Kidney Medicine

Dialysis Modality, Transplant Characteristics, and Incident Atrial Fibrillation After Kidney Transplant: An Observational Study Using USRDS Data

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Rationale & Objective: Atrial fibrillation is the most common arrhythmia and is increasing in prevalence. The prevalence of atrial fibrillation is high among patients receiving dialysis, affecting ~21.3% of the patients receiving hemodialysis and 15.5% of those receiving peritoneal dialysis. The association of previous dialysis modality with incident atrial fibrillation in patients after receiving their first kidney transplant has not been studied.

Study Design: We used the United States Renal Data System to retrospectively identify adult, Medicare-insured patients who received their first kidney transplant between January 1, 2005, and September 30, 2012 and who had not previously been diagnosed with atrial fibrillation.

Setting & Participants: The study included 43,621 patients who were aged 18 years older when receiving a first kidney transplant between January 1, 2005, and September 30, 2012 and whose primary payer was Medicare (parts A and B) at the time of transplantation and the 6 months preceding it.

Exposure: Dialysis modality used before transplant.

Outcome: Time to incidence of atrial fibrillation up to 3 years posttransplant.

Analytical Approach: Multivariable Cox regression was used to estimate HRs.

Results: Of 43,621 patients, 84.9% received hemodialysis and 15.1% received peritoneal dialysis before transplant. The mean ± SD age was 51 ± 13.6 years; 60.8% were male, 55.6% White, and 35.8% Black race. The mean dialysis vintage was 4.3 ± 2.8 years. Newly diagnosed atrial fibrillation after kidney transplant occurred in 286 patients (during 15,363 person-years) who had received peritoneal dialysis and in 2,315 patients (during 83,536 person-years) who had received hemodialysis. After multivariable adjustment, atrial fibrillation was 20% (95% CI, 4%-38%) more likely in those who had been receiving hemodialysis versus peritoneal dialysis, regardless of whether death was considered a competing risk or a censoring event. Each year of pretransplant dialysis vintage increased the risk of posttransplant atrial fibrillation by 6% (95% CI, 3%-9%).

Limitations: Residual confounding; data from billing claims does not specify the duration of atrial fibrillation or whether it is valvular.

Conclusions: Pretransplant hemodialysis, as compared with peritoneal dialysis, was associated with higher risk of newly diagnosed atrial fibrillation after a first kidney transplant.

Visual Abstract included

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A close association exists between kidney disease and cardiovascular disease.[1] Patients diagnosed with chronic kidney disease (CKD) are at higher risks of coronary disease, heart failure, cerebrovascular disease, peripheral artery disease, and arrhythmias as compared with patients without CKD, and this risk increases at more advanced stages of CKD.[2] Atrial fibrillation (AF) is the most common arrhythmia in the general population and is increasing in prevalence.[3] The prevalence of AF is higher in the kidney failure population than in the general population and its incidence increases with lower estimated glomerular filtration rate and increasing proteinuria.[4,5] Individuals with kidney failure receiving dialysis are at particularly high risk of AF where as many as 1 in 3 patients receiving hemodialysis had an episode of AF during 6 months of rhythm monitoring using loop recorder devices.[6] Patients newly diagnosed with AF are at elevated risk of ischemic stroke and mortality, especially soon after AF diagnosis.[7,8] The risk of developing AF differs between dialysis modalities: patients receiving hemodialysis have higher AF incidence than those receiving peritoneal dialysis, which is most pronounced in the first 90 days after dialysis initiation.[9,10]

Patients selected to undergo kidney transplantation have a lower burden of AF than that which has been reported for the broader population receiving dialysis, which is reflective of the selection process toward generally healthier patients satisfying appropriate criteria to be suitable candidates for transplantation; one US study found that only 6.4% of kidney transplant recipients had been diagnosed with AF before their transplant.[11] Although kidney transplant recipients enjoy reduced longer-term cardiovascular mortality compared with patients with kidney failure receiving dialysis,[12] cardiovascular disease remains the leading cause of death and accounts for 30%-50% of mortality after kidney transplantation.[13] New-onset AF occurs in 7% of kidney transplant recipients in the first 3 years after transplantation,[14] occurring more

PLAIN-LANGUAGE SUMMARY

New-onset atrial fibrillation (AF) occurs in 7% of kidney transplant recipients in the first 3 years posttransplantation. We conducted this study to determine whether pretransplant dialysis modality was associated with posttransplant AF. We identified 43,621 patients; 84.9% used hemodialysis and 15.1% used peritoneal dialysis pretransplant. Multivariable Cox regression was used to estimate hazard ratios. We found that patients receiving hemodialysis pretransplant were at 20% increased risk of developing posttransplant AF as compared with patients receiving peritoneal dialysis. As our understanding of transplant-specific risk factors for AF increases, we may be able to better risk-stratify transplant patients and develop monitoring and management strategies that can improve outcomes.

commonly in the peritransplant period.[15] The association of pretransplant dialysis modality with incident AF in patients receiving their first kidney transplant has not been studied and might represent an unexplored risk factor on top of other previously identified risk factors.[16] We conducted this study to determine whether pretransplant dialysis modality, specifically hemodialysis versus peritoneal dialysis, was associated with risk of posttransplant AF.

METHODS

Data Sources

We used information procured by the US Renal Data System (USRDS), the national registry of all persons with kidney failure who receive regularly scheduled dialysis or a kidney transplant in the United States. The USRDS standard analytical files contain all billing claims submitted to the Centers for Medicaid & Medicare Services (CMS) for services covered through fee-for-service Medicare (parts A, B, and D) and baseline information collected in forms that are mandated to be submitted regardless of insurance status (medical evidence report; form CMS-2728). It also contains detailed transplant-related information provided by the United Network for Organ Sharing. Dates of death and the presumed cause(s) of death as reported in the end-stage renal disease Death notification (form CMS-2746) are also recorded. The dialysis modality is recorded in a detailed treatment history file.

