Incidence, Predictors, and Associated Outcomes of Atrial Fibrillation after Kidney Transplantation

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The risk for and predictors of atrial fibrillation (AF) after kidney transplantation are not well described. Registry data that were collected by the United States Renal Data System were used to investigate retrospectively new-onset AF among adult first renal allograft recipients and transplant candidates who received a transplant or were wait-listed in 1995 to 2001 with Medicare as the primary payer. AF events were ascertained from billing records, and participants were followed until loss of Medicare coverage or December 31, 2001. Cox hazards analysis was used to identify independent correlates of posttransplantation AF (adjusted hazard ratio [AHR]; 95% confidence interval [CI]) and to examine AF as an outcomes predictor. Among 31,136 eligible transplant recipients, the cumulative incidence of new-onset AF was 3.6% (95% CI 3.4 to 3.8%) and 7.3% (95% CI 7.0 to 7.6%) at 12 and 36 mo and declined below the demographics-adjusted cumulative incidence on the waiting list by approximately 17 mo. Risk factors for posttransplantation AF included older recipient age, male gender, white race, renal failure from hypertension, and coronary artery disease. Extended pretransplantation dialysis duration, posttransplantation diabetes, and graft failure were identified as potentially modifiable correlates of AF. In separate analyses, AF independently predicted death (AHR 3.2; 95% CI 2.9 to 3.6) and death-censored graft loss (AHR 1.9; 95% CI 1.6 to 2.3). As the population of renal transplant recipients grows older, the incidence and prevalence of AF among these patients will likely increase. Appropriate risk stratification may identify transplant recipients who are in need of close monitoring for and management of this adverse cardiovascular event.

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Patients with kidney failure face increased risk for cardiac arrhythmias. The enhanced arrhythmogenicity of renal disease seems to stem from a complex interplay of comorbidities that are prevalent in people with kidney disease (1), electrolyte and volume disturbances (2), and abnormalities in myocardial structure function that result from uremia and dialytic therapy (3). The net impact of this arrhythmic substrate is elevated risk for a variety of cardiac conduction abnormalities. Graded increases in the risks for ventricular arrhythmias and heart block were predicted independently by severity of renal dysfunction in a cohort of critically ill medical patients (4). Atrial fibrillation, the most common supraventricular arrhythmia, is reported to occur more often in dialysis patients than in the general population (5–7). Although often considered a relatively benign arrhythmia, complications of atrial fibrillation (AF) include hemodynamic destabilization and thromboembolism. Whether AF predicts "hard" adverse outcomes such as mortality among ESRD patients independent of other comorbidities is controversial (5,7).

Kidney transplantation may reduce cardiovascular risk in general compared with chronic dialysis (8). However, cardiovascular disease remains the leading cause of death after transplantation, accounting for 30 to 50% of mortality (9,10). The relative contribution of cardiac arrhythmias to posttransplantation morbidity and mortality is incompletely defined. Using primary hospitalization diagnosis codes, Abbott *et al.* (11) estimated the rate of AF after transplantation at approximately six events per 1000 person-years and found that AF was independently associated with a 34% increase in all-cause mortality. As AF is commonly managed in the outpatient setting or occurs in the hospital as a complication of other conditions, a broader definition is needed to estimate the risk for and implications of this arrhythmia in its usual presentations.

Prompted by the limited information on the risk for and outcomes of atrial arrhythmias after kidney transplantation, 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 all presentations of AF and a related arrhythmia, atrial flutter,

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among allograft recipients and among transplant candidates who were on the waiting list. We also sought to identify clinically relevant risk factors for new diagnoses of this arrhythmia class after transplantation and to estimate the prognostic implications of the diagnosis for subsequent mortality and graft loss.

Materials and Methods

Data Sources

We performed sample selection, outcomes ascertainment, and covariate determinations using registry data that were collected by the USRDS and that incorporate 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, were described previously (12,13).

Participant Selection

We included adult (≥18 yr of age) first renal allograft recipients who received a transplant from January 1, 1995, to December 31, 2001, with Medicare as the primary payer at the time of transplantation. We identified eligible Medicare beneficiaries as those with Medicare "primary payer" status indicated in the "Payhist" file of the USRDS at the time of transplantation; to ensure complete Medicare billing, we also required that the Medicare payment for the initial transplant hospitalization was at least $15,000, as described previously (14). We excluded patients with previous and/or simultaneous multiorgan transplants. Because AF that presents before transplantation may be mediated by different factors and/or have different prognostic implications than arrhythmias that are first diagnosed after transplantation, we limited the sample to those who were at risk for new-onset AF by excluding patients with pretransplantation claims for AF and/or indication of cardiac arrhythmias at ESRD reporting on Center for Medicare and Medicaid Studies Form 2728. Some patients reportedly received combinations of immunosuppressive agents at the time of UNOS registration that more likely reflect data entry errors rather than unusual, experimental regimens. Therefore, we also excluded patients who reportedly received azathioprine plus mycophenolate mofetil and/or more than one calcineurin inhibitor.

