysis duration and cardiovascular risk was not demonstrated. However, in the analyses performed, duration of dialysis was entered in the multivariable model as 5-year incremental categories, which might have been too broad interval. In a publication using the national transplant registry data (11), time spent on dialysis has been not been shown to be significant independent risk factor for ischemic cardiac events occurring within 1.5 to 3 years after renal transplantation, yet it was significantly associated with CHF. In this report, dialysis longer than 1 year prior to transplant was associated not just with cardiac events, but also with patient survival. These differences could be attributed to differences in the observation period, as the present report covered the period immediately post-transplant up to 11.9 years of follow-up. Reducing the time spent on renal dialysis prior to transplantation is also one of the objectives described in the "Healthy People 2010"

report (8). Revisions in the allocation of organs among patients on the waiting list aimed at reducing time on dialysis prior to transplantation have been recently proposed (22).

Modality of Dialysis

Modality of dialysis has been associated with cardiac outcomes as congestive heart failure has been associated with peritoneal dialysis more often than with hemodialysis (11). In a recently published population-based study, a five-fold increased risk for cerebral vascular events in individuals undergoing chronic dialysis therapy, as compared to the general population was described (23). However, the authors made no attempts to further investigate the relationship between the incidence of such events and variables like modality or duration of dialysis therapy. It is common practice in the United States to offer peritoneal dialysis to older patients with a greater number and severity of co-morbid conditions. This factor could have introduced a selection bias in our cohort; however, if this would be the sole explanation for our findings, one should expect cardiac events or deaths to occur more often in this group as well, which was not noted in our results.

Recipient Age

The age of recipients at transplantation and the proportion of transplant recipients with pre-existing cardiovascular disease increased gradually over the past 5 years in the United States (15). Age at transplantation has been described as a risk factor for ischemic cardiovascular disease in other publications (9). With the exception of cardiac events, age of recipients was clearly associated with all other cardiovascular events studied as well as with mortality following renal transplantation. The lack of an association between age and cardiac events is intriguing and may simply reflect the presence of stronger risk

factors for that particular outcome, therefore making an association between this variable and cardiac event less apparent. An alternative explanation would be that older patients are screened more aggressively for asymptomatic cardiac disease (but not necessarily for cerebral or peripheral vascular disease) prior to transplantation and interventions would take place more often in these individuals as compared to younger candidates. These interventions could have prevented some of the cardiac events from happening following transplantation, or could have resulted in loss of candidacy status for transplantation leading to a selection bias in this age group.

Type of Donor, Delayed Graft Function, and Acute Rejection

Type of renal donor and delayed onset of graft function have recently been associated with cardiac events (11). The US national registry data report demonstrated that recipients of a deceased donor organ were at higher risk for cardiovascular events than living-donor transplant recipients (15). Additionally, an association between acute rejection episodes post-transplantation and cardiovascular events have been described previously (9). These variables should be studied more extensively on a prospective fashion.

Prior Cytomegalovirus Infection

Prior publications have suggested that reactivation of CMV latent in arterial wall cells may contribute to atherogenesis: high levels of anti-CMV antibodies were associated with clinically manifested atherosclerosis (24). CMV genome and antigens have been detected in endothelial layers and deeper layers of diseased human aortas by *in-situ* hybridization and immunohistochemical staining (25). High incidence of CMV genetic material has been found in arterial vessels obtained from diabetic patients

undergoing surgical amputation of lower limbs (26). In addition, antibodies directed against CMV have recently been shown to cross-react against a human heat-shock protein (HSP60) and cause endothelial cell death *in vitro* (27). The authors claimed that this phenomenon could be part of the pathophysiologic basis for the association between CMV infection and arteriosclerosis. The presence of an association between CMV infection and cardiovascular outcomes following renal transplantation has been controversial (28; 29). Prior CMV infection has been associated with cardiovascular mortality after renal transplant in a small case-control study (30), yet in a large cohort study (11) the association between prior CMV infection and post-transplant cardiac events was not demonstrated in a short follow-up period (median 2.1 ± 0.95 years, range 0.1 to 3.00 years). Criticisms to most published research have been either the weakness associated with cross-sectional studies or the limited length of follow-up. The present prospective study used a cohort of patients with at least 5 years of observation, with a significant proportion of individuals followed for longer than 10 years.

Study Limitations

This study is not without limitations. Due to the demographics of the OHSU cohort, predominantly composed by Caucasians, caution should be exerted in extrapolating our findings to more diverse populations. Further data regarding the amount and duration of exposure to tobacco would be ideal to attempt to establish a dose-response curve. Likewise, further details regarding the type and duration of diabetes mellitus prior to transplantation are lacking. Unfortunately, these data were not collected and entered into the database.

Future Directions

A validation study utilizing an independent cohort should follow this investigation. A larger cohort and longer observation period would allow for analyses of additional risk factors and provide enough statistical power to further explore subtle interactions. In addition, a more diverse cohort could provide data to explore the effects of exploratory variables across multiple races and ethnicities. The impact of a nonfatal event on overall mortality should be explored using a different analytical strategy such as a time-dependent Cox model. Nevertheless, this research effort lays the groundwork for future work on several fronts. For example, a higher prevalence of serological risk factors for coronary artery disease such as elevated levels of homocysteine, lipoprotein(a), and C-reactive protein have been described in the non transplant chronic kidney disease population (31). The prevalence of such risk factors following transplantation has not been studied on a prospective fashion. Likewise, the potential interactions among serological markers and clinical variables have not been explored. A combination of clinical and laboratory variables could potentially be incorporated into post-transplant cardiovascular risk-scoring tools in an attempt to better identify the patients at highest risk for cardiovascular events.

