Outcomes after Kidney Transplantation of Patients Previously Diagnosed with Atrial Fibrillation

Colin R. Lenihan, MB, BCh, BAO[1], **Maria E. Montez-Rath, PhD**[1], **John D. Scandling, MD**[1], **Mintu P. Turakhia, MD, MAS**[2,3], and **Wolfgang C. Winkelmayer, MD, ScD**[1]

[1]Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA

[2]Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA

[3]Veterans Affairs Palo Alto Health Care System, Palo Alto, CA

Abstract

Little is known about the prevalence and outcomes of patients with atrial fibrillation/flutter (AF) who receive a kidney transplant. We identified all patients who had >1 year of uninterrupted Medicare A+B coverage before receiving their first kidney transplant (1996–2009). The presence of pre-transplant AF was ascertained from diagnosis codes in Medicare physician claims. We studied the post-transplant outcomes of death, all-cause graft failure, death-censored graft failure, and stroke using multivariable Cox regression. Of 62,706 eligible first kidney transplant recipients studied, 3794 (6.4%) were diagnosed with AF prior to kidney transplant. Over a mean follow-up of 4.9 years, 40.6% of AF patients and 24.9% without AF died. All-cause and death-censored graft failure were 46.8% and 16.5%, respectively, in the AF group and 36.4% and 19.5%, respectively, in those without AF. Ischemic stroke occurred in 2.8% of patients with and 1.6% of patients without AF. In patients with AF, multivariable-adjusted hazard ratios (95% confidence intervals) for death, graft failure, death-censored graft failure, and ischemic stroke were 1.46 (1.38–1.54), 1.41 (1.34–1.48), 1.26 (1.15–1.37) and 1.36 (1.10–1.68), respectively. Pre-existing AF is associated with poor post-transplant outcomes. Special attention should be paid to AF in pre-transplant evaluation, counseling, and risk stratification of kidney transplant candidates.

Keywords

arrhythmia; end-stage renal disease; risk assessment; organ allocation

Introduction

Atrial fibrillation/flutter (AF) is a common diagnosis that will affect an estimated 15.6 million people in the US by 2050 and is associated with significantly increased risk of embolic stroke and mortality (1–3). AF is a particular problem the dialysis population where its prevalence has increased from 3.5% in 1992 to 10.7% in 2006 and remains associated

Correspondence to: Wolfgang C. Winkelmayer, MD, ScD, Division of Nephrology, Stanford University School of Medicine, 780 Welch Road, Suite 106, Palo Alto, CA 94304, wcw1@stanford.edu.

with a doubling of one-year mortality (4). In dialysis patients, AF is associated with older age and an increased burden of cardiovascular disease. In addition, the benefits of anticoagulation in AF, which are well established in the general population, have not consistently been demonstrated in end stage renal disease (ESRD) (5–7).

Kidney transplantation is the best treatment for ESRD in terms of life expectancy and quality of life (8). However, the survival benefit of transplantation becomes evident only after an initial increase in short-term mortality from surgery. Detailed pre-transplant evaluation is key in identifying candidates that will benefit from renal transplantation with particular focus on the diagnosis and treatment of cardiovascular disease prior to wait listing and transplantation. While the incidence of new AF after kidney transplantation and associated outcomes have been studied, little is known about how patients with *pre-existing* AF will fare after receipt of their kidney transplant (9,10).

The goal of this study was 1) to establish the prevalence of previously diagnosed AF in U.S. ESRD patients undergoing renal transplantation and 2) to determine its association with post-transplant outcomes.

Materials and Methods

Study Population

We identified all adult patients (18 years) in the US Renal Data System who received their first kidney transplant between January 1997 and December 2009. We restricted the cohort to all patients who had 1) uninterrupted Medicare Part A and B coverage (per payor history file) in the year prior to transplant and 2) in whom at least one valid claim was filed to Medicare during that period.

Variable of Interest

Whether patients had been diagnosed with AF prior to the day of their kidney transplant surgery (= index date) was the variable of interest, which was ascertained from all inpatient and outpatient physician billing claims during the 365 days prior to the index date. We considered patients to have been diagnosed with AF if any International Classification of Diseases, 9th revision, codes of 427.3, 427.31, or 427.32 were listed as diagnoses on 1 inpatient or 2 outpatient claims. Such an approach has been used to identify Medicare patients for the National Registry of Atrial Fibrillation (11) and other claims-based research studies of AF (12, 13). This approach has been shown to have a sensitivity of 94%, specificity of 99% and positive predictive value of 97% (14,15).

Patients Characteristics

We ascertained the following characteristics from the USRDS patient, treatment history and transplant files: recipient age (on transplant date), sex, race (white, black, other), cause of ESRD, body mass index (BMI) at time of transplant, dialysis duration and most recent dialysis modality, patient blood type, transplant type (living, standard deceased, expanded criteria deceased, donation after cardiac death), donor age and sex, HLA-match, panel reactive antibody, and cold ischemia time.

We additionally identified the following co-morbidities using the appropriate ICD-9 codes (see Technical Appendix, Supplemental Table S1): diabetes, cancer, coronary artery disease, cerebrovascular disease, alcohol misuse, peripheral vascular disease (PVD), hypertension, valve disease, heart failure, chronic pulmonary disease, and prior solid organ transplant (heart, lung, liver, pancreas). Co-morbidities were ascertained in the 365 day period prior to the date of transplant surgery and were established by at least 1 inpatient or 2 outpatient

claims not on the same day. We also quantified health care utilization in the year prior to transplant by determining whether the patient was in a skilled nursing facility, the number of days spent in hospital, and the number of non-nephrology outpatient visits.

Outcomes

Our outcomes of interest were death from any cause, graft failure, death-censored graft failure, and ischemic stroke. Graft failure was identified from the USRDS patient files and defined as death, need for dialysis or re-transplant. Ischemic stroke was identified from billing claims and was defined by the presence of one inpatient claim with an ICD-9 primary diagnosis code of 433.x1, 434.x1, 436, or 437.1 or by stroke as cause of death. For the outcomes of death and graft failure, patients were censored at end of study, December 31, 2009. For ischemic stroke, patients were censored at end of study, loss of Medicare Parts A and B coverage and at 3 years post-transplant (when most patients under 65 years of age lose their Medicare coverage).

