Cardiovascular Disease After Renal Transplantation\textsuperscript{1,2}

Bertram L. Kasiske,\textsuperscript{3} Carlos Guijarro, Ziad A. Massy, Michael R. Wiederkehr, and Jennie Z. Ma

B.L. Kasiske, C. Guijarro, Z.A. Massy, M.R. Wiederkehr, J.Z. Ma, The Division of Nephrology, Department of Medicine, University of Minnesota College of Medicine, Hennepin County Medical Center, Minneapolis, MN (J. Am. Soc. Nephrol. 1996; 7:158–165)

ABSTRACT
Although cardiovascular disease is a major cause of morbidity and mortality after renal transplantation, its pathogenesis and treatment are poorly understood. We conducted separate analyses of risk factors for ischemic heart disease, cerebral, and peripheral vascular disease after 706 renal transplants, all of which functioned for at least 6 months. We used Cox proportional hazards analysis to examine the effects of multiple pretransplant and posttransplant risk factors and included time-dependent variables measured at 3, 6, and 12 months, and annually to last follow-up at 7.0 ± 4.2 yr. The independent relative risk (RR) of diabetes was 3.25 for ischemic heart disease, 3.21 for cerebral vascular disease, and 28.18 peripheral vascular disease ($P < 0.05$). The RR of each acute rejection episode was 1.40 for ischemic heart disease and 1.24 for cerebral vascular disease. Among serum lipid levels, high-density lipoprotein cholesterol was the best predictor of ischemic heart disease (RR = 0.80 for each 10 mg/dL). Posttransplant ischemic heart disease was strongly predictive of cerebral (5.80) and peripheral vascular disease (5.22), whereas ischemic heart disease was predicted by pretransplant cerebral (8.25) and peripheral vascular disease (4.58). Other risk factors for vascular disease included age, gender, cigarette smoking, pretransplant splenectomy, and serum albumin. Hypertension and low-density lipoprotein cholesterol had no effect, perhaps because of aggressive pharmacologic treatment. Thus, the incidence of cardiovascular disease continues to be high after renal transplantation, and multiple risk factors suggest a number of possible strategies for more effective treatment and prevention.

Key Words: Hyperlipidemia, coronary heart disease, cerebrovascular disease, peripheral vascular disease, graft rejection

\textsuperscript{1} Received June 8, 1995. Accepted August 21, 1995.
\textsuperscript{2} Portions of this work were presented at the 27th Annual Meeting of the American Society of Nephrology.
\textsuperscript{3} Correspondence to Dr. B.L. Kasiske, Department of Medicine, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55415.
1046-6673/0701-0158$03.00/0
Journal of the American Society of Nephrology
Copyright © 1996 by the American Society of Nephrology

Cardiovascular disease is the most common cause of death after renal transplantation in the United States (1). However, there are surprisingly few reports defining risk factors for cardiovascular disease in renal transplant recipients (2–9). In addition, few studies have separately analyzed risk factors for ischemic heart disease (IHD) (9), cerebral vascular disease (CVD) (6,7,9), and peripheral vascular disease (PVD) (8). Even fewer studies have utilized multivariate statistical techniques to examine risk factors (4,5,9), and we know of no studies that have explored the interrelationships between IHD, CVD, and PVD after renal transplantation. We previously described several risk factors for vascular disease in the era before cyclosporine (CsA) (9). In the analysis presented here, we included a large number of patients treated with CsA, and re-examined risk factors for vascular disease over a longer follow-up period. In addition, we included data and events recorded throughout the late posttransplant period using time-dependent covariates, and carried out separate multivariate analyses for IHD, CVD, and PVD.

METHODS

Patients
Patients who underwent renal transplantation between January 1, 1976 and June 1, 1991 were included. Since we sought to examine possible risk factors for vascular disease events occurring in the late posttransplant period, only patients who survived at least 6 months with a functioning allograft were studied. Some of the patients in our earlier study were included in this analysis (9).