Definitions of Outcomes and Covariates

Posttransplantation AF. New-onset AF and/or flutter events (hereafter referred to as AF) were defined by identification of qualifying posttransplantation Medicare claims with a corresponding diagnosis (*International Classification of Diseases, Ninth Revision* [ICD-9] code 427.3x) in the at-risk sample. Qualifying claims comprised one part A or two part B claims, and the date of the earliest claim defined the date of diagnosis, as per the method previously validated for diabetes (13) and posttransplantation malignancy (15), and used to describe other cardiovascular conditions (16,17) and posttransplantation disorders (18,19). Observations were censored at the earliest of the following events: Loss to follow-up, loss of Medicare, 3 yr after transplantation to avoid censoring bias (the time when Medicare coverage ends after kidney transplantation in the absence of age >65 yr or disability), death, or end of observation (December 31, 2001, the date of the most recent Medicare claims data available at the time of the study).

Recipient, Donor, and Transplant-Related Characteristics and Outcomes. Recipient characteristics and comorbidities were those reported by UNOS at the time of transplantation, supplemented with information on pretransplantation conditions from the Center for Medicare and Medicaid Studies form 2728 when available (Table 1). *De novo* diabetes after transplantation was defined as qualifying posttransplantation claims data (ICD-9 250.x) in patients without a previous indication of diabetes. We also sought posttransplantation claims evidence of hypertension (ICD-9 401.x, 405.x), anemia (ICD-9 281.x, 282.x, 285.x), and acute myocardial infarction (ICD-9 410.x). Donor and transplantation procedure characteristics were derived from UNOS records (Table 1).

We collected induction and maintenance immunosuppression data recorded on the UNOS recipient registration form for analysis on an intention-to-treat basis. Because patients who did not receive maintenance steroids composed a small minority of the sample (<10%), we did not attempt to analyze the associations of steroids with any study outcome. Exposure levels and thus consequences of immunosuppression may vary with co-immunosuppression (20,21). We therefore considered the effects of maintenance immunosuppression in terms of calcineurin inhibitor–antimetabolite combinations. Tacrolimus-azathioprine was used in only 1.5% of the sample and so was combined with tacrolimus–mycophenolate mofetil for analysis. Among regimens that were not composed solely of a calcineurin inhibitor–antimetabolite pair (with or without steroids), we identified those that included rapamycin.

Statistical Analyses

We estimated unadjusted event incidence (95% confidence interval [CI]) by the product-limit (Kaplan-Meier) method and adjusted incidence by Cox regression. To evaluate associations of individual baseline clinical characteristics with the risk for AF, we compared posttransplantation AF incidence among patients stratified by baseline factors; because age is a potent correlate of AF and many baseline comorbidities, we also adjusted these incidence estimates to the average age of the study sample. Continuous variables were categorized into clinically relevant groupings to form clinical strata. Missing categorical covariate data were grouped with the absence of a characteristic when such categories were 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 hazards analysis to obtain covariate-adjusted estimates of the risk for newly diagnosed posttransplantation AF (adjusted hazards ratio [AHR]) 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 models. We tested for two-way interactions between significant predictors and all other variables. We examined the association of AF diagnoses with subsequent death-censored graft failure, all-cause graft loss, and mortality by Cox hazards analysis with AF as a time-varying covariate. We examined candidate final models for collinearity as previously reported (22).

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 interaction 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 9 (SAS Institute Inc., Cary, NC).

Sensitivity Analysis. We assessed the robustness of our estimate of the incidence of *new-onset* AF after transplantation to the duration of availability of pretransplantation claims information in a sensitivity analysis. This analysis was conducted among a subsample with a uniform period for pretransplantation claims ascertainment on the basis of submission of continuous Medicare claims for dialysis above a threshold of $675/mo for at least 12 mo, as described previously (23).