Table 1. Demographics of the Study Cohort.

Variable	Categories	N
Year of transplantation	1991 to 1994	444 (48.2%)
	1995 to 1998	478 (51.8%)
Age group	18 to 45 years	495 (53.6%)
	Older than 45 years	427 (46.3%)
Gender	Female	402 (43.6%)
	Male	520 (56.4%)
Race and ethnicity*	Caucasian	786 (85.2%)
	Black	40 (4.3%)
	Hispanic	37 (4 %)
	Asians or other	59 (6.4%)
Re-transplantation status	Primary	791 (85.8%)
	Re-transplant	131 (14.2%)
Diabetes pre-transplant	No	657 (71.9%)
	Yes	265 (28.1%
Tobacco prior to transplant	No	603 (65.4%)
	Yes	319 (34.6%)
Prior cardiovascular event	No	770 (83.5%)
	Yes	152 (16.5%)
BMI at transplantation	Normal (lower than 25kg/m^2)	503 (54.6%)
	Overweight (25 to 30kg/m^2)	279 (30.2%)
	Obese (greater than 30kg/m^2)	140 (15.2%)
Dialysis status	No dialysis	153 (16.6%)
	Dialysis less than 1 year	277 (30%)
	Dialysis 1 to 2 years	249 (27%)
	Dialysis longer than 2 years	243 (26.4%)
Prior CMV infection*	No	354 (38.4%)
	Yes	563 (61.1%)

*Some sums of percentages are not equal to 100% because of rounding or missing data.

Table 2. Cardiac Events. Univariate Analysis.

Variable	Categories	N at risk	Events	Event-Free Survival			p-value
				1yr	3yr	5yr	
Transplant era	1991 - 1994	444	53	97	95	92	
	1995 - 1998	478	58	96	93	89	0.037
Age at transplant	Younger than 45	495	44	98	96	93	
	45 and older	427	67	95	92	87	0.007
Gender	Female	402	39	97	94	92	
	Male	520	72	97	94	89	0.047
Re-transplantation status	Primary	791	96	97	94	90	
	Retransplant	131	15	98	93	90	0.82
Donor type	Living	243	16	98	97	94	
	Deceased	679	95	96	93	89	0.017
Prior CMV infection	No	354	39	97	95	92	
	Yes	563	72	96	93	89	0.49
Graft function	Immediate	704	77	98	95	92	
	Delayed	218	34	93	89	85	0.003
Diabetes pre-transplant	No	657	56	98	95	93	
	Yes	265	55	95	90	84	<0.001
Tobacco pre-transplant	No	603	43	98	96	94	
	Yes	319	68	95	90	83	<0.001
Prior cardiovascular event	No	770	66	98	96	93	
	Yes	152	45	90	84	75	<0.001
Obesity at transplant	Normal	503	42	98	97	94	
	Overweight	279	39	95	92	89	
	Obese	140	30	94	90	83	<0.001
Hypertension at transplant	No	404	44	97	94	91	
	Yes	518	67	97	93	90	0.28
Hypertension at 3 months	No	388	36	99	97	94	
	Yes	433	44	99	95	92	0.67
High cholesterol at transplant	No	445	47	97	95	92	
	Yes	456	59	97	94	90	0.38

Variable	Categories	N at risk	Events	Event-Free Survival			p-value
				1yr	3yr	5yr	
High cholesterol at 3 mo	No	177	16	99	97	91	
	Yes	664	70	99	96	93	0.65
Duration of dialysis	No dialysis	153	12	98	96	93	
	Less than 1 yr	277	22	97	96	95	
	Between 1 and 2 yr	249	42	95	92	85	
	Longer than 2 years	243	35	97	92	88	0.007
Rejection at 3 months	None	576	53	99	97	93	
	Single	173	20	99	96	91	
	Multiple	112	16	98	93	90	0.16
Creatinine at 3 months	1.3 or lower	370	38	98	95	92	
	1.4 to 1.6	223	21	99	98	94	
	1.7 or higher	264	28	99	96	93	0.74
Pulse pressure at transplant	48 or lower	310	29	98	95	92	
	49 to 60	305	36	96	93	91	
	61 or higher	307	46	97	93	88	0.036
Pulse pressure at 3 months	45 or lower	245	23	99	96	93	
	46 to 58	306	26	99	97	94	
	59 or greater	270	31	99	95	91	0.39
Type of calcineurin inhibitor	Cyclosporine	781	91	97	95	91	
	Tacrolimus	109	12	94	92	89	0.15
Modality of dialysis	Hemodialysis	519	70	96	93	89	
	Peritoneal dialysis	198	20	97	95	92	
	Both	80	13	96	93	88	0.29

