Kidney Medicine

Association Between Type of Vascular Access Used in Hemodialysis Patients and Subsequent Kidney Transplant Outcomes

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Rationale & Objective: Vascular access type (arteriovenous fistula [AVF] vs arteriovenous graft [AVG] vs central venous catheter [CVC]) associates with clinical outcomes in patients with end-stage kidney disease undergoing hemodialysis. Whether a similar association exists with outcomes after kidney transplantation is unknown. We hypothesized that AVGs would associate with worse outcomes, perhaps owing to persistent subclinical inflammation.

Study Design: Retrospective cohort study.

Setting & Participants: Using US registry data merged with electronic health records of a large dialysis organization (2006-2011), we selected patients receiving a first-ever kidney transplant after undergoing more than 30 days of hemodialysis.

Exposure: Hemodialysis access used during the patient's last pretransplantation hemodialysis session.

Outcomes: Patients were followed up from kidney transplantation for all-cause mortality, kidney allograft loss from any cause, and allograft loss not from death.

Analytical Approach: Time-to-event analysis including Kaplan-Meier plots and Cox proportional hazards regression estimated cause-specific HRs and 95% CIs.

Results: Among 9,291 patients who underwent kidney transplantation between 2006 and 2011, a total of 65.3% used an AVF, 20.4% used an AVG, and 14.3% used a CVC for hemodialysis before transplantation. Multivariable regression models adjusted for demographic variables, comorbid conditions, transplant characteristics, and laboratory parameters identified no independent associations between vascular access type and all-cause mortality (HR_{AVG}, 1.13 [95% CI, 0.97-1.33]; HR_{CVC}, 1.00 [95% CI, 0.83-1.21]). Similarly, AVG and CVC use were not independently associated with all-cause allograft loss compared with AVF use (HR_{AVG}, 1.13 [95% CI, 1.00-1.28]; HR_{CVC}, 1.12 [95% CI, 0.96-1.29]). CVC use was associated with 30% higher risk for allograft loss from causes other than death compared with AVF use (HR_{CVC}, 1.30 [95% CI, 1.06-1.57]), but AVGs were not (HR_{AVG}, 1.17 [95% CI, 0.98-1.39]).

Limitations: Nonrandomized exposure leading to potential residual confounding.

Conclusions: No association was found for AVG use before kidney transplantation with mortality, all-cause allograft loss, and allograft loss from all causes other than death, compared with AVF use. The association of CVC use with allograft loss from causes other than death requires further investigation.

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End-stage kidney disease (ESKD) is a significant public health problem, with 678,383 patients reported prevalent in the United States in December 2014.[1] Among the options for kidney replacement therapy, kidney transplantation is preferred because it is associated with better patient outcomes and lower costs.[1-3] However, only 2.6% of incident patients with ESKD received a preemptive kidney transplant,[1] indicating that the majority of patients must receive dialysis for variable periods of time before they can receive a transplant, with center hemodialysis being the predominant modality in the United States.[1] Hemodialysis requires a vascular access such as an arteriovenous fistula (AVF), arteriovenous graft (AVG), or tunneled central venous catheter (CVC).

Several studies[4-6] have established AVFs as the preferred access in hemodialysis patients. A recent systematic review and meta-analysis by Ravani et al[4] included 67 studies and showed that patients using CVCs had 53% higher all-cause mortality, more than twice as many fatal infections, and 38% higher risk for cardiovascular events compared with patients with AVFs. The study also reported worse outcomes with hemodialysis catheter access when compared with AVGs, with 38% higher mortality, 49% more fatal infection rates, and 26% higher cardiovascular event rates. Hence, catheters were associated with poorer outcomes compared with both AVFs and AVGs. When directly comparing AVGs with AVFs, grafts were noted to have worse clinical outcomes, with 18% higher all-cause mortality and 36% higher rates for fatal infection, although no difference was reported for cardiovascular outcomes.

When patients on hemodialysis receive a kidney transplant, AVFs and AVGs remain in place, whereas CVCs are usually removed. However, the putative effects of dialysis access type on clinical outcomes after transplantation have not been studied. Such associations could plausibly exist. Studies have found higher levels of inflammatory markers in transplant

recipients with CVCs and AVGs.[7-9] The increased cardiac output caused by a patent AVF and AVG may impose greater cardiovascular burden and contribute to poorer outcomes in transplant recipients. Overall, the effect of vascular access pretransplantation on outcomes posttransplantation is not known and needs to be better understood.