Table 1. 36-month age-adjusted cumulative incidences of new-onset AF after kidney transplantation, stratified by baseline recipient, donor, and transplant characteristics[a]

Characteristic	No. with Characteristic (%; n = 31,136)	Age-Adjusted Incidence among Those with Characteristic (%; 95% CI)	Age-Adjusted Incidence among Those without Characteristic or Unknown Status (%; 95% CI)	P Value
Recipient characteristics				
demographics				
female gender	12,523 (40.2)	4.8 (4.4 to 5.2)	6.5 (6.1 to 6.9)	<0.0001
race				
white	19,705 (63.2)	5.9 (5.5 to 6.2)		Reference
black	9,572 (30.7)	6.0 (5.5 to 6.6)		0.61
nonwhite, nonblack	1,887 (6.1)	4.3 (3.4 to 5.3)		0.008
Hispanic ethnicity	4,201 (13.5)	4.6 (3.8 to 5.2)	6.0 (5.6 to 6.4)	0.0005
college education	2,964 (9.5)	4.9 (4.1 to 5.7)	5.9 (5.6 to 6.2)	0.02
employed at transplantation	9,178 (29.5)	5.6 (5.1 to 6.1)	5.9 (5.5 to 6.3)	0.37
BMI category (kg/m^2)				
nonoverweight, nonobese (BMI <25)	13,025 (41.8)	5.4 (4.9 to 5.8)		Reference
overweight (BMI ≥ 25 < 30)	12,094 (38.8)	5.8 (5.4 to 6.3)		0.13
obese (BMI ≥30)	6,017 (19.3)	6.7 (6.0 to 7.4)		0.0004
primary cause of ESRD				
hypertension	7,231 (23.2)	6.7 (6.1 to 7.3)		0.0007
diabetes	7,978 (25.6)	5.4 (4.9 to 6.0)		0.38
glomerulonephritis	5,460 (17.5)	5.8 (5.1 to 6.5)		0.87
other	10,467 (33.6)	5.8 (5.4 to 6.1)		Reference
pretransplantation dialysis duration				
none (preemptive)	1,256 (4.0)	3.6 (2.7 to 4.5)		0.46
0 to 12 mo	3,420 (11.0)	4.0 (3.4 to 4.7)		Reference
13 to 24 mo	6,067 (19.5)	4.0 (3.4 to 4.4)		0.84
25 to 60 mo	15,053 (48.3)	5.5 (5.1 to 5.9)		0.0003
60+ mo	5,340 (17.2)	5.7 (5.4 to 6.0)		<0.0001
Comorbidities, pretransplantation				
hypertension	23,400 (75.2)	6.1 (5.5 to 6.6)	5.7 (5.3 to 6.1)	0.21
diabetes	8,721 (28.0)	5.6 (5.1 to 6.1)	5.9 (5.5 to 6.3)	0.26
angina/coronary disease, without known MI	3,262 (10.5)	7.4 (6.5 to 8.3)	5.6 (5.3 to 6.0)	<0.0001
MI	354 (1.1)	8.0 (5.4 to 10.5)	5.8 (5.5 to 6.1)	0.05
congestive heart failure	1750 (5.6)	6.4 (5.2 to 7.5)	5.8 (5.4 to 6.1)	0.32
peripheral vascular disease	1804 (5.8)	6.0 (4.9 to 7.0)	5.8 (5.5 to 6.1)	0.79
cerebral vascular disease	1024 (3.3)	6.7 (5.2 to 8.1)	5.8 (5.4 to 6.1)	0.21
chronic obstructive pulmonary disease	464 (1.5)	6.6 (4.5 to 8.7)	5.8 (5.5 to 6.1)	0.43
smoking history	915 (2.9)	5.8 (4.0 to 7.5)	5.8 (5.5 to 6.2)	0.98
alcohol abuse	168 (0.5)	7.1 (2.8 to 11.3)	5.8 (5.5 to 6.1)	0.51
Donor characteristics				
age				
0 to 30 yr	9,960 (32.0)	5.1 (4.6 to 5.5)		Reference
31 to 44 yr	11,188 (35.9)	5.9 (5.4 to 6.4)		0.01
45 to 59 yr	7,541 (24.2)	6.4 (5.8 to 7.0)		0.0003
60+ years	2,447 (7.9)	7.1 (6.1 to 8.1)		<0.0001
deceased	24,143 (77.5)	6.1 (5.7 to 6.5)	4.8 (4.2 to 5.3)	<0.0001
death caused by stroke	9,779 (31.4)	6.8 (6.2 to 7.3)	5.3 (5.0 to 5.7)	<0.0001
hypertension history	4,408 (14.2)	7.4 (6.6 to 8.2)	5.5 (5.2 to 5.9)	<0.0001
CMV positive	16,434 (52.8)	6.1 (5.7 to 6.6)	5.4 (5.0 to 5.9)	0.01
Transplantation factors				
0 HLA mismatches	2719 (8.7)	4.9 (4.1 to 5.8)		Reference
1 HLA mismatches	1,831 (5.9)	6.0 (4.9 to 7.1)		0.12
2 HLA mismatches	3,500 (11.2)	6.1 (5.3 to 6.9)		0.05