Endpoints
A major IHD event was defined as a myocardial infarction, coronary artery revascularization (percutaneous balloon angioplasty or bypass grafting), or death as a result of IHD. Deaths were considered attributable to IHD if autopsy was consistent with that diagnosis and if events preceding death made IHD the most likely cause. Angina pectoris, arrhythmias, and/or congestive heart failure by themselves were not considered reliable enough to include as end points, but were used in the assessment of the likelihood of pretransplant IHD (see below). We defined CVD as a thrombotic/embolic stroke or documented transient ischemic attack. Intracranial hemorrhage per se (e.g., subarachnoid hemorrhage) was not included in this definition of CVD. We defined PVD as amputation resulting from vascular insufficiency or a peripheral revascularization procedure (bypass or endarterectomy).

Predictor Variables
Variables recorded at the time of transplantation included: age, gender, race, cause of ESRD (including diabetes, autosomal dominant polycystic kidney disease [ADPKD], and glomerulonephritis), weight, height, body mass index (kg/m$^2$), donor age, donor gender, pretransplant splenectomy, pretransplant bilateral nephrectomy, prior transplant, pretransplant blood transfusions, percent panel reactive anti-
bodies at peak and at transplant, number of AB and DR mismatches, evidence of pretransplant IHD (angina pectoris, myocardial infarction, or revascularization), pretransplant CVD, pretransplant PVD, revascularization), delayed graft function.

Major posttransplant event variables included: acute rejection episodes, the development of posttransplant diabetes (requiring treatment with insulin or an oral hypoglycemic agent), withdrawal of CsA, and the reduction of prednisone from 15 mg/day to 15 mg every other day. In addition, variables that could assume the same or different values repetitively posttransplant included laboratory parameters recorded at 3 months, 6 months, 1 yr, and annually thereafter for values for: serum creatinine, creatinine clearance, serum albumin, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and urine protein excretion (g/24 h). All lipid determinations were made after an overnight fast. Hypertension was defined as 2 for blood pressure less than 130/90 mm Hg while receiving no antihypertensive medications, 1 for increased blood pressure treated with at most one medication, and 2 for increased blood pressure treated with more than one medication. Diuretics were included as an antihypertensive medication if given for treatment of blood pressure. Also recorded was whether or not patients were being treated with converting enzyme inhibitors, β-adrenergic blocking agents, calcium antagonists, diuretics, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or other antilipemic agents.

**Missing Values**

Missing values for posttransplant variables were imputed as the average of values occurring immediately before and after the missing value, whenever these values were known. Others were randomly imputed assuming a normal distribution of missing values with the same mean and standard deviation as the known values at the same time of follow-up (10). The percentages of values that were estimated as the means of values before and after the missing value were: 5.7% for cholesterol, 6.4% for triglycerides, 16.8% for HDL, 6.0% for serum albumin, 5.3% for urine protein, 1.3% for creatinine, and 7.2% for creatinine clearance. The percentages of values that were randomly imputed were: 4.8% for cholesterol, 5.1% for triglycerides, 24.3% for HDL, 5.2% for serum albumin, 8.5% for urine protein, 2.6% for serum creatinine, and 9.4% for creatinine clearance. There were 6029 values for each posttransplant variable.

The only pretransplant variable with missing values was the degree of DR mismatching. Values for DR were not known for 125 transplants performed before 1980. Because the number of DR mismatches was associated with the number of AB mismatches among the 581 cases in whom both were determined, unknown DR mismatches were randomly imputed by using the conditional probabilities based on known AB mismatches. The effects of the randomly imputed missing values were examined by comparing the results derived from five separate data sets, each with different randomly imputed missing values. In every case, the final Cox proportional hazards models derived from the different randomly imputed data sets were virtually identical, indicating that the random imputation had little impact on the final results.

**Analysis**

Possible risk factors were examined by using univariate Cox proportional hazards analysis. Covariates that tended to correlate with end points on univariate analysis (P < 0.15) were also examined by using multivariate Cox analysis. Separate analyses were carried out for IHD, CVD, and PVD. For each analysis, patients dying or returning to dialysis before a cardiovascular disease event were censored at that time.