We therefore conducted this study to determine whether posttransplantation outcomes of first-time kidney transplant recipients differed by type of vascular access used for the last outpatient hemodialysis treatment before the kidney transplantation surgery.

METHODS

This study adheres to the Declaration of Helsinki and was approved by institutional review boards at Stanford University School of Medicine (protocol #17904) and Baylor College of Medicine (protocol #H-36408). The need for informed consent was waived owing to the use of deidentified data. The clinical and research activities being reported are consistent with the principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Sources of Data

We used individual-level data from 2 merged databases to conduct this study: (1) the US Renal Data System (USRDS),[1,10] the national registry of patients with ESKD; and (2) the electronic health records of a large dialysis organization. Following approval by the Institutional Review Board at Stanford University School of Medicine and a Data Use Agreement from the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK), the databases were cross-linked using a Health Insurance Portability and Accountability Act (HIPAA)-compliant approach.

The USRDS contains detailed information about the timing and modalities used for the treatment of ESKD, information for sociodemographics and comorbid conditions at onset of ESKD treatment, and detailed kidney transplant–related information from the United Network for Organ Sharing. The electronic health records of the large dialysis organization contain detailed information on each dialysis session provided within their facilities, as well as results of laboratory tests conducted in their patients.

Study Population

We conducted a retrospective cohort study of hemodialysis patients receiving a first kidney transplant. Patients who underwent their first kidney transplantation between 2006 and 2011 were included in the study if they had received at least 30 days of in-center hemodialysis in the facilities of the large dialysis organization (Fig 1).

Exposure of Interest

We identified the hemodialysis access used during the most recent outpatient dialysis treatment before these patients' transplantation surgeries from the electronic health records, in which this information is documented by clinical staff in each dialysis facility for each patient and each session. We categorized these into AVF, AVG, and CVC.

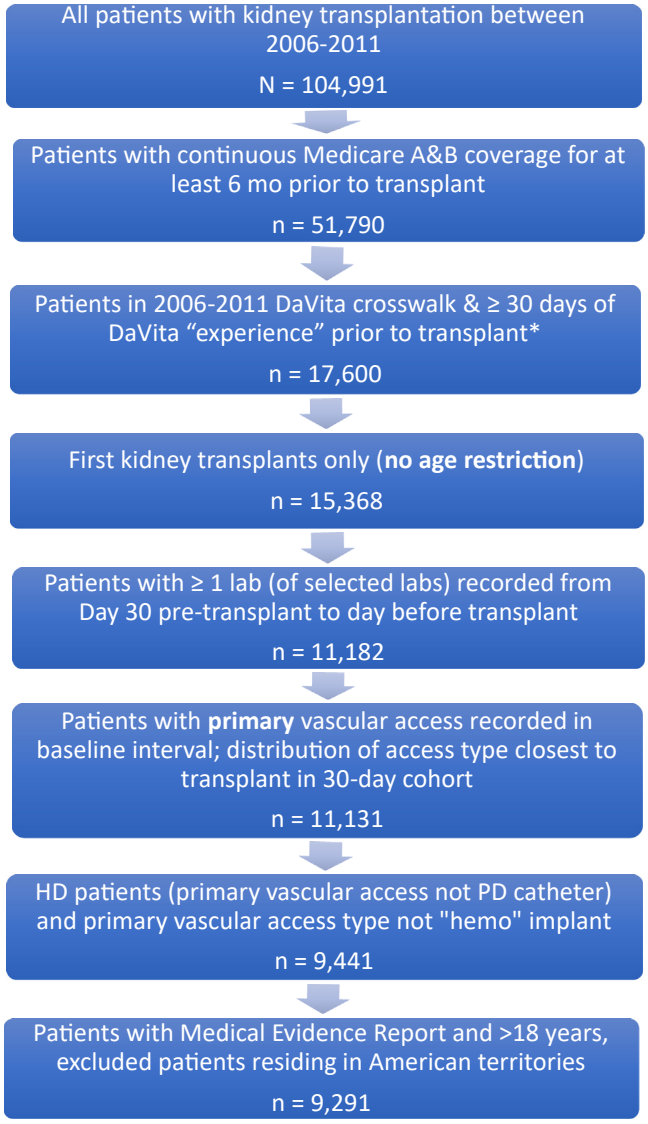

Figure 1. Flow diagram for cohort selection. *Defined as first recorded DaVita dialysis date before day 30 pretransplantation. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

