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Explained and Unexplained Ischemic Heart Disease Risk after Renal Transplantation

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Abstract. Whether the high incidence of ischemic heart disease (IHD) among renal transplant patients can be attributed to the same risk factors that have been identified in the general population is unclear. The risk for major IHD events occurring >1 yr after transplantation among 1124 transplant recipients was estimated by using the risk calculated from the Framingham Heart Study (FHS). The FHS risk predicted IHD (relative risk, 1.28; 95% confidence interval, 1.20 to 1.40; $P < 0.001$); however, the FHS risk tended to underestimate the risk of IHD for renal transplant recipients. This was largely attributable to increased risks associated with diabetes mellitus and, to a lesser extent, age and cigarette smoking for renal transplant recipients. For men, the relative risks for diabetes mellitus were 2.78 (1.73 to 4.49) and 1.53 for the transplant recipient and FHS populations, respectively; the relative risks for age (in years) were 1.06 (1.04 to 1.08) and 1.05, respectively, and those for smoking were 1.95 (1.20 to 3.19) and 1.69, respectively. For women, the relative risks for diabetes mellitus were 5.40 (2.73 to 10.66) and 1.82, respectively. There was a tendency for the risk associated with cholesterol levels to be higher for transplant recipients, compared with the FHS population, but the risks associated with high-density lipoprotein cholesterol levels and BP appeared to be comparable. Independent of these and other risk factors, the adjusted risk of IHD for the transplant recipient population has decreased. Compared with the era before 1986, transplantation between 1986 and 1992 was associated with a lower relative risk of 0.60 (0.39 to 0.92); transplantation after 1992 was associated with an even lower relative risk of 0.27 (0.11 to 0.63) for IHD. Of concern was the fact that dihydropyridine calcium channel antagonists were associated with an increased risk for IHD (relative risk, 2.26; 95% confidence interval, 1.24 to 4.12; $P = 0.008$), and this association was independent of other antihypertensive agents and risk factors. Therefore, although the FHS risk predicts IHD after renal transplantation, it tends to underestimate the risks, especially the risk associated with diabetes mellitus. The unexpected finding that dihydropyridine calcium channel antagonists were associated with an increased IHD risk merits further evaluation.

A number of observational studies have suggested that cardiovascular disease is more common among renal transplant recipients than in the general population (1–8). Recently, a National Kidney Foundation task force on cardiovascular disease reviewed the available evidence and concluded that renal transplant recipients were at high risk for cardiovascular disease and that a number of potentially modifiable risk factors could be targeted for intervention (9). Indeed, several risk factors have been found to be correlated with the incidence of cardiovascular disease events (1–8), and it is possible that the increased incidence of posttransplant cardiovascular disease is the result of an increase in the prevalence of traditional risk factors, such as diabetes mellitus, hypertension, cigarette smoking, and hyperlipidemia. If so, this would suggest that aggressive management of these risk factors could reduce the incidence of cardiovascular disease in this population. Conversely, if the incidence of cardiovascular disease is higher than predicted by traditional risk factors, then this would suggest that other factors, *e.g.*, direct toxic effects of immunosuppression, rejection, or infection, may play significant roles.

Although we previously reported that the incidence of cardiovascular disease is higher among renal transplant recipients, compared with age- and gender-matched control subjects (1), no studies have examined the incidence after adjustment for multiple risk factors. In this study, we compared the observed and expected incidences of ischemic heart disease (IHD) in a population of renal transplant recipients. The expected incidence was calculated using equations based on the relationship between risk factors and IHD in the Framingham Heart Study (FHS) (10).

Materials and Methods

Study Population and End Points

We reviewed clinical records for 1500 transplants performed at Hennepin County Medical Center between February 13, 1963, and July 31, 1997. All patients were eligible for at least 12 mo of follow-up monitoring.

We defined IHD as myocardial infarction (documented by elevated enzyme levels, with or without electrocardiographic changes), coronary artery revascularization (by angioplasty or bypass grafting), or death most likely attributable to IHD. We did not include patients whose only evidence of IHD was angina pectoris or congestive heart failure. In this analysis, we excluded patients who exhibited evidence

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of pretransplant IHD ($n = 107$), patients who developed IHD in the first posttransplant year ($n = 43$, 10 of whom also exhibited pretransplant IHD), and patients who exhibited neither pretransplant IHD nor IHD in the first posttransplant year but failed to survive with a functioning graft for at least 1 yr ($n = 236$). We selected this population to exclude patients with advanced IHD at the time of transplantation, thereby enabling us to study the relationship between posttransplant conditions (measured during the first posttransplant year) and subsequent primary IHD events. There were 1124 transplants available for this analysis. In a secondary analysis, we also examined risk factors for IHD events that occurred at any time after transplantation, in the entire patient population. For this analysis, we examined risk factors determined at or before the time of transplantation. There were 1500 transplants available for this secondary analysis.

We used IHD risk-prediction equations from the FHS to calculate IHD risks for renal transplant recipients (10). The definition of IHD used in the FHS was more inclusive than the definition used for our transplant recipient population. Specifically, in the FHS the definition of IHD included angina pectoris, unrecognized myocardial infarction, and coronary insufficiency. It is probable that our definition of IHD for transplant recipients underestimates the incidence of IHD, as defined in the FHS. Although the sensitivity of the definition used for transplant recipients is no doubt lower than that used in the FHS, the specificity is probably higher. We thought that data on angina pectoris and other conditions considered in the FHS would be difficult to extract consistently and accurately using a retrospective chart review. Therefore, we elected to use a more conservative definition of IHD, keeping in mind the possibility that the incidence of IHD might be underestimated in our transplant recipient population, compared with the FHS.