Cohort Selection

From the USRDS, we retrospectively identified patients who were aged 18 years older when receiving a first kidney transplant between January 1, 2005, and September 30, 2012 and further restricted the sample to patients whose primary payer was Medicare (parts A and B) at the time of transplantation and during the 6 months preceding it (Fig 1). We excluded patients who had simultaneous kidney-pancreas transplant. We excluded patients with a diagnosis of AF (International Classification of Diseases, Ninth Revision: 427.3#, where # could be any number or missing) during the 2 years before their kidney transplant.

Outcome: Time to Posttransplantation AF

Patients were followed from the date of transplantation until the earliest occurrence of death, graft failure, loss of Medicare fee-for-service coverage, or 3 years after transplantation. Graft failure, defined as the return to maintenance dialysis or retransplant, was identified from the USRDS patient file and was treated as a censoring event.

Newly diagnosed AF postkidney transplantation was identified by a single International Classification of Diseases, Ninth Revision code 427.3# (# being any number, or missing entirely) from any inpatient claim, or from any outpatient claim provided a second inpatient or outpatient code was subsequently present.

Exposure of Interest: Dialysis Modality Before Kidney Transplant

Modality of kidney replacement therapy at each point in time is a predefined variable in the USRDS. We recorded the type and duration of the most recently used dialysis modality before kidney transplant. We categorized individuals receiving center hemodialysis, center-self

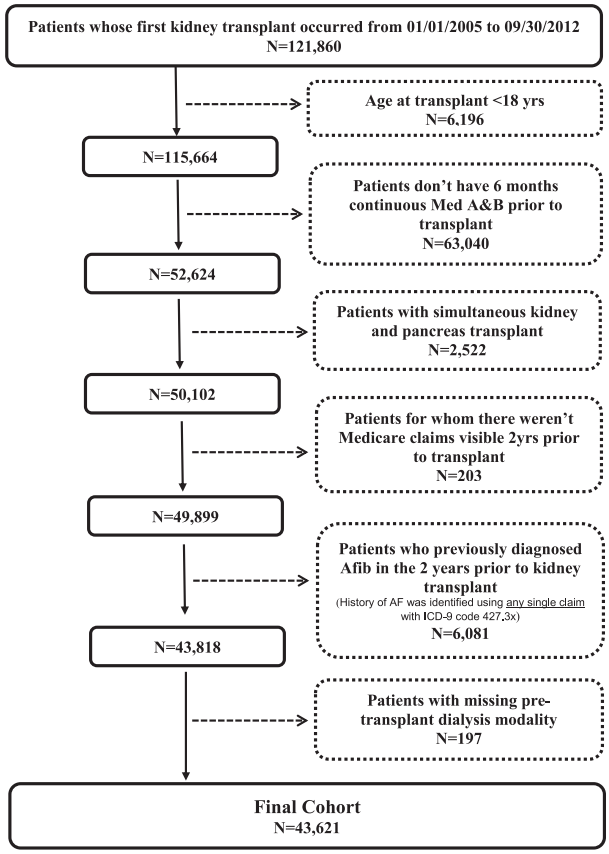

Figure 1. Flow chart of cohort selection.

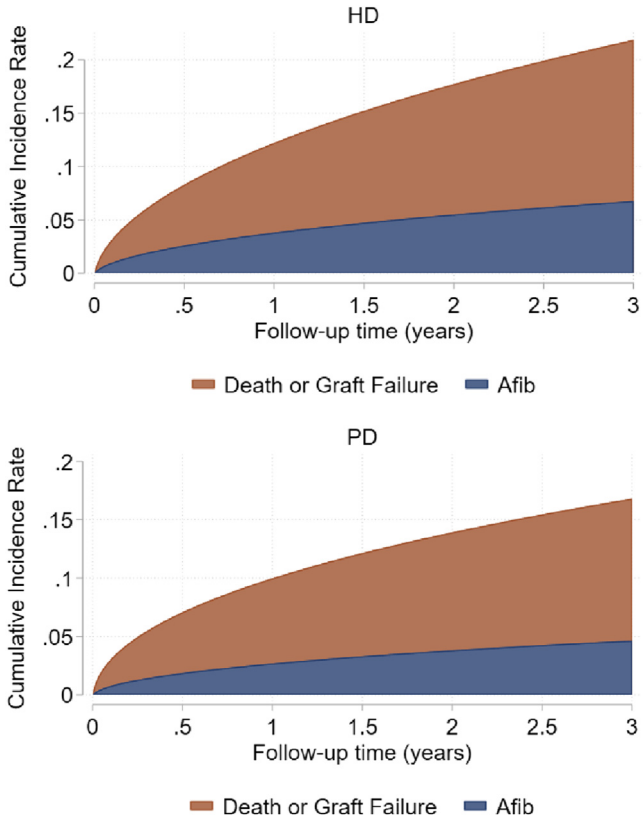

Figure 2. Three-year cumulative incidences of atrial fibrillation and death or graft failure in patients receiving peritoneal dialysis (PD) or hemodialysis (HD) before kidney transplant.

hemodialysis, or home hemodialysis as hemodialysis and those using continuous ambulatory peritoneal dialysis, continuous cyclic peritoneal dialysis, or another type of peritoneal dialysis as peritoneal dialysis.

