Early Renal Insufficiency and Hospitalized Heart Disease after Renal Transplantation in the Era of Modern Immunosuppression

KEVIN C. ABBOTT,* CHRISTINA M. YUAN,* ALLEN J. TAYLOR,† DAVID F. CRUESS,‡ and LAWRENCE Y. C. AGODOA§

**Nephrology Service, Walter Reed Army Medical Center, Washington, DC, and Uniformed Services University of the Health Sciences, Bethesda, Maryland; †Cardiology Service, Walter Reed Army Medical Center, Washington, DC; ‡Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland; and §National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.*

Abstract. Renal insufficiency has been identified as a risk factor for graft loss and death after renal transplantation but has not been consistently linked to early, nonfatal, hospitalized heart disease (HHD). With the United States Renal Data System database, 29,597 patients who received a kidney transplant between January 1, 1996, and July 31, 2000, with Medicare as the primary payer, and were monitored until December 31, 2000, were studied. Cox proportional-hazards regression models were used to calculate the association of recipient estimated GFR (eGFR) at 1 yr after renal transplantation, as determined with the Modification of Diet in Renal Disease formula, with hospitalization for treatment of acute coronary syndromes (ACS) (International Classification of Diseases, version 9, code 410.x or 411.x) or congestive heart failure (CHF) (code 428.x) 1 to 3 yr after renal transplantation. Rates of ACS and CHF were 2.2 and 4.9%, respectively, for patients with eGFR of <44.8 ml/min per 1.73 m^2, compared with 1.2 and 1.4% for patients with eGFR of >69.7 ml/min per 1.73 m^2. Reduced eGFR (<44.8 ml/min per 1.73 m^2, compared with >69.7 ml/min per 1.73 m^2) at the end of the first 1 yr after transplantation was independently associated with increased risks of both ACS (adjusted hazard ratio, 2.16; 95% confidence interval, 1.39 to 3.35) and CHF (adjusted hazard ratio, 2.95; 95% confidence interval, 2.24 to 3.90). It was concluded that early renal insufficiency (approximately stage 3 chronic kidney disease) was associated with higher rates of HHD 1 to 3 yr after kidney transplantation. Preservation of renal function after renal transplantation may reduce the rates of HHD, and renal transplant recipients with reduced eGFR should be considered at high risk of developing cardiovascular disease.

The renal transplant community has traditionally focused on renal insufficiency occurring early after renal transplantation as a risk factor for graft loss (1). It has been assumed that the effects of renal insufficiency on cardiovascular disease occurring after renal transplantation, if any, develop during a long period. Published screening guidelines for ischemic heart disease after renal transplantation do not address posttransplantation renal allograft insufficiency as a potential cardiac risk factor (2). However, evidence from the general population indicates that renal insufficiency is a risk factor (either independently or because of its association with other risk factors) for all-cause death and particularly cardiovascular disease-related death (3,4). Patients who receive renal transplants may have a lower risk of ischemic heart disease, compared with comparable dialysis patients on the renal transplant waiting list (5) or patients who later experience renal allograft failure (6). However, studies have yielded conflicting results on whether posttransplantation renal insufficiency, which has been assessed by using different methodologies (7,8), is associated with an increased risk of nonfatal cardiovascular disease among renal transplant recipients.

Certain immunosuppressive medications used for renal transplantation have a stronger association with nephrotoxicity than do others (9–11). Maintenance immunosuppressive agents have differing effects on BP, lipid levels, and the risk of posttransplantation diabetes mellitus (12–15). Diabetes mellitus seems to make a greater contribution to ischemic heart disease after renal transplantation than would be predicted by the Framingham model (16); therefore, surrogate outcomes based on the unadjusted Framingham model should be considered with caution, if at all, for assessment of cardiovascular disease after renal transplantation (17).

Because any single-center clinical study might not have a sample size able to account or match for substantial confounding variables, we conducted an historical cohort study of the United States renal transplant population from January 1, 1996, to July 31, 2000. The objectives were to determine the asso-

Received March 7, 2003. Accepted June 4, 2003.
Correspondence to Dr. Kevin C. Abbott, Nephrology Service, Walter Reed Army Medical Center, Washington, DC 20307-5001. Phone: 202-782-6462/6463/6288; Fax: 202-782-0185; E-mail: kevin.abbott@na.amedd.army.mil
1046-6673/1409-2358
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000083008.25305.67

ciation of early (by the end of the first 1 yr after renal transplantation) renal insufficiency with hospitalized heart disease (HHD) and to assess whether this risk is affected by differences in baseline factors, especially differences in baseline maintenance immunosuppression. The null hypothesis was that the estimated GFR (eGFR) by the end of the first 1 yr after renal transplantation had no significant association with HHD, after adjustment for potentially confounding variables.

Materials and Methods

Patients

Details of the files used for data abstraction for this study and the limitations of hospitalization data have been described previously and differ according to the year of selection and the limitations of key variables, notably the use of Centers for Medicare/Medicaid Studies (CMS) medical evidence form 2728 (6,18). Files used and merged in analyses were SAF.TXUNOS for the basic transplant information, SAF.TXFUUNOS for follow-up information, SAF.TXIUNOS for medication information, SAF.PATIENTS for dates and causes of death, SAF.RXHIST60 for follow-up dates and information on dialysis modalities before the transplant date, SAF.MEDEVID for information on comorbid conditions and laboratory results at the time of first treatment for ESRD, and SAF.HOSP for hospitalization information. Files were merged by using unique identifiers. The most recent files released by the United States Renal Data System (USRDS) include follow-up data (including dates of death) until October 31, 2001. However, the most recent date for available data on hospitalization is December 31, 2000. This study limited analysis to kidney transplants (including repeat transplants or multiple-organ transplants) performed for individual recipients (one transplant assessed per recipient) between January 1, 1996, and July 31, 2000, with documentation of Medicare as the primary payer. Hospitalization and comorbidity data (from CMS form 2728) were merged with transplant files by using unique patient identifiers.