Risk Factors

In addition to the risk factors used in the FHS risk calculations, we collected data on a number of other possible risk factors. Patient characteristics recorded at the time of transplantation included recipient age, gender, race/ethnicity (Caucasian, African American, Native American, Asian American, Hispanic, and other), body weight, height, body mass index (weight in kilograms divided by height in meters squared), body surface area, cause of renal failure (type I diabetes mellitus, type II diabetes mellitus, primary glomerulonephritis, nephrosclerosis including hypertension and renovascular disease, polycystic kidney disease, systemic lupus erythematosus, and other), total duration of end-stage renal disease (ESRD) before transplantation, and previous transplants. In addition to pretransplant IHD, we collected data on cerebral vascular disease (transient ischemic attacks and strokes), peripheral vascular disease (revascularization procedures and amputations), and malignancies. We also recorded who had undergone bilateral nephrectomies before transplantation.

To examine the effects of changes with time, before analysis we arbitrarily defined three transplantation eras, on the basis of major changes in the prophylactic immunosuppression protocols used during the period of study. Era 1 (39.1% of transplants) was before February 1986, before the introduction of cyclosporine A (CsA) (Sandimmune; Novartis, Basel, Switzerland). During that era, prophylactic immunosuppression included the use of Minnesota antilymphocyte globulin (MALG) (University of Minnesota, Minneapolis, MN), azathioprine, and corticosteroids. Era 2 (34.7% of transplants) extended from February 1986 through August 1992. During that era, CsA was added for prophylactic immunosuppression. Also during era 2, MALG was used as induction therapy until renal function was established and CsA administration was initiated. Azathioprine and corticosteroids continued to be used. Era 3 (26.2% of transplants) extended from September 1992 through July 1997; during that era, MALG was no longer available. MALG was initially replaced by antithymocyte globulin (ATG) (Upjohn, Kalamazoo, MI). During that era, the use of ATG was eventually abandoned; instead, CsA administration was initiated at the time of transplantation. Also during era 3, Neoral (Novartis) was substituted for Sandimmune and mycophenolate mofetil (Cellcept; Roche, Nutley, NJ) was substituted for azathioprine. Corticosteroids continued to be used, albeit in reduced doses.

We recorded when acute rejection episodes occurred after transplantation. Fasting laboratory parameters were recorded during visits made at 3, 6, and 12 mo. These included white blood counts, hemoglobin, serum albumin, cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, glucose, and creatinine levels, and 24-h urinary protein excretion. Chemical values were all measured after an overnight fast. In addition, sitting, resting, systolic, and diastolic BP were recorded at 3, 6, and 12 mo. In the analysis of factors predicting new IHD events after the first posttransplant year, we used the average of laboratory and BP values recorded at 3, 6, and 12 mo.

In the multivariate analysis, total and HDL cholesterol categories were defined according to the National Cholesterol Education Program Adult Treatment Panel II guidelines (11). BP categories were defined according to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (12). Patients were defined as being diabetic if their renal failure was caused by type I or type II diabetes mellitus or if they required treatment with insulin and/or an oral hypoglycemic agent at 3, 6, or 12 mo after transplantation. These three categories were analyzed separately, to study their relationship with posttransplant IHD.

Missing Values

Data collected at the time of transplantation were complete for all patients. All patients were monitored regularly at the center, including at least annual visits after the first posttransplant year, for as long as they maintained functioning allografts. When a patient was hospitalized at another institution, the records were obtained. Therefore, data on IHD events and acute rejection episodes are accurate and complete. Some of the posttransplant laboratory and BP values were not available for all of the 1124 patients included in the primary analysis. Therefore, we included a "missing value" category along with other categories for each variable in the multivariate analyses (for example, serum cholesterol levels could be "high," "not high," or "missing"). This allowed us to avoid possible bias from exclusion of patients with one or more missing values but allowed us to examine in each case whether there was some characteristic of the patients with missing data that influenced IHD. However, we also repeated the analysis for the subset of patients with no missing data, to confirm that missing values did not have major effects on the results and conclusions. In general, there were relatively few missing values. For example, data on total cholesterol levels were available for 1006 patients (89.5%) and data on HDL cholesterol levels were available for 848 patients (75.4%). Data on BP were available for 1019 patients (90.7%). Data on smoking at the time of transplantation were available for 1035 patients (92.1%). For the secondary analysis of both early and late posttransplant IHD events ($n = 1500$ transplants), no posttransplant variables were included. This obviated problems with missing values for patients who experienced graft failure or an IHD event before these data were collected.

Analysis

We used a Cox proportional-hazards analysis to examine the relationship between several known risk factors and IHD in our renal transplant recipient population. For this analysis, we used the same covariate definitions that were used in a recent Cox analysis of the FHS population (10). This enabled us to qualitatively compare the relationship between traditional risk factors and IHD in a normal population with that found in a renal transplant recipient cohort.