Continues

Table 1. (Continued)

Characteristic	No. with Characteristic (%; n = 31,136)	Age-Adjusted Incidence among Those with Characteristic (%; 95% CI)	Age-Adjusted Incidence among Those without Characteristic or Unknown Status (%; 95% CI)	P Value
3 HLA mismatches	7,467 (24.0)	5.4 (4.9 to 6.0)		0.34
4 HLA mismatches	6,548 (21.0)	5.9 (5.3 to 6.5)		0.07
5 HLA mismatches	5,818 (18.7)	5.9 (5.3 to 6.6)		0.07
6 HLA mismatches	3,253 (10.4)	6.6 (5.7 to 7.6)		0.008
delayed graft function	9,067 (29.1)	7.7 (6.9 to 8.2)	5.2 (4.8 to 5.5)	<0.0001
sensitized recipient	2383 (7.6)	6.2 (5.2 to 7.3)	5.8 (5.4 to 6.1)	0.38
induction immunosuppression	12,585 (40.4)	5.9 (5.4 to 6.4)	5.8 (5.4 to 6.2)	0.66
maintenance immunosuppression				
cyclosporine-MMF	11,657 (37.4)	5.7 (5.3 to 6.2)		Reference
cyclosporine-azathioprine	5,101 (16.4)	5.9 (5.3 to 6.5)		0.66
tacrolimus-(MMF or azathioprine)	6,416 (20.6)	4.8 (4.2 to 5.4)		0.02
rapamycin-based	1,847 (5.9)	6.9 (5.5 to 8.3)		0.08
other regimens	6,115 (19.6)	6.5 (5.8 to 7.1)		0.05

[a]AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; MI, myocardial infarction; MMF, mycophenolate mofetil. Incidence estimates are adjusted to the average age of the study sample.

Incidence of Posttransplantation AF on the Waiting List. To provide context for the estimated incidence of posttransplantation AF, we estimated the incidence of first qualifying arrhythmic events after wait-listing among first-time kidney transplant candidates, adjusted to the average age, gender, race, and ethnic composition of the study sample that received a transplant, according to previously described methods (24). Eligible candidates joined the waiting list in 1995 to 2001, had Medicare as the primary payer during time at risk, and did not have prelisting evidence of AF within the registry.

Results

Characteristics of the Sample

We identified 35,359 eligible Medicare beneficiaries who received their first renal allograft during the study period. After exclusion of 2934 (8.3%) patients with previous indications of AF within the registry and 1289 (3.6%) patients who were treated with improbable immunosuppressive drug combinations, the final sample comprised 31,136 patients. The similarities and differences of patients in the USRDS with and without Medicare as their primary payer have been described previously (15,18,25). Observed frequencies of major demographic and clinical characteristics of the study sample are displayed in the second column of Table 1. Waiting list analyses were conducted among 57,389 Medicare-insured transplant candidates without prelisting evidence of AF.

Incidence of AF after Transplantation

The cumulative incidence of new-onset AF after transplantation within the study sample was 2.6% (95% CI 2.5 to 2.8%), 3.6% (95% CI 3.4 to 3.8%), and 7.3% (95% CI 7.0 to 7.6%) at 6, 12, and 36 mo, respectively (Figure 1). Scaled according to observed time at risk, this equates with an event rate of 27.4 events per 1000 patient-years at risk (30.9 and 22.1 first diagnoses per 1000 patient-years in men and women, respectively). Cumulative incidence was similar and also rose most sharply in the peritransplantation period among a subsample with at least 12 mo of continuous pretransplantation Medicare coverage: 2.8% (95% CI 2.6 to 3.0%), 3.8% (95% CI 3.5 to 4.1%), and 7.9% (95% CI 7.4 to 8.3%) at 6, 12, and 36 mo, respectively). By comparison, the incidence of new-onset AF among eligible transplant candidates, adjusted to average demographic characteristics of the study sample that received a transplant, was

