Incidence and Predictors of Myocardial Infarction after Kidney Transplantation

Krista L. Lentine,* Daniel C. Brennan,† and Mark A. Schnitzler*

Department of Medicine, Center for Outcomes Research, Saint Louis University School of Medicine, St. Louis, Missouri; and †Departments of Medicine and Transplant Nephrology, Division of Nephrology, Washington University School of Medicine, St. Louis, Missouri

The risk and predictors of post–kidney transplantation myocardial infarction (PTMI) are not well described. Registry data collected by the United States Renal Data System were used to investigate retrospectively PTMI among adult first renal allograft recipients who received a transplant in 1995 to 2000 and had Medicare as the primary payer. PTMI events were ascertained from billing and death records, and participants were followed for up to 3 yr after transplant or until the end of observation (December 31, 2000). Extended Cox's hazards analysis was used to identify independent clinical correlates of PTMI (hazard ratio [HR]) and to examine PTMI as an outcomes predictor. Among 35,847 eligible participants, the cumulative incidence of PTMI was 4.3% (95% confidence interval [CI], 4.1 to 4.5%), 5.6% (95% CI, 5.3 to 5.8%), and 11.1% (95% CI, 10.7 to 11.5%) at 6, 12, and 36 mo, respectively. Risk factors for PTMI included older recipient age, pretransplantation comorbidities (diabetes, angina, peripheral vascular disease, and MI), transplantation from older donors and deceased donors, and delayed graft function. Women, blacks, Hispanics, and employed recipients experienced reduced risk. The hazard of PTMI rose after a diagnosis of posttransplantation diabetes (HR, 1.60; 95% CI, 1.35 to 1.88) and markedly increased after graft failure (HR, 2.78; 95% CI, 2.41 to 3.19). In separate analyses, PTMI predicted death-censored graft failure (HR, 1.89; 95% CI, 1.63 to 2.20) and strongly predicted death in a manner that declined with time after PTMI. Risk factors for PTMI include potentially modifiable posttransplantation complications. Because PTMI in turn predicts graft failure and death, reducing the risk for PTMI may improve outcomes after kidney transplantation.

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Recent studies demonstrate that myocardial infarction (MI) and renal dysfunction form a "high-risk combination" (1,2). Patients with mild chronic renal insufficiency faced more than twofold higher death rates after MI than those with normal renal function in one center's experience (2), and post-MI mortality increases explosively among ESRD patients on dialysis (1,2). Although kidney transplantation may reduce the risk for MI and improve post-MI survival (1,3), mortality rates after hospitalization for acute coronary syndromes among renal allograft recipients remain sobering, ranging from approximately 24% at 1 yr (1,4), to 30 to 38% at 2 yr (1,4,5), to >45% at 5 yr (1,4). Furthermore, as a leading cause of death (and thus graft loss) in patients with functioning renal transplants (6), posttransplantation MI (PTMI) has important implications for allograft longevity in this population.

Several investigations have approached estimation of the incidence and predictors of MI after kidney transplantation by modeling primary hospital discharge diagnoses (5,7). These studies are limited by the quantity of available information for many clinical variables and, in not ascertaining other presentations including secondary diagnoses and fatal MI, underestimate risk. Candidate risk factors for PTMI include characteristics of the recipient, the kidney donor, transplantation management, and transplant course. Renal allograft recipients have a higher prevalence of "traditional" Framingham atherosclerotic vascular disease risk factors, including advanced age, diabetes, hypertension, and dyslipidemia (8). Time on dialysis before transplantation (9), donor history of hypertension (10), immunosuppressive regimen (11), quality of allograft function (12), and posttransplantation diabetes (13,14) also are implicated as mediators of cardiovascular risk in this population. Along with current uncertainty for the magnitude of PTMI incidence rates, the independent predictive values of putative posttransplantation cardiovascular risk factors for PTMI specifically, potential for risk modification, and the spectrum of clinical consequences after this complication are not yet known.

Prompted by the limited available evidence on the risk and outcomes of PTMI, we undertook a retrospective study of a large cohort of recent kidney transplant recipients recorded in the United States Renal Data System (USRDS). We aimed to quantify the risk for PTMI in all presentations, identify clinically relevant risk factors, and estimate the impact of this complication on posttransplantation outcomes including graft loss and death.

Materials and Methods

Data Sources

We performed sample selection, outcomes ascertainment, and covariate determinations using registry data collected by the USRDS that

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Address correspondence to: Dr. Krista L. Lentine, Saint Louis University Center for Outcomes Research, 3545 Lafayette Avenue, Salus Center, 2nd Floor, St. Louis, MO 63104. Phone: 314-977-9477; Fax: 314-977-1101; E-mail: lentine.krista@stanfordalumni.org

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incorporates information from the United Network for Organ Sharing (UNOS) and Medicare billing claims records. Details of the source USRDS data files, as well as limitations of Medicare claims data, have been described previously (7,15).

Participant Selection

We included adult (≥18 yr of age) first renal allograft recipients who received a transplant in 1995 to 2000 and had Medicare as the primary payer at the time of transplant. We restricted the study to recipients who received a transplant after 1995 because the quantity of potentially predictive data elements available from the UNOS database expanded in that year. We did not study patients who received a transplant after 2000 because the most recent files released by the USRDS at the time of the study included follow-up until December 31, 2000. Patients without Medicare as their primary payer were excluded because of lack of claims data that would reliably indicate the presence or absence of PTMI and certain covariates. Also, we excluded patients with previous and/or simultaneous multiorgan transplants because of potential influence of this experience on subsequent cardiovascular risk and mortality.

Definitions of Outcomes and Covariates

PTMI. PTMI was defined by identification of a posttransplantation Medicare claim (Part A or B) with an MI diagnosis (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 410.x) or by death after transplantation with MI specified as a cause. For patients with multiple qualifying events, we selected the earliest event date as the date of PTMI. Observations were censored at the earliest of the following events: Loss to follow-up, loss of Medicare, 3 yr after transplant (the time when Medicare coverage ends after kidney transplantation in the absence of extenuating disability) to avoid censoring bias, death not caused by PTMI, or end of observation (December 31, 2000).