Figure 1.Interaction Between Pre-Transplant Diabetes and Cardiovascular Disease

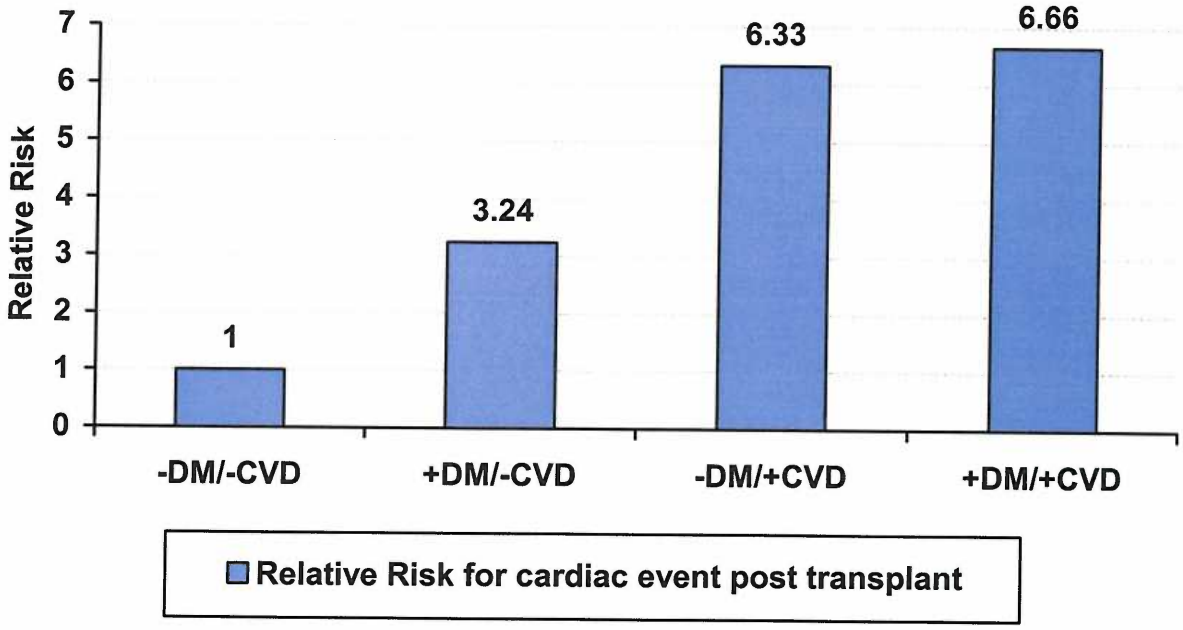

Table 3. Cardiac Events Post-Transplant. Multivariable Analysis.

Complete Model.

Variable	Relative Risk*	95% confidence interval	p-value
Prior cardiovascular event and diabetes	4.62	2.58 to 8.29	<0.001
Prior cardiovascular event (no diabetes)	4.59	2.56 to 8.25	<0.001
Diabetes (no prior cardiovascular event)	3.94	2.37 to 6.55	<0.001
Tobacco history	2.89	1.92 to 4.34	<0.001
Obesity at transplant	2.67	1.60 to 4.45	<0.001
Dialysis longer than 1 year	1.79	1.15 to 2.80	0.01
Overweight at transplant	1.54	0.98 to 2.43	0.06
Transplant after 1994	1.38	0.89 to 2.12	0.14
Delayed graft function	1.23	0.78 to 1.93	0.38
Deceased donor	1.23	0.69 to 2.18	0.49
Male gender	1.14	0.75 to 1.72	0.54
Age older than 45 years	1.11	0.72 to 1.71	0.64
Hypercholesterolemia	1.08	0.73 to 1.60	0.71

*Relative risk adjusted by all the variables listed in addition to: hypertension, level of pulse pressure, type of calcineurin inhibitor, and modality of dialysis.

Table 4. Cardiac Events. Multivariable Analysis.

Reduced Model.

Variable	Relative Risk*	95% confidence interval	p-value
Prior cardiovascular event and diabetes	4.95	2.78 to 8.82	<0.001
Prior cardiovascular event (no diabetes)	4.91	2.82 to 8.56	<0.001
Diabetes (no prior cardiovascular event)	3.89	2.36 to 6.43	<0.001
Tobacco history	3.01	2.01 to 4.52	<0.001
Obesity at transplant	2.93	1.81 to 4.76	<0.001
Dialysis longer than 1 year	1.91	1.25 to 2.91	0.003
Overweight at transplant	1.59	1.01 to 2.50	0.04

*Relative risk adjusted by the other variables listed in the table.

Table 5. Cardiac Events. Reduced Model with "Rejection at 3 Months".

Variable	Relative Risk*	95% confidence interval	p-value
Prior cardiovascular event and diabetes	4.91	2.59 to 9.31	<0.001
Prior cardiovascular event (no diabetes)	4.77	2.55 to 8.93	<0.001
Diabetes (no prior cardiovascular event)	4.29	2.48 to 7.41	<0.001
Tobacco history	3.61	2.30 to 5.67	<0.001
Obesity at transplant	3.13	1.82 to 5.39	<0.001
Multiple rejections	2.05	1.16 to 3.62	0.014
Dialysis longer than 1 year	1.94	1.21 to 3.11	0.006
Overweight at transplant	1.68	1.02 to 2.76	0.04

*Relative risk adjusted by the other variables listed in the table.

Table 6. Cerebral Vascular Events. Univariate Analysis.

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
Transplant era	1991 - 1994	444	33	99	97	94	
	1995 - 1998	478	16	100	99	96	0.12
Age at transplant	Younger than 45	495	9	100	100	98	
	45 and older	427	40	99	96	92	<0.001
Gender	Female	402	18	100	100	97	
	Male	520	31	99	96	94	0.23
Re-transplantation status	Primary	791	47	99	98	95	
	Retransplant	131	3	99	98	97	0.11
Donor type	Living	243	5	100	99	98	
	Deceased	679	44	99	97	94	0.005
Prior CMV infection	No	354	14	99	98	96	
	Yes	563	35	99	98	94	0.03
Graft function	Immediate	704	40	99	98	95	
	Delayed	218	9	99	99	96	0.77
Diabetes pre-transplant	No	657	19	99	99	98	
	Yes	265	30	99	95	88	<0.001
Tobacco pre-transplant	No	603	28	99	98	96	
	Yes	319	21	98	97	94	0.07
Prior cardiovascular event	No	770	27	99	99	97	
	Yes	153	22	98	93	88	<0.001
Obesity at transplant	Normal	503	32	99	97	94	
	Overweight	279	13	99	98	96	
	Obese	140	4	100	98	97	0.34
Hypertension at transplant	No	404	19	100	99	96	
	Yes	518	30	99	97	95	0.36
Hypertension at 3 months	No	396	19	99	98	95	
	Yes	434	24	100	98	96	0.65