We calculated the risk attributable to traditional covariates of the FHS (FHS risk) using coefficients from a Cox proportional-hazards model (10). The FHS risk equaled $e^A - 3.0975$ (for male patients) or $e^B - 9.92545$ (for female patients), where $A = 0.04826 \times$ age $-$ 0.65945 (for cholesterol levels of $<$160 mg/dl) + 0.17692 (for cholesterol levels of 200 to 239 mg/dl) + 0.50539 (for cholesterol levels of 240 to 279 mg/dl) + 0.65713 (for cholesterol levels of $\geq$280 mg/dl) + 0.49744 (for HDL levels of $<$35 mg/dl) + 0.24310 (for HDL levels of 35 to 44 mg/dl) $-$ 0.05107 (for HDL levels of 50 to 59 mg/dl) $-$ 0.48660 (for HDL levels of $\geq$60 mg/dl) $-$ 0.00226 (for BP of $<$120 mmHg and $<$80 mmHg) + 0.28320 (for BP of 130 to 139 mmHg or 85 to 89 mmHg) + 0.52168 (for BP of 140 to 159 mmHg or 90 to 99 mmHg) + 0.61859 (for BP of $\geq$160 mmHg or $\geq$100 mmHg) + 0.42839 (if diabetic) + 0.52337 (if smoked cigarettes) and $B = 0.33766 \times$ age $- 0.00268 \times$ age^2 $-$ 0.26138 (for cholesterol levels of $<$160 mg/dl) + 0.20771 (for cholesterol levels of 200 to 239 mg/dl) + 0.24385 (for cholesterol levels of 240 to 279 mg/dl) + 0.53513 (for cholesterol levels of $\geq$280 mg/dl) + 0.84312 (for HDL levels of $<$35 mg/dl) + 0.37796 (for HDL levels of 35 to 44 mg/dl) + 0.19785 (for HDL levels of 45 to 49 mg/dl) $-$ 0.42951 (for HDL levels of $\geq$60 mg/dl) $-$ 0.53363 (for BP of $<$120 mmHg and $<$80 mmHg) $-$ 0.06773 (for BP of 130 to 139 mmHg or 85 to 89 mmHg) + 0.26288 (for BP of 140 to 159 mmHg or 90 to 99 mmHg) + 0.46573 (for BP of $\geq$160 mmHg or $\geq$100 mmHg) + 0.59626 (if diabetic) + 0.29246 (if smoked cigarettes), where age is in years.

We used the FHS risk as a covariate in a Cox proportional-hazards model that also included each individual covariate in the FHS risk calculation. We did this to further examine how well the relationship between IHD and these traditional risk factors was predicted by the relationship defined in a normal population. Finally, we included other covariates (potentially unique to transplant recipients) along with traditional IHD risk factors, to examine whether any of these factors might be associated with IHD among renal transplant recipients. For each of the major covariates included in the Cox proportional-hazards analyses, we tested the assumption of proportionality by visually inspecting the hazard functions and by using time-dependent covariates in bivariate models, *e.g.*, $\exp[V_i + V_i \cdot \ln(T)]$, where V_i is the i-th covariate and T is time. The only time-interaction covariate that was statistically significant was ESRD caused by type I diabetes mellitus ($P = 0.03$). The hazard function plot for this covariate did not "cross" or otherwise appear to seriously violate the proportionality assumption. Nevertheless, we also analyzed the results of the final model using stratification for type I diabetes mellitus, to assess the effects of this violation on the results for other covariates.

In addition to examining direct correlations between risk factors and IHD in the Cox models, we also examined the effects of interactions with gender and (in the case of pretransplant bilateral nephrectomy) interactions with the cause of ESRD. We tested for interactions by including multiplicative interaction terms. For example, to test the interaction between variables A and B, we included $A \times B$ as a covariate with both A and B. All analyses were performed with Statistical Package for the Social Sciences software (SPSS, Inc., Chicago, IL). Results of the Cox analyses are expressed as relative risks and 95% confidence intervals. In general, covariates were only included in models at $P < 0.05$.

Results

There were similarities and differences between the renal transplant recipient and FHS populations. Among 1124 transplant recipients, 56.4% were male, whereas 46.6% of the FHS population ($n = 5345$) were male subjects (10). The age at transplantation among male patients in our population was 40.1 $\pm$ 12.8 yr, compared with 48.6 $\pm$ 11.7 yr for men in the FHS (10). The age at transplantation among women was 40.6 $\pm$ 13.7 yr, compared with 49.8 $\pm$ 12.0 yr for women in the FHS (10). The prevalence of diabetes mellitus among male transplant recipients was 29.0%, compared with 5.2% in the FHS. The prevalence of diabetes mellitus among female transplant recipients was 28.4%, compared with 4.0% in the FHS (10). The prevalence of cigarette smoking at the time of transplantation among male patients was 24.6%, compared with 40.4% in the FHS. The prevalence of smoking among women transplant recipients was 25.1%, compared with 37.7% in the FHS (10).

There were 123 patients (81 men and 42 women) who experienced their first IHD event more than 1 yr after transplantation. Among this group of patients, 84 experienced documented myocardial infarctions, and these were the only IHD events for 49 patients. In 81 of the 84 cases, the myocardial infarction was the first IHD event. Percutaneous angioplasty was performed for 24 patients, but in only 8 cases was this the only IHD event and in only 12 was it the first IHD event. Bypass grafting was performed in 37 cases; this was the only IHD event in 19 cases and the first event in 19. There were 22 deaths that were thought to be attributable to IHD. In 11 cases, this was the first and only IHD event.

The most striking difference in the relationship between IHD and risk factors in the FHS and transplant recipient populations was for diabetes mellitus (Table 1). For men in the FHS, the risk of IHD was 53% greater for diabetic patients, compared with nondiabetic subjects, whereas for male transplant recipients the risk associated with diabetes mellitus was almost threefold higher, compared with nondiabetic subjects. Even more dramatic was the difference for women, for whom diabetes mellitus was associated with an 82% increased risk of IHD in the FHS cohort, compared with a fivefold increase among transplant recipients. In this analysis, diabetes mellitus was a composite including type I diabetes mellitus that caused ESRD (17.7% of the transplant recipient population), type II diabetes mellitus that caused ESRD (6.8% of the transplant recipient population), and diabetes mellitus that did not cause ESRD (4.5% of the transplant recipient population).