Statistical Analysis

Our cohort was divided according to the presence or absence of AF prior to transplant. Categorical variables were expressed as counts and percentages and continuous variables as medians with an interquartile range. Differences between the two groups were tested using the Chi-squared test for categorical and the Kolmogorov-Smirnov test for continuous variables. Unadjusted incidence rates, defined as the number of events over person-time observed, were calculated for each outcome.

We used multivariate Cox proportional hazards models, stratified by year of transplant, to calculate adjusted hazard ratios (HR) for each outcome. Hazard ratios were generated using three incrementally adjusted models: model 1, adjusted for demographic variables; model 2, additionally adjusted for BMI, comorbidities, healthcare utilization and dialysis history; and model 3, additionally adjusted for transplant related variables. The large sample size and number of outcomes allowed us to present comprehensive models without selecting from the available set specific variables based on significance thresholds or confounding criteria. We used log (− log) survival curves and plots of Loess smoothed scaled Schoenfeld residuals to assess the adequacy of the Cox proportional hazards models. We also analyzed death as a competing risk for both graft loss and ischemic stroke. To do this the same series of Cox proportional hazards models were fit with death as a censoring event. Detailed description of the analysis is available in the Technical Appendix.

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Missing Data

About 42% of patients had at least one variable missing, with the proportion of variables with data missing ranging from less than 1% (recipient race) to 20% (BMI; table 1). To handle the missing data we used standard multiple imputation (MI) techniques (using SAS proc mi) to obtain 9 imputed datasets. One dataset was used for model checking and to the remaining 8 we fitted the stratified Cox proportional hazard models. The results of the 8 fitted models were then combined using the rules described by Roderick and Little (16) (using SAS proc mianalyze). The imputation model included all variables. To help the imputation of BMI at transplant, we also included BMI at time of transplant wait-listing or, if missing, BMI from the Medical Evidence Report, and time between BMI reporting and transplantation. For technical details, see the Technical Appendix.

All estimates are accompanied by their corresponding 95% confidence intervals (CI). Analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC) and R (The R Project for Statistical Computing; Vienna, Austria). The Institutional Review Board of Stanford University approved the study.

Results

We identified 62,706 patients undergoing their first kidney transplant between 1997 and 2009 who met our study inclusion criteria (Figure 1). Of those, 3794 (6.4%) patients were diagnosed with AF prior to transplantation. Patients with atrial fibrillation (AF+) were older and had a higher burden of comorbidities than patients without atrial fibrillation (AF−). Donor age was also higher in patients with AF reflecting the higher number of expanded criteria kidneys performed in this group. Most comorbid conditions, especially cardiovascular ones, were much more prevalent among AF+ patients. Baseline characteristics for the cohort as a whole and stratified according to presence of AF at baseline are shown in Table 1.

During a mean follow-up period of 4.9 years 1539 (40.6%) of AF+ patients and 14,642 (24.9%) of AF− patients died. All-cause graft loss occurred in 1775 (46.8%) in AF+ and 21,466 (36.4%) AF− patients, while death-censored graft failure occurred in 624 (16.5%) in AF+ and 11,482 (19.5%) AF− patients. During a mean follow-up period of 2.2 years, 107 (2.8%) of AF+ patients and 921 (1.6%) of patients AF− patients had an ischemic stroke (all p<0.001; Table 2).

Patient, graft and death-censored graft survival were calculated using the Kaplan-Meier method and are shown in Figure 2. We used multivariable Cox regression to compare the outcomes of death, all-cause graft failure, death-censored graft failure, and stroke in the AF+ and AF− groups, while controlling for important confounding characteristics. We used three different models; model 1 was adjusted for demographic factors only, model 2 for demographics and co-morbidities and model 3 for demographics, co-morbidities and transplant covariates, Figure 3. The estimates of association for all co-variables are shown in the Technical Appendix, Supplemental Table S2.

In the AF+ group, estimated 1- and 5-year patient survival rates were 85.7% (CI, 84.5%− 86.8%) and 59.3% (CI, 57.4% to 61.2%) respectively. In the AF− group, 1- and 5-year patient survival rates were 94.4% (CI, 94.2% to 94.6%) and 80.2% (CI, 79.8% to 80.5%) respectively. The hazard ratio for death in the AF+ group compared to AF− was 2.40 (CI, 2.28 to 2.54), which was attenuated to 1.46 (CI, 1.38 to 1.54) after multivariate adjustment in model 3.

In the AF+ group, estimated 1- and 5-year graft survival rates were 79.4% (CI, 78.1% to 80.7%) and 51.7% (CI, 49.7% to 53.6%) respectively and for the AF− group were 89.1% (CI, 88.9 to 89.4) and 67.6% (CI, 67.2% to 68.1%) respectively. The unadjusted hazard ratio for all-cause graft failure comparing the AF+ to AF− group was 1.76 (CI, 1.68 to 1.85), and 1.41 (CI, 1.34 to 1.48) after adjustment for all observed factors.

In the AF+ group, estimated 1- and 5-year death-censored graft survival rates were 90.9% (CI, 89.9% to 91.8%) and 79.0% (CI, 77.2% to 80.7%) respectively and in the AF− group were 93.8% (CI, 93.6% to 94%) and 80.6% (CI, 80.2% to 81%). The unadjusted hazard ratio for death-censored graft failure comparing the AF+ to AF− group was 1.14 (CI, 1.05 to 1.23), and 1.26 (CI, 1.15 to 1.37) after adjustment.

