Acute Myocardial Infarction and Kidney Transplantation

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Although the risk for acute myocardial infarction (AMI) is lower after transplantation than on the waiting list, this risk may vary by patient population and may be different early *versus* late after transplantation. Risk factors for AMI were examined among 53,297 Medicare beneficiaries who were placed on the deceased-donor waiting list in 1995 to 2002. Early (≤3 mo) and late (>3 mo) effects of receiving a deceased- or living-donor kidney transplant were examined using time-dependent covariates in Cox nonproportional hazards analysis. Overall, transplantation was associated with a 17% lower adjusted risk for AMI (0.83; 95% confidence interval [CI] 0.77 to 0.90) *versus* the waiting list. However, the relative risk (*versus* the waiting list) for AMI was greater for deceased- compared to living-donor transplants, with both being much greater early (deceased-donor 3.57 [95% CI 3.21 to 3.96] compared to living-donor 2.81 [95% CI 2.31 to 3.42]) than late (deceased-donor 0.45 [95% CI 0.41 to 0.50] compared to living-donor 0.39 [95% CI 0.33 to 0.47]) posttransplantation. Individuals who were ≥65 yr of age had a much higher risk (*versus* 18- to 34-yr-olds) for AMI early posttransplantation (8.01; 95% CI 5.12 to 12.53) compared with the waiting list (3.68; 95% CI 3.98 to 4.54) or late posttransplantation (4.37; 95% CI 3.07 to 6.20). Black patients had less reduction in AMI risk (*versus* white patients) late posttransplantation (0.78; 95% CI 0.64 to 0.95) compared with early posttransplantation (0.60; 95% CI 0.48 to 0.74) or on the waiting list (0.62; 95% CI 0.56 to 0.68). The AMI risk that was associated with chronic kidney disease from diabetes (*versus* glomerulonephritis) was relatively greater on the waiting list (1.64; 95% CI 1.45 to 1.85) compared with early (1.34; 95% CI 1.08 to 1.68) and late (1.39; 95% CI 1.12 to 1.72) posttransplantation. Thus the risk reduction for AMI with transplantation *versus* the waiting list varies by patient population and time after transplantation.

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Cardiovascular disease (CVD) is the major cause of death for patients with stage 5 chronic kidney disease (CKD) (1), and it is important to understand differences in CVD among comparable patients who are treated with dialysis compared with transplantation. This comparison is important for several reasons: (*1*) To inform patients better of the risk of transplantation *versus* remaining on dialysis, (*2*) to inform physicians better of the need for CVD screening and prevention as part of the transplant evaluation, and (*3*) to understand better the pathogenesis of CVD by comparing risk factors for dialysis *versus* transplant patients. Nevertheless, few studies with adequate statistical power have compared the incidence and risk for CVD in dialysis and transplant patients.

Part of the problem in making comparisons between dialysis and transplant patients is that the latter are screened and selected on the basis of their risk for CVD. Indeed, most patients undergo screening and some undergo coronary artery revascularization as part of their routine kidney transplant evaluation (2,3). Nevertheless, the risk for CVD events may be transiently increased in the early postoperative period but ultimately lower compared with dialysis. Also confusing is that in many studies, CVD mortality included patients who were dying of cardiac arrest and congestive heart failure. A larger proportion of CVD deaths in dialysis compared with transplant patients may be due to arrhythmias or cardiomyopathy, rather than atherosclerotic ischemic heart disease (IHD) *per se* (1).

We used data that were collected by the United Network for Organ Sharing (UNOS) and the United States Renal Data System (USRDS) to determine the incidence and risk factors for acute myocardial infarction (AMI) among patients who were accepted for kidney transplantation. To be certain that we identified patients who had AMI, we limited the analysis to patients who had Medicare as their primary payer (approximately 45% of patients). We hypothesized that if the pathogenesis of IHD were similar in dialysis and kidney transplantation recipients, then risk factors for AMI also should be similar. We tested this hypothesis by comparing rates and risk factors for AMI among transplant recipients *versus* patients who were on the deceased-donor transplant waiting list. We did not have data that were acceptable for analysis of several traditional risk factors, such as cholesterol, BP, and cigarette smoking. Nevertheless, we were able to compare patients who were on the waiting list and those who had received a transplant using a number of risk factors that are associated with IHD in the general population, including age, gender, ethnicity, obesity, and diabetes.

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Materials and Methods

Patient Population

We included all Medicare patients who were listed for deceased-donor kidney transplantation or patients who were never listed but underwent kidney transplantation between 1995 and 2002. We did not include patients who were listed for pancreas transplantation. Of these 53,297 patients, 49,288 (92%) were placed on the deceased-donor waiting list, whereas 4009 (8%) received a transplant without ever being listed. Patients were followed to AMI (3335 [6%]), loss of Medicare coverage (3891 [7%]), 3 yr posttransplantation (10,030 [19%]), transplant failure (excluding death; 2651 [5%]), death (other than AMI; 6410 [12%]), or December 31, 2002 (26,980 [51%]).

Patient and Transplantation Characteristics

We tabulated data on patients at the time of listing or first transplant without listing, including age, gender, ethnicity, body mass index (BMI; weight in kilograms divided by height in meters squared), years of previous ESRD, primary cause of ESRD, comorbidities listed on the Medicare 2728 form (diabetes independent of what caused primary kidney disease, congestive heart failure, ischemic heart disease or AMI, peripheral vascular disease, or cerebral vascular disease), and employment status. We also recorded the date of transplantation with either a deceased- or living-donor kidney.