Other Patient Characteristics

All characteristics were ascertained from standard analytical files in the USRDS and ascertained at the time of or during the 6-month period preceding the first transplant. Several comorbid conditions (from corresponding diagnoses in medical claims within 2 years before baseline), and health care utilization parameters 6 months before the baseline as listed in Table 1. We also recorded the time between first treatment for kidney failure and kidney transplant (vintage). Several standard characteristics relevant for kidney transplantation were also ascertained, including recipient characteristics (blood type and panel-reactive antibodies), donor source (living vs deceased), donor characteristics (age and sex), any history of previous nonkidney solid organ transplant, and HLA-mismatch and cold ischemia time.

Statistical Analysis

We described baseline characteristics among all patients and by dialysis modality, hemodialysis versus peritoneal dialysis, using means and standard deviations (SDs) or medians and 25th and 75th percentiles for continuous variables and counts and percent for categorical variables. Patients were followed for incident AF from the date of transplantation until the earliest occurrence of death, graft failure, loss of Medicare fee-for-service coverage, or 3 years after transplantation. We computed unadjusted incidence rates of AF by pretransplant modality type. We graphed cumulative incidence function plots to compare 3-year cumulative incidence of AF, graft failure, and death by pretransplant modality type. We estimated unadjusted and incrementally adjusted hazard ratios (HRs) for AF by pretransplant dialysis modality (with peritoneal dialysis being the reference). Estimates were adjusted in 4 nested multivariable models. All models were stratified by the era of transplant: 2005-2006, 2007-2008, 2009-2010, and 2011-2012. Models 1–4 were incrementally adjusted as follows: model 1—modality type; model 2—model 1 plus age at time of transplant, sex, race, body mass index, cause of kidney failure, dialysis vintage, and duration of last pretransplant dialysis modality; model 3—model 2 plus comorbid conditions, health care utilization metrics (nursing home stay, number of hospital days, and number of nonnephrology clinic visits), and previous nonkidney solid organ transplant status and; model 4—model 3 plus transplant characteristics. The primary analysis treated graft failure and death as a censoring event to compute cause-specific HRs. A secondary analysis treated graft failure and death as a competing risk and generated fine and gray subdistribution HRs (Table S1, Table S2, and Table 2).[17] We examined the correlation of the scaled Schoenfeld residuals with time and found no evidence that the log-hazard ratio changed with follow-up time for any of the variables included in model 4 (Schoenfeld test global $P > 0.05$).

Missing Data

In the final study cohort, 22% of patients had at least 1 variable missing. Calculated panel-reactive antibody titer was the variable with the most observations missing (15% of the cohort). Data were assumed to be missing at random and handled using multiple imputation by fully conditional specification as implemented in SAS. In addition to the exposure and all covariates included in the analysis model, the imputation model also included the event indicator and the Nelson-Aalen estimator of the cumulative marginal hazard. Imputation models were stratified by treatment modality, and 23 data sets were generated.[18,19] Imputation models were run separately for the cause-specific and fine and gray subdistribution model analyses.[19,20] The analyses models were run on each imputed data set separately and coefficients and corresponding standard errors were combined using the Rubin's rules.[21]

The study was approved by institutional review boards at Stanford University (#51697) and at Baylor College of Medicine (H-36408), which waived the requirement for informed consent, and a Data Use Agreement with the National Institutes of Diabetes and Digestive and Kidney Diseases was in place. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc), R version 3.1.2, and Stata MP,

Table 1. Baseline Characteristics of US Patients who Underwent Their First Kidney Transplant Between 2005 and 2012, Altogether and Stratified by Pretransplant Dialysis Modality

Baseline Characteristics	All N = 43,621	Hemodialysis n = 37,055	Peritoneal Dialysis n = 6,566
Female (%)	17,116 (39.2%)	13,945 (37.6%)	3,171 (48.3%)
Age (y)			
Mean ± SD	51.1 ± 13.6	51.4 ± 13.4	49.2 ± 14.3
Median (IQR)	52.0 (41.0-62.0)	53.0 (42.0-62.0)	50.0 (39.0-60.0)
Race			
White	24,274 (55.6%)	20,045 (54.1%)	4,229 (64.4%)
Black	15,629 (35.8%)	13,989 (37.8%)	1,640 (25.0%)
Other	3,718 (8.5%)	3,021 (8.2%)	697 (10.6%)
Cause of kidney failure			
Diabetes	13,226 (30.3%)	11,887 (32.1%)	1,339 (20.4%)
Hypertension	11,152 (25.6%)	9,643 (26.0%)	1,509 (23.0%)
Glomerulonephritis	10,246 (23.5%)	8,136 (22.0%)	2,110 (32.1%)
Other	8,868 (20.3%)	7,281 (19.6%)	1,587 (24.2%)
Year of kidney failure			
2005-2006	11,260 (25.8%)	9,531 (25.7%)	1,729 (26.3%)
2007-2008	11,205 (25.7%)	9,606 (25.9%)	1,599 (24.4%)
2009-2010	11,419 (26.2%)	9,731 (26.3%)	1,688 (25.7%)
2011-2012	9,737 (22.3%)	8,187 (22.1%)	1,550 (23.6%)
BMI at transplant (kg/m^2)			
Mean ± SD	27.9 ± 5.2	27.9 ± 5.2	27.6 ± 5.1
Median (IQR)	27.5 (24.0-31.6)	27.6 (24.0-31.6)	27.3 (23.8-31.2)
<18.5	865 (2.0%)	716 (1.9%)	149 (2.3%)
18.5-24.9	12,927 (29.6%)	10,919 (29.5%)	2,008 (30.6%)
25-29.9	14,716 (33.7%)	12,436 (33.6%)	2,280 (34.7%)
≥30	14,407 (33.0%)	12,359 (33.4%)	2,048 (31.2%)
Dialysis vintage (time since initiation of dialysis, y)			
Mean ± SD	4.3 ± 2.8	4.5 ± 2.8	3.7 ± 2.4
Median (IQR)	3.9 (2.4-5.6)	4.0 (2.5-5.7)	3.4 (1.9-4.8)
<2.5	11,579 (26.5%)	9,384 (25.3%)	2,195 (33.4%)
2.5-5	18,031 (41.3%)	15,125 (40.8%)	2,906 (44.3%)
5-9	11,507 (26.4%)	10,215 (27.6%)	1,292 (19.7%)
≥9	2,504 (5.7%)	2,331 (6.3%)	173 (2.6%)
Duration of last dialysis modality (y)			
Mean ± SD	3.8 ± 2.6	4.0 ± 2.7	2.7 ± 1.9
Median (IQR)	3.4 (1.9-5.1)	3.6 (2.1-5.3)	2.4 (1.2-3.8)
<2.5	15,293 (35.1%)	11,866 (32.0%)	3,427 (52.2%)
2.5-5	16,985 (38.9%)	14,609 (39.4%)	2,376 (36.2%)
5-9	9,604 (22.0%)	8,895 (24.0%)	709 (10.8%)
≥9	1,739 (4.0%)	1,685 (4.5%)	54 (0.8%)
Comorbid conditions			
Diabetes mellitus	19,219 (44.1%)	17,142 (46.3%)	2,077 (31.6%)
Alcohol dependence	554 (1.3%)	518 (1.4%)	36 (0.5%)
CAD	13,026 (29.9%)	11,624 (31.4%)	1,402 (21.4%)
COPD	6,745 (15.5%)	5,895 (15.9%)	850 (12.9%)
CVD	2,960 (6.8%)	2,646 (7.1%)	314 (4.8%)
Cerebral bleed	328 (0.8%)	299 (0.8%)	29 (0.4%)
Cancer	2,372 (5.4%)	2,077 (5.6%)	295 (4.5%)
Hypertension	39,813 (91.3%)	34,151 (92.2%)	5,662 (86.2%)
VHD	5,970 (13.7%)	5,362 (14.5%)	608 (9.3%)
PVD	8,022 (18.4%)	7,417 (20.0%)	605 (9.2%)
Liver disease	6,338 (14.5%)	5,658 (15.3%)	680 (10.4%)
Tobacco use	3,493 (8.0%)	3,074 (8.3%)	419 (6.4%)
Arrhythmia	1,895 (4.3%)	1,707 (4.6%)	188 (2.9%)