Posttransplant variables that could assume different values at different times, e.g., cholesterol and triglycerides, were treated as time-averaged, time-dependent covariates in the Cox analysis, whereby the value at any time was the average of all values that occurred before that time. For some unadjusted comparisons between groups we assigned a single value to each patient that was the average of all values measured from the time of transplantation to the time of the vascular disease event or last follow-up. Discrete posttransplant events, e.g., acute rejection, were handled as time-dependent covariates in the Cox analysis, and were treated as being absent until the time of occurrence and then present thereafter. Pretransplant variables were used as fixed (discrete or parametric) covariates in the univariate and multivariate Cox analysis. Because most cytomegalovirus infections occurred within the first 6 months posttransplant when few end points occurred, this was also treated as a fixed covariate. Data were analyzed using the statistical software packages SPSS (SPSS, Inc., Chicago, IL) and BMDP (University of California Press, Berkeley, CA) (11,12). Final results were considered significant for P < 0.05. Values are reported as mean ± SD.

**RESULTS**

**Patient Characteristics**

There were 706 transplants performed in 675 patients. Mean age was 40.6 ± 13.2 yr, 56.4% were men, 4.1% were black, and 3.1% were American Indian. The cause of ESRD was diabetes in 28.2%, chronic glomerulonephritis in 33.9%, and ADPKD in 9.6%. There were 11.6% who had received a previous transplant and 11.2% who had live donors. Pretransplant splenectomy was performed in 68.1%, but was largely abandoned in later years. Bilateral nephrectomy was performed before transplant in 30.9%.

All patients received azathioprine and corticosteroid-based immunosuppression. Minnesota antilymphocyte globulin was used for induction therapy in 88.7%. In 35.4%, CsA was used as prophylactic immunosuppression once renal function was established. The CsA was electively withdrawn in 80% of these patients at 1.2 ± 0.4 yr after transplantation. An attempt was made to convert 63.8% of patients to alternate-day prednisone at 1.9 ± 1.2 yr after transplantation. However, 36.1% of these patients returned to daily prednisone some time later. The time to death, return to dialysis, or last follow-up (January 1, 1995) was 7.0 ± 4.2 yr. At the time of last follow-up, 24.2% had died and 20.1% had returned to dialysis. Cholesterol, LDL and triglycerides were high throughout the posttransplant period (Table 1). Posttransplant hypertension and proteinuria were also common (Table 1).
TABLE 1. Selected values for possible posttransplant cardiovascular disease risk factors\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>3 Months ((N = 706))</th>
<th>1 Yr ((N = 682))</th>
<th>2 Yr ((N = 631))</th>
<th>10 Yr ((N = 161))</th>
<th>Mean of All Posttransplant Values ((N = 706))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>247 ± 63</td>
<td>252 ± 66</td>
<td>242 ± 66</td>
<td>247 ± 55</td>
<td>245 ± 48</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td>141 ± 95</td>
<td>155 ± 60</td>
<td>149 ± 58</td>
<td>153 ± 56</td>
<td>148 ± 45</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>226 ± 423</td>
<td>196 ± 146</td>
<td>181 ± 126</td>
<td>174 ± 139</td>
<td>194 ± 146</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>62 ± 24</td>
<td>58 ± 20</td>
<td>56 ± 18</td>
<td>59 ± 17</td>
<td>58 ± 13</td>
</tr>
<tr>
<td>Serum Albumin (g/dL)</td>
<td>3.74 ± 0.48</td>
<td>3.96 ± 0.38</td>
<td>3.95 ± 0.39</td>
<td>3.79 ± 0.43</td>
<td>3.84 ± 0.32</td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min)</td>
<td>1.44 ± 0.53</td>
<td>1.49 ± 0.74</td>
<td>1.56 ± 0.90</td>
<td>1.45 ± 0.65</td>
<td>1.60 ± 0.63</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>8.5</td>
<td>9.2</td>
<td>9.5</td>
<td>5.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75</td>
<td>74</td>
<td>69</td>
<td>53</td>
<td>69</td>
</tr>
</tbody>
</table>

\(^a\) Values are mean ± SD. Values at 6 months, 3 yr, 4 yr, etc., are not shown. All values up to time of death, return to dialysis, or last follow-up are included whether or not vascular disease events had occurred. Proteinuria is defined as greater than 500 mg/day. LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