Recipient, Donor, and Transplant-Related Characteristics and Outcomes. We collected the following recipient demographics and clinical characteristics for evaluation: Age, race, Hispanic ethnicity, gender, primary cause of ESRD, time from first dialysis until transplantation, college education, employment (full or part time), obesity (body mass index ≥30 kg/m^2), and comorbid conditions. The date of first dialysis was defined as the earliest dialysis start date identified among records of UNOS, the Center for Medicare and Medicaid Studies (CMS Form 2728), and the USRDS treatment history file. Recipient characteristics and comorbidities were those reported by UNOS at the time of transplantation, supplemented with information on pretransplantation conditions from the CMS 2728 when available (*i.e.*, conditions known at the time of ESRD reporting) and with pretransplantation claims data in cases of diabetes (ICD-9 250.x), MI, peripheral vascular disease (ICD9 440.2x, 443.9), hypertensive heart disease (ICD-9 402.x), dyslipidemia (ICD-9 272.0 to 272.5), cardiac arrhythmia (ICD-9 427.x), and tobacco use (ICD-9 305.1x). A diagnosis of diabetes was identified from claims data on the basis of one inpatient or two outpatients claims, with the date of onset set at the earliest claim, as previously validated for diabetes (Hebert method) (16). We distinguished diabetes related and unrelated to ESRD. Posttransplantation diabetes was defined as qualifying posttransplantation claims data in patients without an indication of diabetes before transplantation (related or unrelated to renal failure). After confirming with a sensitivity analysis that use of single claims produced similar diagnosis rates and risk associations with PTMI for dyslipidemia as the Hebert method (2% absolute difference in diagnosis rates and 3% absolute risk difference), we required single claims for other conditions. Donor and transplant procedure characteristics were derived from UNOS records, including donor age, race, gender, source (deceased *versus* living), the year of transplantation, recipient sensitization (panel of reactive antibodies ≥50%), the number of donor–recipient human leukocyte antigen mismatches, donor–recipient cytomegalovirus (CMV) seropairing, cold ischemia time, and delayed graft function defined as dialysis during the first 7 d posttransplantation. We collected immunosuppression data recorded on the UNOS recipient registration form for analysis on an intention-to-treat basis. We defined induction therapy as recorded administration of any of the following during the transplant hospitalization for the specified purpose of induction: Anti-thymocyte globulins, anti-CD3 monoclonal antibodies, and anti-CD25 antibody preparations. We ascertained maintenance immunosuppression on the basis of recorded use for maintenance therapy at transplantation discharge.

Statistical Analyses

We estimated the incidence of PTMI by the product-limit method. Bivariate comparisons of the cumulative incidence of PTMI were performed with the log-rank test. To form clinical strata, we categorized continuous variables into clinically relevant groupings. Missing categorical covariate data were grouped with the absence of a characteristic when such a category was relevant or into a category distinct from the reference group, allowing estimation of the effect of the known and indicated presence of specified conditions. We used multivariate Cox's hazards analysis to obtain covariate-adjusted estimates of the risk for PTMI (hazard ratio [HR]) associated with recipient-, donor-, and transplant-related factors. The proportionality of hazards over time was assessed by testing interactions between predictors and a continuous linear function of years after transplantation, and nonproportionality was adjusted by entry of significant time interactions in final extended Cox models. We tested for two-way interactions between significant predictors (positive and negative) and all other variables.

In the prediction of PTMI, we did not consider cases in which graft failure, PTMI, and death occurred on the same day as cases of graft failure (because of possibility that PTMI was the primary event). We examined the impact of PTMI on death-censored graft failure, all-cause graft loss, and mortality by extended Cox's hazards analysis with PTMI as a time-varying covariate. Because death records were used in the ascertainment of PTMI, we analyzed only "survived MI" (cases in which the participant did not die on date of MI) as a predictor of subsequent death and graft loss.

For main effects, we considered a $P < 0.01$ to be statistically significant, because of the large sample and large number of covariates considered. The criteria for statistical significance of interactions terms reflected the number of comparisons performed with each covariate: $P < 0.01$ for time and $P < 0.0002$ for between-variable interactions, allowing the total probability of type I error in each case to be no greater than 0.01. All analyses were performed with SAS for Windows software, version 8 (SAS Institute, Cary, NC).

Incidence of MI on the Waiting List. To provide context for the estimates of PTMI incidence, we estimated the incidence of first MI after wait-listing among transplant candidates who had Medicare as the primary payer and joined the waiting list in 1995 to 2000. We used Cox regression to estimate a probability distribution function adjusted to the average age, gender, race, and ethnic composition of the study sample that received a transplant. Participants for whom Medicare coverage began after the start of the waiting period were entered into the risk set by left truncation (17). Observations were censored at removal from the waiting list (including time of transplantation or death not due to MI), loss to follow-up, loss of Medicare, and end of study observation.

Results

Characteristics of the Sample

We identified 35,847 eligible Medicare beneficiaries who received their first renal allograft during the study period. The similarities and differences of patients in the USRDS with and without Medicare as their primary payer have been described previously (15,18,19). Observed frequencies of major demographic and clinical characteristics are displayed in the first column of Table 1.

Incidence of PTMI

The cumulative incidence of PTMI was 4.3% (95% CI, 4.1 to 4.5%), 5.6% (95% CI, 5.3 to 5.8%), and 11.1% (95% CI, 10.7 to 11.5%) at 6, 12, and 36 mo, respectively. Scaled according to observed time at risk, this equates to an event rate of 45 MI per 1000 patient-years at risk (51 and 38 MI per 1000 patient-years among men and women, respectively). By comparison, the incidence of MI among 70,066 eligible transplant candidates, adjusted to average demographic characteristics of the study sample who received a transplant, was 5.0% (95% CI, 4.8 to 5.2%) at 1 yr and 16.7% (95% CI, 16.1 to 17.2%) at 3 yr after joining the waiting list, respectively. Table 1 shows the cumulative incidence of PTMI, stratified by significant positive and negative predictors of PTMI risk.