(Continued)

Table 1 (Cont'd). Baseline Characteristics of US Patients who Underwent Their First Kidney Transplant Between 2005 and 2012, Altogether and Stratified by Pretransplant Dialysis Modality

Baseline Characteristics	All N = 43,621	Hemodialysis n = 37,055	Peritoneal Dialysis n = 6,566
Heart failure	11,000 (25.2%)	10,135 (27.4%)	865 (13.2%)
Previous solid organ transplant	929 (2.1%)	847 (2.3%)	82 (1.2%)
Patient blood type			
O	20,822 (47.7%)	17,690 (47.7%)	3,132 (47.7%)
A	14,289 (32.8%)	12,073 (32.6%)	2,216 (33.7%)
B	6,415 (14.7%)	5,487 (14.8%)	928 (14.1%)
AB	1,775 (4.1%)	1,527 (4.1%)	248 (3.8%)
Living donation	8,489 (19.5%)	6,988 (18.9%)	1,501 (22.9%)
Donor characteristics			
Age (y)			
Mean ± SD	39.3 ± 15.8	39.5 ±15.7	38.5 ± 16.0
Median (IQR)	41.0 (27.0-51.0)	41.0 (27.0-52.0)	40.0 (26.0-51.0)
Female donor	19,234 (44.1%)	16,284 (43.9%)	2,950 (44.9%)
HLA mismatch			
0	3,241 (7.4%)	2,720 (7.3%)	521 (7.9%)
1-3	9,919 (22.7%)	8,302 (22.4%)	1,617 (24.6%)
4-6	29,656 (68.0%)	25,336 (68.4%)	4,320 (65.8%)
Panel-reactive antibody titer, mean ± SD	15.6 ± 27.7	15.6 ± 27.7	15.6 ± 27.8
Median (IQR)	0.0 (0.0-16.0)	0.0 (0.0-16.0)	0.0 (0.0-16.0)
Cold ischemia time (hrs), mean ± SD	15.5 ± 10.7	15.6 ± 10.7	14.4 ± 10.5
Median (IQR)	15.0 (8.0-21.6)	15.0 (8.2-22.0)	14.0 (6.3-21.0)
Nursing home stay	448 (1.0%)	418 (1.1%)	30 (0.5%)
Hospital days, mean ± SD	3.3 ± 5.5	3.3 ± 5.7	3.1 ± 4.7
Hospital days, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	1.0 (1.0-2.0)
Nonnephrology clinic visits, mean ± SD	14.9 ± 13.3	15.2 ± 13.4	13.3 ± 12.7
Nonnephrology clinic visits, median (IQR)	12.0 (6.0-20.0)	12.0 (6.0-21.0)	10.0 (5.0-18.0)

Note: Several variables had incomplete data, specifically the proportion of observations missing the following variables were: sex (<0.1%); cause of kidney failure (0.3%); body mass index (1.6%); blood type (0.7%); donor type (0.7%); donor age (0.7%); donor sex (0.7%); HLA mismatch (1.8%); calculated panel-reactive antibody titer (15.0%); cold ischemia time (8.1%); and living donation (0.7%).
Abbreviation: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HLA, human leukocyte antigen; IQR, interquartile range; PAD, peripheral arterial disease; SD, standard deviation; VHD, valvular heart disease.

version 17.1 (StataCorp). Significance was at 2-sided $\alpha = 0.05$.