Outcomes

Our primary outcome was HHD after renal transplantation. Specific causes of HHD were chosen because of their known differences in risk factors and prognoses, as well as their independent contributions to morbidity and quality of life. Hospitalizations selected were for treatment of acute coronary syndromes (ACS) (International Classification of Diseases, version 9, primary discharge diagnosis code 410.x or 411.x) or congestive heart failure (CHF) (International Classification of Diseases, version 9, primary discharge diagnosis code 428.x).

Survival Times

The time to HHD was primarily calculated as the time from the transplant date to the date of the first hospitalization for treatment of heart disease during the study period, with recipients being censored at the time of death, the time of loss to follow-up monitoring, or the end of the study period (December 31, 2000, the most recent date for available hospitalization data). Such calculations required survival for hospitalization and thus could not assess patients who died as a result of sudden cardiac death (a significant ACS factor).

Independent Variables

Renal function after transplantation was assessed by using the Modification of Diet in Renal Disease eGFR formula (19). The serum creatinine level used was the most recent serum creatinine level measurement available before the end of the first 1 yr after renal transplantation. Patient characteristics and treatment factors used were those at the time of transplantation. BP data and blood lipid levels were not available, whereas cigarette smoking status was available for a fraction of the patients, from CMS form 2728 (see below). The USRDS information on maintenance immunosuppressive medications did not include total doses and, because almost all recipients were receiving corticosteroid therapy (20), corticosteroid use was not included in this analysis. The duration of dialysis before transplantation was defined as the time from the first recorded dialysis treatment to the transplant date. The variables assessed included donor and recipient ages, race, gender, weight, body mass index (calculated from height and weight), induction and maintenance immunosuppressive medications, graft loss, previous transplants, delayed graft function, network, state of transplantation, duration of dialysis before transplantation, and allograft rejection, in accordance with previous studies (16). The specific cause of ESRD assessed was diabetes mellitus (other causes were not excluded but were not specifically identified). Treatment with peritoneal dialysis for any 60-d period before transplantation was determined from patient treatment files. Data from CMS form 2728 were available for more than one-half of the cohort (Table 1), whose first date of ESRD was on or after April 1, 1995; because of the time elapsed from presentation of ESRD to renal transplantation, this disproportionately included recipients of living-donor kidneys. The form included information on pertinent laboratory values and baseline comorbidities.

Statistical Analyses

All analyses were performed with SPSS 9.0 (SPSS, Inc., Chicago, IL). Files were merged and converted to SPSS files by using DBMS/Copy (Conceptual Software, Houston, TX). Univariate analyses of factors associated with primary hospitalizations for treatment of ACS were performed with chi-squared tests for categorical variables (Fisher's exact test was used for violations of Cochran's assumptions) and *t* tests for continuous variables (the Mann-Whitney test was used for non-normally distributed variables). Statistical significance for univariate comparisons was defined as $P < 0.05$. Variables with $P < 0.10$ in univariate analyses testing for a relationship with a first ACS hospitalization were entered into multivariate analyses as covariates, because of the possibility of negative confounding. Variables considered to have a known clinical reason for association with ACS were introduced into multivariate models even if univariate *P* values were >0.10, in accordance with established epidemiologic principles (21). Continuous variables were explored, and values thought to be inconsistent with clinical experience were excluded.

The independent associations between patient factors and HHD were examined in multivariate analyses with stepwise Cox regression (likelihood ratio method) (22,23) for time until the first ACS hospitalization during the study period, controlling for variables entered into the model as described above. Log[−log(survival time)] *versus* log(survival time) plots were inspected and were parallel for all covariates in the final models, confirming the existence of proportional hazards. Multivariate analyses excluded all patients with missing values, which resulted in models substantially smaller than the entire study population. Continuous variables that were non-normally distributed were also assessed according to quartiles. Hierarchically well formed models were used for assessments of interaction terms. Because the Food and Drug Administration approved sirolimus for use in kidney transplantation on September 15, 1999, analysis limited to patients who received transplants on or after that date was also performed. To account for the possibility of miscoding of antirejection

Table 1. Factors associated with HHD after renal transplantation for renal transplant recipients treated January 1, 1996, to July 31, 2000, with Medicare as primary payer[a]