Ninety patients received an HMG-CoA reductase inhibitor at some time after transplantation. As a group, those treated with an HMG-CoA reductase inhibitor had higher (mean of all values after transplant) cholesterol (278 ± 41 versus 240 ± 47 mg/dL, \(P < 0.001\)) and triglycerides (272 ± 301 versus 183 ± 102, \(P < 0.001\)) compared with patients who did not receive an HMG-CoA reductase inhibitor. Because the patients who received an HMG-CoA reductase inhibitor were selected because they were at high risk for cardiovascular disease, it was not possible to examine the effect of HMG-CoA reductase inhibition on vascular disease in this retrospective analysis. Neither could these patients be excluded, because doing so would bias the results by selectively excluding the highest-risk patients. However, the risk factors for vascular disease in this study were each shown to be independent of the effects of HMG-CoA reductase inhibition in multivariate analysis. This was also true for antihypertensive agents.

**Ischemic Heart Disease**

There were 85 patients who developed a major IHD event. By actuarial analysis, 23% of patients who survived with a functioning allograft for 15 yr developed IHD (Figure 1). There were 32 patients who died of IHD (18.7% of all deaths). Although there were too few IHD deaths to analyze separately, the major risk factors for IHD described below also tended to be risk factors for IHD death (data not shown).

To better define independent risk factors, we used both univariate and multivariate Cox proportional hazards analysis. Because some of the same risk factors for IHD may be risk factors for CVD and PVD, we examined multivariate models with and without other pretransplant and posttransplant vascular disease events included as independent predictor variables (Table 2). Not surprisingly, age, diabetes, and gender were strong independent risk factors for posttransplant IHD. Acute rejection episodes and their treatment also independently predicted IHD. Pre-transplant IHD and posttransplant PVD and CVD were strong predictors of major IHD events after transplantation (Table 2).

Interestingly, pretransplant splenectomy was an independent risk factor for IHD. However, splenectomy...
TABLE 2. Independent risk factors for ischemic heart disease

<table>
<thead>
<tr>
<th>Independent Risk Factors</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (each decade)</td>
<td>1.49 (0.000)</td>
<td>1.88 (0.000)</td>
</tr>
<tr>
<td>Diabetes at Transplant</td>
<td>2.09 (0.001)</td>
<td>3.25 (0.000)</td>
</tr>
<tr>
<td>Male</td>
<td>2.28 (0.001)</td>
<td>2.68 (0.000)</td>
</tr>
<tr>
<td>Pretransplant Splenectomy</td>
<td>1.65 (0.090)</td>
<td>2.07 (0.038)</td>
</tr>
<tr>
<td>Each Acute Rejection</td>
<td>1.26 (0.010)</td>
<td>1.40 (0.000)</td>
</tr>
<tr>
<td>HDL (each 10 mg/dL)</td>
<td>0.80 (0.010)</td>
<td>0.82 (0.017)</td>
</tr>
<tr>
<td>Pretransplant IHD</td>
<td>6.00 (0.000)</td>
<td>Excluded</td>
</tr>
<tr>
<td>Posttransplant PVD</td>
<td>9.06 (0.000)</td>
<td>Excluded</td>
</tr>
<tr>
<td>Posttransplant CVD</td>
<td>15.61 (0.000)</td>
<td>Excluded</td>
</tr>
</tbody>
</table>

a Relative risk and (in parentheses) P value for univariate and multivariate Cox proportional hazard models. Relative risk is the risk of IHD compared with no risk = 1.00. Pretransplant and/or posttransplant vascular disease were excluded from Models 1 and 2. HDL, high-density lipoprotein cholesterol; IHD, ischemic heart disease; PVD, peripheral vascular disease; CVD, cerebral vascular disease.

was less frequently performed on patients who had received transplants more recently, and was less frequently performed on patients who received living donor kidneys than in patients who did not (39% versus 72%, P < 0.001). Patients who underwent splenectomy were more likely to have undergone bilateral nephrectomy than patients who did not undergo splenectomy (43% versus 4%, P < 0.001). Finally, patients with splenectomy had higher mean (time-averaged) posttransplant cholesterol levels compared with patients who did not undergo splenectomy (249 ± 52 versus 239 ± 43, P = 0.012).