Independent Risk Factors for PTMI

Independent clinical correlates of PTMI identified among the candidate characteristics are shown in Table 2. Recipient factors associated with increased risk for PTMI included older age and histories of angina, peripheral vascular disease, and dyslipidemia. Pretransplantation MI history predicted a nearly fourfold increase in the risk for PTMI, but risk decreased with time after transplantation by approximately 30% of the baseline risk per year. Cardiac arrhythmia history was linked with 41% increased PTMI risk at transplantation, which declined approximately 11% each posttransplantation year. Pretransplantation diabetes (related or unrelated to primary cause of renal failure) was a weak baseline risk factor, but risk rose further over observation by approximately 19% each year. As diabetes as primary cause of ESRD was an additional independent PTMI risk factor, patients with this diagnosis faced risk that incorporated both the diabetes comorbidity and ESRD as a result of diabetes-related estimates to yield a 56% risk increase.

Recipient factors that reduced the risk for PTMI included black race, Hispanic ethnicity, and employment. Female recipients had 36% lower risk compared with male recipients at transplantation, but the relative gap associated with female compared with male gender narrowed at approximately 14% per year posttransplantation.

Donor and transplant-related risk factors for PTMI included older donor age, deceased donor, and delayed graft function. The risk for PTMI was 60% higher after a diagnosis of posttransplantation diabetes and rose nearly threefold after graft failure. The unadjusted 36-mo cumulative incidences of posttransplantation diabetes and graft failure were 14.8% (95% CI, 14.3 to 15.3%) and 13.3% (95% CI, 12.8 to 13.8%), respectively.

Outcomes after PTMI

Unadjusted mortality after PTMI was 14.8% (95% CI, 13.4 to 16.1%) at 30 d, 28.4% (95% CI, 26.6 to 30.2%) at 1 yr, and 36.1% (95% CI, 34.0 to 38.2%) at 2 yr after infarction event. After adjustment for a variety of clinically important risk factors, "survived" PTMI independently and potently predicted death in a manner that decreased with time (Table 3). Specifically, the HR for subsequent death after a survived PTMI was 18.9 (15.3 to 23.2) in the first week at risk, 8.59 (7.05 to 10.46) in the next 3 wk, and 2.72 (2.41 to 3.06) thereafter.

Unadjusted rates of death-censored graft failure after PTMI were 8.7% (95% CI, 7.4 to 10.0%) at 1 yr and 12.9% (95% CI, 11.0 to 14.7%) at 2 yr after infarction. The unadjusted incidence of all-cause graft loss after PTMI was 30.7% (95% CI, 28.8 to 32.6%) at 1 yr and 38.8% (95% CI, 36.5 to 41.1%) at 2 yr. Survived PTMI independently predicted subsequent death-censored graft failure and all-cause graft loss, with risk relationships that were highest within the first week at risk but persisted over observation (Table 3).

Discussion

Prognosis after MI is known to be dramatically worsened by comorbid renal dysfunction, but the epidemiology of MI after kidney transplantation is not well described. We report the largest and most detailed investigation to date of the incidence, predictors, and outcomes of MI among kidney transplant recipients.

Incidence of PTMI

In this large retrospective cohort study of Medicare beneficiaries who recently received a transplant, we found that PTMI is a common complication, affecting approximately 11.1% of patients by 3 yr posttransplantation, and that much of this risk is experienced early, within the first 6 mo of transplantation. Beyond the early posttransplantation period, the incidence of PTMI was somewhat lower than the demographics-adjusted incidence of MI among transplant candidates (11.1 *versus* 16.7% at 3 yr), consistent with previous evidence that transplantation may reduce the risk for MI (3). However, wait-listed patients who do not have an up-to-date cardiac evaluation when an organ becomes available may be passed over, thereby compromising the comparability of transplanted and wait-listed groups. Contrasted with estimated general population risk, gender-stratified incidences of MI after transplantation were approximately six- and 10-fold higher than recent population-based estimates of MI among adult men and women in the United States, respectively (20).

Use of broad sources for outcomes ascertainment in this study including all available Medicare billing records and death record evidence of MI yielded a higher observed rate of posttransplantation coronary events than previously published. The overall rate of PTMI standardized by patient-time at risk is five times the rate of hospitalization for posttransplantation acute coronary syndromes detected by Abbott *et al.* (5) and 50% more than the rate of coronary syndrome hospitalization that these authors identified among a smaller cohort of incident dialysis patients (21). Despite derivation from broader data sources,

Table 1. 36-month unadjusted cumulative incidences of PTMI, stratified by clinical predictors of increased or reduced incidence rates[a]