Covariates: Other Patient Characteristics

We defined each patient's age (at transplantation), sex, race (white, black, and other), Hispanic ethnicity, and residential Census Division from the USRDS, which also provided information for several comorbid conditions and body mass index at the time of ESKD. We additionally identified several laboratory measurements from the 30 days preceding the transplantation, as well as donor and recipient characteristics commonly used in kidney transplant outcomes research. Table 1 lists all characteristics used for this study.

Table 1. Patient Characteristics Before First Kidney Transplant, According to Most Recent HD Access Type Used, 2006-2011

	Primary HD Access Type			
	AVF	AVG	CVC	*P*
N (row %)	6,068 (65.3%)	1,894 (20.4%)	1,329 (14.3%)	
Age, y	52.5 (13.7)	54.3 (12.4)	50 (14.5)	<0.001
Male sex	4,201 (69.2%)	959 (50.6%)	716 (53.9%)	<0.001
Race (<10 missing)				<0.001
White	3,477 (57.3%)	768 (40.5%)	781 (58.8%)	
Black	2,090 (34.5%)	982 (51.8%)	456 (34.3%)	
Asian	324 (5.3%)	88 (4.6%)	58 (4.4%)	
Other	174 (2.9%)	56 (3.0%)	33 (2.5%)	
Hispanic ethnicity (14 missing)	1,153 (19.0%)	285 (15.1%)	200 (15.0%)	<0.001
Geographic region				<0.001
Northeast	874 (14.4%)	268 (14.1%)	215 (16.2%)	
Midwest	1,170 (19.3%)	318 (16.8%)	297 (22.3%)	
South	2,604 (42.9%)	923 (48.7%)	532 (40.0%)	
West	1,420 (23.4%)	385 (20.3%)	285 (21.4%)	
Comorbid conditions				
Diabetes (13 missing)	3,217 (53.1%)	1,190 (62.9%)	689 (52.0%)	<0.001
Hypertension (<10 missing)	5,989 (98.7%)	1,885 (99.6%)	1,315 (99.0%)	0.008
Heart failure (21 missing)	2,789 (46.1%)	968 (51.2%)	602 (45.5%)	<0.001
Arteriosclerotic heart disease (20 missing)	1,814 (30.0%)	674 (35.6%)	375 (28.3%)	<0.001
Cerebrovascular disease (22 missing)	784 (12.9%)	311 (16.4%)	199 (15.0%)	<0.001
Peripheral vascular disease (22 missing)	1,761 (29.1%)	772 (40.8%)	405 (30.6%)	<0.001
History of malignancy (22 missing)	558 (9.2%)	196 (10.4%)	125 (9.4%)	0.33
BMI, kg/m^2 (429 missing)				<0.001
<18.5	112 (1.9%)	36 (2.0%)	43 (3.4%)	
18.5-24.9	1,695 (29.4%)	464 (25.5%)	432 (33.9%)	
25-29.9	1,987 (34.4%)	588 (32.4%)	378 (29.7%)	
≥30	1,978 (34.3%)	729 (40.1%)	420 (33.0%)	
Time since ESKD, y median (IQR); mean (SD)	3.8 [2.4-5.4]; 4.2 (2.5)	4.6 [3.3-6.6]; 5.1 (2.9)	3.4 [1.6-5.2]; 3.7 (2.7)	<0.001
Donor age, y (138 missing)	39.2 (15.9)	39.4 (16.0)	38.7 (15.0)	0.38
Donor male sex	3,421 (56.4%)	1,093 (57.7%)	750 (56.4%)	0.59
Donor race				0.02
White	3,976 (65.5%)	1,196 (63.1%)	855 (64.3%)	
Black	941 (15.5%)	349 (18.4%)	241 (18.1%)	
Asian	170 (2.8%)	49 (2.6%)	24 (1.8%)	
Other	981 (16.2%)	300 (15.8%)	209 (15.7%)	
Donor type				<0.001
Deceased	5,008 (82.5%)	1,687 (89.1%)	872 (65.6%)	
Living	1,060 (17.5%)	207 (10.9%)	457 (34.4%)	
Cold ischemia time (1,054 missing)				<0.001
<12 h	2,064 (38.1%)	553 (32.6%)	557 (49.5%)	
12-24 h	2,427 (44.8%)	828 (48.8%)	418 (37.1%)	
>24 h	925 (17.1%)	314 (18.5%)	151 (13.4%)	
HLA antigen mismatch (529 missing)				<0.001
0	419 (7.3%)	113 (6.3%)	95 (7.6%)	
1-3	1,320 (23.0%)	336 (18.8%)	354 (28.5%)	
4-6	3,989 (69.6%)	1,342 (74.9%)	794 (63.9%)	
Recipient peak PRA (1,445 missing)				<0.001
0%-10%	3,730 (72.9%)	1,084 (65.7%)	748 (69.3%)	
11%-80%	1,072 (20.9%)	411 (24.9%)	235 (21.8%)	
>80%	315 (6.2%)	155 (9.4%)	96 (8.9%)	
Recipient ABO blood type				0.001
O	2,975 (49.0%)	868 (45.8%)	592 (44.5%)	
A	1,990 (32.8%)	627 (33.1%)	472 (35.5%)	
B	874 (14.4%)	327 (17.3%)	197 (14.8%)	
AB	229 (3.80%)	72 (3.80%)	68 (5.10%)	