Interestingly, low HDL cholesterol levels in women were more strongly associated with IHD for transplant recipients than for FHS subjects; however, only 3.5% of women with transplants (17 of 490) (and 7.9% of men) exhibited low HDL levels. Otherwise, the association between HDL and IHD appeared to be similar in the FHS and transplant recipient populations. In general, there appeared to be a somewhat greater risk of IHD associated with elevated total cholesterol levels in

Table 1. Relative risk for IHD among control subjects (FHS) *versus* patients >1 yr after renal transplantation[a]

Variable	Men		Women	
	FHS	Transplant	FHS	Transplant
Age (yr)	1.05	1.06 (1.04 to 1.08)[b]	1.40	1.10 (0.91 to 1.32)
Age^2 (yr)			0.997	0.999 (0.997 to 1.002)
Cholesterol (mg/dl)				
<160	0.52	0.00 (0.00 to 2×10^{77})	0.77	0.00 (0.00 to 0.00)
160 to 199	*1.00*	*1.00*	*1.00*	*1.00*
200 to 239	1.19	2.39 (0.97 to 5.91)	1.23	2.07 (0.25 to 16.99)
240 to 279	1.66	2.02 (0.81 to 5.04)	1.28	2.44 (0.30 to 19.86)
>280	1.93	2.25 (0.88 to 5.76)	1.71	1.84 (0.22 to 15.62)
HDL (mg/dl)				
<35	1.64	1.02 (0.32 to 3.29)	2.32	9.16 (2.18 to 38.48)[b]
35 to 44	1.28	1.37 (0.54 to 3.46)	1.46	1.48 (0.42 to 5.24)
45 to 49	*1.00*	*1.00*	1.00	0.37 (0.04 to 3.29)
50 to 59	0.95	1.32 (0.53 to 3.28)	*1.00*	*1.00*
≥60	0.61	1.07 (0.45 to 2.54)	0.65	0.99 (0.37 to 2.70)
BP (mmHg)				
<120 and <80	1.00	0.25 (0.03 to 2.14)	0.59	0.56 (0.13 to 2.54)
120 to 129 or 80 to 84	*1.00*	*1.00*	*1.00*	*1.00*
130 to 139 or 85 to 89	1.33	1.05 (0.46 to 2.41)	0.93	1.26 (0.46 to 3.48)
140 to 159 or 90 to 99	1.68	1.19 (0.56 to 2.55)	1.30	1.63 (0.64 to 4.17)
≥160 or ≥100	1.86	1.47 (0.61 to 3.55)	1.59	0.31 (0.06 to 1.56)
Diabetes mellitus (Y/N)	1.53	2.78 (1.73 to 4.49)[b]	1.82	5.40 (2.73 to 10.66)[b]
Cigarette use (Y/N)	1.69	1.95 (1.20 to 3.19)[b]	1.34	1.82 (0.87 to 3.81)

[a] Shown are relative risks (95% confidence intervals). A relative risk greater or less than 1.00 indicates a higher or lower risk for ischemic heart disease (IHD), respectively. For example, among Framingham Heart Study (FHS) men, the risk is 5% higher for each 1-yr increase in age. Reference risks for cholesterol levels, high-density lipoprotein (HDL) levels, and BP are indicated by *1.00*. Included in the model (but not in the table) were variables testing the effects of missing values (each $P > 0.2$). *P* values and confidence intervals for FHS coefficients are not indicated (10).

[b] $P < 0.05$.

the transplant recipient cohort, compared with the FHS population (Table 1). It is noteworthy that 58.4% of men (370 of 634) and 64.1% of women (314 of 490) exhibited fasting total cholesterol levels that averaged >240 mg/dl during the first posttransplant year. However, in the transplant recipient population, even borderline cholesterol elevations of 200 to 239 mg/dl (present in 27.8% of men and 25.1% of women) appeared to be associated with an increased incidence of IHD. There were probably too few patients (2.1% of men and 2.9% of women) with low (<160 mg/dl) cholesterol levels to reliably assess the association of low levels with IHD among renal transplant patients.

The association of IHD with cigarette smoking also appeared to be somewhat greater for transplant recipients than for the FHS population. The association of IHD with age for men was also qualitatively greater among transplant recipients. For each year of age, the risk of IHD was 4.9% higher among men in the FHS population, whereas it was 5.9% higher among male transplant recipients. The association of IHD with age for women was not substantially different among the transplant recipients, compared with the FHS population. Virtually identical results were obtained in an analysis that excluded all patients with any missing data, so these results do not seem to have been influenced by missing values.