Characteristic	No. with Characteristic (%)	Incidence among Those with Characteristic, % (CI)	Incidence among Those without Characteristic or Unknown Status, % (CI)	*P* Value[b]
Predictors of increased unadjusted PTMI incidence				
recipient characteristics	n = 35,847			
demographics				
age (yr)				
18–30	4498 (12.6%)	2.7 (2.1–3.3)		reference
31–44	10,093 (28.2%)	7.1 (6.4–7.7)		<0.0001
45–60	13211(36.8%)	12.6 (11.8–13.3)		<0.0001
60+	8045 (22.4%)	18.4 (17.3–19.5)		<0.0001
obesity	5157 (14.4%)	13.4 (12.1–14.7)	10.8 (10.4–11.2)	0.0006
primary cause of ESRD				
diabetes	8912 (24.9%)	17.4 (16.4–18.4)	9.1 (8.7–9.5)	<0.0001
pretransplantation dialysis duration (mo)				
none (preemptive)	2533 (7.1%)	2.1 (1.7–2.4)		0.03
0–12	5458 (15.2%)	8.8 (7.9–9.8)		reference
13–24	7269 (20.3%)	11.1 (10.2–12.0)		0.0003
25–60	15,704 (43.8%)	12.1 (11.5–12.8)		<0.0001
60+	4883 (13.6%)	12.2 (11.0–13.5)		<0.0001
comorbidities				
diabetes	16,038 (44.7%)	15.4 (14.7–16.2)	7.7 (7.2–8.2)	<0.0001
pretransplant MI	2887 (8.0%)	30.2 (28.1–32.3)	9.4 (9.0–9.9)	<0.0001
angina/coronary disease, without known MI	3254 (9.1%)	19.1 (17.3–20.9)	10.3 (9.9–10.8)	<0.0001
peripheral vascular disease	7578 (21.1%)	18.9 (17.8–20.1)	9.1 (8.6–9.5)	<0.0001
dyslipidemia	12,059 (33.6%)	14.7 (13.9–15.6)	9.4 (8.9–9.8)	<0.0001
cardiac arrhythmia	11,675 (32.6%)	15.5 (14.7–16.3)	9.0 (8.5–9.4)	<0.0001
hypertensive heart disease	6081 (17.0%)	14.5 (13.4–15.7)	10.4 (10.0–10.8)	<0.0001
smoking history	2963 (8.3%)	13.8 (12.0–15.6)	10.9 (10.5–11.3)	0.0034
donor characteristics				
age (yr)				
0–30	11,440 (31.9%)	9.4 (8.7–10.0)		reference
31–44	9081 (25.3%)	10.5 (9.7–11.3)		0.12
45–59	8827 (24.6%)	11.8 (11.0–12.6)		<0.0001
60+	2876 (8.0%)	17.0 (15.3–18.7)		<0.0001
unknown	3623 (10.1%)			
deceased	26,874 (75.0%)	12.1 (11.1–12.6)	7.9 (7.1–8.6)	<0.0001
CMV seropositive	18,547 (51.7%)	11.7 (11.1–12.2)	10.4 (9.8–11.0)	0.0005
transplantation factors				
CMV seropairing				
donor −/recipient −	4874 (13.6%)	8.9 (7.8–9.8)		reference
donor +/recipient −	5723 (16.0%)	11.3 (10.2–12.3)		0.0004
donor −/recipient +	7270 (20.3%)	11.3 (10.4–12.2)		0.0009
donor +/recipient +	12,824 (35.8%)	11.8 (11.1–12.6)		<0.0001
unknown	5156 (14.4%)			
delayed graft function	9376 (26.2%)	14.3 (13.4–15.3)	10.1 (9.6–10.5)	<0.0001
Predictors of decreased unadjusted PTMI incidence				
recipient demographics				
female gender	14,347 (40.0%)	9.6 (9.0–10.3)	12.1 (11.5–12.6)	<0.0001
black race	10,327 (28.8%)	10.1 (9.4–10.8)	11.5 (11.0–12.0)	0.002
Hispanic ethnicity	4550 (12.7%)	8.5 (7.5–9.6)	11.4 (10.9–11.8)	<0.0001
working full or part time	11,382 (31.8%)	8.1 (7.4–8.7)	12.5 (12.0–13.0)	<0.0001
primary cause of ESRD				
glomerulonephritis	7655 (21.4%)	7.8 (7.1–8.6)	12.0 (11.5–12.5)	<0.0001
transplantation factors				
maintenance immunosuppression				
corticosteroids	32,609 (91.0%)	10.9 (10.5–11.3)	13.0 (11.4–14.6)	<0.0001

[a]CI, confidence interval; PTMI, posttransplantation myocardial infarction; CMV, cytomegalovirus. There were no significant differences in the unadjusted cumulative incidences of PTMI after stratification according to any of the following characteristics: recipient education; hypertension as a cause of renal failure; donor gender or race; zero donor-recipient human leukocyte antigen mismatches; administration of induction therapy; or maintenance immunosuppression with cyclosporine micro-emulsions, cyclosporine suspensions, tacrolimus, azathioprine, mycophenolate mofetil, or rapamycin.

[b]*P* value by log-rank statistic for comparison to specified reference group (in cases of recipient and donor ages, dialysis duration, and CMV seropairing) or to those without characteristic or unknown status.

Table 2. Independent clinical correlates of PTMI[a]

Characteristic	HR for PTMI (95% CI)	*P* Value
Recipient characteristics		
demographics		
age (yr)		
18–30	1.00 = reference	
31–44	1.97 (1.55–2.49)	<0.0001
45–60	3.20 (2.54–4.02)	<0.0001
60+	3.96 (3.14–5.01)	<0.0001
gender		
female	0.73 (0.66–0.82)	<0.0001
female × time (yr)[b]	1.14 (1.05–1.24)	0.002
male	1.00 = reference	
race		
black	0.79 (0.72–0.88)	<0.0001
other/unknown	0.80 (0.67–0.96)	0.02
white	1.00 = reference	
ethnicity		
Hispanic	0.71 (0.62–0.81)	<0.0001
non-Hispanic	1.00 = reference	
employment		
working full or part time	0.84 (0.76–0.92)	0.0001
unemployed	1.00 = reference	
primary cause of ESRD		
diabetes	1.38 (1.23–1.55)	<0.0001
hypertension	1.06 (0.95–1.19)	>0.2
glomerulonephritis	0.96 (0.85–1.09)	>0.2
other or unknown cause	1.00 = reference	
comorbidities		
diabetes	1.13 (1.00–1.28)	0.05
diabetes × time (yr)[b]	1.19 (1.09–1.29)	0.0001
pretransplant MI	3.77 (3.34–4.25)	<0.0001
pretransplant MI × time (yr)[b]	0.70 (0.62–0.78)	<0.0001
angina/coronary disease, without known MI	1.66 (1.48–1.85)	<0.0001
peripheral vascular disease	1.23 (1.13–1.34)	<0.0001
dyslipidemia	1.22 (1.12–1.32)	<0.0001
cardiac arrhythmia	1.41 (1.27–1.57)	<0.0001
cardiac arrhythmia × time (yr)[b]	0.89 (0.82–0.97)	0.007
Donor characteristics		
source		
deceased	1.17 (1.05–1.31)	0.006
living	1.00 = reference	
donor age (yr)		
0–30	1.00 = reference	
31–44	1.10 (0.99–1.23)	0.07
45–59	1.16 (1.05–1.29)	0.005
60+	1.28 (1.13–1.46)	0.0002
unknown	1.11 (0.94–1.32)	0.2
Transplantation complications		
delayed graft function	1.15 (1.06–1.25)	0.001
graft failure[c]	2.78 (2.41–3.19)	<0.0001
posttransplantation diabetes[c]	1.60 (1.35–1.88)	<0.0001