For post-transplant ischemic stroke, 1- and 3- year incidence estimates, computed using the 1-KM method, were 1.72% (CI, 1.33% to 2.24%) and 4.07% (CI, 3.36% to 4.92%),

respectively, in the AF+ group and 0.72% (CI, 0.65% to 0.80%) and 2.07% (CI, 1.92% to 2.19%), respectively, in the AF− group (Figure 2, Panel D). The ischemic stroke incidence curves crossed immediately (within 30 days) post-transplant violating the proportional hazards assumption, therefore as a sensitivity analysis, we re-fitted the models excluding stroke and death occurring within the first 30 days post-transplant and found a clear separation of the curves. Moreover, hazard ratio estimates from this conditional model did not differ substantially from those utilizing the entire data. The multivariable adjusted HR for stroke was 1.36 (CI, 1.10–1.68) for AF+ patients compared with those without the arrhythmia.

As a sensitivity analysis, we compared results using multiple imputation with a complete case analysis. Complete-case analysis is a commonly used alternative to handling missing data in which only subjects without missing data are utilized for analysis. While complete-case analysis is a simple approach, it does make greater assumptions about missing data than multiple imputation and is generally considered an inferior method (17,18). With the exception of ischemic stroke, the results were very similar for all outcomes. For post-transplant ischemic stroke there is a loss of efficiency due to the loss of 42% of the sample in complete case analysis and the HR are biased towards the null and not significant.

We also analyzed death as a competing risk for both graft loss and ischemic stroke. The same series of models were fitted with death as a censoring event. For both outcomes, the adjusted hazard ratios remained similar and statistically significant. Results from all sensitivity analysis as well as competing risk analysis are available in Supplemental Tables S3–S6 and Supplemental Figure S1 in the Technical Appendix.

Discussion

In our large population of US kidney transplant recipients, pre-existing AF was strongly associated with adverse post-transplant outcomes. To our knowledge, this is the first study to focus on patients with known AF prior to transplant surgery. In the hemodialysis population, AF is associated with increased mortality (4). However, ESRD patients who undergo kidney transplantation are highly selected individuals that have passed through rigorous pre-transplant screening and have in many cases, survived long deceased donor waiting times (19). Nonetheless, we found that post-transplant death, graft failure and ischemic stroke were all significantly more likely in patients with pre-existing AF.

We found patients with AF to be older and have a higher burden of cardiovascular and non-cardiovascular comorbidities. Several of these, including diabetes, heart failure, coronary artery disease and COPD, are independently associated with poor transplant outcomes (20,21). Patients with AF also received more kidneys from expanded criteria donors, a reflection of the older age and higher burden of diabetes in the group, which have a shorter median half-life than standard deceased donor kidneys (22). However, the presence of AF remained strongly associated with poor outcomes even after adjustment for demographics, co-morbidities and transplant variables.

Although AF could simply be a marker of patient frailty or advanced cardiovascular disease not otherwise captured in the dataset, there are several plausible explanations for a causal relationship between AF and poor post-transplant outcomes. It is well-established that AF causes stroke, and CKD has been shown to increase the risk of stroke in AF (7). Furthermore, CKD is a strong predictor of mortality after stroke (23,24). In our study, patients with baseline AF had a 37% higher risk of post-transplant stroke than patients without AF, which is consistent with these prior observations. The association between AF and increased risk of graft failure is consistent with findings in patients without chronic

kidney disease, in whom AF was associated with the new development of chronic kidney disease (first decline of eGFR to <60 mL/min/1.73m^2 and decline of >10 mL/min/1.73m^2 or development of new proteinuria)(25). This association may be explained by a higher risk of recurrent microembolism into the (transplant) kidney in patients with AF.

In addition, the therapies used to treat AF may themselves be harmful. The use of anticoagulation in renal transplant recipients with atrial fibrillation has not been well studied and it is not clear whether their AF management is in line with current guidelines (26). Post-transplant patients may be particularly predisposed to proarrhythmia from antiarrhythmic and rate-control drugs, particularly for drugs that are excreted by the kidney. The risk of proarrhythmia may be heightened from irreversible ventricular hypertrophy and myocardial fibrosis that develops in ESRD pre-transplant (27,28). AF is also associated with increased systemic inflammation (29,30), which along with decreased cardiac output (31), may potentiate decline in renal graft function.

Our study further emphasizes the association of AF with poor outcomes in ESRD patients. The findings complement previous studies that demonstrate increased mortality associated with the arrhythmia in the hemodialysis population and increased mortality and graft loss in patients who develop the arrhythmia post-transplant as previously described by Lentine and colleagues. (4,10). However, prospective studies are necessary to determine whether interventions such as rate or rhythm control will improve outcome.

Our findings also impact the pre-transplant evaluation process. The evaluation is designed to both select patients that will gain a survival advantage from transplant and to maximize the benefit to society of a very scarce resource. While there are relatively few absolute medical contraindications to kidney transplantation, the identification of markers for high-risk candidates is vital to guide the frequency of pre-transplant follow-up, pre-transplant diagnostic testing and decision-making in borderline candidates (19).

Our study has a number of strengths; it was designed to capture medical claims data in the year preceding transplantation in a large population of US ESRD patients. The use of Medicare Parts A and B claims data allows us to ascertain detailed medical and health care utilization data and link it to transplant outcomes through the US Renal Data System. Limitations of the study include the use of diagnosis codes, which likely underestimate the prevalence of AF in the ESRD population because AF may be overlooked in patients with numerous other co-morbidities. In addition, diagnostic coding for AF does not distinguish among persistent, paroxysmal or transient atrial fibrillation, although all forms of atrial fibrillation are associated with increased stroke risk (32,33). As all observational studies, we cannot rule out the presence of residual confounding by unobserved or inaccurately measured characteristics. By limiting our study group to patients with 1 year of Medicare Part A and B coverage we are selecting patients of relatively longer dialysis vintage, which is itself associated with poor transplant outcome (34). In addition, we do not have data on medication use, and specifically anti-coagulation and anti-platelet medications that impact the outcome of atrial fibrillation in the general population (5).

In fact our study serves to highlight the great number of unanswered questions about atrial fibrillation management in renal transplant recipients. The role of anticoagulation, of questionable benefit in the dialysis population [35], has not been studied at all in those ESRD patients that go on to receive a transplant. Practical questions about the optimal peri-operative management of atrial fibrillation and the timing of anticoagulation initiation post-transplant also arise. In addition evidence for the benefit of cardio-protective drugs such ACE inhibitors or angiotensin receptor blockers, which may ameliorate left ventricular

hypertrophy and myocardial fibrosis, both risk factors for AF, is conflicting in kidney transplant recipients [36,37].