Among the lipid parameters examined, only HDL levels were independently correlated with IHD (Table 2). However, there was an inverse relationship between HDL and triglyceride levels (r = -0.23, P < 0.001), as well as a correlation between HDL and total cholesterol (r = 0.15, P < 0.001). Patients with high triglycerides had an increased incidence of IHD (Figure 2). In the univariate Cox analysis, triglyceride values were not significantly correlated with IHD (Table 2). However, logarithmically transformed triglycerides were associated with IHD in the univariate (RR = 2.15, P = 0.032), but not in the multivariate Cox analysis. Total and LDL cholesterol did not predict IHD. Posttransplant diabetes occurred in 50 patients (7.1%), and was a strong predictor of IHD in univariate analysis (RR = 2.22, P = 0.029). However, posttransplant diabetes was associated with a number of other variables, and was not independent of these other risk factors for IHD in multivariate models. For example, patients who developed posttransplant diabetes had higher (time-averaged) posttransplant cholesterol (262 ± 55 versus 244 ± 47 mg/dL, P = 0.025) and triglycerides (294 ± 358 versus 186 ± 111 mg/dL, P = 0.036), but lower HDL (53.7 ± 13.8 versus 58.1 ± 13.3 mg/dL, P = 0.023) compared with patients who did not develop diabetes. Patients who developed posttransplant diabetes were also older than those who did not (51 ± 11 versus 40 ± 13 years, P < 0.001).

By univariate analysis, there was a tendency for...
posttransplant hypertension to be associated with IHD \( (P = 0.083) \). However, hypertension and its treatment with different antihypertensive agents were not independent predictors of IHD in the multivariate analysis. Similarly, ADPKD was marginally associated with an increased incidence of posttransplant IHD in univariate \( (P = 0.055) \), but not multivariate, analysis. Serum albumin (g/dL) was also highly correlated with IHD on univariate analysis \( (RR = 0.19, P < 0.001) \). The effects of serum albumin on IHD were independent of acute rejection episodes, HDL, and diabetes, but were not independent of age in multivariate models. Cigarette smoking (each 10 pack-yr at transplant) was associated with IHD on univariate \( (RR = 1.14, P = 0.010) \), but not multivariate analysis. Body mass index, cytomegalovirus infection, proteinuria, serum creatinine, creatinine clearance value, the use of a living related donor, the use of CsA, conversion to alternate-day prednisone, and other variables were not associated with IHD in multivariate analysis.

**Cerebral Vascular Disease**

There were 54 patients who had a major CVD event. By actuarial analysis, 15% of patients who survived with a functioning allograft for 15 yr experienced a major CVD event (Figure 1). Major independent risk factors for CVD included diabetes, cigarette smoking, pretransplant splenectomy, acute rejection episodes, and posttransplant serum albumin value (Table 3). Pretransplant IHD and CVD and posttransplant IHD were also strong independent risk factors for CVD after renal transplantation.

In univariate analysis, age correlated with CVD \( (RR = 1.31 \text{ for each decade, } P = 0.009) \). However, the effect of age on CVD was not independent of serum albumin value in multivariate models. Neither posttransplant lipids nor posttransplant hypertension predicted CVD. Similarly, values for urine protein excretion, serum creatinine, creatinine clearance, body mass index, and other variables failed to independently predict posttransplant CVD.

**Peripheral Vascular Disease**

There were 71 patients who had major PVD complications. By actuarial analysis, 15% of those who survived with a functioning allograft for 15 yr developed PVD (Figure 1). Diabetes, gender, cigarette smoking, posttransplant serum albumin value, pretransplant PVD, and posttransplant IHD were all independent risk factors for PVD (Table 4). None of the other pretransplant or posttransplant variables were independent predictors of PVD.

**DISCUSSION**

The results of this study confirm that cardiovascular disease continues to be a major complication after renal transplantation. Although the incidence of clinically apparent pretransplant vascular disease likely underestimates the true prevalence of vascular disease at transplantation, it is clear that the risk for vascular disease is not just a result of events occurring early after transplantation, but rather continues to accrue in the late posttransplant period (Figure 1). In addition, we could find no evidence that the use of CsA has reduced the incidence of vascular disease complications, although patients treated with CsA have not been followed as long as those treated with conventional immunosuppression. The fact that CsA was electively withdrawn in the majority of patients makes it less likely that we could have detected any long-term effects of CsA on vascular disease.