	No. or Mean ± SD	No. Missing	No. of or Mean for Patients with Factor With	
			ACS	CHF
Follow-up time (yr)	2.11 ± 0.95	(0.1 to 3.00)		
Total no.	29,597		553 (1.9%)	889 (3.0%)
Demographic factors				
Male recipient (*versus* female)	17,739 (59.9%)	0	368 (2.1%)[b]	527 (3.0%)
African-American recipient (*versus* all other races)	8031 (27.1%)	0	127 (1.6%)[b]	342 (4.3%)[b]
Mean age (yr) (risk per older year)	45.4 ± 14.6	0	52.4 ± 11.5[c]	52.3 ± 12.9[c]
Quartiles of age (*versus* < 33 yr)				
>56.8 yr			206 (2.8%)[b]	428 (5.1%)[b]
45.2 to 56.8 yr			195 (2.6%)[b]	228 (3.3%)[b]
33.7 to 45.2 yr			120 (1.6%)[b]	129 (1.8%)[b]
<33.7 yr			32 (0.4%)	104 (1.5%)
Mean serum creatinine level at 1 yr after transplantation (mg/dl)[d]	1.60 ± 1.05	6096 (20.6%)	1.70 ± 0.8[c]	1.98 ± 1.04[c]
Median serum creatinine level at 1 yr after transplantation (mg/dl)[d]	1.4			
Quartiles of serum creatinine levels at 1 yr after transplantation				
<1.1 mg/dl			83 (1.5%)	106 (1.9%)
1.1 to <1.4 mg/dl			94 (1.7%)	90 (1.6%)
1.4 to 1.8 mg/dl			104 (1.9%)	141 (2.5%)
>1.8 mg/dl			117 (2.2)[b]	274 (5.0%)[b]
MDRD GFR at 1 yr after transplantation[d]	58.7 ± 24.8	7422 (25%)	53.3 ± 19.2[c]	47.9 ± 19.5[c]
Median (ml/min per 1.73 m^2)	56.6			
Quartiles				
>69.4 (ml/min per 1.73 m^2)			72 (1.2%)	81 (1.4%)
>56.6 to 69.4 (ml/min per 1.73 m^2)			92 (1.6%)	110 (1.9%)
44.9 to 56.7 (ml/min per 1.73 m^2)			119 (2.0%)	118 (2.0%)
<44.9 (ml/min per 1.73 m^2)			128 (2.2)[b]	285 (4.9%)[b]
Duration of dialysis before transplantation				
Mean (yr)	4.09 ± 3.97	1074 (3.6%)	3.7 ± 3.5	4.1 ± 3.5
Median (yr)	2.9			
Quartiles				
>2.98 yr			108 (1.5%)	211 (3.0%)
>1.79 to 2.98 yr			143 (2.0%)	268 (3.8%)
1.00 to 1.79 yr			167 (2.3%)[b]	243 (3.4%)
<1.00 yr			123 (1.7%)	158 (2.2%)[b]
Maintenance immunosuppression (*versus* other medications)				
Cyclosporine	19,936 (71.7%)		399 (2.0%)[b]	593 (3.0%)
Tacrolimus	11,252 (40.5%)		184 (1.6%)[b]	316 (2.8%)
Mycophenolate	21,964 (79%)		390 (1.8%)[b]	606 (2.8%)[b]
Azathioprine	7224 (26.0%)		158 (2.2%)[b]	209 (2.9%)
Sirolimus	1629 (5.9%)		33 (2.0%)	54 (3.3%)
BMI (kg/m^2)	25.9 ± 24.8	4906 (16.6%)	26.5 ± 5.4[c]	27.1 ± 16.1[c]
BMI of >30 kg/m^2 (*versus* lower)	4737 (19.2%)		98 (2.1%)	209 (4.4%)[b]
PD (*versus* HD)	9942 (33.6%)		187 (1.9%)	260 (2.6%)[b]
Cause of ESRD				
Diabetes mellitus	7145 (28.2%)	4220 (14.3%)	215 (3.0%)[b]	294 (4.1%)[b]
Transplant-related factors				
Donor age (yr)	36.4 ± 16.1	2616 (8.8%)	39.1 ± 16.1[c]	40.8 ± 17.5[c]
Quartiles of donor age				
>47.7 yr			170 (2.5%)[b]	300 (4.4%)[b]
>36.7 to 47.7 yr			119 (1.8%)	208 (3.1%)
22.8 to 36.7 yr			125 (1.9%)	169 (2.5%)
<23.8 yr			109 (1.6%)	158 (2.3%)
African-American donor (*versus* donors of all other races)	3668 (12.4%)	0	53 (1.4%)[b]	141 (3.8%)[b]
Graft loss (*versus* continued graft function)	2025 (6.8%)	Presumed 0	60 (3.0%)[b]	162 (8.0%)[b]
Cadaveric donor (*versus* living donor)	22,896 (77.4%)	0	453 (2.0%)[b]	835 (2.6%)[b]
Kidney-pancreas transplant (*versus* all other transplant types)	1040 (3.5%)	0	31 (3.0%)[b]	16 (1.5%)[b]
Dialysis in the first 1 wk after transplantation (delayed graft function, *versus* absence of delayed graft function)	6494 (22.1%)	198 (0.7%)	156 (2.4%)	318 (4.9%)[b]
Episodes of rejection in the first 1 yr after transplantation (*versus* lack of rejection)	5993 (20.2%)	Presumed 0	125 (2.1%)[b]	251 (4.2%)[b]
Previous transplant (*versus* primary transplant)	3857 (13.2%)	293 (1.0%)	61 (1.6%)	105 (2.7%)[b]
Donor CMV-positive (*versus* donor CMV-negative)	15,987 (60.8%)	3309 (11.2%)	324 (2.0%)	547 (3.4%)[b]
Recipient CMV-positive (*versus* recipient CMV-negative)	13,095 (65.3%)	9553 (32.3%)	294 (2.2%)	496 (3.8%)[b]
Recipient HCV-positive (*versus* recipient HCV-negative)	1882 (7.0%)	2778 (9.4%)	27 (1.4%)	79 (4.2%)[b]
Donor HCV-positive (*versus* donor HCV-negative)	630 (2.1%)	0	12 (1.9%)	34 (5.4%)[b]
Information from medical evidence form 2728, baseline laboratory value, or history of condition in prior 10 yr[e]				
Ischemic heart disease (*versus* absence)	1280 (7.5%)	12,622 (42.6%)	55 (4.3%)[b]	79 (6.2%)
Myocardial infarction (*versus* absence)	450 (2.7%)	12,622 (42.6%)	20 (4.4%)[b]	23 (5.1%)
Congestive heart failure (*versus* absence)	1898 (11.2%)	12,622 (42.6%)	56 (3.0%)[b]	116 (6.1%)
Hypertension (*versus* absence)	12,042 (70.9%)	12,622 (42.6%)	213 (1.8%)[b]	321 (2.7%)
Stroke (*versus* absence)	449 (2.6%)	12,622 (42.6%)	15 (3.3%)[b]	22 (4.9%)[b]
Smoking (*versus* nonsmoking)	892 (5.8%)	12,622 (42.6%)	24 (2.1%)	37 (3.8)[b]
Hematocrit (%)	28.1 ± 5.8	13,757 (46.5%)	28.9 ± 5.6[c]	28.8 ± 5.8[c]
Serum albumin level (g/dl)	3.4 ± 0.7	15,919 (53.8%)	NS	NS