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
High cholesterol at transplant	No	445	15	100	99	97	
	Yes	456	33	99	97	94	0.02
High cholesterol at 3 mo	No	181	7	100	98	96	
	Yes	669	37	100	98	96	0.43
Duration of dialysis	No dialysis	153	5	99	98	97	
	Less than 1 yr	277	18	99	97	95	
	Between 1 and 2 yr	249	9	100	98	96	
	Longer than 2 years	243	17	99	98	93	0.13
Rejection at 3 months	None	580	26	99	98	96	
	1	175	12	100	99	96	
	More than 1	114	8	99	96	93	0.23
Creatinine at 3 months	1.3 or lower	375	19	100	99	96	
	1.4 to 1.6	223	8	100	99	98	
	1.7 or higher	266	19	99	98	93	0.08
Pulse pressure at transplant	48 or lower	310	11	99	99	97	
	49 to 60	305	18	99	97	95	
	61 or higher	307	20	99	97	93	0.13
Pulse pressure at 3 months	45 or lower	249	8	99	98	97	
	46 to 58	310	14	100	99	96	
	59 or greater	271	21	100	98	93	0.03
Type of calcineurin inhibitor	Cyclosporine	781	44	99	98	95	
	Tacrolimus	109	5	100	99	94	0.33
Modality of dialysis	Hemodialysis	519	20	100	98	97	
	Peritoneal dialysis	198	23	98	95	90	
	Both	80	3	99	99	96	0.002

Figure 2. Relative Risk for Post-Transplant Cerebral Vascular Events. Interaction Between Diabetes Mellitus and Peritoneal Dialysis.

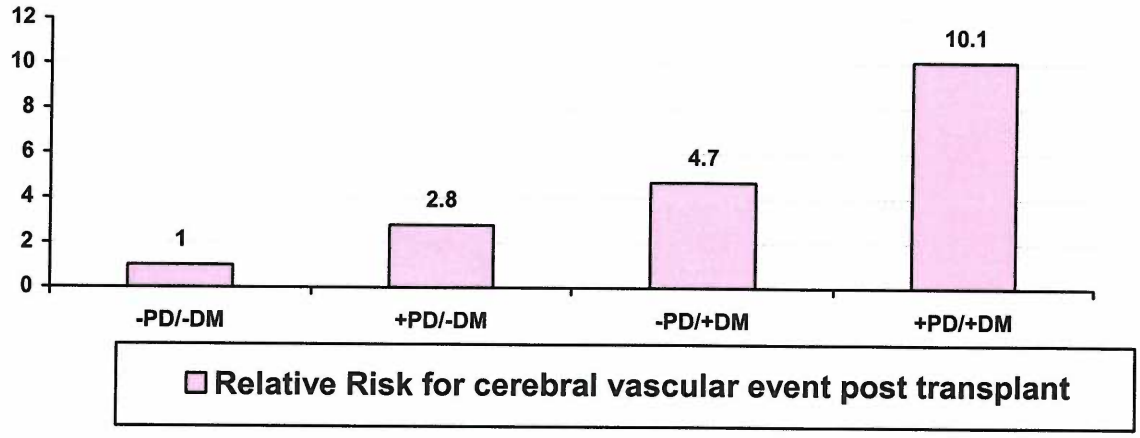

Table 7. Cerebral Vascular Events Post-Transplant. Multivariable Analysis.

Complete Model.

Variable	Relative Risk*	95% confidence interval	p-value
Diabetes and peritoneal dialysis	11.02	4.63 to 26.21	<0.001
Age older than 45 years	5.47	2.44 to 12.26	<0.001
Diabetes (no peritoneal dialysis)	4.21	1.78 to 9.94	0.001
Prior cardiovascular event	3.51	1.86 to 6.62	<0.001
Peritoneal dialysis (no diabetes)	2.73	1.04 to 7.15	0.004
Obese at transplant	0.24	0.08 to 0.73	0.01
Overweight at transplant	0.42	0.21 to 0.85	0.02
Dialysis longer than 1 year	0.55	0.3 to 1.02	0.06
Hypertension	1.78	0.95 to 3.31	0.07
Prior CMV infection	1.68	0.88 to 3.23	0.12
Transplant after 1994	0.66	0.34 to 1.28	0.22
Re-transplant status	0.44	0.1 to 1.91	0.27
Deceased donor	1.73	0.64 to 4.71	0.28
Hypercholesterolemia	1.36	0.72 to 2.58	0.34
Male gender	1.26	0.66 to 2.4	0.49
Tobacco history	1.15	0.62 to 2.15	0.66

*Relative risk adjusted by all the variables listed on the table.

Table 8. Cerebral Vascular Events. Multivariable Analysis. Reduced Model.

Variable	Relative Risk*	95% confidence interval	p-value
Peritoneal dialysis and diabetes	12.91	5.51 to 30.2	<0.001
Age older than 45 years	6.76	3.09 to 14.82	<0.001
Diabetes (no peritoneal dialysis)	4.03	1.72 to 9.44	0.001
Prior cardiovascular event	3.72	2.01 to 6.89	<0.001
Obesity at transplantation	0.20	0.07 to 0.6	0.004
Overweight at transplantation	0.41	0.2 to 0.81	0.011
Peritoneal dialysis (no diabetes)	3.08	1.2 to 7.89	0.019
Hypertension	1.74	0.95 to 3.18	0.07

*Relative risk adjusted by the other variables listed in the table.

Table 9. Cerebral Vascular Events with "Creatinine Level at 3 Months". Reduced Model.