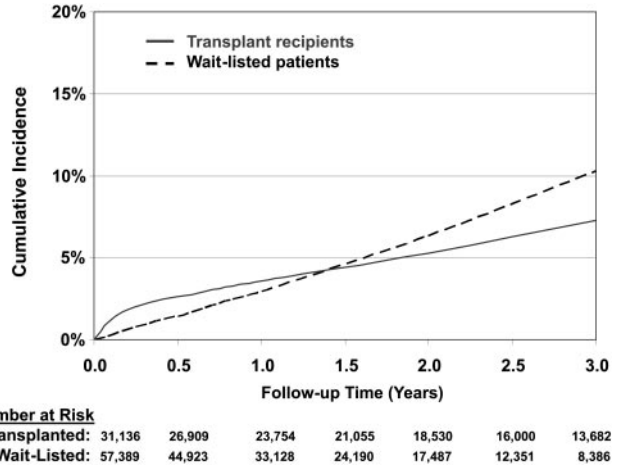

Figure 1. Cumulative incidence of new-onset atrial fibrillation (AF) among kidney transplant recipients and among transplant candidates on the waiting list. Incidence was estimated after entry on the waiting list among transplant candidates and after transplantation among allograft recipients, respectively. Waiting-list estimates are adjusted to the average age, gender, racial, and ethnic composition of the study sample that received a transplant.

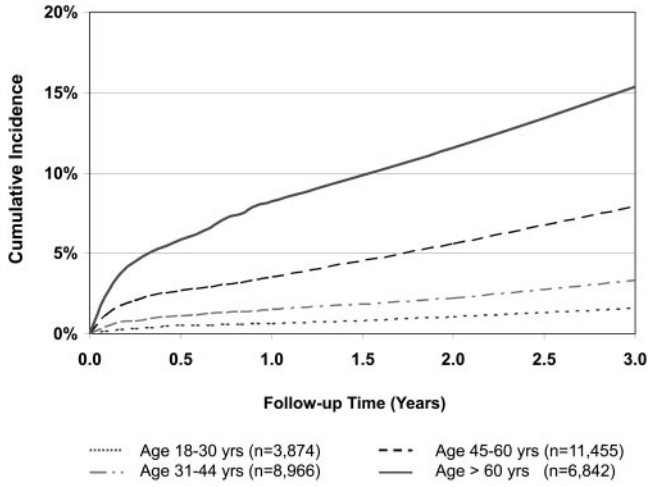

Figure 2. Cumulative incidence of new-onset AF after transplantation, stratified by recipient age at transplantation.

1.4% (95% CI 1.3 to 1.6%) at 6 mo, 3.0% (95% CI 2.8 to 3.2%) at 1 yr, and 10.3% (95% CI 9.8 to 10.7%) at 3 yr after joining the waiting list. In terms of incidence density, this equates with an event rate of 35.6 events per 1000 patient-years at risk (38.8 and 31.2 events among men and women, respectively) on the waiting list.

Table 1 displays the age-adjusted cumulative incidence of new-onset AF stratified by baseline clinical characteristics. There were no significant differences in the age-adjusted incidence of AF according to year of transplantation. The age-stratified cumulative incidence of posttransplantation AF is displayed in Figure 2. Table 2 provides the cumulative incidences of important posttransplantation complications and bivariate associations with subsequent AF.

Risk Factors for Posttransplantation AF

Independent predictors of posttransplantation AF that were identified among the candidate characteristics are shown in Table 3. We observed a marked increase in risk with advancing age, such that participants who were older than 60 yr faced more than eight times the risk of those aged 18 to 30 yr. Other recipient factors that were associated with increased risk included male gender, white race, non-Hispanic compared with Hispanic ethnicity, ESRD caused by hypertension, and extended pretransplantation dialysis duration. Among the candidate baseline comorbidities, only pretransplantation angina/coronary disease was identified as an independent correlate—the presence of this condition was associated with an approximately 34% risk increase.

Among the baseline donor and transplantation factors that bore age-adjusted relationships with AF, advanced donor age and delayed graft function persisted as modest risk factors after full multivariate adjustment. Several posttransplantation complications were associated with increased subsequent risk for AF, including diagnoses of hypertension, anemia, and new-onset diabetes. Risk was more than two times higher after a posttransplantation myocardial infarction and increased approximately 2.9 times after graft failure.

Outcomes after Posttransplantation AF

Age-adjusted mortality after diagnosis of AF was 17.8% (95% CI 15.4 to 20.1%) at 1 yr and 23.7% (95% CI 20.7 to 26.7%) at 2 yr. Cumulative rates of age-adjusted, death-censored graft failure after AF were 10.3% (95% CI 8.2 to 12.4%) at 1 yr and 13.8% (95% CI 11.1 to 16.4%) at 2 yr after diagnosis (Figure 3). After adjustment for recipient, donor, and transplant characteristics (as in the full model described in Table 3), new onset atrial fibrillation independently and potently predicted death (AHR 3.25; 95% CI 2.92 to 3.63), subsequent death-censored graft loss (AHR 1.93; 95% CI 1.63 to 2.29), and all-cause graft loss (AHR 2.88; 95% CI 2.60 to 3.12).