The FHS risk predicted actual IHD events among renal transplant recipients (relative risk, 1.28; 95% confidence interval, 1.20 to 1.40; $P < 0.0001$). However, we also investigated how well the FHS risk predicted IHD among renal transplant recipients and whether the relationships between the risk factors making up the FHS risk predictor were different in the transplant recipient population, compared with the FHS population. In this analysis, we excluded all transplant patients with any missing data, because otherwise it would have been impossible to exactly calculate the FHS risk. In a Cox proportional-hazards model that included each of the individual risk factors from the FHS risk-prediction equations, the FHS risk was no longer a statistically significant predictor of IHD. In this model, age, diabetes mellitus, cigarette smoking, and low HDL levels in women appeared to be the best predictors of IHD (data not shown). In a Cox proportional-hazards model that included only age, diabetes mellitus, and cigarette smoking, the FHS risk did not independently predict IHD (Table 2). This suggests that the relationships of age, gender, and diabetes mellitus with IHD among the renal transplant patients differ

Table 2. Failure of the calculated FHS risk to predict IHD among renal transplant patients, independent of age, diabetes mellitus, and cigarette smoking[a]

Variable	Relative Risk	95% CI	*P* Value
Age (yr)	1.06	1.04 to 1.08	0.000
Age of women (yr)	0.97	0.96 to 0.98	0.000
Diabetic (Y/N)	1.03	1.00 to 1.05	0.034
Diabetic women (Y/N)	6.56	3.44 to 12.5	0.000
Smoking (Y/N)	1.78	1.19 to 2.68	0.005
FHS risk	1.08	0.95 to 1.23	0.230

[a] Cox proportional-hazards model ($n = 1035$ transplants and 117 IHD events) was used. Shown are relative risks, 95% confidence intervals, and *P* values. A relative risk greater or less than 1.00 indicates a higher or lower risk for IHD, respectively. For example, the risks are approximately 6% higher for each 1-yr increase in age for men and 3% higher for women (add effects of age + age in women). The FHS risk is defined by a Cox proportional-hazards model that includes age, diabetes, and other risk factors (see Materials and Methods for details). Cases with any missing data were excluded. CI, confidence interval.

from those for the FHS population. However, these results should be interpreted with caution, because the relatively small sample size and other factors might have affected the ability of the FHS risk to predict IHD among transplant recipients.

We investigated whether other non-FHS risk factors unique to renal transplant recipients were also associated with late posttransplant IHD (Table 3). In this analysis, we examined the relationships for three categories of diabetes mellitus and found that in men the risk associated with non-ESRD-producing diabetes mellitus was similar to the risk associated with diabetes mellitus that resulted in ESRD. Conversely, in women the risk associated with diabetes mellitus that caused ESRD appeared to be significantly greater than the risk associated with non-ESRD-producing diabetes mellitus. However, it should be kept in mind that the proportions of the population with non-ESRD-producing diabetes mellitus were only 27 of 490 women (5.5%) and 23 of 634 men (3.6%). Therefore, the power to detect associations with non-ESRD-producing diabetes mellitus was probably small.

As in the FHS, age, cigarette smoking, and serum cholesterol levels were independently associated with IHD (Table 3). However, hypertriglyceridemia was also independently associated with IHD in our transplant recipient cohort. In contrast, HDL levels were not an independent risk factor when total cholesterol and triglyceride levels were taken into account. Much of the risk of hypercholesterolemia appeared to be attributable to elevated LDL levels. Indeed, substituting increased LDL levels (>160 mg/dl) for high total cholesterol levels revealed an almost identical independent association with IHD (data not shown).

When there were two or more acute rejection episodes during the first year, the risk for subsequent IHD was also increased (Table 3). The severity of acute rejection and how

Table 3. Risk factors for IHD events occurring >1 yr after renal transplantation[a]

Variable	Full Model			Stratified Model		
	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
ESRD, type I diabetes mellitus (0.18)	3.03	1.75 to 5.24	0.000			
ESRD, type I diabetes mellitus in women (0.07)	2.31	1.09 to 4.86	0.028	2.30	1.09 to 4.85	0.029
ESRD, type II diabetes mellitus (0.07)	2.79	1.26 to 6.17	0.012	2.76	1.24 to 6.14	0.013
ESRD, type II diabetes mellitus in women (0.03)	3.35	0.99 to 11.3	0.052	3.23	0.96 to 10.9	0.033
Nonrenal disease diabetes (0.04)	2.54	1.15 to 5.60	0.021	2.59	1.17 to 5.71	0.051
Age (1.00, mean = 41.8 yr)	1.06	1.04 to 1.08	0.000	1.06	1.04 to 1.08	0.000
Age in women (0.44, mean = 41.5 yr)	0.99	0.97 to 0.99	0.000	0.98	0.97 to 0.99	0.000
Smoking at transplant (0.25)	1.85	1.23 to 2.76	0.003	1.87	1.25 to 2.80	0.002
Transplant in 1986 to 1992 (0.35)	0.60	0.39 to 0.92	0.019	0.59	0.38 to 0.91	0.018
Transplant after 1992 (0.26)	0.27	0.11 to 0.63	0.002	0.26	0.11 to 0.61	0.002
Two or more 1st year rejections (0.16)	1.62	1.04 to 2.53	0.034	1.62	1.04 to 2.53	0.034
Bilateral nephrectomy (0.29)	0.45	0.26 to 0.77	0.004	0.45	0.26 to 0.78	0.004
Bilateral nephrectomy for PKD (0.04)	3.45	1.50 to 7.95	0.004	3.50	1.52 to 8.06	0.003
Serum albumin levels of <4.0 mg/dl (0.54)	1.71	1.10 to 2.65	0.017	1.71	1.10 to 2.66	0.017
Proteinuria (0.17)	1.69	1.08 to 2.64	0.022	1.65	1.06 to 2.58	0.028
Cholesterol levels of >200 mg/dl (0.77)	2.18	1.01 to 4.72	0.048	2.18	1.01 to 4.73	0.048
Triglyceride levels of >350 mg/dl (0.07)	1.90	1.04 to 3.47	0.038	1.88	1.03 to 3.44	0.040