Variable	Relative Risk*	95% confidence interval	p-value
Diabetes and peritoneal dialysis	11.28	4.66 to 27.3	<0.001
Age older than 45 years	6.11	2.76 to 13.52	<0.001
Diabetes (no peritoneal dialysis)	5.35	2.18 to 13.14	<0.001
Creatinine > 1.6mg/dl at 3 months	3.33	1.65 to 6.71	0.001
Prior cardiovascular event	3.10	1.60 to 6.01	0.001
Peritoneal dialysis (no diabetes)	3.03	1.10 to 8.36	0.03
Obesity at transplantation	0.33	0.11 to 0.99	0.049
Transplant after 1994	0.54	0.27 to 1.10	0.08

*Relative risk adjusted by the other variables listed in the table.

Table 10. Peripheral Vascular Events. Univariate Analysis.

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
Transplant era	1991 - 1994	444	22	99	97	95	
	1995 - 1998	478	19	99	97	96	0.97
Age at transplant	Younger than 45	495	12	99	99	98	
	45 and older	427	29	98	96	93	0.009
Gender	Female	402	12	99	98	97	
	Male	520	29	99	96	95	0.05
Re-transplantation status	Primary	791	38	99	97	95	
	Retransplant	131	3	100	100	98	0.21
Donor type	Living	243	11	100	97	96	
	Deceased	679	30	99	97	96	0.91
Prior CMV infection	No	354	10	99	98	97	
	Yes	563	31	99	97	95	0.11
Graft function	Immediate	704	29	99	98	96	
	Delayed	218	12	98	96	94	0.15
Diabetes pre-transplant	No	657	9	100	100	99	
	Yes	265	32	96	91	89	<0.001
Tobacco pre-transplant	No	603	15	99	98	98	
	Yes	319	26	98	96	92	<0.001
Prior cardiovascular event	No	770	23	99	99	98	
	Yes	153	18	96	91	87	<0.001
Obesity at transplant	Normal	503	23	99	98	96	
	Overweight	279	14	99	97	95	
	Obese	140	4	99	97	97	0.63
Hypertension at transplant	No	404	20	100	98	96	
	Yes	518		98	97	96	0.59
Hypertension at 3 months	No	395	21	99	96	96	
	Yes	435	17	99	99	96	0.33

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
High cholesterol at transplant	No	445	17	99	98	96	
	Yes	456	23	99	97	95	0.46
High cholesterol at 3 mo	No	182	6	99	98	97	
	Yes	668	32	99	98	96	0.43
Duration of dialysis	No dialysis	153	5	100	99	99	
	Less than 1 yr	277	11	99	98	96	
	Between 1 and 2 yr	249	16	99	96	96	
	Longer than 2 years	243	9	98	96	96	0.34
Rejection at 3 months	None	582	30	99	97	95	
	1	174	6	100	99	97	
	More than 1	114	3	99	99	98	0.43
Creatinine at 3 months	1.3 or lower	374	19	98	97	93	
	1.4 to 1.6	225	9	100	98	97	
	1.7 or higher	266	11	100	98	97	0.84
Pulse pressure at transplant	48 or lower	310	15	99	97	96	
	49 to 60	305	10	99	98	97	
	61 or higher	307	16	99	96	94	0.45
Pulse pressure at 3 months	45 or lower	248	7	100	99	99	
	46 to 58	310	15	98	96	96	
	59 or greater	272	16	99	97	94	0.19
Type of calcineurin inhibitor	Cyclosporine	781	36	99	97	96	
	Tacrolimus	109	4	98	96	96	0.89
Modality of dialysis	Hemodialysis	519	18	99	98	96	
	Peritoneal dialysis	198	16	97	94	92	0.012

Figure 3. Relative Risk for Post-Transplant Peripheral Vascular Events.

Interaction Between Tobacco Smoking and Prior CMV Infection.

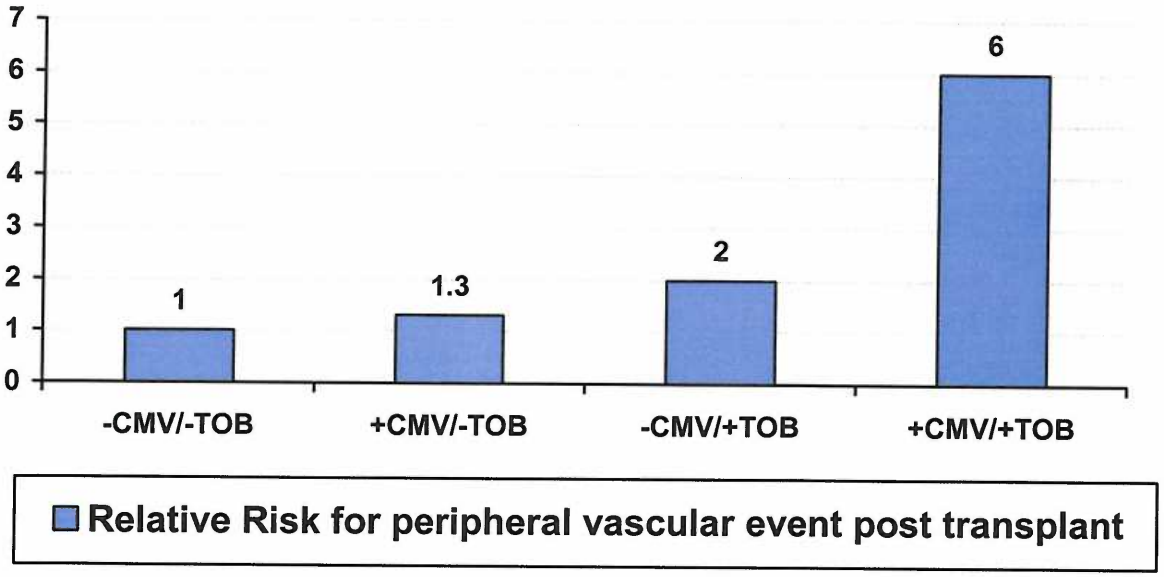

Table 11. Peripheral Vascular Events. Multivariable Analysis. Complete Model.