AMI

AMI was defined as the first occurrence of (*1*) one inpatient 410.x billing code; no outpatient codes were used and 410.x2 (subsequent episodes of care) was excluded; (*2*) cause of death on the ESRD death notification form; or (*3*) cause of death on the UNOS follow-up form. Of a total of 3335 AMI patients, 2659 (80%) were identified from claims, 527 (16%) were identified from ESRD death notification forms, and 149 (4%) were identified from UNOS as cause of death. The use of Medicare claims to detect patients with MI was validated previously (4).

Statistical Analyses

The (unadjusted) cumulative incidences of AMI were determined using the Kaplan-Meier method. Risk factors for AMI were analyzed using Cox nonproportional hazards analysis, with transplantation as a time-dependent covariate. The Cox nonproportional hazards model allowed for changing hazard ratios during each of three time periods: Waiting list, early posttransplantation (first 3 mo), and late posttransplantation. Adjustment was made for age, gender, race, Hispanic ethnicity, primary cause of renal disease, comorbidities at or before listing, employment status, previous ESRD time, and year. Tests of interactions between various patient characteristics and treatment (waiting list *versus* transplant) were done using the likelihood ratio χ^2 test comparing the reduced Cox model (without interaction terms) with the full Cox model (with interaction terms). The AMI rates within specific demographic groups were calculated using an unadjusted interval Poisson model, again allowing for separate rate estimations during time on the waiting list, early posttransplantation, and late posttransplantation. All analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Incidence of AMI after Listing

The cumulative (Kaplan-Meier) incidence of AMI after listing was 0.67, 1.36, 2.77, 5.73, and 8.71% at 3, 6, 12, 24, and 36 mo, respectively (Figure 1). In patients who received a transplant before any AMI occurrence, the cumulative incidence of AMI after deceased-donor transplantation was 2.27, 2.74, 3.35, 4.69, and 6.09% at 3, 6, 12, 24, and 36 mo, respectively; and the cumulative incidence of AMI after living-donor transplantation was 1.51, 1.84, 2.27, 3.13, and 4.24% at 3, 6, 12, 24, and 36 mo, respectively.

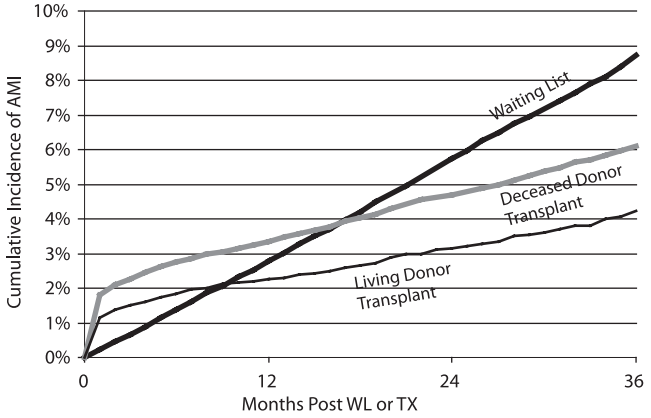

Figure 1. Cumulative (Kaplan-Meier) incidence of acute myocardial infarction (AMI) on the waiting list and after kidney transplantation. Most transplant recipients also spent time on the waiting list, but time was reset to "0" at transplantation. Most of the difference in AMI incidence in recipients of deceased- *versus* living-donor kidney transplants occurred very early after transplantation. Thereafter, the incidence of AMI was similar in deceased- and living-donor transplant recipients, with both eventually having a lower incidence than patients on the waiting list.

Risk Factors for AMI after Listing

We examined risk factors for AMI after patients were listed for a deceased-donor transplant (or received a transplant without ever being listed). These AMI occurred either on the waiting list or after transplantation. Older age; male gender; diabetes as a cause of CKD (compared with glomerulonephritis); duration of previous ESRD; and history of hypertension, congestive heart failure, IHD, and cerebral vascular disease each were independently associated with a greater risk for AMI after listing (Table 1). There was also a slightly higher risk for AMI in the most recent transplant era. Causes of CKD other than diabetes were associated with a lower risk for AMI (compared with glomerulonephritis). Black and Asian patients had a lower risk than white patients, and Hispanic patients had a lower risk compared with non-Hispanic patients. Being employed was also associated with a lower risk for AMI. Neither obesity nor being underweight was associated with AMI (Table 1).

Overall, transplantation (*versus* the waiting list) was associated with a 17% lower adjusted risk for AMI (0.83; 95% confidence interval [CI] 0.77 to 0.90; $P < 0.0001$). The adjusted relative risk (RR) for AMI after transplantation (*versus* the waiting list) was 0.89 (95% CI 0.81 to 0.97; $P = 0.0060$) for deceased-donor transplants and 0.69 (95% CI 0.60 to 0.79; $P < 0.0001$) for living-donor transplants. However, the RR was increased in the first 3 mo and lower thereafter (Table 1, Figure 2). The RR for AMI (*versus* the waiting list) was greater for recipients of de-

Table 1. Risk factors of AMI after being placed on the waiting list[a]