Discussion

Incidence of AF after Transplantation

In this large, retrospective, cohort study of Medicare beneficiaries who recently received a transplant, we found that new-onset AF is common, affecting 7% of renal allograft recipients by 3 yr posttransplantation, and that the rate of diagnosis is highest in the peritransplantation period. This pattern is con-

Table 2. Cumulative incidences of selected posttransplantation complications and unadjusted associations of these complications with subsequent new-onset AF[a]

Complication	Cumulative Incidence of Diagnosis (%; 95% CI)[b]			Unadjusted HR for AF (95% CI)
	6 Mo	12 Mo	36 Mo	
Hypertension	85.3 (84.9 to 85.7)	91.5 (91.2 to 91.8)	98.4 (96.8 to 100)	1.51 (1.33 to 1.72)[c]
Anemia	40.6 (40.1 to 41.2)	46.6 (46.1 to 47.2)	60.6 (60.0 to 61.2)	1.73 (1.56 to 1.91)[c]
New-onset diabetes	16.2 (15.8 to 16.6)	19.3 (18.9 to 19.8)	26.4 (25.8 to 26.9)	1.52 (1.38 to 1.68)[c]
MI	2.8 (2.6 to 3.0)	3.6 (3.4 to 3.8)	7.2 (6.9 to 7.6)	4.03 (3.42 to 4.75)[c]
Graft failure[d]	4.0 (3.8 to 4.2)	5.5 (5.2 to 5.7)	12.3 (11.8 to 12.7)	3.28 (2.84 to 3.81)[c]

[a]HR, hazard ratio.
[b]Diagnosis reflects the first indication of each condition after transplantation, based on qualifying billing claims for all conditions except graft failure. Diagnosis of graft failure is based on United Network for Organ Sharing reporting.
[c]$P < 0.0001$.
[d]Indicates graft loss events not due to death.

Table 3. Independent clinical correlates of new-onset AF after kidney transplantation[a]

Characteristic	Adjusted HR for AF (95% CI)	*P* Value
Recipient characteristics		
demographics		
age		
18 to 30 yr	1.00 (reference)	
31 to 44 yr	1.87 (1.37 to 2.56)	<0.0001
45 to 60 yr	4.20 (3.12 to 5.65)	<0.0001
60+ yr	8.10 (6.00 to 10.92)	<0.0001
gender		
female	0.74 (0.67 to 0.83)	<0.0001
male	1.00 (reference)	
race		
black	0.72 (0.64 to 0.82)	<0.0001
white	1.00 (reference)	
nonblack, nonwhite	0.64 (0.50 to 0.81)	<0.0001
ethnicity		
Hispanic	0.66 (0.56 to 0.78)	<0.0001
non-Hispanic	1.00 (reference)	
primary cause of ESRD		
diabetes	0.86 (0.72 to 1.03)	0.11
hypertension	1.23 (1.08 to 1.41)	0.001
glomerulonephritis	1.08 (0.94 to 1.26)	0.27
other or unknown cause	1.00 (reference)	
Pretransplantation dialysis duration		
none (preemptive)	0.99 (0.74 to 1.33)	0.95
0 to 12 mo	1.00 (reference)	
13 to 24 mo	0.95 (0.77 to 1.16)	0.59
25 to 60 mo	1.31 (1.10 to 1.57)	0.003
>60 mo	1.63 (1.32 to 2.00)	<0.0001
comorbidities, pretransplantation		
angina/coronary disease, without known MI	1.34 (1.17 to 1.53)	<0.0001
Donor and transplantation factors		
delayed graft function	1.17 (1.06 to 1.31)	0.003
donor age		
0 to 30 yr	1.00 (reference)	
31 to 44 yr	1.17 (1.03 to 1.33)	0.01
45 to 59 yr	1.18 (1.03 to 1.34)	0.02
60+ yr	1.25 (1.06 to 1.48)	0.008
Posttransplantation complications		
hypertension[b]	1.28 (1.12 to 1.46)	0.004
anemia[b]	1.35 (1.21 to 1.50)	<0.0001
new-onset diabetes[b]	1.36 (1.20 to 1.54)	<0.0001
MI[b]	2.38 (2.01 to 2.81)	<0.0001
graft failure[b]	2.89 (2.47 to 3.38)	<0.0001

[a]Results of multivariate Cox hazards analysis, where AHR > 1.00 indicates an increased risk for posttransplantation AF and AHR < 1.00 indicates reduced risk. 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, employment, BMI category, and sensitization; *recipient* pretransplantation histories of hypertension, diabetes, MI, congestive heart failure, peripheral vascular disease, cerebral vascular disease, chronic obstructive pulmonary disease, smoking, and alcohol abuse; *donor* source (deceased *versus* living), death caused by stroke, hypertension history, and cytomegalovirus positivity; degree of donor–recipient HLA matching; induction and maintenance immunosuppression; and year of transplantation (data not shown).