Variable	Relative Risk*	95% confidence interval	p-value
Diabetes pre-transplant	8.29	3.84 to 17.87	<0.001
Tobacco and prior CMV infection	4.27	1.52 to 12.0	0.006
Prior cardiovascular event	2.12	1.07 to 4.19	0.032
Age older than 45 years	2.13	1.04 to 4.38	0.04
Peritoneal dialysis	1.93	0.62 to 5.95	0.25
Male gender	1.39	0.68 to 2.83	0.36
Delayed graft function	1.34	0.65 to 2.74	0.43
CMV infection (no tobacco)	1.27	0.42 to 3.86	0.66
Tobacco (no CMV)	1.21	0.34 to 4.32	0.77
Hypertension	1.06	0.56 to 2.01	0.86
Hypercholesterolemia	0.93	0.49 to 1.77	0.82
Re-transplantation status	0.84	0.25 to 2.87	0.78

*Relative risk adjusted by all the variables listed on the table.

Table 12. Peripheral Vascular Events. Multivariable Analysis. Reduced Model.

Variable	Relative Risk*	95% confidence interval	p-value
Diabetes pre-transplant	8.48	3.97 to 18.1	<0.001
Tobacco and prior CMV infection	3.88	2.06 to 7.31	<0.001
Age older than 45 years	2.31	1.14 to 4.66	0.019
Prior cardiovascular event	2.25	1.17 to 4.35	0.016
Peritoneal dialysis	2.13	0.71 to 6.42	0.18

*Relative risk adjusted by the other variables listed in the table.

Table 13. First Cardiovascular Events. Univariate Analysis.

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
Transplant era	1991 - 1994	444	91	95	90	85	
	1995 - 1998	478	85	95	89	83	0.19
Age at transplant	Younger than 45	495	57	97	94	91	
	45 and older	427	119	92	84	76	<0.001
Gender	Female	402	63	96	92	87	
	Male	520	113	94	88	82	0.012
Re-transplantation status	Primary	791	156	94	89	84	
	Retransplant	131	20	98	91	87	0.26
Donor type	Living	243	30	98	94	89	
	Deceased	679	146	94	88	82	0.012
Prior CMV infection	No	356	57	96	91	87	
	Yes	563	119	94	88	82	0.029
Graft function	Immediate	704	132	96	91	85	
	Delayed	218	44	90	85	80	0.08
Diabetes pre-transplant	No	657	80	97	94	90	
	Yes	265	96	89	78	68	<0.001
Tobacco pre-transplant	No	603	76	97	93	90	
	Yes	319	100	91	83	72	<0.001
Prior cardiovascular event	No	770	102	97	93	89	
	Yes	153	74	84	70	57	<0.001
Obesity at transplant	Normal	503	82	96	92	87	
	Overweight	279	59	93	88	82	
	Obese	140	35	93	85	79	0.017
Hypertension at transplant	No	404	74	96	91	85	
	Yes	518	102	94	89	83	0.44
Hypertension at 3 months	No	385	64	97	91	86	
	Yes	432	72	98	93	87	0.91

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
High cholesterol at transplant	No	445	68	96	92	88	
	Yes	456	100	95	89	81	0.02
High cholesterol at 3 mo	No	176	23	99	94	88	
	Yes	661	118	97	92	86	0.16
Duration of dialysis	No dialysis	153	21	97	93	89	
	Less than 1 yr	277	43	96	92	88	
	Between 1 and 2 yr	249	57	93	87	80	
	Longer than 2 years	243	55	94	87	79	0.046
Rejection at 3 months	None	572	93	97	92	87	
	1	172	32	99	94	86	
	More than 1	112	24	97	90	84	0.29
Creatinine at 3 months	1.3 or lower	367	67	96	91	85	
	1.4 to 1.6	221	33	98	94	89	
	greater than 1.6	264	46	98	92	86	0.49
Pulse pressure at transplant	48 or lower	310	48	97	91	87	
	49 to 60	305	60	94	89	84	
	61 or greater	307	68	94	88	80	0.036
Pulse pressure at 3 months	45 or lower	244	33	98	93	91	
	46 to 58	304	49	98	93	88	
	59 or lower	269	54	97	91	82	0.08
Type of calcineurin inhibitor	Cyclosporine	781	148	95	90	84	
	Tacrolimus	109	19	92	87	82	0.63
Modality of dialysis	Hemodialysis	519	94	95	89	85	
	Peritoneal dialysis	198	50	92	85	78	
	Both	80	16	95	92	83	0.04

Figure 4. Relative Risk for Post-Transplant Cardiovascular Events. Interaction Between Diabetes Mellitus and Pre-Transplant Cardiovascular Disease.