Variable	Recipients of Living-Donor Transplants Included (n = 53,297)		Censoring Recipients at Living-Donor Transplant (n = 49,417)	
	% of Total	RR (95% CI) P Value	% of Total	RR (95% CI) P Value
Transplantation status				
on the deceased donor waiting list	93[a]	1.00 (Reference)	100	1.00 (Reference)
deceased-donor transplant ≤3 mo	36[a]	3.57 (3.21 to 3.96) $P < 0.0001$	39	3.47 (3.13 to 3.85) $P < 0.0001$
deceased-donor transplant >3 mo	31[a]	0.45 (0.41 to 0.50) $P < 0.0001$	34	0.45 (0.40 to 0.50) $P < 0.0001$
living-donor transplant ≤3 mo	14[a]	2.81 (2.31 to 3.42) $P < 0.0001$	—	—
living-donor transplant >3 mo	13[a]	0.39 (0.33 to 0.47) $P < 0.0001$	—	—
Listed in 1999 to 2002 (*versus* 1995 to 1998)[b]	54	1.09 (1.01 to 1.19) $P = 0.0333$	54	1.11 (1.02 to 1.20) $P = 0.0209$
Age at listing[b]				
18 to 34 yr	19	1.00 (Reference)	18	1.00 (Reference)
35 to 49 yr	32	2.25 (1.92 to 2.64) $P < 0.0001$	32	2.22 (1.88 to 2.62) $P < 0.0001$
50 to 64 yr	35	3.63 (3.11 to 4.24) $P < 0.0001$	36	3.58 (3.04 to 4.20) $P < 0.0001$
≥65 yr	14	4.30 (3.62 to 5.11) $P < 0.0001$	14	4.08 (3.40 to 4.89) $P < 0.0001$
Race				
white	58	1.00 (Reference)	56	1.00 (Reference)
black	35	0.64 (0.59 to 0.69) $P < 0.0001$	37	0.63 (0.58 to 0.68) $P < 0.0001$
Asian	5	0.83 (0.70 to 0.98) $P = 0.0283$	5	0.83 (0.70 to 1.00) $P = 0.0371$
other/unknown	3	0.62 (0.49 to 0.78) $P < 0.0001$	3	0.60 (0.47 to 0.76) $P < 0.0001$
Hispanic ethnicity (*versus* non-Hispanic)	16	0.66 (0.59 to 0.73) $P < 0.0001$	16	0.66 (0.59 to 0.73) $P < 0.0001$
Male (*versus* female)	59	1.09 (1.02 to 1.17) $P = 0.0160$	60	1.08 (1.01 to 1.17) $P = 0.0339$
Body mass index at listing[b]				
<18.5 kg/m^2	4	0.95 (0.79 to 1.15) $P = 0.6014$	4	0.95 (0.78 to 1.15) $P = 0.5748$
18.5 to 29.9 kg/m^2	47	1.00 (Reference)	47	1.00 (Reference)
≤30 kg/m^2	18	0.95 (0.86 to 1.05) $P = 0.2723$	19	0.93 (0.84 to 1.04) $P = 0.1913$
Unknown	30	1.05 (0.95 to 1.16) $P = 0.3535$	30	1.03 (0.93 to 1.15) $P = 0.5524$
Primary cause of kidney disease				
glomerulonephritis	25	1.00 (Reference)	25	1.00 (Reference)
diabetes	32	1.53 (1.38 to 1.71) $P < 0.0001$	33	1.53 (1.37 to 1.70) $P < 0.0001$
hypertension	19	0.75 (0.66 to 0.85) $P < 0.0001$	19	0.75 (0.66 to 0.85) $P < 0.0001$
cystic kidney disease	5	0.69 (0.56 to 0.84) $P = 0.0002$	5	0.66 (0.54 to 0.82) $P < 0.0001$
other/unknown	19	0.74 (0.66 to 0.84) $P < 0.0001$	18	0.75 (0.66 to 0.85) $P < 0.0001$
Comorbidity at or before listing[b]				
diabetes (*versus* no diabetes)[c]	27	1.08 (0.97 to 1.20) $P = 0.1801$	28	1.08 (0.97 to 1.21) $P = 0.1620$
congestive heart failure (*versus* none)	11	1.19 (1.08 to 1.32) $P = 0.0008$	12	1.19 (1.07 to 1.32) $P = 0.0011$
hypertension (*versus* none)	58	0.91 (0.83 to 0.99) $P = 0.0344$	58	0.90 (0.82 to 0.99) $P = 0.0265$
ischemic heart disease (*versus* none)[d]	8	1.68 (1.51 to 1.87) $P < 0.0001$	8	1.68 (1.51 to 1.87) $P < 0.0001$
peripheral vascular disease (*versus* none)	4	1.12 (0.98 to 1.29) $P = 0.1032$	4	1.08 (0.93 to 1.25) $P = 0.3093$
cerebral vascular disease (*versus* none)	3	1.20 (1.00 to 1.43) $P = 0.0449$	3	1.15 (0.95 to 1.38) $P = 0.1490$
Employment status at listing[b]				
not employed	60	1.00 (Reference)	61	1.00 (Reference)
employed	31	0.84 (0.76 to 0.92) $P = 0.0003$	31	0.84 (0.76 to 0.92) $P = 0.0003$
retired	9	1.01 (0.89 to 1.14) $P = 0.9394$	9	1.03 (0.90 to 1.17) $P = 0.1744$
Duration of previous ESRD				
<1 mo	2	1.06 (0.81 to 1.38) $P = 0.6876$	2	1.12 (0.82 to 1.53) $P = 0.4907$
1 to 12 mo	39	1.00 (Reference)	39	1.00 (Reference)
≥12 mo	58	1.23 (1.14 to 1.33) $P < 0.0001$	59	1.22 (1.13 to 1.32) $P < 0.0001$

[a]Transplant status was considered a time-dependent state. Percentages are those of the original population that contributed time to the particular state. Each variable in this table is adjusted for each other variable. AMI, acute myocardial infarction; CI, confidence interval; RR, relative risk.