In conclusion, we have shown that pre-transplant atrial fibrillation is present in approximately 6% of patients undergoing renal transplantation and is associated with significantly higher post-transplant mortality, graft loss and stroke. Special attention should be paid to patients with AF being evaluated or on the wait-list for kidney transplant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

AF	atrial fibrillation
ESRD	end stage renal disease
CI	confidence interval
HR	hazard ratio
ICD9	International Classification of Diseases, 9th revision
USRDS	US Renal Data System
PVD	peripheral vascular disease
MI	multiple imputation
eGFR	estimated glomerular filtration rate

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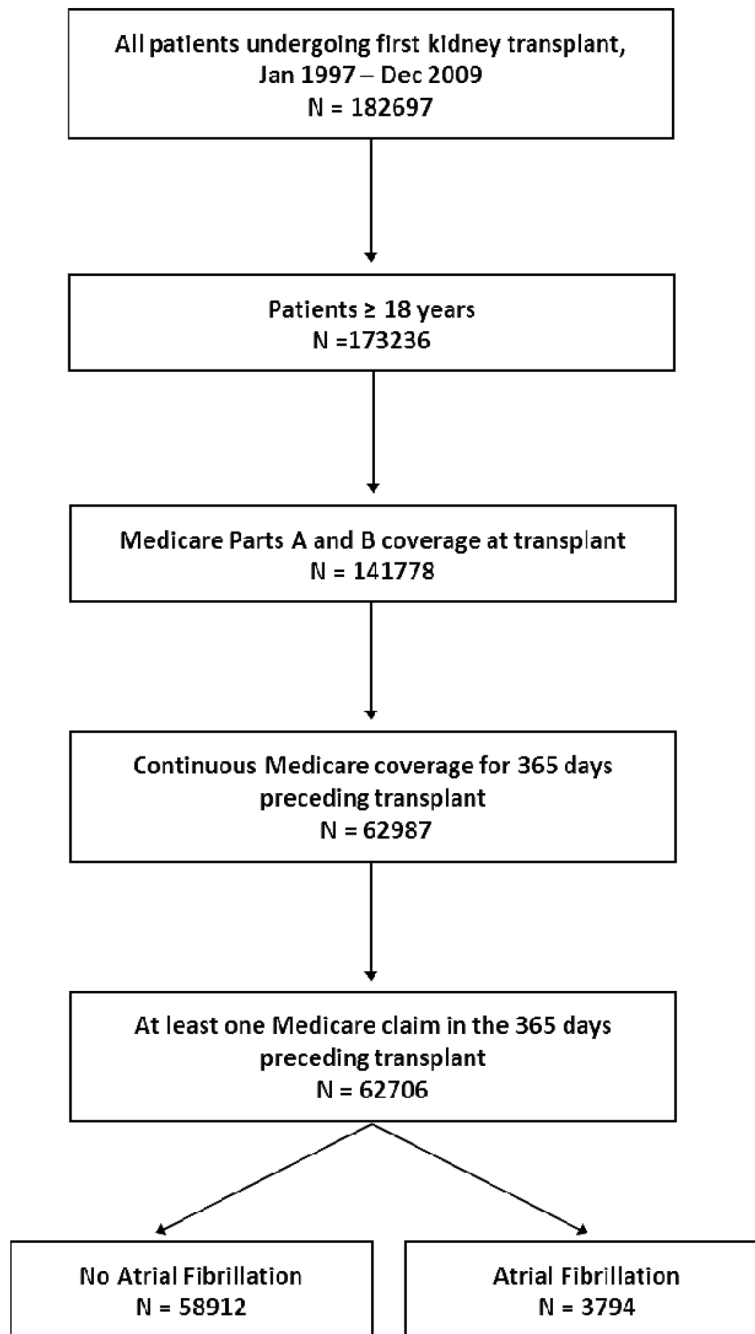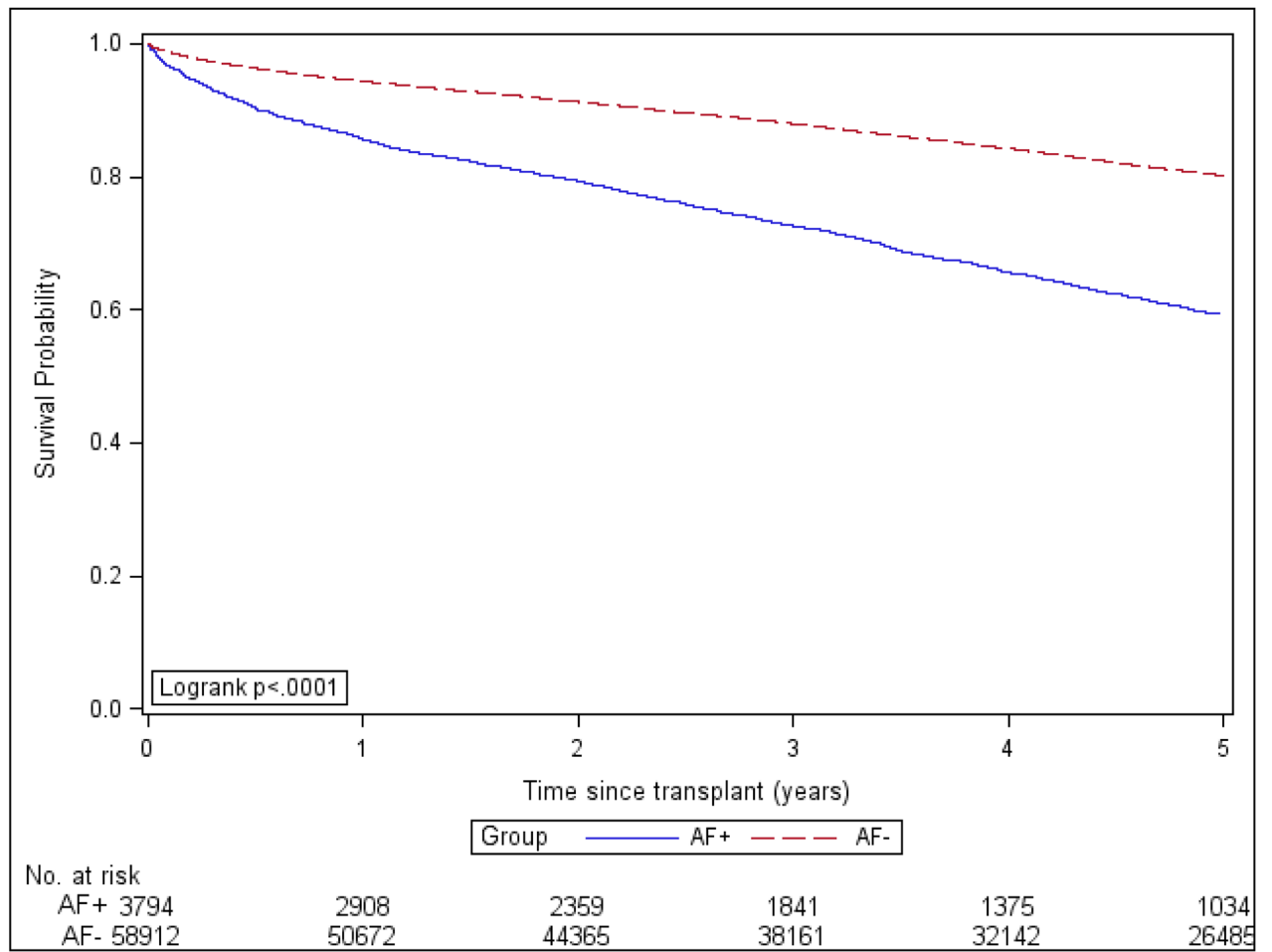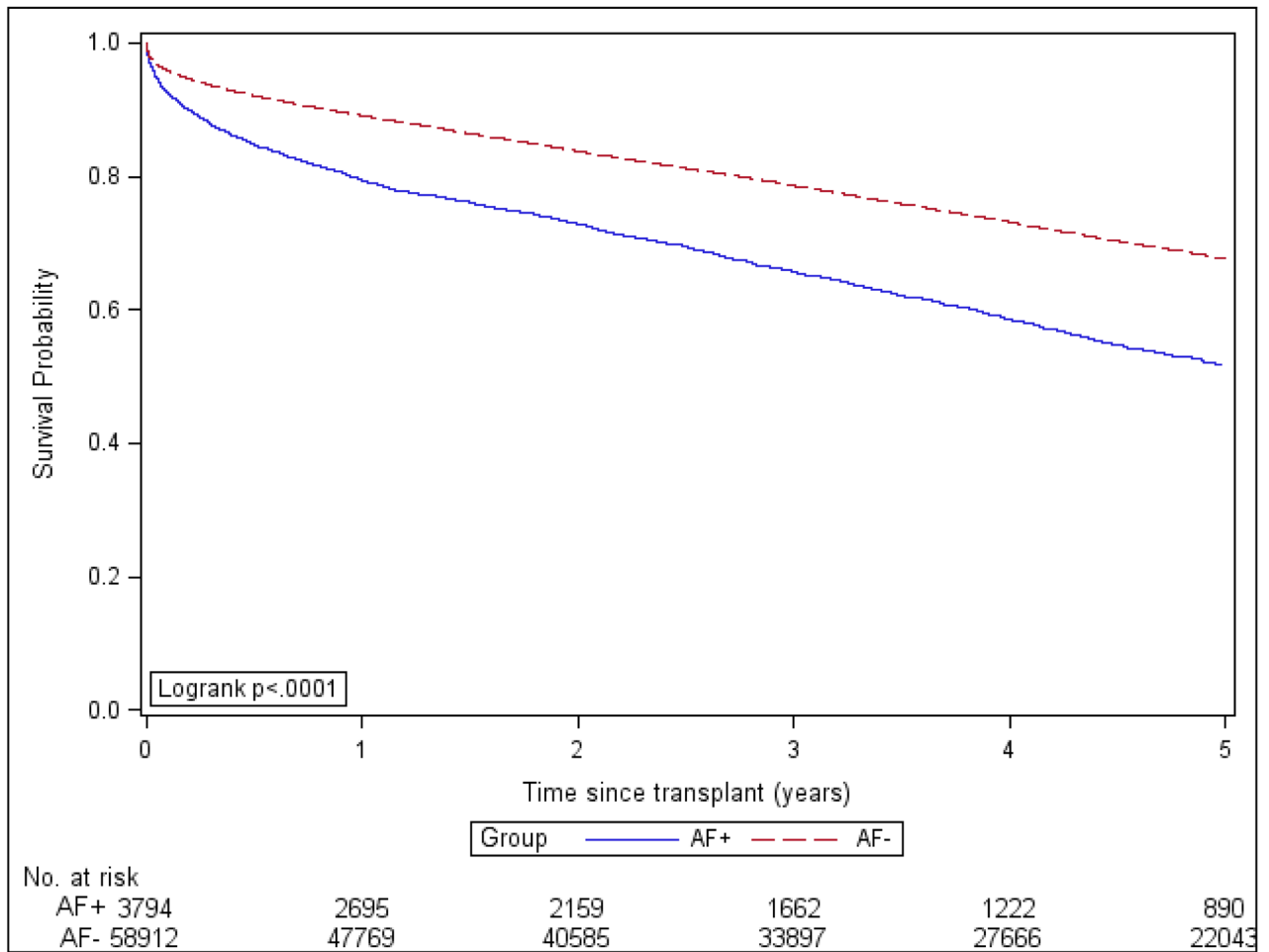
Figure 1.
Cohort Flow Chart