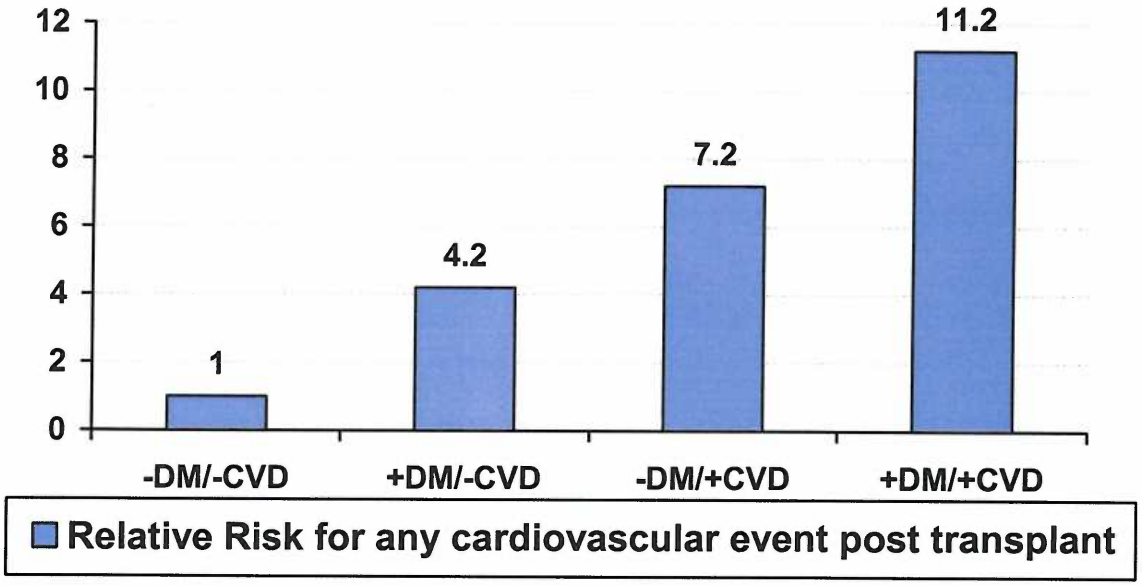

Table 14. First Cardiovascular Event Post-Transplant. Multivariable Analysis.

Complete Model.

Variable	Relative Risk*	95% confidence interval	p-value
Diabetes and prior cardiovascular event	10.29	6.35 to 16.66	<0.001
Diabetes (no prior cardiovascular event)	5.04	3.28 to 7.73	<0.001
Prior cardiovascular event (no diabetes)	4.47	2.74 to 7.29	<0.001
Tobacco history	2.33	1.68 to 3.22	<0.001
Age older than 45 years	2.08	1.44 to 2.99	<0.001
Prior CMV infection	1.39	0.99 to 1.95	0.057
Dialysis longer than 1 year	1.36	0.94 to 1.97	0.10
Pulse pressure 61 or greater	0.71	0.45 to 1.14	0.16
Hypertension	1.27	0.88 to 1.83	0.21
Obesity at transplant	1.24	0.80 to 1.92	0.34
Male gender	1.19	0.85 to 1.66	0.31
Peritoneal dialysis	1.34	0.70 to 2.56	0.38
Hypercholesterolemia	1.14	0.83 to 1.57	0.44
Delayed graft function	1.11	0.76 to 1.63	0.59
Transplant after 1994	1.04	0.74 to 1.47	0.82
Deceased donor	1.01	0.64 to 1.58	0.98

*Relative risk adjusted by all the variables listed on the table.

Table 15. First Cardiovascular Event. Multivariable Analysis. Reduced Model.

Variable	Relative Risk*	95% confidence interval	p-value
Diabetes and prior cardiovascular event	9.56	6.07 to 15.05	<0.001
Diabetes (no prior cardiovascular event)	4.69	3.12 to 7.06	<0.001
Prior cardiovascular event (no diabetes)	4.58	2.84 to 7.38	<0.001
Tobacco history	2.36	1.72 to 3.24	<0.001
Age older than 45 years	2.07	1.47 to 2.93	<0.001
Prior CMV infection	1.38	1.00 to 1.90	0.051
Dialysis longer than 1 year	1.37	0.99 to 1.88	0.056

*Relative risk adjusted by the other variables listed in the model.

Table 16. Patient Survival. Univariate Analysis.

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
Transplant era	1991 - 1994	444	128	96	91	88	
	1995 - 1998	478	64	97	94	89	0.81
Age at transplant	Younger than 45	495	78	98	94	91	
	45 and older	427	114	95	91	85	<0.001
Gender	Female	402	78	98	93	89	
	Male	520	114	96	92	88	0.29
Re-transplantation status	Primary	791	159	97	93	89	
	Retransplant	131	33	98	93	86	0.34
Donor type	Living	243	23	97	96	94	
	Deceased	679	169	96	92	87	<0.001
Prior CMV infection	No	356	71	97	94	91	
	Yes	566	121	96	92	87	0.40
Graft function	Immediate	704	123	97	94	91	
	Delayed	218	69	95	88	79	<0.001
Diabetes pre-transplant	No	657	115	97	94	90	
	Yes	265	77	95	90	84	<0.001
Tobacco pre-transplant	No	603	99	97	94	91	
	Yes	319	93	96	90	84	<0.001
Prior cardiovascular event	No	770	135	97	94	90	
	Yes	153	57	94	89	81	<0.001
Obesity at transplant	Normal	503	98	98	94	90	
	Overweight	279	61	95	91	88	
	Obese	140	33	96	91	86	0.09
Hypertension at transplant	No	404	80	96	92	89	
	Yes	518	112	97	93	88	0.19
Hypertension at 3 months	No	397	64	98	95	92	
	Yes	435	79	98	95	91	0.48