[b]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.

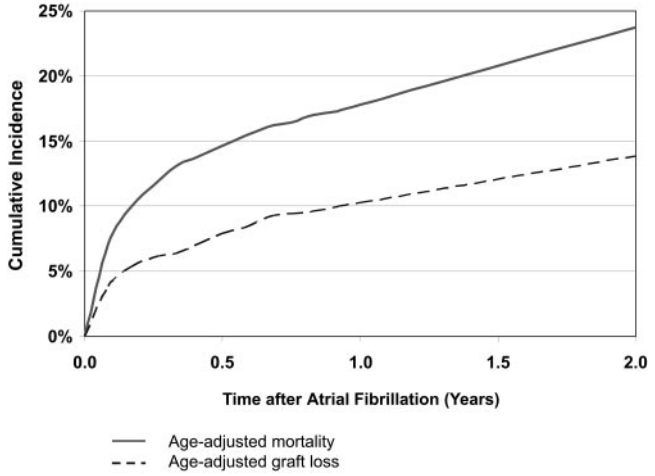

Figure 3. Time course of age-adjusted mortality and death-censored graft loss after diagnosis of new-onset AF after kidney transplantation. Incidence estimates are adjusted to the average age of the study sample.

sistent with known associations of surgical stresses, including anesthesia, excess catecholamine production, and autonomic imbalances with cardiac arrhythmias, especially arrhythmias of atrial origin (26,27). Beyond the early posttransplantation period, the rate of new diagnoses after transplantation declined below the adjusted rate on the waiting list such that cumulative posttransplantation incidence fell below that on the waiting list by approximately 17 mo. Cardiac hypertrophy, a known correlate of arrhythmias in dialysis patients, has been shown to regress over the first 2 yr posttransplantation (28). However, as patients who remain on the waiting list may differ systematically from those who ultimately receive a transplant by factors that are not recorded in the registry, selection may bias the sample of patients who ultimately receive a transplant toward lower cardiac risk. Our observation suggests that transplantation may somewhat reduce but certainly not reverse vulnerability to atrial arrhythmias in the longer term.

The incidence of AF observed in this study was nearly five times that of primary hospitalizations for AF that were reported recently among USRDS registrants during a similar observation period (11). This difference is largely attributable to our inclusion of secondary diagnoses and outpatient events and emphasizes that admissions primarily for AF constitute a minority of presentations. The overall incidence density of AF after transplantation in our study approximated that in the eldest population segment in the Framingham Heart Study (29), demonstrating that along with known concerns about accelerated ischemic and congestive heart disease, arrhythmic cardiac risk is elevated among transplant recipients compared with the general population.

Predictors of AF after Transplantation

The risk for AF increases dramatically with age in the general population (29,30) and after other types of solid-organ transplants (31), perhaps in part because of senile degeneration of the myocardial conduction system. Similarly, we found that age was the strongest risk factor for AF among renal allograft recipients even after adjustment for multiple baseline conditions. Furthermore, risk in the elderly rose most sharply in the first few months after transplantation. These data suggest that elderly transplant recipients warrant close monitoring for AF, particularly early after transplantation.

We identified duration of pretransplantation dialysis as a potentially modifiable risk factor for posttransplantation AF. Patients who are on long-term dialysis are at risk for electrolyte disturbances, and both cardiac dilation and hypertrophy (pro-arrhythmic structural anomalies) have been shown to progress after dialysis initiation (32). This "uremic cardiomyopathy" may be driven by multiple factors, including chronic volume overload, unphysiologic fluid removal volumes during cyclic dialysis sessions, anemia, and uncontrolled hypertension. The observed association of dialysis duration with AF may also in part reflect a surrogate relationship of extended dialysis with the accumulated impacts of unmeasured comorbidities and/or comorbidity severity that advances with time after kidney failure. However, documented improvement in cardiac dimensions after kidney transplantation suggests that superior metabolic and volume status control reverse, at least on a macroscopic scale, components of the myocardial substrate for arrhythmias (28).