[b]Time of placement on the deceased-donor waiting list or time of transplantation if this occurred before placement on the waiting list.

[c]Diabetes independent of diabetes that caused ESRD.

[d]Includes history of AMI.

ceased- *versus* living-donor transplants early (3.57 [95% CI 3.21 to 3.96] *versus* 2.81 [95% CI 2.31 to 3.42]) and late (0.45 [95% CI 0.41 to 0.50] *versus* 0.39 [95% CI 0.33 to 0.47]) after transplantation.

Interaction of Age with Transplantation on the Risk for AMI

There was a positive interaction between older age and the risk for AMI associated with transplantation (test for interaction, $P = 0.03$). Compared with individuals who were 18 to 34

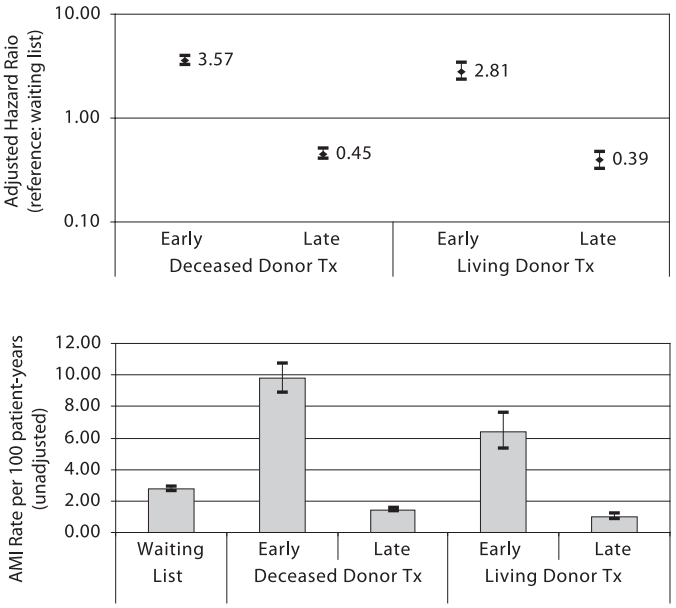

Figure 2. Differences in the relative risks (RR; top) and absolute rates (bottom) of AMI associated with transplantation and donor source. Adjusted RR are with 95% confidence intervals (CI), where failure to cross 1.0 indicates $P < 0.05$ compared with the waiting list. The RR for AMI associated with transplantation is higher early but lower late after transplantation. The risk for AMI (compared with the waiting list) is relatively greater for recipients of deceased-donor than living-donor transplants. WL, waiting list; ET, early (≤3 mo) after transplantation; LT, late (>3 mo) after transplantation.

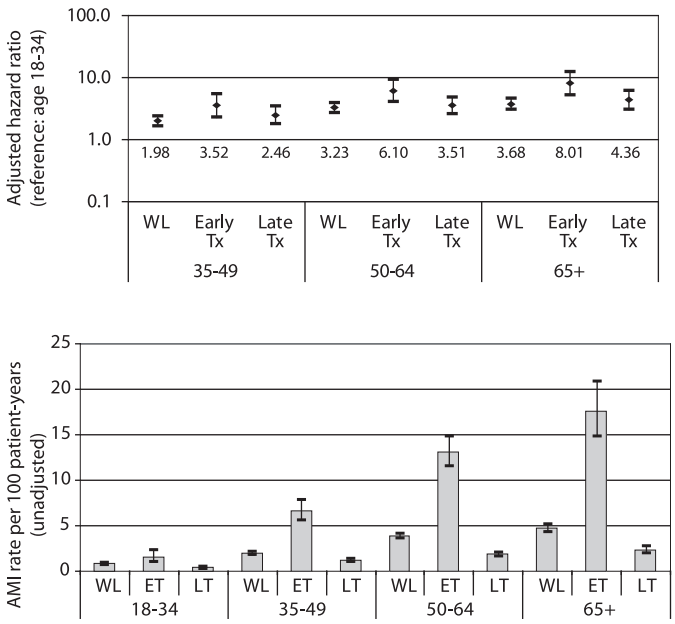

Figure 3. Differences in the RR (top) and absolute rates (bottom) of AMI associated with age. Adjusted RR are with 95% CI, where failure to cross 1.0 indicates $P < 0.05$ compared with the reference age 18 to 34 yr. The increase in RR for AMI associated with older age is greatest early after transplantation. For all ages, rates of AMI were highest early and lowest late after transplantation.

yr of age, AMI risk for those who were 35 to 49 was 1.98 (95% CI 1.62 to 2.41) on the waiting list *versus* 2.87 (95% CI 2.20 to 3.74) after transplantation. The AMI risk for those who were 50 to 64 (compared with 18 to 34) was 3.21 (95% CI 2.65 to 3.88) on the waiting list and 4.55 (95% CI 3.52 to 5.88) after transplantation. The AMI risk for those who were ≥65 yr of age (compared with 18 to 34) was 3.62 (95% CI 2.93 to 4.47) on the waiting list and 5.94 (95% CI 4.51 to 7.83) after transplantation. Most of the interaction was due to a positive interaction between the early (≤3 mo) effect of transplantation on AMI risk and the effect of age on AMI risk. In other words, the increased risk for AMI among individuals who were 35 to 49, 50 to 64, and ≥65 (compared with 18 to 34) was more pronounced early after transplantation than on the waiting list or late after transplantation (Figure 3). The absolute risk for AMI was highest early after transplantation for all age groups (Figure 3).