[a] Cox proportional-hazards models ($n = 1124$ transplants and 123 IHD events), with and without stratification for renal disease from type I diabetes mellitus, which violates the proportional-hazards assumption, were used. Shown are relative risks, 95% confidence intervals, *P* values, and (in parentheses) the proportion of patients having the characteristic indicated by that variable. A relative risk greater or less than 1.00 indicates a higher or lower risk for IHD, respectively. Included in the models, but not in the table, were variables testing the effects of missing values (each with $P > 0.5$). ESRD, end-stage renal disease; PKD, polycystic kidney disease.

rejection episodes were treated were not correlated with IHD (data not shown). Similarly, the presence of proteinuria was associated with a higher risk of IHD. Independent of proteinuria, low serum albumin levels (<4.0 mg/dl) were also correlated with an increased risk of IHD. Removal of both native kidneys before transplantation was associated with a lower incidence of IHD. Splenectomy, which was once frequently performed in conjunction with bilateral nephrectomy, was not an independent predictor of IHD (data not shown). Interestingly, patients who had undergone bilateral nephrectomies of polycystic kidneys were more likely to experience late IHD events (Table 3); however, polycystic kidney disease *per se* was not an independent risk factor for IHD. The association of nephrectomy with IHD was independent of any other type of renal disease, *e.g.*, it was similar in patients with diabetes mellitus and glomerulonephritis (data not shown).

The incidence of posttransplant IHD has decreased (Table 3). Compared with patients who received transplants before 1986, those who received transplants between 1986 and 1992 exhibited a 40% reduction in risk and those who received transplants after 1992 exhibited a 73% reduction in risk (Table 3). The reasons for this decrease in IHD risk are not readily apparent. The different prophylactic immunosuppression protocols, *e.g.*, the use of CsA or antibody induction with MALG or ATG, were not independent predictors of IHD (data not shown).

In a secondary analysis, we also examined risk factors for early and late IHD events (Table 4). In this analysis, we included all cases of IHD after renal transplantation ($n = 189$ events) that occurred in the whole patient population ($n = 1500$ transplants). However, we included only risk factors determined before or at the time of transplantation. Reliable data on lipid levels and BP were not available at the time of transplantation. For the most part, all of the risk factors identified in the primary analysis were also risk factors in this expanded analysis. In addition, pretransplant IHD was an independent risk factor for posttransplant IHD events (Table 4).

Finally, we examined whether the use of specific medications at 1 yr after transplantation was correlated with the risk of subsequent IHD. None of the lipid-lowering or antiplatelet agents were correlated with subsequent IHD (data not shown). However, among the different antihypertensive agents examined, we found that dihydropyridine calcium channel antagonists were associated with an increased risk of IHD (Table 5). The association between dihydropyridine calcium channel antagonists and IHD was independent of all other risk factors for IHD, including BP (data not shown).

Discussion

There are a number of important limitations to this study. The definition of IHD for the renal transplant recipients was different from that used in the FHS. The definition of IHD used in the FHS is likely to be more sensitive but less specific than the definition used for our renal transplant recipient population. However, this bias should decrease, not increase, the apparent risk of IHD among transplant patients, compared with control subjects, and in no case was the risk associated with a covariate less than expected for the renal transplant recipient population. Cholesterol levels, HDL levels, and BP were measured differently for the renal transplant patients, compared with the FHS population, and it is also possible that these risk factors were treated more or less aggressively for the transplant recipients than for the FHS cohort. However, this is an unavoidable limitation of the application of risk factors to clinical practice in general and is not just a limitation of this analysis. Finally, the numbers of transplant patients and IHD events in this study may be too small for adequate assessment of the association of all risk factors with IHD.

Despite these limitations, there were some important findings in this study. In general, most of the risk factors in the FHS also predicted risk when applied to renal transplant recipients (Table 1). However, the tendency was for several of the FHS risk factors to underestimate the risk of IHD among transplant recipients (Figure 1). Diabetes mellitus was the most

Table 4. Risk factors for early and late IHD after renal transplantation (posttransplant covariates were excluded)[a]

Variable	Relative Risk	95% CI	*P* Value
ESRD, type I diabetes mellitus (0.17)	3.23	2.04 to 5.09	0.000
ESRD, type I diabetes mellitus in women (0.07)	1.93	1.04 to 3.58	0.036
ESRD, type II diabetes mellitus (0.09)	2.21	1.27 to 3.82	0.005
ESRD, type II diabetes mellitus in women (0.03)	1.95	0.80 to 4.73	0.140
Age (1.00, mean = 41.8 yr)	1.07	1.05 to 1.08	0.000
Age in women (0.42, mean = 41.5 yr)	0.99	0.98 to 0.99	0.000
Smoking at transplantation (0.24)	1.53	1.11 to 2.13	0.010
Transplant in 1986 to 1992 (0.32)	0.69	0.49 to 0.99	0.042
Transplant after 1992 (0.26)	0.48	0.29 to 0.80	0.004
Bilateral nephrectomy (0.28)	0.54	0.35 to 0.84	0.006
Bilateral nephrectomy in PKD (0.04)	2.39	1.19 to 4.80	0.014
Pretransplant IHD (0.07)	1.98	1.32 to 2.97	0.001

[a] Cox proportional-hazards model ($n = 1500$ transplants and 189 IHD events) was used. Shown are relative risks, 95% confidence intervals, *P* values, and (in parentheses) the proportion of patients having the characteristic indicated by that variable.