Variable	Categories	N at risk	Events	Event-free survival			p-value
				1yr	3yr	5yr	
High cholesterol at transplant	No	445	92	97	92	87	
	Yes	456	89	97	94	91	0.44
High cholesterol at 3 mo	No	182	27	98	94	89	
	Yes	670	122	98	96	92	0.63
Duration of dialysis	No dialysis	153	19	98	95	92	
	Less than 1 yr	277	46	98	95	91	
	Between 1 and 2 yr	249	61	96	92	89	
	Longer than 2 years	243	66	95	89	83	<0.001
Rejection at 3 months	None	590	100	98	95	91	
	1	183	41	98	93	89	
	More than 1	120	29	94	87	84	0.057
Creatinine at 3 months	1.3 or lower	377	60	98	96	93	
	1.4 to 1.6	225	40	99	95	92	
	greater than 1.6	267	53	98	94	89	0.14
Pulse pressure at transplant	48 or lower	310	48	97	94	91	
	49 to 60	305	65	97	93	88	
	61 or greater	307	79	96	92	86	0.006
Pulse pressure at 3 months	45 or lower	249	31	98	96	93	
	46 to 58	312	45	99	95	92	
	59 or lower	272	67	98	94	89	0.002
Type of calcineurin inhibitor	Cyclosporine	781	169	97	93	89	
	Tacrolimus	109	12	99	96	90	0.61
Modality of dialysis	Hemodialysis	519	116	97	92	88	
	Peritoneal dialysis	198	41	97	92	88	
	Both	80	22	95	95	86	0.10

Figure 5. Relative Risk for Post-Transplant Death. Interaction Between Tobacco Smoking and Type of Organ Donor (Living or Deceased).

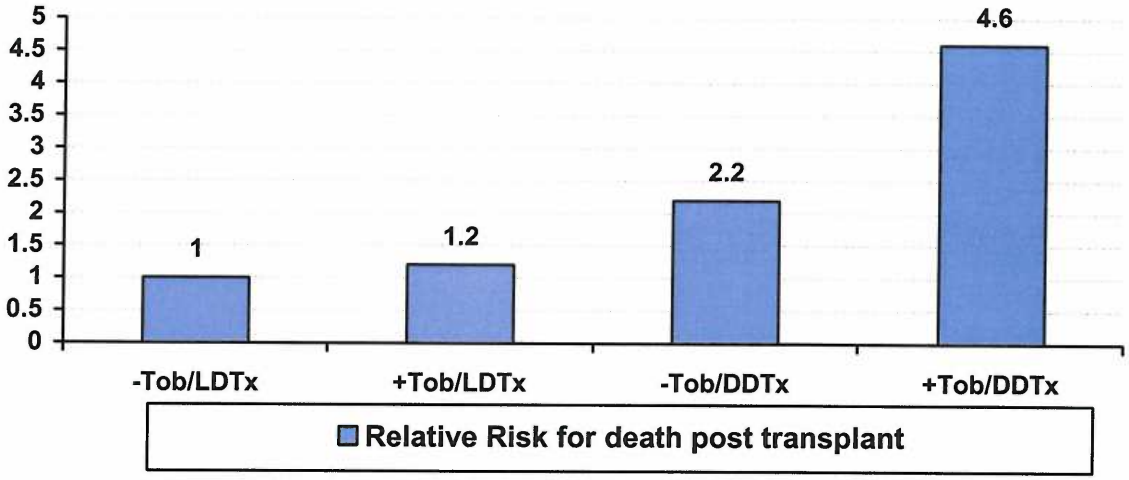

Table 17. Patient Survival. Multivariable Analysis. Complete Model.

Variable	Relative Risk*	95% confidence interval	p-value
Tobacco history and deceased donor	2.42	1.36 to 4.32	0.003
Diabetes pre-transplant	1.78	1.30 to 2.44	<0.001
Age older than 45 years	1.58	1.13 to 2.19	0.007
Prior cardiovascular event	1.57	1.10 to 2.34	0.012
Delayed graft function	1.44	1.03 to 2.01	0.031
Dialysis longer than 1 year	1.40	0.99 to 1.97	0.058
Pulse pressure 61 or greater	1.39	0.89 to 2.17	0.1
Deceased donor (no tobacco history)	1.32	0.79 to 2.32	0.3
Obesity at transplant	1.27	0.83 to 1.94	0.2
Hypertension	1.21	0.88 to 1.65	0.2
Hypercholesterolemia	0.80	0.59 to 1.09	0.2
Tobacco history and living donor	1.04	0.42 to 2.56	0.9

*Relative risk adjusted by all the variables listed on the table and modality of dialysis.

Table 18. Patient Survival. Multivariable Analysis. Reduced Model.

Variable	Relative Risk*	95% confidence interval	p-value
Tobacco history and deceased donor	1.93	1.41 to 2.63	<0.001
Diabetes pre-transplant	1.69	1.24 to 2.29	0.001
Age older than 45 years	1.61	1.17 to 2.21	0.003
Dialysis longer than 1 year	1.57	1.14 to 2.16	0.005
Prior cardiovascular event	1.59	1.12 to 2.25	0.01
Delayed graft function	1.62	1.17 to 3.23	0.04

*Relative risk adjusted by the other variables listed in the table.

Table 19. Patient Survival. Multivariable Analysis Including 3-month Variables.

Reduced Model.

Variable	Relative Risk*	95% confidence interval	p-value
Tobacco history and deceased donor	3.52	1.97 to 6.31	<0.001
Age older than 45 years	1.81	1.25 to 2.63	0.002
Diabetes pre-transplant	1.76	1.24 to 2.51	0.002
Pulse pressure > 58 mmHg	1.64	1.05 to 2.55	0.029
Prior cardiovascular event	1.52	1.02 to 2.26	0.04
Dialysis longer than 1 year	1.47	1.02 to 2.12	0.04
Hypercholesterolemia at transplant	0.7	0.50 to 1.00	0.05
Deceased donor (no tobacco history)	1.60	0.9 to 2.85	0.1

*Relative risk adjusted by the other variables listed in the table.

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