Interaction of Black and Asian Ethnicity with Transplantation on the Risk for AMI

Compared with white patients, black patients had a lower risk for AMI on the waiting list (0.65; 95% CI 0.59 to 0.71) and somewhat less of a risk reduction after transplantation (0.73; 95% CI 0.63 to 0.84; test for interaction, $P = 0.04$). The risk for AMI for black patients (compared with white patients) early after transplantation was similarly reduced, but the reduction in risk was less pronounced ($P = 0.0308$) late after transplantation than it was on the waiting list or early after transplantation (Figure 4). In contrast, Asian patients had a similar risk for AMI as white patients on the waiting list (0.93; 95% CI 0.77 to 1.13) but a relatively lower risk for AMI after transplantation compared with white patients (0.63; 95% CI 0.43 to 0.92).

Interaction of Hispanic Ethnicity with Transplantation on the Risk for AMI

Hispanic ethnicity was tabulated separately on USRDS and UNOS data forms. For Hispanic patients (compared with non-Hispanic patients), a lower risk for AMI on the waiting list (0.72; 95% CI 0.63 to 0.81) tended to be even lower after transplantation (0.58; 95% CI 0.48 to 0.70), although this difference was of borderline statistical significance (test for interaction $P = 0.06$) The posttransplantation reduction in risk for Hispanic patients (compared with non-Hispanic patients) may have been a result of a reduction ($P = 0.0513$) in risk late after transplantation (Figure 5).

Interaction of Causes of CKD with Transplantation on the Risk for AMI

The global test for an interaction between primary causes of CKD and transplantation was nonsignificant (test for interaction, $P = 0.30$). However, considering specific causes, diabetes (compared with the arbitrarily selected reference group with CKD from glomerulonephritis) was associated with a relatively greater risk for AMI on the waiting list (1.70; 95% CI 1.50 to 1.92) than after transplantation (1.33; 95% CI 1.13 to 1.56; $P = 0.0083$). The posttransplantation reduction in risk from diabetes

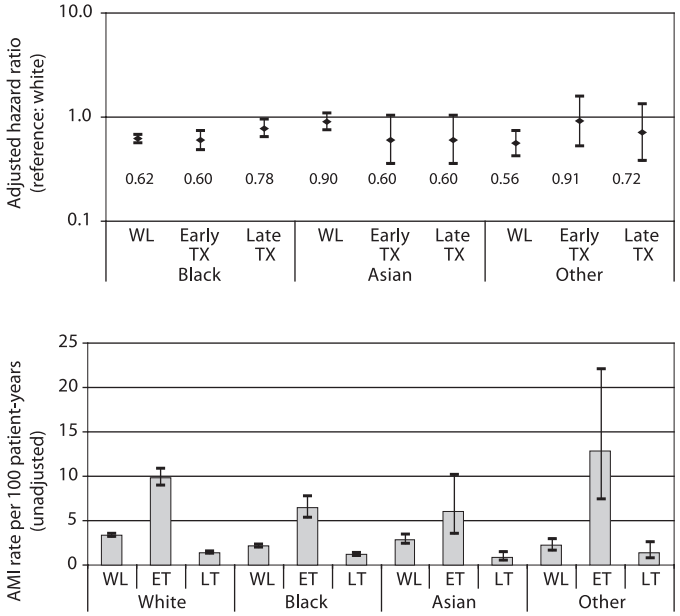

Figure 4. Differences in the RR (top) and absolute rates (bottom) of AMI associated with black and Asian ethnicity. Adjusted RR are with 95% CI, where failure to cross 1.0 indicates $P < 0.05$ compared with the reference white patients. Late after transplantation, black patients (compared with white patients) had less of a reduction in risk for AMI than they enjoyed on the waiting list and early after transplantation. For all ethnicities, rates of AMI were highest early and lowest late after transplantation.