Diabetes is a major risk factor for vascular disease after renal transplantation (3). However, the incidence of vascular disease is also high in nondiabetics. Indeed, 58% of all IHD events, and 50% of all CVD events occurred in patients without diabetes. Thus, restricting the use of intervention strategies to diabetics would miss the majority of patients with IHD and CVD in our population. In contrast, major PVD complications were unusual in nondiabetics. Indeed, only 11% of the major PVD complications occurred in nondiabetics.

Throughout the period of study, all patients were advised to take one adult (325 mg) or child (65 mg) aspirin per day unless contraindicated. Unfortunately, we had no reliable means to assess compliance with this advice. Nevertheless, the high incidence of vascular disease complications in our transplant population is even more remarkable considering

---

**TABLE 3. Independent risk factors for cerebral vascular disease**

<table>
<thead>
<tr>
<th>Independent Risk Factors</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.98 (0.000)</td>
<td>3.21 (0.000)</td>
</tr>
<tr>
<td>Smoking (10 pack-yr)</td>
<td>1.18 (0.003)</td>
<td>1.24 (0.001)</td>
</tr>
<tr>
<td>Pretransplant Splenectomy</td>
<td>2.27 (0.042)</td>
<td>2.79 (0.015)</td>
</tr>
<tr>
<td>Each Acute Rejection</td>
<td>1.26 (0.048)</td>
<td>1.24 (0.009)</td>
</tr>
<tr>
<td>Serum Albumin (g/dL)</td>
<td>0.11 (0.000)</td>
<td>0.15 (0.000)</td>
</tr>
<tr>
<td>Pretransplant IHD</td>
<td>5.06 (0.000)</td>
<td>Excluded</td>
</tr>
<tr>
<td>Pretransplant CVD</td>
<td>7.18 (0.000)</td>
<td>Excluded</td>
</tr>
<tr>
<td>Posttransplant IHD</td>
<td>7.06 (0.000)</td>
<td>Excluded</td>
</tr>
</tbody>
</table>

*See legend to Table 2 for detailed explanation.*
TABLE 4. Independent risk factors for peripheral vascular disease

<table>
<thead>
<tr>
<th>Independent Risk Factors</th>
<th>Univariate Analysis</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>25.74 (0.000)</td>
<td>28.18 (0.000)</td>
<td>22.49 (0.000)</td>
<td>22.44 (0.000)</td>
</tr>
<tr>
<td>Male</td>
<td>1.75 (0.027)</td>
<td>1.81 (0.023)</td>
<td>1.83 (0.021)</td>
<td>1.79 (0.027)</td>
</tr>
<tr>
<td>Smoking (10 pack-yr)</td>
<td>1.09 (0.157)</td>
<td>1.15 (0.048)</td>
<td>1.17 (0.023)</td>
<td>1.14 (0.067)</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>0.25 (0.000)</td>
<td>0.33 (0.011)</td>
<td>0.41 (0.052)</td>
<td>0.38 (0.034)</td>
</tr>
<tr>
<td>Pretransplant PVD</td>
<td>8.07 (0.000)</td>
<td>Excluded</td>
<td>2.55 (0.001)</td>
<td>2.50 (0.000)</td>
</tr>
<tr>
<td>Posttransplant IHD</td>
<td>5.76 (0.000)</td>
<td>Excluded</td>
<td>Excluded</td>
<td>5.22 (0.000)</td>
</tr>
</tbody>
</table>

*See legend to Table 2 for detailed explanation.

the likelihood that many patients utilized aspirin prophylaxis.

The use of time-dependent covariates allowed us to examine the effects of lipids measured throughout the posttransplant period. We and others have previously reported that the serum total cholesterol level is associated with cardiovascular disease after renal transplantation (2,4,5,9). In the study presented here, cholesterol and LDL were not associated with IHD in the univariate or multivariate Cox analysis. However, it is impossible to determine to what extent reductions in cholesterol and LDL among high risk patients treated with HMG-CoA reductase inhibitors confounded the relationship between these lipid parameters and IHD. It is also possible that changes in cholesterol and LDL may have been linked to changes in other variables, e.g., acute rejection episodes, which obscured a relationship between cholesterol and IHD. In any case, these results underscore the fact that only controlled clinical trials can prove that reducing cholesterol and LDL will reduce IHD after renal transplantation.