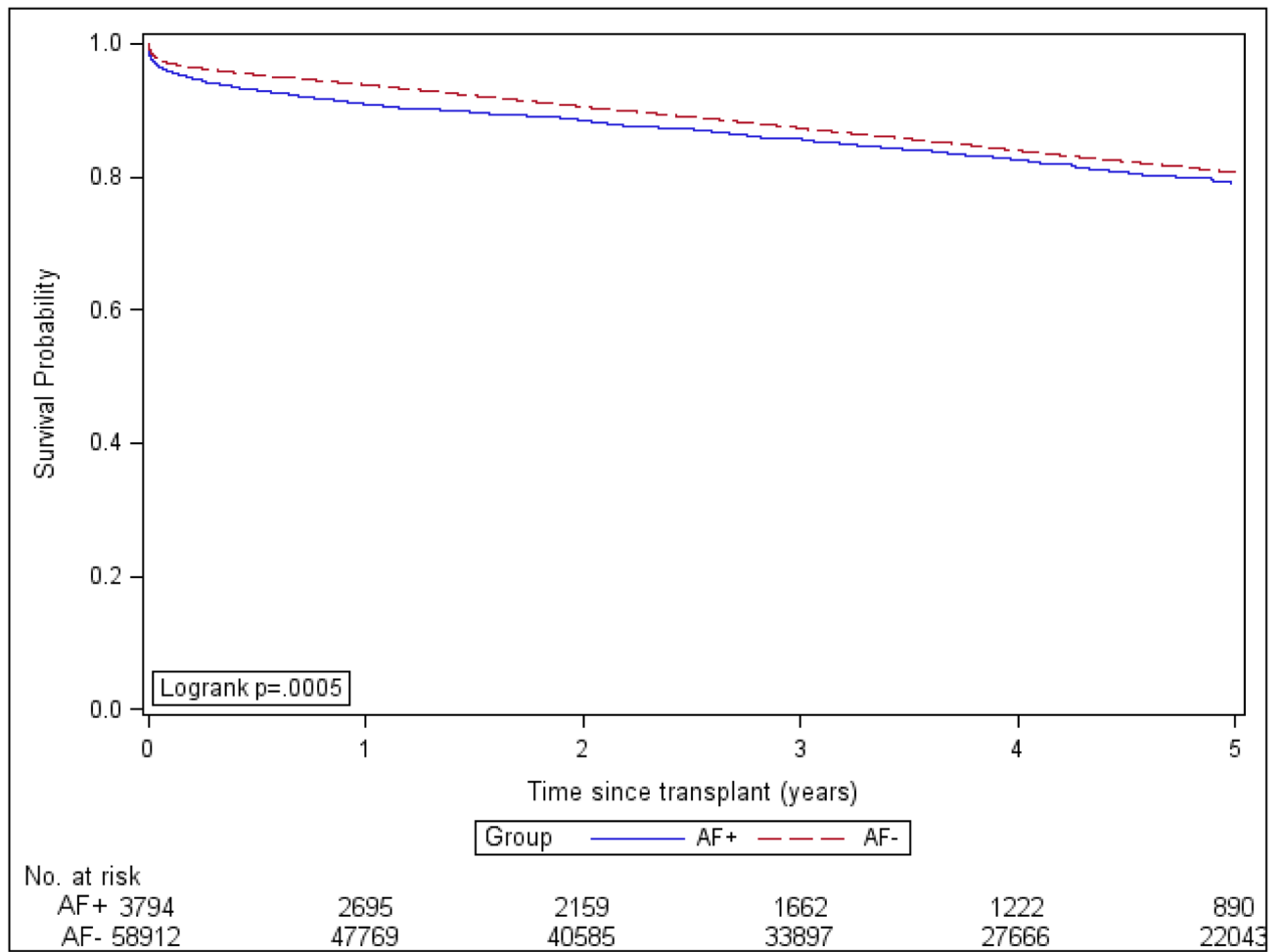## Panel A: Patient Survival

Panel B: Graft Survival

Panel C: Death-Censored Graft

Survival

Panel D: Ischemic Stroke Incidence
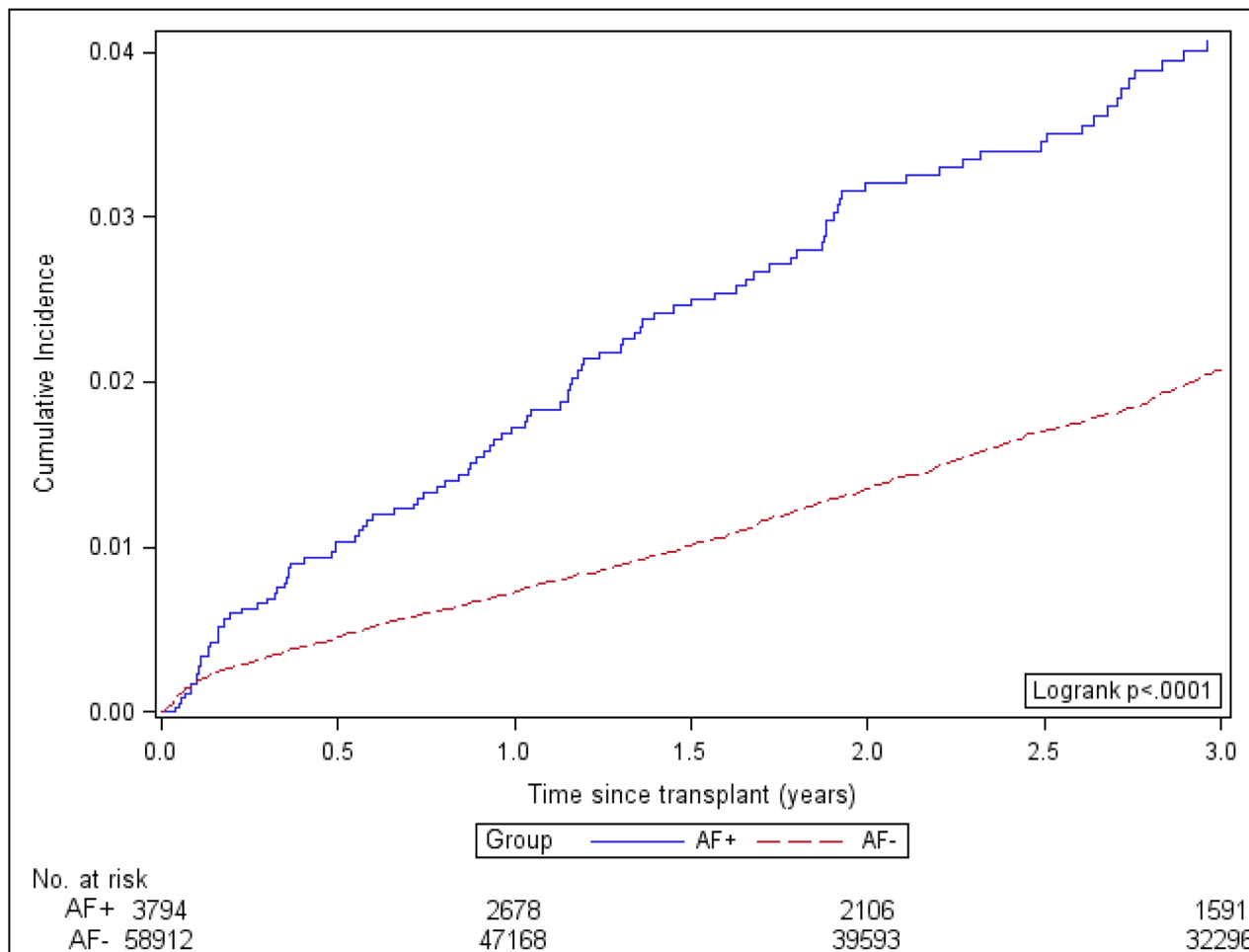
Figure 2. Kaplan-Meier Product Limit Estimates of Study Outcomes
AF+: Patients with atrial fibrillation.
AF−: Patients without atrial fibrillation.
Incidence computed by the Kaplan-Meier method.
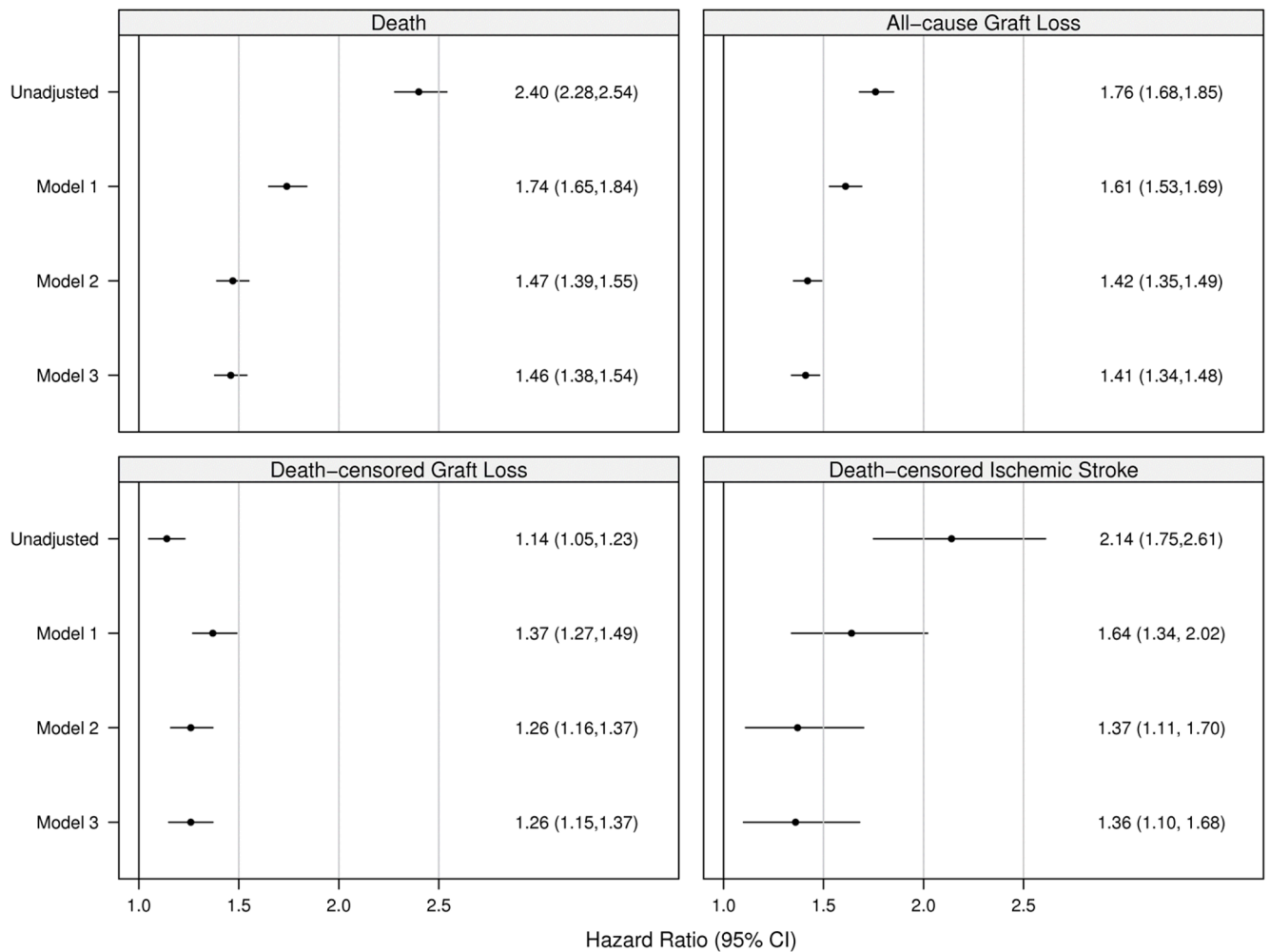
Figure 3. Unadjusted and Adjusted Hazard Ratios for Study Outcomes
Stratified Cox analysis with multiple imputation to handle missing data.
All models stratified by Year of transplant.
Model 1 is adjusted for age, sex, and race.
Model 2 is additionally adjusted for BMI at transplant, cause of ESRD, dialysis vintage, dialysis modality, skilled nursing facility utilization indicator, number of hospital days, number of non-nephrology clinic visits, previous solid organ transplant, and all comorbidities.
Model 3 is additionally adjusted for patient blood type, panel reactive antibody, donor age, donor sex, transplant type, number of HLA mismatches, and cold ischemia time.
Ischemic stroke includes events related to death from any kind of stroke.