RESULTS

Study Cohort

We identified 43,621 patients; 37,055 (84.9%) received hemodialysis and 6,566 (15.1%) received peritoneal dialysis before kidney transplant. The mean ± SD age was 51 ± 13.6 years; 26,505 (60.8%) were male, 24,274 (55.6%) were identified as White, and 15,629 (35.8%) as Black, 14,407 (33%) were obese, and 13,226 (30.3%) had diabetes as their reported cause of kidney failure (Table 1). Heart failure was identified in 11,000 (25.2%), whereas 13,026 (29.9%) had coronary artery disease, and 1,895 (4.3%) had been diagnosed with arrhythmias other than AF. The mean dialysis vintage was 4.3 ± 2.8 years. Previous nonkidney solid organ transplantation was reported in 929 (2.1%) patients. Almost half of the transplant recipients had O as their blood type (20,822, 47.7%). Only 8,489 (19.5%)

Table 2. Association of the Pretransplant Modality and Incident AF Posttransplantation

Dialysis Modality (Type of HR)	Person-Y	Persons With Incident AF	HR (95% CI) Model 1	Model 2	Model 3	Model 4
Peritoneal dialysis	15,363	286	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Hemodialysis (cause-specific HR)	83,536	2,315	1.47 (1.30-1.66)	1.27 (1.12-1.44)	1.14 (1.00-1.29)	1.20(1.04-1.38)

Note: Model 1—calendar year, model 2—model 1 + age at time of transplant, sex, race, BMI, cause of kidney failure and modality duration and dialysis vintage, model 3—model 2 + comorbid conditions, health care utilization metrics and previous solid organ transplant status, model 4—model 3 + transplant characteristics. All models stratified by incidence year categories (2005-2006, 2007-2008, 2009-2010, and 2011-2012).
Abbreviation: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

Table 3. Associations of Transplant Recipient Characteristics With AF After Transplant

Patient Characteristics	Cause-Specific HR (95% CI), Unadjusted	Cause-Specific HR (95% CI), Adjusted
Modality (hemodialysis vs peritoneal dialysis)	1.30 (1.22-1.39)	1.20 (1.04-1.38)
Age (y)	1.02 (1.02-1.02)	1.05 (1.05-1.05)
Female (vs Male)	0.89 (0.85-0.93)	0.86 (0.78-0.95)
Race		
Black (vs White)	0.88 (0.80-0.97)	0.82 (0.74-0.91)
Other (vs White)	0.76 (0.69-0.83)	0.67 (0.56-0.80)
Body Mass Index (kg/m^2)		
18.5-25 (vs <18.5)	0.95 (0.81-1.11)	0.83 (0.58-1.19)
25-29.9 (vs <18.5)	1.03 (0.88-1.20)	1.01 (0.71-1.44)
≥30 (vs <18.5)	1.16 (0.99-1.36)	1.16 (0.82-1.66)
Comorbid conditions		
Diabetes mellitus	1.39 (1.33-1.45)	0.99 (0.88-1.11)
Alcohol dependence	1.27 (1.07-1.51)	1.12 (0.77-1.62)
CAD	1.56 (1.49-1.63)	1.22 (1.11-1.34)
COPD	1.38 (1.31-1.46)	1.04 (0.93-1.16)
CVD	1.24 (1.15-1.34)	0.91 (0.78-1.06)
Cerebral bleed	1.00 (0.78-1.28)	0.59 (0.34-1.03)
Cancer	1.32 (1.21-1.43)	1.09 (0.94-1.27)
Hypertension	1.50 (1.37-1.64)	1.12 (0.92-1.36)
VHD	1.48 (1.40-1.57)	1.22 (1.10-1.36)
PVD	1.61 (1.54-1.69)	1.10 (0.99-1.21)
Liver disease	1.29 (1.22-1.37)	1.10 (0.98-1.23)
Tobacco use	1.26 (1.17-1.35)	1.05 (0.88-1.24)
Arrhythmia	1.54 (1.41-1.68)	1.61 (1.39-1.87)
Heart failure	1.53 (1.46-1.60)	1.31 (1.19-1.44)
Dialysis characteristics		
Cause of kidney failure		
Hypertension (vs diabetes)	0.83 (0.78-0.88)	1.04 (0.91-1.19)
Glomerulonephritis (vs diabetes)	0.70 (0.66-0.75)	1.00 (0.86-1.16)
Other (vs diabetes)	0.74 (0.69-0.78)	1.03 (0.89-1.20)
Dialysis vintage (per y)	1.04 (1.03-1.05)	1.06 (1.03-1.09)
Duration of last dialysis modality (per y)	1.05 (1.04-1.05)	1.00 (0.98-1.03)
Transplant characteristics		
Previous solid organ transplant	1.35 (1.18-1.53)	1.43 (1.13-1.82)
Living donation	0.67 (0.63-0.71)	0.77 (0.66-0.91)
Patient blood type		
A (vs O)	1.05 (1.00-1.10)	1.11 (1.01-1.22)
B (vs O)	1.05 (0.98-1.12)	1.07 (0.95-1.21)
AB (vs O)	1.05 (0.94-1.17)	1.00 (0.79-1.26)
Donor age (y)	1.02 (1.01-1.02)	1.01 (1.00-1.01)
Female donor (vs Male)	1.10 (1.06-1.15)	1.10 (1.01-1.20)
HLA mismatch		
1-3 (vs 0)	1.10 (1.00-1.21)	1.23 (1.01-1.51)
4-6 (vs 0)	1.35 (1.24-1.47)	1.30 (1.08-1.57)
Cold ischemia time (per h)	1.01 (1.01-1.01)	1.00 (0.99-1.00)
Panel-reactive antibody (per 5%)	1.00 (1.00-1.01)	1.00 (1.00-1.01)

Note: Multivariable Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals to estimate the association of modality with incident AF over up to 3 years postkidney transplant.
Abbreviation: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HLA, human leukocyte antigen, PAD, peripheral arterial disease; VHD, valvular heart disease.

had a living donor. The mean donor age was 39.3 ± 15.8, and a total of 18,234 (44.1%) donors were women. The majority (29,656, 68%) had a 4-6 HLA mismatch. The mean panel-reactive antibody titer was 15.6 ± 27.7, mean cold ischemia time was 15.5 ± 10.7 hours.