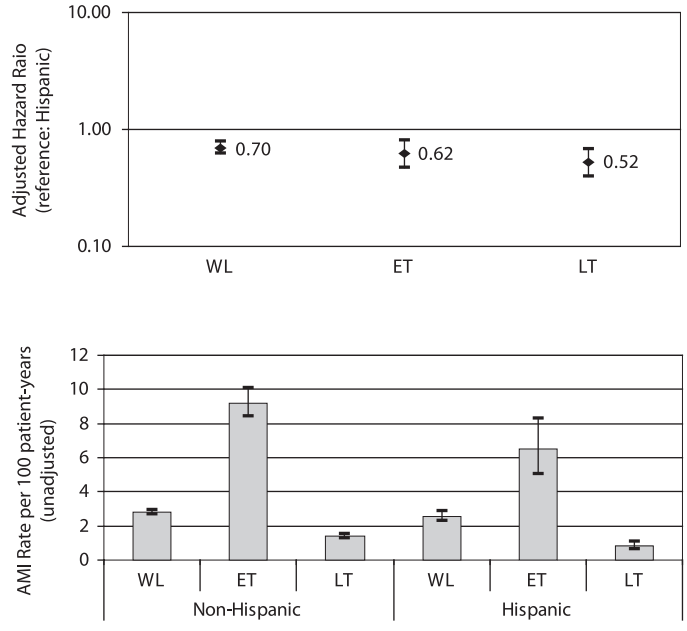

Figure 5. Differences in the RR (top) and absolute rates (bottom) of AMI associated with Hispanic ethnicity. Adjusted RR are with 95% CI, where failure to cross 1.0 indicates $P < 0.05$ compared with the reference white patients. Hispanic patients (compared with non-Hispanic patients) had a relatively greater reduction in risk for AMI late after transplantation than on the waiting list or early after transplantation.

was from reduced risk both early and late after transplantation (Figure 6). It is interesting that the RR for AMI associated with CKD from glomerulonephritis was greater than other causes of CKD, excepting diabetes. Of course, the absolute risk for AMI was highest early after transplantation for all causes of CKD (Figure 6).

Interaction of Gender with Transplantation on the Risk for AMI

Considering the entire study period, men had a slightly higher risk for AMI compared with women (Table 1). Whereas the magnitude of the hazard ratio remained approximately the same when considering the waiting list and posttransplantation periods separately (test for interaction, $P = 0.76$), the differences between men and women were no longer statistically significant.

Interaction of BMI with Transplantation on the Risk for AMI

The risk for AMI after listing was no different for individuals who were either underweight (BMI <18.5 kg/m^2) or overweight (BMI ≥ 30 kg/m^2), compared with individuals with normal BMI (Table 1). The RR for AMI for BMI ≥ 30 kg/m^2 (*versus* BMI <30 kg/m^2) was similar on the waiting list (0.95: 95% CI 0.85 to 1.06) and early (0.95; 95% CI 0.75 to 1.20) or late (0.92; 95% CI 71.2 to 1.18) after transplantation (test for interaction, $P = 0.53$).

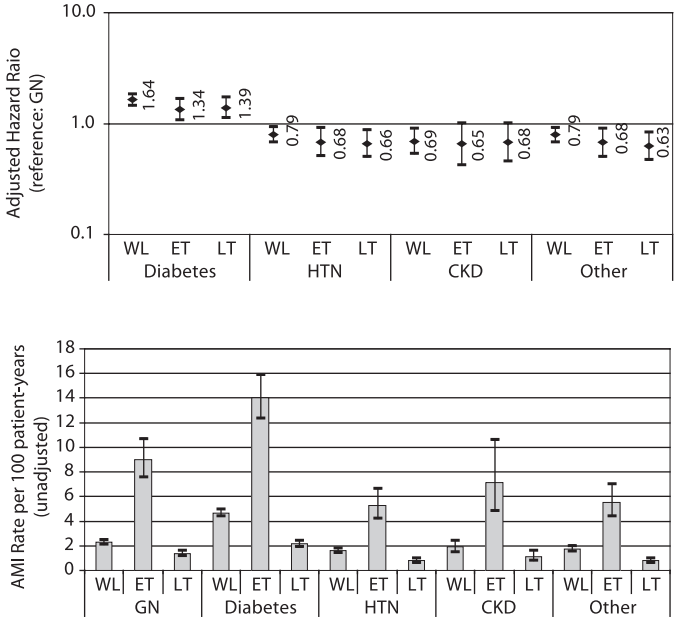

Figure 6. Differences in the RR (top) and absolute rates (bottom) for AMI associated with different causes of chronic kidney disease (CKD). Adjusted RR are with 95% CI, where failure to cross 1.0 indicates $P < 0.05$ compared with the reference CKD from glomerulonephritis (GN). The RR associated with CKD from diabetes (compared with CKD from GN) was greater on the waiting list than early and late after transplantation. For all causes of CKD, rates of AMI were highest early and lowest late after transplantation.

Interaction of Previous ESRD Duration with Transplantation on the Risk for AMI

Individuals who had ESRD for a longer period of time before listing had a higher risk for AMI after listing (Table 1). However, there was no interactive effect of duration of previous ESRD on AMI risk with transplantation (test for interaction, $P = 0.44$). The RR for AMI for those with ≥12 mo of ESRD before listing (compared with 1 to 12 mo of ESRD before listing) was 1.22 (95% CI 1.12 to 1.34) on the waiting list, 1.29 (95% CI 1.07 to 1.55) early after transplantation, and 1.30 (95% CI 1.09 to 1.55) late after transplantation.

Interaction of Previous IHD with Transplantation on the Risk for AMI

Individuals who had evidence of previous IHD or AMI documented on the 2728 form before listing had a higher risk for AMI after listing (Table 1). However, there was no interactive effect of previous IHD/AMI on AMI risk with transplantation (test for interaction, $P = 0.24$). The RR for AMI for those with previous IHD/AMI before listing was 1.64 (95% CI 1.45 to 1.86) on the waiting list, 1.80 (95% CI 1.44 to 2.26) early after transplantation, and 1.66 (95% CI 1.31 to 2.10) late after transplantation (Figure 7).