Unlike total cholesterol, HDL was an independent risk factor for IHD. A relatively high proportion of HDL values were imputed. Nevertheless, 3550 measured HDL values were included in the analysis. Although errors may have been introduced by using estimated and imputed HDL values, there is no reason to believe that this would have created systematic bias. Our confidence in the results is strengthened by the fact that almost identical results were seen when the random imputation procedure was repeated five times. Although HDL levels are generally normal after transplantation, the composition of HDL may not be normal (13), and it is plausible that HDL may directly influence the pathogenesis of atherosclerotic vascular disease. Indeed, at least one other center has reported an inverse relationship between HDL levels and cardiovascular disease after renal transplantation (5). However, changes in HDL may often be indicative of other abnormalities in lipoprotein metabolism (14,15). In many populations, as in the present study, HDL levels are inversely related to triglycerides, and the catabolism of triglyceride-rich lipoproteins may be linked to HDL formation and reverse cholesterol transport (14,15). This relationship between HDL and triglycerides may have obscured an association between triglycerides and IHD in the multivariate analysis. More importantly, the changes in HDL and triglyceride metabolism may be indicative of more generalized metabolic abnormalities, e.g., altered insulin and glucose metabolism.

Posttransplant diabetes was associated with the development of IHD in univariate analysis. Others have found posttransplant diabetes to be associated with increased mortality after transplantation (16,17). It is unclear whether posttransplant diabetes influences the pathogenesis of vascular disease directly, or is merely correlated with other variables associated with IHD, e.g., hyperlipidemia and related metabolic abnormalities. Indeed, it is interesting to speculate that posttransplant diabetes may share many features attributed to “Syndrome X”, the clinical constellation of insulin resistance, hyperlipidemia, hypertension, and obesity that is also associated with IHD in nontransplant patients (18–20).

Why splenectomy was independently associated with both IHD and CVD is unclear. It is possible that splenectomy was a surrogate marker for the effects of several other clinical variables. Indeed, splenectomy was associated with higher serum cholesterol levels, a finding previously reported in normal animals and humans with myeloproliferative disorders (21,22). However, the fact that the associations between splenectomy and vascular disease were statistically independent of cholesterol and other variables, and the fact that splenectomy was an independent predictor of both IHD and CVD, make it more likely that some other effect related to splenectomy is responsible for this association. In at least one case-control study of war veterans, splenectomy was linked to subsequent cardiovascular disease complications (23). In that report, it was suggested that postsplenectomy thrombocytosis and hypercoagulability could have contributed to cardiovascular disease (23). In any case, the recent decrease in the use of pretransplant splenectomy procedures may help to reduce the incidence of cardiovascular disease events in renal transplant recipients.

It was recently reported that transplant recipients with ADPKD had a higher incidence of posttransplant cardiovascular disease than other transplant recipients (4). Although there was a tendency for ADPKD to
be associated with IHD on univariate analysis, ADPKD was not an independent risk factor in our analysis. Why ADPKD was not more strongly correlated to IHD in our study is unclear, although our study population included fewer patients with ADPKD compared with the previous report, and we analyzed IHD and CVD end points separately. We also carefully excluded ADPKD patients with subarachnoid hemorrhage from the analysis of CVD. These and other differences in study design could account for differences in the results of these two studies.

Acute rejection was a consistent independent risk factor for both IHD and CVD. The effects of acute rejection on vascular disease were independent of graft function, proteinuria, and hypertension. However, virtually all patients with acute rejection were treated with high doses of corticosteroids, so that acute rejection may be a surrogate for cumulative corticosteroid dose and metabolic effects not accounted for by the variables included in the multivariate models (9). Alternatively, it is possible that acute rejection and its treatment lead directly to endothelial damage, thereby contributing to the pathogenesis of atherosclerosis.