Among candidate baseline comorbidities, only coronary artery disease and renal failure from hypertension (a surrogate for long-standing hypertension) were significant correlates of posttransplantation AF in the multivariate model. In contrast, posttransplantation diagnoses of several of these conditions, including hypertension, new-onset diabetes, and myocardial infarction, were significantly associated with subsequent AF. These observations likely have several explanations. Pretransplantation comorbidities have been screened such that they were not deemed severe enough to preclude transplantation eligibility and may be remote to the transplantation event; posttransplantation complications are unscreened and may be more severe. Furthermore, because construction of a time-varying covariate requires that patients first develop the predictor of interest to be in the risk set for the modeled outcome, the denominator is smaller than the full sample and is particularly small close to the model origin (33). This reduced risk set will magnify the early hazard but only if the predictor and the outcome are significantly correlated. The strong observed association of graft failure with subsequent AF may reflect a mechanism similar to that of extended dialysis duration, namely electrolyte disturbances and progressive cardiomegaly. Although we lacked information to determine whether the risk for AF bore a graded response to reduced renal function, the high risk for atrial arrhythmias after graft failure resonates with recent observations that cardioprotective benefits of transplantation are blunted by allograft loss (8,24,34).

Outcomes after Diagnosis of AF

The prognostic significance of AF in ESRD is not defined clearly. In a small cohort study of 190 hemodialysis patients who were followed for up to 1 yr, AF independently predicted thromboembolic complications but not death (5). Although co-

morbid clinical conditions may confound estimates of the mortality implications of cardiac arrhythmias, we observed that after adjustment for a variety of clinical characteristics, patients with posttransplantation AF experienced more than three times the risk for subsequent death as those without this arrhythmia. Although we cannot exclude mediation by an unobserved prognostic factor, potential mechanisms for this association include hemodynamic destabilization and fatal thromboembolic events, which may complicate AF even in the postoperative setting (35,36).

The magnitude of the risk relationship between AF and all-cause mortality in this study was more than six times that estimated in the study of patients who were hospitalized for AF by Abbott *et al.* (11), even after adjustment for a broader list of potentially confounding covariates. This difference suggests that consideration of patients with outpatient and secondary inpatient diagnoses as not having AF transfers their mortality risk to the referent sample. Thus, even outside the inpatient setting, AF after kidney transplantation does not seem to portend a benign prognosis.

We found not only that AF predicted posttransplantation death but also that it independently predicted death-censored graft failure. Loss of "atrial kick" may lead to renal hypoperfusion that is synergistic with ischemic injury from calcineurin inhibitors and, like heart failure, may activate a nephrotoxic cytokine cascade (37). Alternatively, the association may reflect deleterious renal consequences of invasive diagnostic procedures or therapies administered to patients with cardiac dysfunction. Whether attributable to a direct effect or a marker for associated conditions or iatrogenic complications, AF after kidney transplantation is an adverse indictor for graft survival.

Limitations

This study is limited by its retrospective design and our inability to confirm objectively clinically coded diagnoses. We also lacked quantitative information on candidate predictors, including levels of BP, and laboratory values such as hemoglobin and serum creatinine. Description of comorbid conditions as dichotomous variables prevents detection of possible prognostic implications of disease severity. Only immunosuppressive agents but not other medications, such as anticoagulants and antiplatelet agents, were available for study. Because we required Medicare coverage for participation only at the time of transplantation, detection of pretransplantation AF by Medicare claims is subject to underascertainment and may lead to overestimation of new posttransplantation diagnoses. However, we found that our estimates of the incidence of new-onset AF after transplantation were robust to a sensitivity analysis among a subsample with a uniform coverage period for pretransplantation claims ascertainment. 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 consideration of a broad list of clinical covariates.

Conclusion

In this large population-based study, we found that new-onset AF is common after kidney transplantation and is associated with markedly increased risk for death and death-censored graft loss. Elderly transplant recipients faced particularly high risk for AF, as did patients after allograft loss. The current literature has no citations on the use or outcomes of therapies such as anticoagulation in transplant patients with AF. As the renal transplant recipient population grows older, we may anticipate the incidence and prevalence of AF also to increase; thus, appropriate risk stratification and management of this complication will assume greater importance.

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Most patients with ESRD who are maintained on dialysis or with a successful transplant have increased risks for coronary artery disease cardiomyopathy and subsequent mortality. This is particularly true in diabetics. An article by Kasiske *et al*. (pages 900–907) in this month's *JASN* discusses risk factors after transplant for acute myocardial infarction compared to patients on the waiting list.