Discussion

There are several potentially important findings in this study. (*1*) The risk for AMI was clearly less for patients after kidney transplantation compared with patients who remained on the waiting list. (*2*) The risk for AMI was relatively higher for recipients of a deceased-donor kidney, compared with living-donor kidney recipients, especially early after transplantation. (*3*) The age-associated risk for AMI was relatively greater after transplantation compared with the waiting list. This was due to an increased age-associated risk for AMI within the first 3 mo after transplantation. (*4*) This study confirmed that black patients who were on the waiting list were at lower risk for AMI compared with white patients. However, this relative advantage was reduced but not eliminated in the late posttransplantation period. Hispanic patients (compared with non-Hispanic patients) had a lower risk for AMI on the waiting list that tended to be even lower after transplantation. (*5*) For patients with CKD that was caused by diabetes (compared with CKD that was caused by glomerulonephritis), the risk for AMI was relatively higher on the waiting list than after transplantation. However, glomerulonephritis was associated with a higher risk for AMI (compared with nondiabetic causes of CKD) both on the waiting list and early and late after transplantation.

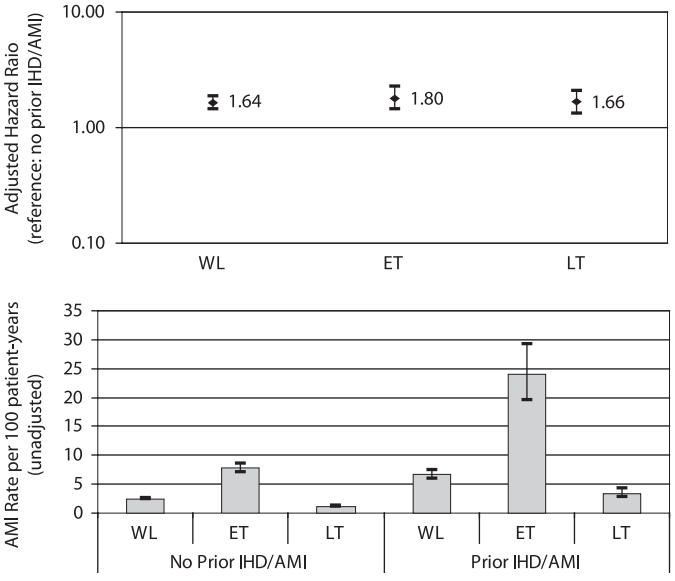

Figure 7. Differences in the RR (top) and absolute rates (bottom) for AMI associated with prior IHD or AMI. Adjusted RR are with 95% CI, where failure to cross 1.0 indicates $P < 0.05$ compared with the reference of no previous ischemic heart disease (IHD)/AMI. The RR associated with documented evidence of previous IHD/AMI was similar on the waiting list compared with early and late after transplantation. For patients with and without previous IHD/AMI, rates of AMI were highest early and lowest late after transplantation.

The risk for AMI was clearly less for patients after kidney transplantation compared with the waiting list. Hypolite *et al.* (5) reported a similar finding for acute coronary syndromes among 11,369 diabetic kidney and/or pancreas transplant candidates who were placed on the UNOS waiting list in July 1994 to June 1997. This is a remarkable finding, given that data from observational studies (6–8) and at least one randomized controlled trial (9) have suggested that traditional risk factors may not predict CVD events in patients who are treated with hemodialysis. In contrast, kidney transplant recipients typically have a higher prevalence of traditional risk factors than dialysis patients, and the relationship between those risk factors and CVD after transplantation is similar to that found in the general population (10–12). One explanation for this difference may be that CVD events in dialysis patients more often may be caused by nonatherosclerotic events, *e.g.*, arrhythmias. However, even when we restricted our analysis to AMI, transplant recipients still have fewer events late after transplantation than patients on the waiting list.

It is worth noting that the incidence of AMI was highest early after transplantation, likely as a result of the stress of surgery, high doses of immunosuppressive medications, early graft dysfunction, and other factors. This occurred despite the screening and preemptive coronary revascularization of asymptomatic kidney transplant candidates that typically is part of the routine, pretransplantation evaluation (2,3). Clearly, studies are needed to evaluate the cost-effectiveness of these screening programs and whether other strategies might be more effective.

Posttransplantation AMI were relatively more common for recipients of a deceased-donor kidney, compared with a living-donor kidney, especially early after transplantation. It is plausible that recipients of a deceased-donor kidney had more delayed graft function and early acute rejection, along with higher doses of immunosuppressive medications and lower kidney function, than recipients of living-donor kidneys. These differences could increase the risk for AMI in the early posttransplantation period (13–15). Despite differences in deceased- and living-donor transplants, the risk for AMI associated with

other characteristics was virtually identical in separate analyses that included or excluded (censoring) living-donor transplants.

Age was one of the strongest risk factors for AMI early after transplantation, and the relative advantage of transplantation (*versus* the waiting list) was diminished for older individuals. Although transplantation still may be the best option for individuals of all ages, these results suggest that older individuals are at particularly high risk for perioperative AMI and should be considered for prophylactic measures.