Serum albumin has not previously been reported to be an independent risk factor for vascular disease events in renal transplant recipients. Although the relationship between albumin and IHD was not independent of HDL, age and other variables, albumin was an independent risk factor for CVD and PVD. In particular, the effects of albumin were independent of urine protein excretion. Albumin is often an indicator of visceral protein stores and overall nutritional status. As such, hypoalbuminemia is a powerful predictor of mortality among hemodialysis patients (24,25).

Serum albumin has also been shown to be an independent risk factor for cardiovascular disease in patients without renal disease (26–28). Possible mechanisms linking low albumin levels to vascular disease events cannot be discerned from the present study. It is possible that low albumin levels are a result of age in addition to a cause of vascular disease, and that patients with low albumin levels had poorer nutrition even before a major vascular disease event occurred. Alternatively, it is possible that low albumin levels reflect vascular damage with increased vascular permeability to albumin, as reported in patients with diabetes (29).

Some investigators have found that cigarette smoking is associated with posttransplant vascular disease (5), but others have not (2). As in our previous analysis (9), smoking at the time of transplantation was associated with posttransplant vascular disease events. Unfortunately, we could not document the number of patients who continued to smoke after transplantation. However, we have previously found that most patients who were smoking at the time of transplant continued to smoke after transplantation (30).

There may be several reasons why hypertension did not appear to be a risk factor for vascular disease in our patient population. Indeed, others have also failed to find a consistent relationship between hypertension and posttransplant vascular disease (4,5). It is possible that the crude index we used to measure the effects of hypertension did not adequately reflect the degree and duration of blood pressure elevation after transplantation. However, it is also possible that aggressive treatment of hypertension effectively reduced adverse events in our patient population. For these and other reasons, the role of hypertension in posttransplant vascular disease is difficult to discern.

The relatively large number of patients and long duration of follow-up in this study permitted us to examine the interrelationship between IHD, CVD, and PVD, independent of diabetes and other shared risk factors. The results demonstrated a close association between IHD, CVD, and PVD after renal transplantation. Thus, patients with IHD events were much more likely to have CVD or PVD complications. Similarly, patients who had a CVD or PVD event after transplantation were more likely to have a subsequent IHD event. These interrelationships could not be explained by the other variables that were included in the analysis, and suggest that pathogenesis of IHD, CVD, and PVD may be similar in many respects. These interrelationships also underscore the importance of aggressive risk factor management in patients who develop a vascular disease event.

Like all epidemiologic studies, these results should be interpreted with caution. Although we used multivariate statistical techniques, it is still difficult to eliminate the possibility of confounding between variables in discerning cause and effect relationships. In addition, we had insufficient data to examine all putative risk factors for cardiovascular disease. Changes in lipoprotein composition, oxidized lipoproteins, plasma homocysteine levels, levels of fibrinogen, and other coagulation parameters could each play a role in the pathogenesis of posttransplant cardiovascular disease.

In summary, despite new immunosuppression protocols and more effective management of risk factors, cardiovascular disease continues to be a major cause of morbidity and mortality after renal transplantation. The results of our analysis suggest that future efforts to improve lipid abnormalities, particularly those related to HDL and triglyceride metabolism may be beneficial. Whether the lack of correlation between cholesterol and cardiovascular disease is the result of our current emphasis on the use of HMG-CoA reductase inhibitors to reduce LDL cholesterol or other factors is unclear. Certainly, it cannot be concluded that efforts to reduce LDL should be abandoned, just as it cannot be concluded that a lack of correlation between hypertension and cardiovascular disease should prompt us to be less vigilant in treating blood pressure. Our results also suggest that the development of new agents and strategies to treat acute rejection episodes may help to reduce cardiovascular disease. In addition, efforts to reduce cigarette smok-
ing need greater emphasis. Finally, the fact that pre-transplant vascular disease continues to be a strong predictor of posttransplant vascular disease events suggests that efforts to prevent posttransplant vascular disease should begin before transplantation.

ACKNOWLEDGMENTS

This work was supported in part by Grant #92-1244 from the American Heart Association, and Fondo de Investigación Sanitaria (FIS 93/5439), from the Spanish Ministry of Health. We thank Ms. Jan Lowick for helping to prepare the manuscript and Dr. Ibrahim Mujir for helping to collect data on cigarette smoking.

REFERENCES