Table 5. Independent association of antihypertensive agents with IHD events occurring >1 yr after renal transplantation[a]

Variable	Relative Risk	95% CI	*P* Value
Dihydropyridine calcium channel blocker (0.19)	2.26	1.24 to 4.12	0.008
Nondihydropyridine calcium channel blocker (0.16)	1.28	0.59 to 2.76	0.526
Beta-blocker (0.29)	0.93	0.60 to 1.44	0.742
Converting enzyme inhibitor (0.20)	0.97	0.48 to 1.95	0.924
Vasodilator (0.10)	0.48	0.22 to 1.06	0.066
Thiazide diuretic (0.13)	1.22	0.74 to 2.01	0.430
Loop diuretic (0.30)	1.41	0.93 to 2.16	0.108
Other antihypertensive (0.20)	1.71	0.99 to 2.93	0.053

[a] Cox proportional-hazards model (n = 969 transplants and 116 IHD events) was used. Shown are relative risks, 95% confidence intervals, *P* values, and (in parentheses) the proportion of patients receiving that antihypertensive medication at 1 yr after transplantation. These covariates were also adjusted for the same covariates shown in Table 3 (but not shown here).

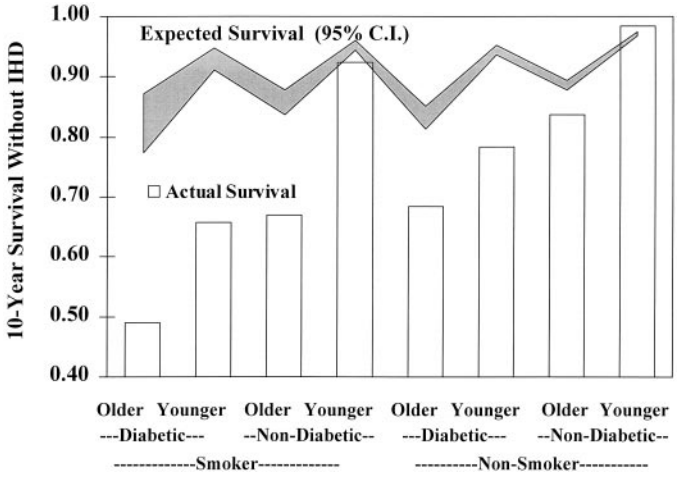

Figure 1. Observed and expected risks for ischemic heart disease (IHD) after renal transplantation. The vertical bars indicate actuarial survival free of IHD after 10 yr of follow-up monitoring, *i.e.*, 11 yr after renal transplantation. The shaded areas above the vertical bars are 95% confidence intervals (C.I.) for the calculated 10-yr IHD risk from the Framingham Heart Study (10).

notable example. We found that the risk of IHD associated with diabetes mellitus was substantially higher for renal transplant recipients than for the FHS population, especially among women (Table 1). Perhaps it should not be surprising that the risk of diabetes mellitus was much greater than expected among renal transplant recipients, because in most cases the diabetes mellitus in renal transplant recipients had already caused ESRD. Therefore, characteristics of diabetes mellitus that may be common to both microvascular disease and systemic atherosclerosis, *e.g.*, the duration of diabetes mellitus, the degree of glycemic control, or poorly understood genetic factors, may have been more prevalent among diabetic renal transplant recipients than among diabetic patients in the FHS cohort. Interestingly, the risks associated with diabetes mellitus that caused ESRD were similar for type I and type II diabetes mellitus (Table 3). For both type I and type II diabetes mellitus, the risk was much higher for women than for men. Although this gender-related difference in risk from diabetes mellitus is evident in the FHS (10), this association appears to be exaggerated for renal transplant recipients. Whether this gender association reflects differences in the underlying pathogenesis of IHD or other differences cannot be determined from these data.

We also separately examined the association between diabetes mellitus that did not cause ESRD and IHD. For men, the prevalence of diabetes mellitus that did not cause ESRD was similar in the transplant recipient population (4.9% of men without diabetic ESRD), compared with the FHS population (5.2% of men) (10). However, among women the prevalence of diabetes mellitus that did not cause ESRD appeared to be somewhat higher in the transplant recipient cohort (7.1% of women without diabetic ESRD), compared with the FHS population (4.0% of women) (10). This slightly higher prevalence among female transplant recipients (despite a younger mean age) may reflect the effects of corticosteroids and other immunosuppressive medications. In any case, diabetes mellitus that did not cause ESRD was associated with a slightly higher risk of IHD, compared with diabetes mellitus in the FHS population (Table 3), but this risk was not exaggerated for women (unlike the risk for diabetes mellitus causing ESRD). These results should be interpreted cautiously, because the number of patients with diabetes mellitus that did not cause ESRD in our study was relatively small.

Like diabetes mellitus, the effects of age and cigarette smoking on IHD seemed to be significantly different for renal transplant patients, compared with FHS participants. Indeed, we found that, among all of the risk factors identified in the FHS, only diabetes mellitus, age, and cigarette smoking were independently associated with IHD when the risk predicted by the FHS equation was taken into account (Table 2). It is quite possible that other risk factors are also different and the number of patients in our study was too small for detection of these differences. Nevertheless, it appeared that most of the difference was attributable to diabetes mellitus, age, and cigarette smoking. Indeed, the risk of IHD for younger, nondiabetic, and nonsmoking renal transplant recipients was similar to the expected risk defined for the FHS population (Figure 1). How-

ever, the risks associated with age, smoking, and diabetes mellitus were substantially greater among renal transplant recipients (Figure 1).