[a] Data are given as number and percentage of total or mean ± 1 SD. Dates for renal transplants were January 1, 1996, to March 3, 1999, with truncation at 3 yrs of follow-up monitoring. ACS, hospitalizations for treatment of acute coronary syndromes, International Classification of Diseases primary discharge code of 410.× (acute myocardial infarction) or 411.× (unstable coronary syndromes); CHF, hospitalizations for treatment of congestive heart failure, International Classification of Diseases primary discharge code of 428.×; PD, history of peritoneal dialysis for any 60-d period before transplantation (*versus* no history of peritoneal dialysis); HHD, hospitalized heart disease; BMI, body mass index; HD, hemodialysis; NA, variable was calculated from multiple other variables, and the number of missing values could not be given accurately; MDRD, Modification of Diet in Renal Disease; HCV, hepatitis C virus; CMV, cytomegalovirus.

[b] $P < 0.05$, by chi-squared test *versus* patients without factor (for example, for male patients, risk is for ACS or CHF *versus* patients).

[c] $P < 0.05$, by *t* test *versus* patients without ACS or CHF.

[d] Obtained from the most recent serum creatinine level before the end of the first 1 yr after renal transplantation.

[e] Limited to patients who developed ESRD on or after April 1, 1995.

drugs as maintenance drugs, we also performed analyses excluding patients who experienced allograft rejection in the first 1 yr after transplantation and using allograft rejection as an interaction term with all medications in the model. Analyses limited to patients who were receiving calcineurin inhibitors (either cyclosporine or tacrolimus) and excluding patients who were noted as receiving both cyclosporine and tacrolimus (possible crossovers, because the database could not reliably indicate the sequence of medication use) were also performed. Analyses substituting the mean values for missing values for continuous variables in multivariate analyses were performed for validation purposes.

Results

The incidence of CHF was 14.2 cases/1000 person-yr, and the incidence of ACS was 8.9 cases/1000 person-yr. Characteristics of the study population are presented in Table 1 and are consistent with current USRDS/United Network for Organ Sharing (UNOS) reports (24). The duration of dialysis before transplantation and serum creatinine levels at the end of the first 1 yr after transplantation were not normally distributed. Immunosuppressive medications were introduced into clinical practice at different times during the 1990s. The rates of ACS and CHF did not change significantly with time during the study period.

In unadjusted analyses (Table 1), factors associated with ACS included male gender, reduced eGFR at 1 yr, older age, longer duration of dialysis before transplantation, cyclosporine and azathioprine use, ESRD attributable to diabetes mellitus, older donor age, cadaveric kidney transplantation, kidney-pancreas transplantation, delayed graft function, graft loss, allograft rejection in the first 1 yr after transplantation, and cytomegalovirus-positive recipient. Among comorbid conditions noted in form 2728, cardiovascular comorbid conditions were generally associated with ACS and higher hematocrit levels but not low serum albumin levels.

In unadjusted analyses, factors associated with CHF included recipient African-American race, older recipient age, reduced eGFR at 1 yr, longer duration of dialysis before transplantation, nonuse of calcineurin inhibitors, use of sirolimus with cyclosporine, use of OKT3, elevated body mass index, older donor age, donor African-American race, delayed graft function, graft loss, rejection, cytomegalovirus-positive donor or recipient, and hepatitis C virus-positive donor or recipient. Cardiovascular comorbid conditions were generally associated with CHF, including higher hematocrit levels.

Table 2 presents the results of adjusted analyses of factors associated with ACS. Inspection of log[−log(survival time)] *versus* log(survival time) plots demonstrated a deviation from the proportional-hazards assumption at 1.5 yr after transplantation. Therefore, multivariate models assessed factors associated with ACS occurring ≥1.5 yr after transplantation. In the model that did not include comorbid conditions from CMS form 2728, the patients with eGFR in quartiles 1 to 3 at 1 yr after transplantation were all at significantly increased risk of ACS, compared with patients with eGFR in the highest quartile (Figure 1). However, in the model accounting for comorbid conditions (which also contained fewer patients), only patients with eGFR in the lowest quartile (<44.8 ml/min per 1.73 m^2) were independently at increased risk of ACS. Other factors that were significant in the analyses included older age, a history of peritoneal dialysis treatment, and diabetes mellitus. Rejection occurring in the first 1 yr after transplantation was significant only as an interaction term with cyclosporine use in the larger model but was significant with adjustment for

Table 2. Cox regression analysis of factors independently associated with ACS occurring 1.5 to 3 yr after renal transplantation[a]

	Model without CMS Form 2728		Model with CMS Form 2728	
	P Value	Adjusted Rate Ratio for ACS in Cox Regression	*P* Value	Adjusted Rate Ratio for ACS in Cox Regression
Quartiles of MDRD GFR at 1 yr after transplantation				
>69.4 ml/min per 1.73 m^2		Reference		Reference
>56.6 to 69.4 ml/min per 1.73 m^2	0.023	1.70 (1.08 to 2.69)	0.089	1.79 (0.93 to 3.46)
44.9 to 56.7 ml/min per 1.73 m^2	0.002	2.05 (1.31 to 3.19)	0.086	1.78 (0.92 to 3.46)
<44.9 ml/min per 1.73 m^2	0.001	2.16 (1.39 to 3.35)	0.005	2.44 (1.30 to 4.58)
Quartiles of age (*versus* <33 yr)				
>57 yr	<0.001	6.62 (3.32 to 13.20)	<0.001	8.15 (2.90 to 22.90)
45 to 57 yr	<0.001	6.47 (3.23 to 12.97)	<0.001	7.75 (2.73 to 21.95)
35 to 45 yr	<0.001	4.31 (2.26 to 8.21)	0.003	5.09 (1.76 to 14.68)
Diabetes mellitus	<0.001	2.23 (1.71 to 2.91)	0.002	1.84 (1.26 to 2.69)
Comorbid conditions from CMS form 2728				
Prior ischemic heart disease	NA		<0.001	2.47 (1.56 to 3.93)
Smoking history	NA		0.032	1.94 (1.06 to 3.56)
No. in final model	17,576		10,214	

[a] NA, not included in model; MDRD, Modification of Diet in Renal Disease; CMS, Centers for Medicare/Medicaid Studies.