Incidence of Posttransplant AF by Predialysis Modality

Newly diagnosed AF occurred in 286 patients (during 15,363 person-years) receiving peritoneal dialysis and in 2,315 patients (during 83,536 person-years) receiving

hemodialysis before their first kidney transplant. Table 2 shows the HR estimates for dialysis modality across the different adjustment steps. Model 1, which only adjusted for time-varying graft failure estimated a higher rate (HR, 1.47; 95% CI, 1.30-1.66) of AF among persons who had been receiving hemodialysis before transplant compared with those previously receiving peritoneal dialysis. This association was attenuated after adjusting for all available characteristics, but AF remained significantly more likely in those who had been receiving hemodialysis versus peritoneal dialysis, (multivariable-adjusted HR, 1.20; 95% CI, 1.04-1.38; Table 2, model 4, Fig 2). Results were not materially changed when death was treated as a competing event instead of a censoring risk event (Table S1).

Other Risk Factors for Posttransplant AF

We identified several additional characteristics that were associated with the development of postkidney transplant AF (Table 3). Longer pretransplant dialysis vintage was associated with higher risk of AF (HR, 1.06; 95% CI, 1.03-1.09, per additional year) posttransplant, whereas no independent association was identified for the duration of the most recent dialysis modality. Transplant factors, such as a previous solid organ transplant (HR, 1.43; 95% CI, 1.13-1.82), a female donor (HR, 1.10; 95% CI, 1.01-1.20), and HLA mismatch (1-3 vs 0, HR 1.23; 95% CI, 01.01-1.51; 4-6 vs 0, HR 1.30; 95% CI, 1.08-1.57) were independently associated with increased risks of AF, whereas having a living donor was associated with a lower risk of AF (HR, 0.77; 95% CI, 0.66-0.91).

DISCUSSION

Using a large United States registry of persons with kidney failure undergoing kidney transplantation, we examined potential differences in the incidence of AF posttransplantation by pretransplant dialysis modality and other transplant-specific factors. In this study we found that kidney transplant recipients who had been receiving hemodialysis before transplantation were at a 20% higher risk of developing AF posttransplantation than those who had been receiving peritoneal dialysis. This finding arose from a large, representative cohort of US patients with kidney failure and from analyses carefully adjusted for several demographic characteristics and comorbid conditions that were known to associate with AF risk in the general population,[22,23] and in persons with CKD, including those with kidney failure requiring kidney replacement therapy.[24-27] Our findings extend our recent analysis, which found that persons with incident kidney failure newly initiating hemodialysis compared with peritoneal dialysis had higher rates of AF during the first 90 days of kidney failure treatment, but that these differences in AF risk attenuated and were no longer significant at later time points.[9]

Why might patients with kidney failure treated with peritoneal dialysis have a lower AF risk than patients treated with hemodialysis before kidney transplant? Pretransplant hemodialysis is associated with a higher risk of posttransplant heart failure as compared with peritoneal dialysis,[28] and this may likely translate into a higher risk of posttransplant AF. An enlarged left atrium is a significant risk for AF in patients receiving dialysis.[27] In patients receiving hemodialysis, left atrial ejection fraction and inadequate contractility reserve develop and persist even when the patients' volume status has improved.[29] Myocardial electrical activity also appears to be more stable in patients receiving peritoneal dialysis as compared with patients receiving hemodialysis.[30] In addition, the arteriovenous fistula used for hemodialysis access poses significant hemodynamic and structural cardiovascular challenges that have been well-described in the literature to date and that are specific to the patients receiving hemodialysis. Arteriovenous fistulas increase cardiac output with subsequent increases in circulating volume, consequently affecting atrial and ventricular size and function, predisposing to arrhythmias, including AF.[31,32] Although no association was found between vascular access type and mortality among patients receiving a kidney transplant after previously undergoing hemodialysis,[33] the potential role of vascular access (or access ligation) relative to incident AF is unclear. Another potential contributor to the discrepancy between patients receiving hemodialysis versus peritoneal dialysis may relate to residual kidney function. Residual kidney function, especially in patients receiving peritoneal dialysis, is associated with improved outcomes, including lower mortality and improved cardiovascular and nutritional health.[34] Finally, patients receiving peritoneal dialysis tend to be overall healthier than patients receiving hemodialysis, and in our analysis patients receiving hemodialysis had a higher prevalence of all measured comorbid conditions. As can be seen clearly in this study, important differences in risk status remain by dialysis modality among patients undergoing successful kidney transplantation. Although we adjusted for all these factors, residual confounding is possible.

Several other dialysis and transplant-related factors were associated with incident AF in this study. Knowledge about longer dialysis vintage, having a female donor, or having (more) HLA mismatches associated with AF will not factor into an organ acceptance decision, but may motivate more proactive arrhythmia screening after a transplant in persons possessing these characteristics. Screening for AF in the general population has limited evidence[35] but given the association of AF with mortality,[14,36] the lack of data on anticoagulation in patients with AF and kidney disease, the greater risk of hemorrhagic transformation poststroke in patients with CKD,[37,38] and the associated risk of bleeding with biopsy posttransplant when investigating rejection in transplant recipients, screening strategies may be impactful in our population, which is at high risk for adverse events.