[a]HR, hazards ratio. Results of extended Cox hazards analysis, where HR >1.00 or <1.00 indicate an increased or reduced risk for PTMI, respectively. Each risk estimate was adjusted for all other characteristics in the model, including those shown along with the following characteristics with $P \geq 0.01$ (recipient education, pretransplantation dialysis duration, obesity, tobacco use history, hypertensive heart disease history, and panel reactive antibody status; donor race and gender; transplant year, number of donor-recipient HLA mismatches, donor–recipient CMV seropairing, administration of induction therapy, and maintenance immunosuppression [cyclosporine microemulsions, cyclosporine suspensions, tacrolimus, azathioprine, mycophenolate mofetil, and rapamycin]; data not shown).

[b]Term indicating HR associated with the parameter estimate for the interaction of a given predictor with each 1-yr interval since transplantation. At a given time, the HR associated with a time-dependent predictor is calculated as *e* raised to the sum of [ln(HR at time zero) + ln(HR for interaction term) × (years from time zero)].

[c]Indicates a time-varying covariate, defined as a variable that may change in value during the observation interval on the basis of the diagnosis of a condition after transplantation.

Table 3. Independent effects of PTMI on graft loss and death[a]

Characteristic	Death-Censored Graft Failure HR (95% CI)	All-Cause Graft Loss HR (95% CI)	Death HR (95% CI)
"Survived" PTMI[b,c]			
within 1 wk of PTMI	4.24 (2.96–6.07)[e]	11.5 (9.3–14.2)[e]	18.9 (15.3–23.2)[e]
1 wk to 1 mo after PTMI	2.61 (1.74–3.93)[e]	6.72 (5.46–8.25)[e]	8.6 (7.0–10.5)[e]
>1 mo after PTMI	1.61 (1.35–1.91)[e]	2.55 (2.27–2.86)[e]	2.72 (2.41–3.06)[e]
PTMI × DGF	—	0.68 (0.58–0.81)[e]	—
PTMI × graft failure	—	—	0.67 (0.54–0.83)[f]
Recipient characteristics			
demographics			
age (yr)			
18–30	1.00 = reference	1.00 = reference	1.00 = reference
31–44	0.73 (0.65–0.81)[e]	0.81 (0.73–0.89)[e]	1.30 (1.08–1.57)[g]
45–60	0.68 (0.59–0.79)[e]	0.92 (0.82–1.03)	2.26 (1.86–2.75)[e]
age 45–60 yr × time (yr)[d]	0.80 (0.74–0.88)[e]	0.86 (0.81–0.92)[e]	0.88 (0.81–0.95)[g]
60+	0.66 (0.56–0.78)[e]	0.97 (0.88–1.08)	3.02 (2.52–3.62)[e]
age >60 yr × time (yr)[d]	0.72 (0.64–0.81)[e]	—	—
Race			
black	1.03 (0.92–1.12)	0.93 (0.85–1.02)	0.86 (0.79–0.94)[f]
black × time (yr)[c]	1.32 (1.22–1.43)[e]	1.23 (1.16–1.31)[e]	—
other/unknown	0.68 (0.56–0.83)[f]	0.76 (0.66–0.87)[e]	0.80 (0.67–0.95)[h]
white	1.00 = reference	1.00 = reference	1.00 = reference
ethnicity			
Hispanic	0.80 (0.70–0.91)[f]	0.76 (0.69–0.84)[e]	0.71 (0.62–0.80)[e]
employment			
working full or part time	0.94 (0.87–1.02)	0.87 (0.82–0.93)[e]	0.72 (0.63–0.82)[e]
working × time (yr)[c]	—	—	1.15 (1.05–1.25)[g]
primary cause of ESRD			
diabetes	0.82 (0.73–0.93)[g]	1.09 (1.00–1.19)[h]	1.41 (1.27–1.58)[e]
hypertension	1.08 (0.97–1.19)	1.12 (1.03–1.20)[g]	1.15 (1.04–1.27)[g]
glomerulonephritis	1.01 (0.92–1.12)	0.99 (0.91–1.07)	0.93 (0.83–1.04)
pretransplantation dialysis duration (mo)			
none (preemptive)	0.88 (0.71–1.08)	0.88 (0.75–1.02)	0.85 (0.68–1.05)
0–12	1.0 = reference	1.00 = reference	1.0 = reference
13–24	0.96 (0.84–1.09)	1.08 (0.98–1.19)	1.17 (1.02–1.34)[h]
25–60	0.90 (0.80–1.01)	1.06 (0.97–1.16)	1.24 (1.10–1.41)[f]
>60	0.91 (0.78–1.05)	1.14 (1.02–1.27)[h]	1.44 (1.24–1.69)[e]
comorbidities			
diabetes	1.11 (1.01–1.22)[h]	1.15 (1.07–1.24)[f]	1.07 (0.95–1.21)
diabetes × time (yr)[c]	—	—	1.20 (1.11–1.29)[e]
peripheral vascular disease	1.05 (0.96–1.16)	1.16 (1.09–1.23)[e]	1.21 (1.12–1.31)[e]
dyslipidemia	0.89 (0.82–0.97)[g]	0.92 (0.87–0.98)[g]	0.97 (0.90–1.04)
cardiac arrhythmia	1.06 (0.98–1.15)	1.31 (1.21–1.42)[e]	1.25 (1.16–1.35)[e]
arrhythmia × time (yr)[c]	—	0.89 (0.84–0.94)[f]	—
smoking	1.01 (0.84–1.23)	0.99 (0.86–1.14)	1.02 (0.85–1.23)
smoking × time (yr)[c]	1.31 (1.15–1.49)[e]	1.29 (1.16–1.42)[e]	1.22 (1.07–1.38)[g]
Donor characteristics			
deceased source	1.54 (1.32–1.79)[e]	1.42 (1.27–1.59)[e]	1.19 (1.04–1.36)[g]
deceased donor × DGF	0.52 (0.42–0.65)[e]	0.62 (0.52–0.74)[e]	—
age (yr)			
0–30	1.00 = reference	1.00 = reference	1.00 = reference
31–44	1.09 (0.98–1.21)	1.08 (1.00–1.16)	1.04 (0.94–1.15)
45–59	1.35 (1.22–1.49)[e]	1.32 (1.22–1.41)[e]	1.18 (1.08–1.30)[f]
60+	1.96 (1.74–2.22)[e]	1.63 (1.49–1.79)[e]	1.29 (1.15–1.45)[e]
unknown	1.36 (1.14–1.62)[f]	1.35 (1.19–1.53)[e]	1.26 (1.07–1.47)[g]
gender			
female	1.11 (1.03–1.19)[g]	1.10 (1.04–1.16)[f]	1.06 (0.98–1.13)
race			
black	1.33 (1.20–1.47)[e]	1.25 (1.16–1.35)[e]	1.11 (1.00–1.24)
white	1.00 = reference	1.00 = reference	1.00 = reference
Transplantation factors			
year 1995	1.00 = reference	1.00 = reference	1.00 = reference
year 2000	0.51 (0.41–0.64)[e]	0.65 (0.56–0.75)[e]	0.88 (0.73–1.07)
0 HLA mismatches	1.00 = reference	1.00 = reference	1.00 = reference
1 HLA mismatch	1.20 (1.03–1.39)[h]	1.10 (0.99–1.22)	1.03 (0.90–1.17)
2 HLA mismatches	1.14 (0.96–1.34)	1.17 (1.06–1.29)[g]	1.08 (0.95–1.22)
2 HLA mismatches × time (yr)[e]	1.14 (1.05–1.24)[g]	—	—