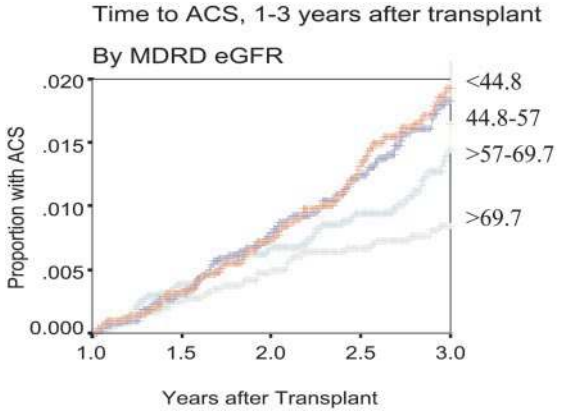

Figure 1. Kaplan-Meier plot of time to hospitalized acute coronary syndromes (ACS) (International Classification of Diseases, version 9, primary discharge diagnosis code 410.x or 411.x), according to quartiles of Modification of Diet in Renal Disease estimated GFR (eGFR), as indicated by the most recent available serum creatinine level measured <1 yr after renal transplantation. There was no distinct difference in the risk of ACS according to GFR until approximately 2 yr after renal transplantation, when the lowest GFR quartile (<44.8 ml/min per 1.73 m^2) was significantly different from the highest GFR quartile (>69.7 ml/min per 1.73 m^2) ($P < 0.01$, log rank test). This difference remained significant in an adjusted Cox regression analysis (Table 2).

comorbid conditions. Notably, the duration of dialysis before transplantation had no independent relationship with ACS in either model.

In adjusted analyses of CHF (Table 3), eGFR did not seem to have as consistent a relationship with CHF, although patients with eGFR in the lowest quartile had a significantly higher risk of CHF, compared with those with higher eGFR (Figure 2), regardless of whether comorbid conditions were included in the model. In contrast to ACS, the duration of dialysis before transplantation had a significant stepwise relationship with CHF, regardless of whether comorbid conditions were included. Other significant factors included older age, diabetes mellitus, and delayed graft function.

The results of the analyses were not substantially different in models limited to patients who received transplants on or after September 15, 1999 (the date of Food and Drug Administration approval of sirolimus for use in kidney transplantation), limited to patients receiving calcineurin inhibitors, or excluding patients who were noted as receiving both cyclosporine and tacrolimus. Results were also not substantially different in models using quartiles of serum creatinine levels (instead of eGFR) or using interpolation of mean values for missing values for continuous variables.

Table 3. Cox regression analysis of factors independently associated with CHF occurring 1 to 3 yr after renal transplantation[a]

	Model without CMS Form 2728		Model with CMS Form 2728	
	P Value	Adjusted Rate Ratio for CHF in Cox Regression	*P* Value	Adjusted Rate Ratio for CHF in Cox Regression
African-American recipient	<0.001	1.61 (1.33 to 1.95)	0.015	1.42 (1.07 to 1.89)
Quartiles of MDRD GFR at 1 yr after transplantation				
>69.4 ml/min per 1.73 m^2		Reference		Reference
>56.6 to 69.4 ml/min per 1.73 m^2	0.12	1.26 (0.91 to 1.74)	0.18	1.40 (0.86 to 2.28)
44.9 to 56.7 ml/min per 1.73 m^2	0.25	1.21 (0.88 to 1.66)	0.33	1.28 (0.78 to 2.11)
<44.9 ml/min per 1.73 m^2	<0.001	2.95 (2.24 to 3.90)	<0.001	3.37 (2.16 to 5.27)
Duration of dialysis before transplantation (*versus* <1.0 yr)				
>2.98 yr	<0.001	2.61 (1.74 to 3.93)	<0.001	2.95 (2.06 to 7.07)
>1.79 to 2.98 yr	<0.001	2.55 (1.72 to 3.78)	<0.001	2.88 (2.39 to 6.67)
1.00 to 1.79 yr	<0.001	2.32 (1.55 to 3.48)	<0.001	2.34 (1.80 to 4.67)
<1.00 yr		Reference		Reference
Quartiles of age, (*versus* (>33 yr)				
>57 yr	<0.001	3.70 (2.68 to 5.11)	<0.001	2.95 (1.89 to 4.60)
45 to 57 yr	<0.001	2.37 (1.69 to 3.32)	NS	
33 to 44 yr	0.79	1.02 (0.63 to 1.65)	NS	
Diabetes mellitus	<0.001	1.93 (1.60 to 2.32)	0.027	1.36 (1.04 to 1.79)
BMI of ≥30 kg/m^2	0.001	1.62 (1.21 to 2.16)	0.013	1.59 (1.10 to 2.30)
Comorbid conditions from CMS form 2728				
Prior congestive heart failure	NA		<0.001	3.56 (2.48 to 5.09)
No. in final model	15,687		8724	

[a] NA, not included in model; BMI, body mass index; MDRD, Modification of Diet in Renal Disease; CMS, Centers for Medicare/Medicaid Studies.