This study has important limitations that need to be considered. First, there is the potential for residual confounding as discussed above. Second, we relied on information submitted in billing claims to Medicare to ascertain AF and not on direct measurement of cardiac activity through monitors. Third, Medicare claims do not specify whether AF was persistent, permanent, or paroxysmal or whether it should be considered valvular.

In conclusion, we found that patients receiving hemodialysis before transplantation were at increased risk of developing new-onset postkidney transplant AF compared with patients who were receiving peritoneal dialysis. The presence of classic AF risk factors in the recipient plays an important role but identification of and knowledge about transplant-related factors is important. As our understanding of transplant-specific risk factors for AF increases, we may be able to better risk-stratify the kidney transplant population and develop monitoring and management strategies that can improve outcomes.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Association of the Pretransplant Dialysis Modality and Incident AF Posttransplantation Using Subdistribution Hazard Ratio.

Table S2: Associations of Transplant Recipient Characteristics with AF After Transplant Using Subdistribution Hazard Ratio.

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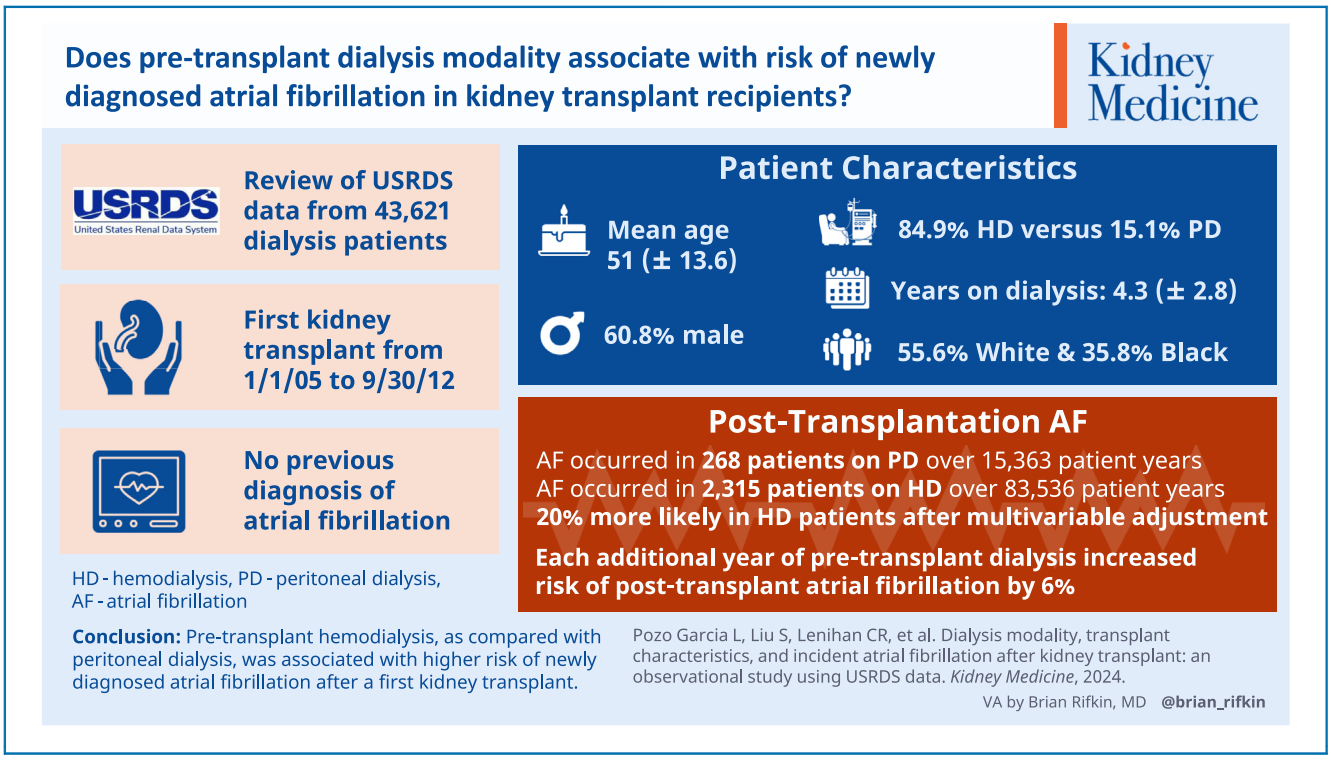
REFERENCES

1. Weiner DE, Tabatabai S, Tighiouart H, et al. Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. *Am J Kidney Dis*. 2006;48(3):392-401.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke Statistics-2022 update: A report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639.
3. Tanaka Y, Shah NS, Passman R, Greenland P, Lloyd-Jones DM, Khan SS. Trends in cardiovascular mortality related to atrial fibrillation in the United States, 2011 to 2018. *J Am Heart Assoc*. 2021;10(15):e020163.
4. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123(25):2946-2953.
5. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(6):572-586.
6. Koplan BA, Winkelmayer WC, Costea AI, et al. Implantable loop recorder monitoring and the incidence of previously unrecognized atrial fibrillation in patients on hemodialysis. *Kidney Int Rep*. 2022;7(2):189-199.
7. Airy M, Chang TI, Ding VY, et al. Risk profiles for acute health events after incident atrial fibrillation in patients with end-stage renal disease on hemodialysis. *Nephrol Dial Transplant*. 2018;33(9):1590-1597.
8. Vazquez E, Sanchez-Perales C, Garcia-Garcia F, et al. Atrial fibrillation in incident dialysis patients. *Kidney Int*. 2009;76(3):324-330.
9. Niu J, Shah MK, Perez JJ, et al. Dialysis modality and incident atrial fibrillation in older patients with ESRD. *Am J Kidney Dis*. 2019;73(3):324-331.
10. Chang CH, Fan PC, Lin YS, et al. Atrial fibrillation and associated outcomes in patients with peritoneal dialysis and hemodialysis: a 14-year nationwide population-based study. *J Nephrol*. 2021;34(1):53-62.
11. Lenihan CR, Montez-Rath ME, Scandling JD, Turakhia MP, Winkelmayer WC. Outcomes after kidney transplantation of