The results of this study suggest that the risks associated with lipid abnormalities and elevated BP are at least as high among renal transplant patients as they are in the general population (Table 1). This is particularly important, because lipid abnormalities and hypertension are very common among renal transplant patients. As in the FHS population and other populations, total cholesterol levels were associated with an increased risk for IHD among renal transplant recipients and much of the risk from total cholesterol levels could be attributed to LDL cholesterol levels. Among our renal transplant patients, the relationship between HDL levels and IHD appeared to be similar to that found in the FHS (Table 1), although the relatively small number of transplant patients in this study may have prevented us from detecting small differences. Interestingly, we found that hypertriglyceridemia was also an independent risk factor for IHD among renal transplant recipients (Table 3). Although not included in the FHS risk-prediction equations, triglyceride levels were found to be associated with IHD for subsets of the FHS population (13). In general, there is growing appreciation of the role of hypertriglyceridemia as a risk factor for IHD in the general population (14).

It is difficult to determine the possible effects of therapeutic interventions in retrospective cross-sectional analyses, because the same patients who are at highest risk for IHD may be those selected for therapy. Nevertheless, it is very encouraging that the (adjusted) relative risk of IHD seems to be decreasing (Table 3). Of concern, however, is the association between the use of nondihydropyridine calcium channel antagonists and the risk for IHD events. That this association was not attributable to chance is suggested by the following factors: (*1*) the strength of the association, (*2*) the absence of similar associations with other antihypertensive agents, and (3) the fact that similar associations have been noted in other studies.

Potential adverse effects of calcium channel antagonists have been noted in meta-analyses of randomized controlled trials (15,16) and in observational studies, *e.g.,* the Nurses' Health Study (17). The Appropriate Blood Pressure Control in Diabetes Trial was recently halted by the Data and Safety Monitoring Board because of an increase in fatal and nonfatal myocardial infarctions (not a primary end point) among patients randomly allocated to receive the calcium channel antagonist nisoldipine (18). Although the mechanism for these putative adverse effects of calcium channel blockers is unclear, recent studies documented increases in catecholamine levels with dihydropyridine calcium channel antagonists (19). A number of ongoing randomized controlled trials will ultimately resolve the controversy surrounding calcium channel blockers in the treatment of hypertension (20).

We previously reported that acute rejection episodes are associated with an increased risk of IHD (1,2). This association is independent of other known risk factors. Whether this association is attributable to the invariable high-dose corticosteroid treatment of acute rejection, the resulting graft dysfunction, or other factors is difficult to determine in a retrospective analysis. It is possible that an increased incidence of clinically apparent (or unapparent) infections after treatment of acute rejection could contribute to the pathogenesis of atherosclerosis. It is also possible that immune system activation associated with acute rejection causes a generalized inflammatory response that exacerbates systemic atherosclerosis. Low serum albumin levels may be one possible manifestation of a chronic inflammatory state. We previously reported that low serum albumin levels were associated with cardiovascular disease among renal transplant recipients (2). The association of serum albumin levels with IHD in this study was statistically independent of proteinuria and other risk factors.

Why pretransplant bilateral nephrectomy was associated with a reduced risk of IHD is unclear. The presence of native kidneys is associated with hypertension (21), and better BP control could theoretically reduce the incidence of IHD. The association of nephrectomy with IHD was independent of splenectomy. Splenectomy was performed for 534 of 1124 patients (47.5%) but was performed at the same time as nephrectomy for 286 of 321 patients (89.1%) who underwent nephrectomies. In general, the type of underlying kidney disease did not influence the relationship between pretransplant nephrectomy and IHD. However, nephrectomy for patients with polycystic kidney disease was independently associated with a higher risk of IHD (Table 3). Other authors reported that polycystic kidney disease is itself associated with an increased risk for IHD after renal transplantation and that pretransplant bilateral nephrectomies may reduce the risk of IHD among patients with polycystic kidney disease (22). However, we failed to find any independent association of polycystic kidney disease *per se* with IHD in our transplant recipient population. Rather, only patients with polycystic kidney disease who underwent pretransplant bilateral nephrectomies appeared to be at increased risk. It should be kept in mind that the number of patients with polycystic kidney disease who underwent bilateral nephrectomies in our study was relatively small, *i.e.*, 47 of 1124 patients (4.2%) in the primary analysis and 64 of 1500 patients (4.3%) in the secondary analysis (approximately equal numbers of patients with polycystic kidney disease did not undergo pretransplant bilateral nephrectomies). There is no reason to think that bilateral nephrectomies for patients with polycystic kidney disease would cause IHD. It seems more plausible that the patients with polycystic kidney disease who underwent bilateral nephrectomies were already at increased risk for IHD. These may have been patients with very large kidneys, *i.e.,* patients with greater expression of the polycystic kidney disease gene(s). Why such patients should be at increased risk for IHD is unclear but deserves further investigation.

We previously reported that pretransplant splenectomy was weakly associated with IHD after renal transplantation (2). In this study, we found pretransplant splenectomy to be associated with an increased risk of IHD in univariate analysis (data not shown), but this association was not statistically significant after adjustment for multiple risk factors (Table 3). There was no single risk factor that seemed to explain the difference

between the univariate and multivariate results for splenectomy.

In summary, this study demonstrated that many of the risk factors defined for the FHS cohort appear to be associated with qualitatively similar risks of IHD for renal transplant recipients. However, the risks associated with age, cigarette smoking, and especially diabetes mellitus appeared to be higher than expected for renal transplant recipients. It is encouraging that the risk of IHD is decreasing, although the reasons for this decrease are unclear. Finally, it is of concern that dihydropyridine calcium channel antagonists were associated with an increased risk of IHD among renal transplant recipients. Perhaps these agents should be used with caution, pending the results of large, ongoing, randomized, controlled trials in the general population.

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