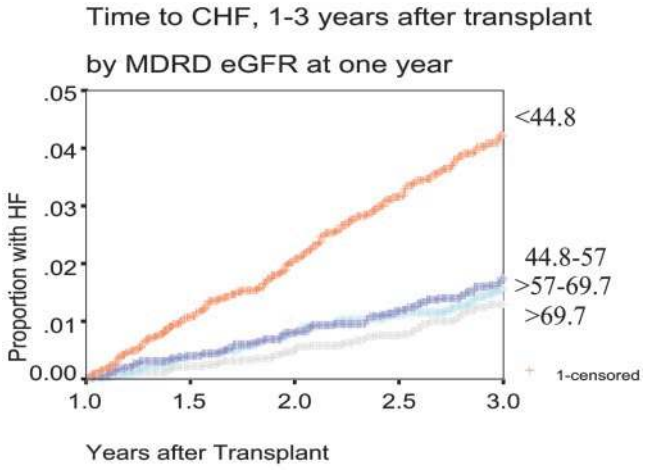

Figure 2. Kaplan-Meier plot of time to hospitalized congestive heart failure (CHF) (International Classification of Diseases, version 9, primary discharge diagnosis code 428.x), according to quartiles of Modification of Diet in Renal Disease eGFR, as indicated by the most recent available serum creatinine level measured <1 yr after renal transplantation. There was a distinct difference in the risk of CHF according to GFR immediately after renal transplantation; the lowest GFR quartile (<44.8 ml/min per 1.73 m^2) was significantly different from the highest GFR quartile (>69.7 ml/min per 1.73 m^2) ($P < 0.01$, log rank test). This difference remained significant in an adjusted Cox regression analysis (Table 3).

Discussion

Decreased eGFR at the end of the first 1 yr after transplantation was independently associated with HHD 1 to 3 yr after renal transplantation. The threshold eGFR of 44.8 ml/min per 1.73 m^2 corresponded to a serum creatinine level of 1.8 mg/dl for most patients and is in the middle range of stage 3 chronic kidney disease, as defined by Kidney Disease Outcomes Quality Initiative guidelines (25). This finding is remarkably similar to the association of reduced GFR with death among patients in the general population with known CHF; a "eGFR" of <44 ml/min (calculated with the Cockroft-Gault method and thus representing a creatinine clearance) was associated with a threefold increased risk of death (26). This relationship manifested 1 to 2 yr after transplantation for ACS and immediately after the first posttransplantation year for CHF. Because we did not have access to BP and lipid levels, we could not determine whether the risk of HHD associated with decreased eGFR was independent of those factors. However, even large cohort studies of the general population have been unable to determine whether renal insufficiency is truly an independent risk factor for cardiovascular disease. Although both conditions were considered HHD, the risk factors for ACS and CHF were not entirely congruent, consistent with studies of the general population. Remarkably, in this study the association between decreased eGFR and HHD persisted after adjustment for known cardiovascular risk factors, as determined from CMS form 2728. In the search for unifying risk factors for heart disease after renal transplantation that might be subject to intervention, eGFR thus seems promising. Findings on other risk factors for ACS and CHF after renal transplantation in this study were consistent with previously published results (5–7,27).

Elevated serum creatinine levels (>1.4 mg/dl) have been associated with recurrent ischemic heart disease in the general population (28,29), as well as death after HHD (30,31). Elevated serum creatinine levels after renal transplantation have been linked to graft failure (1) and to cardiac disease-related death (32). In the renal transplant population, Ducloux *et al.* (8) observed that elevations in baseline serum creatinine levels were associated with composite cardiovascular outcomes, including death. More recently, however, Ducloux *et al.* (33) reported that serum creatinine levels were not independently associated with cardiovascular events, after accounting for $CD4^+$ cell lymphopenia, serum homocysteine levels, age, and tobacco use. Those authors suggested the intriguing theory that immunodeficiency, which might be a "lurking variable" associated with renal insufficiency, is an independent predictor of atherosclerotic events among renal transplant recipients. Our study was obviously not able to measure $CD4^+$ cell counts, C-reactive protein levels, or other unconventional risk factors.

There are additional reasons why renal insufficiency might contribute to the risk of HHD after renal transplantation. Cohort studies of the general population recently demonstrated that standard prevention and management therapies are less likely to be used for patients with renal insufficiency who also have or develop cardiovascular disease (34,35). Beneficial medications such as HMG-CoA reductase inhibitors and β-blockers are dramatically underused for patients with chronic renal failure (36,37), even for those with known cardiovascular disease (38). The same may be true for renal transplant recipients with renal insufficiency, but that remains to be determined. Hariharan *et al.* (1) directly attributed improvements in graft survival rates with time to improved posttransplantation renal function. It has yet to be determined whether improvements in posttransplantation cardiovascular disease, as noted by Herzog *et al.* (39) and Meier-Kriesche *et al.* (40), could also be related to better kidney function or to other factors.

Several factors that were associated with ischemic heart disease after renal transplantation in other studies, namely, male gender and allograft rejection occurring in the first 1 yr after transplantation (5,7,16), were not significantly associated with ACS after adjustment for eGFR at 1 yr, suggesting that the effects of male gender and rejection might be partially mediated by changes in eGFR. In contrast, both African-American race and body mass index, which we previously reported as being associated with CHF after renal transplantation (41), were significant independently of eGFR at 1 yr. Whether this increased risk of CHF among African-American and obese recipients was attributable to higher BP or other factors that were not measured could not be determined. Cohort studies of CHF after renal transplantation have been limited to Caucasian populations (7,42); it is now appropriate to plan similar trials for African-American renal transplant recipients.

We did not observe that any specific immunosuppressive agent was independently associated with ACS or CHF. Be-

cause of the limitations of the USRDS/UNOS database and substantial changes in immunosuppressive agent use (43), with considerable crossover of medications, it is almost impossible to account for the immunosuppressive regimens and associate them with the risk of CHF and ACS. We therefore used information on immunosuppression to adjust for possible confounding effects on renal function. In any case, differences in cardiovascular outcomes mediated by differing immunosuppressive regimens would be unlikely by 3 yr after transplantation. In particular, we did not observe that any specific immunosuppressive agents demonstrated adverse interactions with decreased renal function among renal transplant recipients, in terms of risk for cardiovascular disease.