Table 3. Continued.

Characteristic	Death-Censored Graft Failure HR (95% CI)	All-Cause Graft Loss HR (95% CI)	Death HR (95% CI)
3 HLA mismatches	1.40 (1.22–1.62)[e]	1.40 (1.24–1.58)[e]	1.12 (0.98–1.27)
3 HLA mismatches × time (yr)[e]		0.90 (0.84–0.96)[g]	—
4 HLA mismatches	1.48 (1.27–1.73)[e]	1.30 (1.17–1.45)[e]	1.16 (1.01–1.34)[h]
5 HLA mismatches	1.86 (1.54–2.25)[e]	1.59 (1.38–1.82)[e]	1.32 (1.10–1.58)[g]
6 HLA mismatches	1.32 (0.96–1.81)	1.22 (0.98–1.52)	1.26 (0.95–1.65)
sensitized recipient	1.27 (1.12–1.44)[f]	1.17 (1.06–1.29)[g]	1.09 (0.96–1.23)
CMV seropairing			
donor −/recipient −	1.00 = reference	1.00 = reference	1.00 = reference
donor +/recipient −	1.15 (1.00–1.32)[h]	1.18 (1.07–1.32)[g]	1.18 (1.03–1.36)[h]
donor −/recipient +	1.18 (1.03–1.35)[h]	1.16 (1.05–1.28)[g]	1.10 (0.96–1.25)
donor +/recipient +	1.12 (0.99–1.27)	1.12 (1.02–1.23)[h]	1.09 (0.96–1.23)
unknown	0.86 (0.72–1.02)	0.98 (0.86–1.10)	1.06 (0.91–1.25)
Maintenance immunosuppression			
corticosteroids	0.89 (0.76–1.04)	0.54 (0.48–0.62)[e]	0.45 (0.38–0.54)[e]
corticosteroids × time (yr)[e]	—	1.54 (1.38–1.73)[e]	1.40 (1.23–1.60)[e]
corticosteroids × graft failure	—	—	1.84 (1.40–2.42)[e]
cyclosporine microemulsion	0.60 (0.52–0.70)[e]	0.68 (0.61–0.76)[e]	0.82 (0.73–0.92)[g]
microemulsion × time (yr)[e]	1.22 (1.11–1.34)[e]	1.10 (1.03–1.17)[g]	—
cyclosporine suspension	0.83 (0.73–0.95)[g]	0.86 (0.78–0.95)[g]	0.92 (0.81–1.05)
tacrolimus	0.64 (0.53–0.64)[e]	0.73 (0.66–0.81)[e]	0.73 (0.63–0.84)[e]
tacrolimus × time (yr)[e]	1.23 (1.09–1.39)[f]	—	—
tacrolimus × graft failure	—	—	1.59 (1.26–2.02)[e]
azathioprine	1.04 (0.92–1.16)	1.00 (0.92–1.09)	0.99 (0.89–1.11)
MMF	0.73 (0.63–0.83)[e]	0.77 (0.70–0.85)[e]	0.90 (0.81–1.11)
MMF × time (yr)[e]	1.16 (1.06–1.26)[g]	1.12 (1.05–1.19)[f]	—
rapamycin	1.31 (1.07–1.61)[g]	1.03 (0.88–1.22)	0.81 (0.64–1.03)
Complications			
DGF	6.60 (5.28–8.26)[e]	4.06 (3.40–4.84)[e]	1.64 (1.46–1.83)[e]
DGF × time (yr)[e]	0.58 (0.53–0.63)[e]	0.70 (0.66–0.75)[e]	0.88 (0.81–0.95)[g]
DGF × graft failure	—	—	0.62 (0.51–0.74)[e]
DGF × deceased donor	0.52 (0.42–0.65)[e]	0.62 (0.52–0.7)[e]	—
DGF × PTMI	—	0.68 (0.58–0.81)[e]	—
graft failure[c]	—	—	3.31 (2.49–4.39)[e]
graft failure × corticosteroids	—	—	1.84 (1.40–2.42)[e]
graft failure × tacrolimus	—	—	1.59 (1.26–2.02)[f]
graft failure × DGF	—	—	0.62 (0.51–0.74)[e]
graft failure × PTMI	—	—	0.67 (0.54–0.83)[e]
posttransplantation diabetes[c]	1.46 (1.28–1.66)[e]	1.38 (1.25–1.52)[e]	1.41 (1.23–1.61)[e]

[a]DGF, delayed graft function; HLA, human leukocyte antigens; MMF, mycophenolate mofetil. Results of extended Cox hazards analysis, where HR > or <1.00 indicate an increased or reduced risk for the modeled outcome (graft failure, all-cause graft loss, or death, respectively). Each risk estimate was adjusted for all other characteristics in the model, including those shown along with characteristics with $P \geq 0.01$ (data not shown for variables that are nonsignificant in all models: recipient gender, obesity, and education; recipient histories of pretransplant MI, angina and/or coronary disease, and hypertensive heart disease; administration of induction therapy; and transplant cold ischemia time). In the case of two-way interactions, the net risk associated with two predictors is calculated as e raised to the sum of [ln(HR for predictor 1) + ln (HR for predictor 2) + ln (HR for interaction term)].