Table 1

Characteristics of First Kidney Transplant Recipients, by Presence of Atrial Fibrillation

	All N = 62,706	No Atrial Fibrillation N=58,912	Atrial Fibrillation N=3,794	P-value[1]
Patient Demographics				
Patient age	51 (40–61)	50 (39–60)	60 (52–67)	<0.001
Female	39.3	39.8	31.2	<0.001
Race[2]				
White	57.5	56.7	70.3	<0.001
Black	34.8	35.5	23.9	
Other	7.7	7.8	5.7	
BMI at transplant (kg/m²)				
< 20	2.0	2.0	1.6	<0.001
20– 25	27.7	28.0	23.6	
26–30	26.7	26.6	29.1	
>30	22.9	22.6	27.0	
Missing	20.7	20.8	18.8	
Cause of ESRD				
Diabetes	31.6	31.4	33.9	<0.001
Hypertension	24.3	24.2	25.4	
Glomerulonephritis	25.0	25.2	21.1	
Other	18.2	18.1	18.6	
Missing	1.0	1.0	1.1	
Dialysis Vintage (years)				
< 2.5 years	26.2	26.1	26.7	0.01
2.5 – 5 years	43.6	43.7	41.4	
> 5 years	30.3	30.1	31.9	
Dialysis Modality				
Hemodialysis	85.7	85.4	90.9	<0.001
Peritoneal Dialysis	14.2	14.5	8.9	
Missing	0.2	0.2	0.2	
Skilled Nursing Facility Utilization	2.5	2.2	7.0	<0.001
Hospital days (N)	4 (2–10)	4 (2–9)	10 (4–20)	<0.001
Non-nephrology clinic visits (N)	18 (9–30)	17 (9–29)	27 (16–42)	<0.001
Comorbidities				
Diabetes	42.3	39.3	49.0	<0.001
Cancer	3.7	3.3	6.0	<0.001
Coronary artery disease	11.8	9.2	24.0	<0.001
Cerebrovascular disease	8.4	7.2	16.2	<0.001
Cerebral hemorrhage	0.5	0.5	1.2	<0.001
Alcohol	1.1	0.8	1.0	0.12
Tobacco	6.3	4.5	5.0	0.23
PVD	16.6	13.6	26.6	<0.001

	All N = 62,706	No Atrial Fibrillation N=58,912	Atrial Fibrillation N=3,794	P-value[1]
Hypertension	95.4	80.5	95.0	<0.001
Valve disease	12.6	9.7	29.8	<0.001
Heart failure	22.8	18.1	44.9	<0.001
Chronic pulmonary disease	13.0	10.3	22.9	<0.001
Previous Solid Organ Transplant				
Heart transplant	0.6	0.6	1.0	<0.001
Lung transplant	0.1	0.1	0.4	<0.001
Liver transplant	0.9	0.8	1.5	<0.001
Pancreas transplant	0.4	0.4	0.2	0.03
Patient blood type				
O	48.5	48.6	45.7	<0.001
A	33.0	32.8	37.1	
B	14.6	14.7	13.0	
AB	3.8	3.7	4.1	
Missing	0.1	0.1	0.1	
Panel reactive antibody				
0–10%	65.2	65.2	67.5	0.001
11–80%	18.6	18.6	18.3	
>80%	6.3	6.3	6.0	
Missing	9.9	10.0	8.2	
Transplant Characteristics				
Donor age	39 (24–51)	39 (24–50)	43 (28–53)	<0.001
Missing	7.2	7.2	6.1	
Donor Gender				
Female	43.5	43.4	44.7	0.03
Missing	0.2	0.2	0.1	
Transplant type				
Living donor	16.6	16.5	17.6	<0.001
Standard deceased donor	62.5	62.7	58.2	
Expanded criteria donor	8.6	8.4	11.7	
Donation after cardiac death	5.3	5.2	6.6	
Missing	7.2	7.3	5.9	
Number HLA mismatches				
0	8.7	8.6	10.0	<0.001
1–3	26.2	26.2	25.6	
4–6	59.0	58.9	60.2	
Missing	6.1	6.3	4.3	
Cold ischemia time (hours)				
<10	20.2	20.1	21.0	<0.001
10 – 23	41.0	41.0	40.7	
> 23	21.9	21.8	23.5	

	All N = 62,706	No Atrial Fibrillation N=58,912	Atrial Fibrillation N=3,794	P-value[1]
Missing	17.0	17.1	14.8	

All values are presented as percent or median (interquartile range).

[1] p-values based on Chi-square tests for categorical variables and Kolmogorov-Smirnov test for continuous variables.

[2] Fourteen patients had missing race all belonging to the No Atrial Fibrillation group.

Table 2

Follow-up and Study Outcomes

Outcome	No Atrial Fibrillation N=58,912	Atrial Fibrillation N=3,794
Death		
Number of events	14,642	1,539
Person-time at risk (years)	292,976	13,403
Incidence rate (events/100 person-years)	4.998	11.482
All cause graft loss		
Number of events	21,446	1,775
Person-time at risk (years)	254,538	12,052
Incidence rate (events/100 person-years)	8.43	14.73
Death-censored graft loss		
Number of events	11,482	624
Person-time at risk (years)	254,538	12,052
Incidence rate (events/100 person-years)	4.51	5.18
Death-censored Ischemic stroke [1]		
Number of events	921	107
Person-time at risk (years)	131,126	7336
Incidence rate (events/100 person-years)	0.70	1.46

[1] Ischemic stroke includes non-fatal events and death from any type of stroke