This study has several limitations that were previously discussed in published reports of studies that used the USRDS database, including the inability to monitor hematocrit levels, BP, glycemic control, and lipid levels with time (6). Discontinuation of calcineurin inhibitor or corticosteroid use, continuation of (rather than a history of) cigarette smoking, and treatment of hyperlipidemia, hypertension, or hyperglycemia, all of which could affect rates of cardiovascular disease, could not be assessed. Nevertheless, this study noted many of the same risk factors for ACS and CHF after transplantation as did previous studies (6–8,16). Although information on BP was recently introduced into the UNOS transplant database, this information was available for only a small number of patients, and information on lipid levels and proteinuria was not available. Longenecker *et al.* (18) observed that the specificity of CMS form 2728 for cardiovascular disease was >90%, although its sensitivity was considerably lower. Cardiovascular disease may certainly present after initiation of dialysis (and thus after documentation in CMS form 2728), but it is often occult and is usually detected earlier with serial echocardiography than on the basis of clinical manifestations. Because most patients have substantial cardiovascular disease after 2 yr of dialysis, the duration of dialysis before transplantation might be a reasonable surrogate measure for underlying cardiovascular disease (33,42). The strongest predictors of future acute coronary events for the general population are oxidized LDL levels (44) or a combination of C-reactive protein and LDL levels (45), which were not available in the database. The USRDS will likely never be able to determine differences in hospitalization rates on the basis of long-term follow-up data, because of Medicare reporting regulations being limited to 3 yr after transplantation. Despite these limitations, our analysis is strengthened by the completeness and large size of the database, its population-based character, its use of actual outcomes (hospitalized ACS and death), and its relatively complete follow-up data.

In conclusion, analysis of data for the national renal transplant population demonstrated that reduced eGFR (which would be considered approximately stage 3 chronic kidney disease in the general population) 1 yr after transplantation was independently associated with an increased risk of HHD 1 to 3 yr after renal transplantation. Because of the decreasing rates of allograft rejection and graft failure with time (46), the relative importance of death with graft function, of which HHD is a harbinger, will likely increase with time. Evidence from the general and dialysis populations demonstrates that beneficial treatments for cardiovascular disease seem underused for patients with renal insufficiency, regardless of the presence of conventional cardiovascular risk factors. The same is likely true for the renal transplant population. It remains an intriguing possibility that preservation of renal function after kidney transplantation could affect HHD and thus death with graft function.

Acknowledgments

The opinions stated are solely those of the authors and do not represent an endorsement by the Department of Defense or the National Institutes of Health. This is a United States government work, and there are no restrictions on its use.

References

1. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP: Post-transplant renal function in the first 1 yr predicts long-term kidney transplant survival. *Kidney Int* 62: 311–318, 2002
2. Bostom AD, Brown RS Jr, Chavers BM, Coffman TM, Cosio FG, Culver K, Curtis JJ, Danovitch GM, Everson GT, First MR, Garvey C, Grimm R, Hertz MI, Hricik DE, Hunsicker LG, Ibrahim H, Kasiske BL, Kennedy M, Klag M, Knatterud ME, Kobashigawa J, Lake JR, Light JA, Matas AJ, McDiarmid SV, Miller LW, Payne WD, Rosenson R, Sutherland DE, Tejani A, Textor S, Valantine HA, Wiesner RH: Prevention of post-transplant cardiovascular disease: Report and recommendations of an ad hoc group. *Am J Transplant* 2: 491–500, 2002
3. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134: 629–636, 2001
4. Garg AX, Clark WF, Haynes RB, House AA: Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. *Kidney Int* 61: 1486–1494, 2002
5. Hypolite IO, Bucci J, Hshieh P, Cruess D, Agodoa LY, Yuan CM, Taylor AJ, Abbott KC: Acute coronary syndromes after renal transplantation in patients with end-stage renal disease resulting from diabetes mellitus. *Am J Transplant* 2: 274–281, 2002
6. Abbott KC, Bucci JR, Cruess D, Taylor AJ, Agodoa LY: Graft loss and acute coronary syndromes after renal transplantation in the United States. *J Am Soc Nephrol* 13: 2560–2569, 2002
7. Rigatto C, Parfrey P, Foley R, Negrijn C, Tribula C, Jeffery J: Congestive heart failure in renal transplant recipients: Risk factors, outcomes, and relationship with ischemic heart disease. *J Am Soc Nephrol* 13: 1084–1090, 2002
8. Ducloux D, Motte G, Challier B, Gibey R, Chalopin JM: Serum total homocysteine and cardiovascular disease occurrence in chronic, stable renal transplant recipients: A prospective study. *J Am Soc Nephrol* 11: 134–137, 2000
9. Keunecke C, Rothenpieler U, Zanker B, Schneeberger H, Illner WD, Theodorakis J, Stangl M, Land W: Mycophenolate mofetil monotherapy: An example of a safe nephrotoxicity/atherogenicity-free immunosuppressive maintenance regimen in a selected group of kidney-transplanted patients. *Transplant Proc* 2[Suppl]: 6S–8S, 2000
10. Galiatsou E, Morris ST, Jardine AG, Rodger RS, Watson MA, Elliott HL: Cardiac and vascular abnormalities in renal transplant patients: Differential effects of cyclosporin and azathioprine. *J Nephrol* 13: 185–192, 2000
11. Montagnino G, Tarantino A, Segoloni GP, Cambi V, Rizzo G, Altieri P, Castagneto M, Salvadori M, Cossu M, Pisani F, Car-