[b]"Survived PTMI" indicates cases in which the participant did not die on date of MI.

[c]Indicates a time-varying covariate, defined as a variable that may change in value during the observation interval on the basis of the diagnosis of a condition after transplantation.

[d]Term indicating change in hazard of death associated with given predictor for each 1-yr interval posttransplantation. At a given time, the HR associated with a time-dependent predictor is calculated as e raised to the sum of [ln(HR at time zero) + ln(HR for interaction term) × (years from time zero)].

[e]$P < 0.0001$; [f]$0.0001 = P < 0.001$; [g]$0.001 = P < 0.01$; [h]$0.01 = P < 0.05$.

our outcome was somewhat more disease specific in that we studied only MI and did not include preinfarction syndromes.

Predictors of PTMI

Recipient Factors. Traditional risk calculators do not fully explain late ischemic heart disease risk in selected renal allograft recipients who are free of previous vascular events (22,23). In this study of MI risk from the time of transplantation, dominant risk factors aside from advanced age included pretransplantation MI and allograft failure. Nonetheless, traditional risk factors including male gender, diabetes, and dyslipidemia each were independently predictive of MI after transplantation, and smoking, obesity, and hypertensive heart disease [our surrogate for long-standing hypertension (24)] were unadjusted pre-

dictors. The time dependence and nested nature of some observed effects afford more detailed insight into the epidemiology of PTMI.

Although women faced a lower risk for PTMI than men, this relative protection diminished with time after transplantation for the study cohort as a whole. Taken with the absence of interactions between gender and age categories, this finding suggests that dissipation of the gender differential in general coronary heart disease risk may begin at a younger age after transplantation than in the general population (25,26). Diabetes without comorbid nephropathy was a relatively weak predictor of PTMI in this study, but risk increased to >50% above baseline in the substantial subset with diabetes as the cause of renal failure, and risk among all individuals with diabetes rose with time after transplantation. Although these effect sizes are lower than those of other recent reports of diabetes-related coronary syndrome risk after transplantation (5), this likely reflects our adjustment for a variety of independently predictive cardiovascular comorbidities that may be confounded with diabetes if not individually considered. Although we did not have information to adjust risk for pretransplantation diabetes duration, a diagnosis of diabetes as the cause of kidney failure is a reasonable surrogate for long-standing diabetes (27,28). Therefore, these patterns support increased risk for PTMI with longer duration of diabetes both before and after kidney transplantation. Whether more quantitative variable descriptions incorporating posttransplantation information would prevent the adjustment-related loss of predictive value of smoking, hypertension/hypertensive heart disease, and obesity was not discernible with the available data.

Race and ethnicity have been identified as important factors in the detection of cardiovascular events in the general population, but the direction of racial trends in diagnosis are inconsistent across studies (29,30). Our observation of reduced risk for PTMI among nonwhite individuals parallels the lower reported rates of coronary event hospitalizations among nonwhite dialysis patients (21). Further study is needed to determine whether these patterns reflect differential ascertainment, as from differential access to care, or true racial and ethnic risk variation.

The risk for PTMI among our study cohort was independently increased by detection of a variety of cardiovascular comorbidities before transplantation, including angina, peripheral vascular disease, and arrhythmias, and pretransplantation MI was a particularly strong predictor. In contrast, whereas Abbott *et al.* (5) found bivariate links between the risk for hospitalization for posttransplantation acute coronary syndromes and pretransplantation cardiovascular events, these associations attenuated to nonsignificance with covariate adjustment in their study. Possible explanations for such discrepancies include the interstudy differences in outcome measures and distinctions in the ascertainment of covariates themselves. In this work of Abbott *et al.* (5) and other studies (5,7,31), information on comorbidity is limited to that provided by CMS 2728, a data source with demonstrated specificity for cardiovascular diagnoses but low sensitivity as a result of underreporting and missing information (32). We combined CMS 2728 diagnoses with billing evidence of comorbid conditions, markedly increasing the frequencies of detected conditions and likely contributing to increased precision of condition-related effect estimates.

Donor- and Transplant-Related Factors. We found that donor age, deceased source, delayed graft function, and allograft failure were independently predictive of PTMI. Donor hypertension may be a predisposing factor for cardiovascular disease after transplantation (10) and, given potential confounding of age and hypertension, may at least partially mediate the rise in PTMI risk with older donor age. The present study extends and confirms evidence of associations between renal failure and cardiovascular risk after transplantation (33), most specifically, corroborating the recent finding of Abbott *et al.* (5) that graft loss is a potent predictor of posttransplantation hospitalizations for coronary disease events. Although this association may indicate that factors that promote graft loss also promote PTMI, direct causality is plausible given consistent observation of azotemia as a precursor to increased cardiovascular risk in general (34) and MI risk specifically (2) in patients without transplants. Furthermore, because delayed graft function and graft failure are potentially modifiable complications, they are putative targets for PTMI risk reduction.