patients previously diagnosed with atrial fibrillation. *Am J Transplant*. 2013;13(6):1566-1575.
12. Meier-Kriesche HU, Schold JD, Srinivas TR, Reed A, Kaplan B. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. *Am J Transplant*. 2004;4(10):1662-1668.
13. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. *Kidney Int*. 2000;57(1):307-313.
14. Lentine KL, Schnitzler MA, Abbott KC, et al. Incidence, predictors, and associated outcomes of atrial fibrillation after kidney transplantation. *Clin J Am Soc Nephrol*. 2006;1(2):288-296.
15. Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2012;60(5):434-480.
16. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725-1730.
17. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med*. 2017;36(27):4391-4400.
18. Montez-Rath ME, Winkelmayer WC, Desai M. Addressing missing data in clinical studies of kidney diseases. *Clin J Am Soc Nephrol*. 2014;9(7):1328-1335.
19. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377-399.
20. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med*. 2009;28(15):1982-1998.
21. Little RJ, Rubin DB. Statistical analysis with missing data. In: John Wiley & Sons; 2002.
22. Vlachos K, Letsas KP, Korantzopoulos P, et al. Prediction of atrial fibrillation development and progression: current perspectives. *World J Cardiol*. 2016;8(3):267-276.
23. Brunner KJ, Bunch TJ, Mullin CM, et al. Clinical predictors of risk for atrial fibrillation: implications for diagnosis and monitoring. *Mayo Clin Proc*. 2014;89(11):1498-1505.
24. Fabbian F, Catalano C, Lambertini D, et al. Clinical characteristics associated to atrial fibrillation in chronic hemodialysis patients. *Clin Nephrol*. 2000;54(3):234-239.
25. Ananthapanyasut W, Napan S, Rudolph EH, et al. Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(2):173-181.
26. Zelnick LR, Shlipak MG, Soliman EZ, et al. Prediction of incident atrial fibrillation in chronic kidney disease: the chronic renal insufficiency cohort study. *Clin J Am Soc Nephrol*. 2021;16(7):1015-1024.
27. Abuhasira R, Mizrakli Y, Shimony A, Novack V, Shnaider A, Haviv YS. Atrial fibrillation characteristics in patients on haemodialysis vs. peritoneal dialysis. *Sci Rep*. 2018;8(1):2976.
28. Lenihan CR, Liu S, Airy M, Walther C, Montez-Rath ME, Winkelmayer WC. The association of pre-kidney transplant dialysis modality with de novo posttransplant heart failure. *Cardiorenal Med*. 2021;11(5-6):209-217.
29. Malik J, Lachmanova J, Kudlicka J, et al. Left atrial dysfunction in end-stage renal disease patients treated by hemodialysis. *Nephron*. 2016;133(3):169-174.
30. Zhang W, Liang Y, Lv J, Li Y, Sun J. The effects of peritoneal dialysis on QT interval in ESRD patients. *BMC Nephrol*. 2022;23(1):69.
31. Ori Y, Korzets A, Katz M, Perek Y, Zahavi I, Gafter U. Haemodialysis arteriovenous access—a prospective haemodynamic evaluation. *Nephrol Dial Transplant*. 1996;11(1):94-97.
32. Iwashima Y, Horio T, Takami Y, et al. Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. *Am J Kidney Dis*. 2002;40(5):974-982.
33. Airy M, Lenihan CR, Ding VY, et al. Association between type of vascular access used in hemodialysis patients and subsequent kidney transplant outcomes. *Kidney Med*. 2019;1(6):383-390.
34. Wang AY, Lai KN. The importance of residual renal function in dialysis patients. *Kidney Int*. 2006;69(10):1726-1732.
35. Kahwati LC, Asher GN, Kadro ZO, et al. Screening for atrial fibrillation: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2022;327(4):368-383.
36. Abbott KC, Reynolds JC, Taylor AJ, Agodoa LY. Hospitalized atrial fibrillation after renal transplantation in the United States. *Am J Transplant*. 2003;3(4):471-476.
37. Cherng YG, Lin CS, Shih CC, et al. Stroke risk and outcomes in patients with chronic kidney disease or end-stage renal disease: two nationwide studies. *PLOS ONE*. 2018;13(1):e0191155.
38. Chelluboina B, Vemuganti R. Chronic kidney disease in the pathogenesis of acute ischemic stroke. *J Cereb Blood Flow Metab*. 2019;39(10):1893-1905.


Does pre-transplant dialysis modality associate with risk of newly diagnosed atrial fibrillation in kidney transplant recipients?
Kidney Medicine
USRDS
United States Renal Data System
Review of USRDS data from 43,621 dialysis patients
First kidney transplant from 1/1/05 to 9/30/12
No previous diagnosis of atrial fibrillation
HD - hemodialysis, PD - peritoneal dialysis, AF - atrial fibrillation
Patient Characteristics
Mean age 51 (± 13.6)
60.8% male
84.9% HD versus 15.1% PD
Years on dialysis: 4.3 (± 2.8)
55.6% White & 35.8% Black
Post-Transplantation AF
AF occurred in 268 patients on PD over 15,363 patient years
AF occurred in 2,315 patients on HD over 83,536 patient years
20% more likely in HD patients after multivariable adjustment
Each additional year of pre-transplant dialysis increased risk of post-transplant atrial fibrillation by 6%
Conclusion: Pre-transplant hemodialysis, as compared with peritoneal dialysis, was associated with higher risk of newly diagnosed atrial fibrillation after a first kidney transplant.
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