mellini M, Mastrangelo F, Ferrara R, Ponticelli C: Long-term results of a randomized study comparing three immunosuppressive schedules with cyclosporine in cadaveric kidney transplantation. *J Am Soc Nephrol* 12: 2163–2169, 2001
12. Shaheen FA, Souqiyyeh MZ, Shiek IA, Fedhail H, al-Sulaiman M, Mousa D, al-Hawas F, al-Khader AA: Hypercholesterolemia in renal transplantation. *Ann Transplant* 6: 9–13, 2001
13. Curtis JJ: Treatment of hypertension in renal allograft patients: Does drug selection make a difference? *Kidney Int Suppl* 63: S75–S77, 1997
14. Bloom RD, Rao V, Weng F, Grossman RA, Cohen D, Mange KC: Association of hepatitis C with posttransplant diabetes mellitus in renal transplant patients on tacrolimus. *J Am Soc Nephrol* 13: 1374–1380, 2002
15. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ: Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 3: 178–185, 2003
16. Kasiske BL, Chakkera HA, Roel J: Explained and unexplained ischemic heart disease risk after renal transplantation. *J Am Soc Nephrol* 11: 1735–1743, 2000
17. Margreiter R: Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: A randomised multicentre study. *Lancet* 359: 741–746, 2002
18. Longenecker JC, Coresh J, Klag MJ, Levey AS, Martin AA, Fink NE, Powe NR: Validation of comorbid conditions on the end-stage kidney disease medical evidence report: The CHOICE study: Choices for Healthy Outcomes in Caring for ESRD. *J Am Soc Nephrol* 11: 520–529, 2000
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation: Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470, 1999
20. Ojo AO, Meier-Kriesche HU, Hanson JA, Leichtman AB, Cibrik D, Magee JC, Wolfe RA, Agodoa LY, Kaplan B: Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. *Transplantation* 69: 2405–2409, 2000
21. Szklo M, Nieto FJ: *Epidemiology: Beyond the Basics*, Gaithersburg, MD, Aspen Publishers, 2000, p 257
22. SPSS: *SPSS 9.0 Advanced Models: Application Guide*, Chicago, SPSS Inc., 1999
23. Kleinbaum DG: *Survival Analysis: A Self-Learning Text* (Statistics in the Health Sciences), New York, Springer Verlag, 1996
24. http://www.usrds.org, accessed March 5, 2003
25. http://www.kidney.org/professionals/doqi/kdoqi/p4_class_g1.htm, accessed March 7, 2003
26. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 102: 203–210, 2000
27. Ganesh SK, Hulbert-Shearon T, Port FK, Eagle K, Stack AG: Mortality differences by dialysis modality among incident ESRD patients with and without coronary artery disease. *J Am Soc Nephrol* 14: 415–424, 2003
28. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134: 629–636, 2001
29. Ritz E, Dikow R, Ruilope LM: Renal dysfunction as a cardiovascular risk factor. *Curr Hypertens Rep* 4: 365–368, 2002
30. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R: Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: A population-based study. *J Am Soc Nephrol* 13: 1928–1936, 2002
31. Walsh CR, O'Donnell CJ, Camargo CA Jr, Giugliano RP, Lloyd-Jones DM: Elevated serum creatinine is associated with 1-year mortality after acute myocardial infarction. *Am Heart J* 144: 1003–1011, 2002
32. Meier-Kriesche HU, Baliga R, Kaplan B: Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation* 75: 1291–1295, 2003
33. Ducloux D, Challier B, Saas P, Tiberghien P, Chalopin JM: CD4 cell lymphopenia and atherosclerosis in renal transplant recipients. *J Am Soc Nephrol* 14: 767–772, 2003
34. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB: Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 137: 555–562, 2002
35. Wright RS, Reeder GS, Herzog CA, Albright RC, Williams BA, Dvorak DL, Miller WL, Murphy JG, Kopecky SL, Jaffe AS: Acute myocardial infarction and renal dysfunction: A high-risk combination. *Ann Intern Med* 137: 563–570, 2002
36. Tonelli M, Moye L, Sacks FM, Kiberd B, Curhan G: Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med* 138: 98–104, 2003
37. Seliger SL, Weiss NS, Gillen DL, Kestenbaum B, Ball A, Sherrard DJ, Stehman-Breen CO: HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. *Kidney Int* 61: 297–304, 2002
38. Trespalacios FC, Taylor AJ, Agodoa LY, Abbott KC: Incident acute coronary syndromes in chronic dialysis patients in the United States. *Kidney Int* 62: 1799–1805, 2002
39. Herzog CA, Ma JZ, Collins AJ: Long-term survival of renal transplant recipients in the United States after acute myocardial infarction. *Am J Kidney Dis* 36: 145–152, 2000
40. Meier-Kriesche HU, Ojo AO, Port FK, Arndorfer JA, Cibrik DM, Kaplan B: Survival improvement among patients with end-stage renal disease: Trends over time for transplant recipients and wait-listed patients. *J Am Soc Nephrol* 12: 1293–1296, 2001
41. Abbott KC, Hypolite IO, Hshieh P, Cruess D, Taylor AJ, Agodoa LY: Hospitalized congestive heart failure after renal transplantation in the United States. *Ann Epidemiol* 12: 115–122, 2002
42. Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P: Electrocardiographic left ventricular hypertrophy in renal transplant recipients: Prognostic value and impact of blood pressure and anemia. *J Am Soc Nephrol* 14: 462–468, 2003
43. Helderman JH, Bennett WM, Cibrik DM, Kaufman DB, Klein A, Takemoto SK: Immunosuppression: Practice and trends. *Am J Transplant* 3[Suppl 4]: 41–52, 2003
44. Tsimikas S, Bergmark C, Beyer RW, Patel R, Pattison J, Miller E, Juliano J, Witztum JL: Temporal increases in plasma markers of oxidized low-density lipoprotein strongly reflect the presence of acute coronary syndromes. *J Am Coll Cardiol* 41: 360–370, 2003
45. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347: 1557–1565, 2002
46. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D: Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 342: 605–612, 2000