We also identified posttransplantation diabetes as a potentially modifiable risk factor for PTMI. Posttransplantation diabetes has been proposed to amplify cardiovascular risk after transplantation (13), but to our knowledge, ours is the first study to link this complication with cardiac events and with PTMI specifically. Framed in the context of recently reported associations of posttransplantation diabetes and all-cause death risk (14,18), our findings also suggest that PTMI may partially mediate the mortality excess observed after diagnosis of *de novo* diabetes in transplant recipients. Although posttransplantation diabetes maintained independent predictive value for death, this effect was weakened when considered with PTMI in our study. Of note, the lower cumulative incidence of posttransplantation diabetes in this study compared with that estimated by Kasiske *et al.* (18) from USRDS data sources using a similar method (15 *versus* 24% over 36 mo) is largely explained by sampling criteria. In contrast to Kasiske, we included patients who had pretransplantation diabetes and by definition are not at risk for the *de novo* complication and, in comprising nearly half of the sample, markedly dilute incidence percentages.

Several bivariate predictors of PTMI warrant mention. We observed higher PTMI risk among recipients who were CMV seropositive or received kidneys from seropositive donors compared with those with donor-negative/recipient-negative seropairings. Adjusted risk for the seropair with the highest risk for posttransplantation CMV disease (donor-positive/recipient-negative) approached but did not reach our chosen level of statistical significance ($P = 0.03$). In accordance with these unadjusted risk estimates, CMV infection has been linked with atherosclerotic risk among heart transplant recipients (35) and general patients without transplants (36). As approximately 15% of serologic pairing information was missing, failure to detect an independent association of CMV seropairing with

PTMI may reflect misclassification error, which tends to reduce the estimated statistical significance of effects.

Increased time on dialysis has been associated with angiographic progression of coronary artery disease and noninvasive measures of coronary calcification in small cohorts (37,38). We found that although the unadjusted incidence of PTMI was lowest among patients who received a preemptive transplant and higher with dialysis duration beyond 1 yr compared with <1 yr, these associations were nonsignificant after covariate adjustment. In a study of late cardiac hospitalizations after transplantation that incorporated estimated renal function, Abbott *et al.* (7) found that pretransplantation dialysis duration independently predicted heart failure but not coronary syndrome events. These findings suggest that the impact of dialysis duration on PTMI risk may be accounted for, at least statistically, by the accumulation of comorbid conditions and/or overshadowed by the importance of allograft function.

The potential to modify posttransplantation cardiovascular risk with immunosuppressive regimens is actively debated. Whereas choice of immunosuppression has not been shown to reduce cardiovascular mortality, specific agents, including calcineurin inhibitor type, sirolimus, and corticosteroids, seem to have a variable impact on traditional cardiovascular risk mediators such as BP, serum lipids, and glycemic control (11,39). Our observation of a bivariate association between maintenance corticosteroid use and reduced risk for PTMI may seem surprising given the known adverse effects of steroids on cardiovascular risk factors, including hypertension, dyslipidemia, and glucose intolerance. Given the role of inflammation in cardiovascular risk (40), this association could reflect benefit via anti-inflammatory pathways. Alternatively, the association may be driven by selection factors, as patients who received a transplant without maintenance steroids between 1995 and 2000 represent a highly selected minority (<10% of the cohort) whose cardiovascular risk is unknown. As in the report of posttransplantation coronary syndrome hospitalizations (5), we did not detect independent associations between PTMI and maintenance or induction immunosuppressive agents analyzed on an intention-to-treat basis. Possible explanations for the lack of association include changes in immunosuppressive agents during follow-up, confounding by uncontrolled factors related to initial agent choice, or absence of differential net impact on PTMI risk perhaps as a result of an effective balance of distinct adverse effects.

Outcomes after PTMI

Patients who developed PTMI faced significantly higher graft failure risk and markedly increased death risk, particularly early after the infarction event. Notably, unadjusted mortality after PTMI was highly consistent with average post-MI death rates reported for transplant recipients who were hospitalized for PTMI from 1977 to 1996 (1,4). In that study, which spanned 20 yr of post–kidney transplantation experience, crude mortality after PTMI did not vary by event era, but after adjustment for higher comorbidity among patients who received a more recent transplant, recent death rates were improved. Our results strengthen the conclusion that among the types of patients who currently receive a transplant, PTMI remains a strong predictor of short- and long-term mortality. To our knowledge, ours is the first study to report an independent association of PTMI with subsequent death-censored or all-cause graft loss.

Limitations

This study is limited by its retrospective design and lack of quantitative information on candidate predictors including cigarette use and levels of BP, lipids, glycemic control, and laboratory values such as hemoglobin and inflammatory markers. C-reactive protein levels were recently shown in several small studies to predict posttransplantation coronary events and cardiovascular mortality independent of some traditional risk factors, but these analyses did not include other important factors studied in the current work, such as allograft failure and posttransplantation diabetes (23,40). We were unable to control for medication use over time, including changes in immunosuppressive agents and doses along with any use of antihypertensives, statins, and aspirin. Because we required Medicare coverage for participation only at the time of transplantation, detection of pretransplantation comorbidities with Medicare claims is subject to underascertainment with increased time before transplantation. The primary outcome measure is a surrogate for clinical events, and although external validation would be required to determine accuracy of USRDS records for PTMI specifically, the method of ICD-9–based outcome ascertainment was validated for diabetes (16) and has been used to describe a variety of important clinical events in patients with kidney disease (15,18,19). We defined our outcome measure to capture all available evidence of PTMI within USRDS databases and thereby produce the most comprehensive available estimate of PTMI in all forms of clinical presentation. Despite its limitations, this study is strengthened by basis in a large, population-based sample; by relatively complete follow-up of Medicare beneficiaries; and by inclusion of a broad list of potential predictors using more comprehensive covariate detection methods than are generally published.

Conclusion

In this large population-based study, we found that PTMI is common after kidney transplantation and that PTMI risk is linked with potentially modifiable factors, including delayed graft function, posttransplantation diabetes, and graft failure. In turn, occurrence of PTMI predicts graft failure and strongly predicts death. Although many predictors of PTMI are relatively fixed, we have identified a collection of risk factors for PTMI that may allow more accurate risk determination and focused allocation of screening and preventive measures. There remains a need to develop accurate and reliable multivariable-based estimates of the risk for other posttransplantation cardiovascular complications (41). Understanding and reducing the risk for PTMI and other cardiovascular events may improve outcomes after kidney transplantation.

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