Although black patients had a lower risk for AMI (compared with white patients) both before and after transplantation, this lower risk for black patients diminished with time after transplantation. Hispanic patients, conversely, had a relatively lower risk for AMI after transplantation, although this result was of borderline statistical significance ($P = 0.0513$). Unlike black and Hispanic patients, the AMI risk reduction for Asian patients (compared with white patients) was similar on the waiting list and at all times after transplantation. The reasons for these ethnic differences in AMI risk before and after transplantation are not clear, but these differences in the risk for AMI parallel the known risk for rejection and graft dysfunction associated with ethnicity (16–20). Therefore, it is possible that the interaction between ethnicity and transplantation on the risk for AMI reflects differences (genetic or other) in risks for graft dysfunction, which in turn may increase the risk for AMI. Indeed, it was reported previously that posttransplantation graft function is a risk factor for major adverse cardiac events (15), acute coronary syndromes (14), and death from CVD (13). However, it also is possible that socioeconomic differences that are associated with ethnicity cause AMI to be diagnosed less frequently, and this could account for some or all of the observed differences.

It is not surprising that diabetes, as a cause of CKD, was associated with the highest risk for AMI. It was interesting, however, that glomerulonephritis was associated with a higher risk for AMI (compared with nondiabetic causes of CKD). It is possible that traditional risk factors, especially dyslipidemias, are more common in patients with chronic glomerulonephritis as a result of long-standing proteinuria and the use of therapeutic agents such as corticosteroids.

It is interesting that employment status was associated with AMI after placement on the waiting list. Specifically, the 31% of patients who were employed at the time of listing or preemptive transplantation had a 16% lower risk for AMI than patients who were not employed (Table 1). Employment status may be a surrogate for socioeconomic status and thereby influence the risk for AMI. Conversely, it also is plausible that unemployed patients already had CVD (that was not reflected in the comorbidity indicators) at the time of listing and that being employed was a result and not a cause of CVD.

To the best of our knowledge, there have been no other systematic comparisons of AMI on the waiting list with AMI after kidney transplantation. As previously mentioned, Hypolite *et al.* (5) reported a reduced incidence of acute coronary syndromes (including AMI) among kidney transplant recipients with diabetes compared with the waiting list. Our results extend theirs to patients who did not have diabetes as a cause of CKD. A recent, comprehensive analysis by Lentine *et al.* (21) catalogued risk factors for AMI after kidney transplantation using USRDS data from 1995 to 2000. However, their analysis examined multiple risk factors for AMI without focusing on interactions and comparisons between the waiting list and kidney transplantation *per se*. We did not include a number of the risk factors that they examined from data on the Medicare 2728 form, given the large proportion of missing values for variables such as dyslipidemia, hypertension, and cigarette smoking.

Although our analysis is the largest of its kind, it has a number of obvious weaknesses: (*1*) As previously mentioned, the USRDS registry does not contain accurate data on traditional CVD risk factors, such as dyslipidemias, hypertension, and cigarette smoking. (*2*) Medicare beneficiaries who were used in this analysis are not a random sample of the whole population of patients who are placed on the transplant waiting list. Nevertheless, we previously demonstrated that Medicare beneficiaries are more alike than different from patients who are not Medicare beneficiaries (22). Therefore, it is unlikely that the results of this study would not be applicable to the whole population of patients who are placed on the waiting list. (*3*) Although we limited the comorbidity data used from the Medicare 2728 Form to variables that seemed to have the least amount of missing data, even these data may be inaccurate. (*4*) Perhaps most concerning is the assumption that patients on the waiting list are truly comparable to patients who undergo kidney transplantation. This assumption, although common in published analyses, has never been validated. It is likely that there is at least some selection bias that could lead to an underestimation of AMI risk after transplantation compared with the waiting list. This would occur to the extent that there are patients on the waiting list who did not receive a transplant when a kidney was offered, because they were at increased risk for CVD. Such patients may have been placed on "internal hold" or simply were not discovered to have had a recent CVD event and were removed from the list before a kidney was offered.

Conclusion

Although the incidence of AMI is reduced after kidney transplantation compared with the waiting list, it is more frequent early than late after transplantation. In addition, the RR difference between the waiting list and transplantation varies in different patient populations. In particular, older individuals have a relatively greater risk for AMI after transplantation compared with the waiting list than younger individuals, largely as a result of a higher risk for AMI early after transplantation. In contrast, patients with CKD as a result of diabetes (compared with glomerulonephritis) had a relatively greater risk for AMI on the waiting list than after transplantation. Finally, several factors that may adversely affect graft function (*e.g.*, deceased *versus* living donor and black *versus* white ethnicity) increased the RR for AMI after transplantation compared with the waiting list. Further study and comparison of the risks for AMI in different patient populations on the waiting list and after transplantation may better inform patients and physicians of the risk of transplantation *versus* remaining on dialysis and improve our understanding of the pathogenesis of CVD in patients with stage 5 CKD. Finally, this study provides valuable guidance to practicing health care professionals by directing their attention to appropriate monitoring and, when

possible, implementation of risk reduction strategies for patients who are at increased risk for AMI. Close attention should be directed to people in the early posttransplantation period (<3 mo), those who have experienced >1 yr of dialysis before listing, older people, and transplant recipients who have diabetes.

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This paper defines the relative risk of an acute myocardial infarct after kidney transplant in different patient groups compared to patients on the waiting list. It is related to three papers in this month's issue of *CJASN*, which establish the risk of atrial fibrillation posttransplant (pages 288–296), review the unique clinical aspects of heart failure in patients with diabetic nephropathy (pages 193–208), and discuss approaches to coronary revascularization in diabetic dialysis patients (pages 209–220).