(Continued)

Table 1 (Cont'd). Patient Characteristics Before First Kidney Transplant, According to Most Recent HD Access Type Used, 2006-2011

	Primary HD Access Type			
	AVF	AVG	CVC	*P*
Immunosuppression drug use (597 missing)				
Thymoglobulin	2,920 (51.4%)	894 (50.4%)	640 (51.6%)	0.71
Alemtuzumab	671 (11.8%)	221 (12.5%)	107 (8.60%)	0.002
Muromonab-CD3	15 (0.30%)	[a]	[a]	0.85
Basiliximab	1,217 (21.4%)	339 (19.1%)	269 (21.7%)	0.09
Daclizumab	373 (6.6%)	150 (8.5%)	112 (9.0%)	0.001
Tacrolimus	5073 (89.3%)	1570 (88.5%)	1082 (87.3%)	0.09
Cyclosporin	427 (7.5%)	147 (8.3%)	101 (8.1%)	0.50
Sirolimus/everolimus	234 (4.1%)	75 (4.2%)	56 (4.5%)	0.82
Mycophenolate mofetil	5,309 (93.5%)	1,657 (93.4%)	1,160 (93.5%)	0.97
Azathioprine	34 (0.6%)	10 (0.6%)	[a]	0.89
Corticosteroids[b]	5,376 (94.7%)	1,693 (95.4%)	1,187 (95.7%)	0.20
Most recent laboratory results (no. missing)				
Albumin, g/dL (42)	4.1 (0.3)	4 (0.3)	4 (0.4)	<0.001
Hemoglobin, g/dL (<10)	11.8 (1.3)	11.8 (1.2)	11.9 (1.4)	0.09
Platelet count, 10^3/μL (62)	224 (72.7)	221.1 (70.6)	235 (82.7)	<0.001
WBC count, 10^3/μL (58)	6.6 (2)	6.7 (2.1)	6.8 (2.1)	0.02
Ferritin, ng/mL (135)	617 (406.8)	623.6 (359)	513.2 (386)	<0.001
Calcium, mg/dL (29)	9.1 (0.7)	9 (0.7)	9.1 (0.8)	0.35
Potassium, mg/dL (37)	4.9 (0.6)	4.8 (0.6)	4.9 (0.7)	<0.001
Intact parathyroid hormone, ng/L (201)	389 (333)	393.(354)	440 (479)	0.89
Phosphorus, mg/dL (32)	5.5 (1.6)	5.4 (1.5)	5.8 (1.8)	<0.001
Creatinine, mg/dL (210)	10.3 (3)	10.2 (3)	10 (3.4)	0.01

Note: N = 9,291. Values for categorical variables are given as N (percent of nonmissing); values for continuous variables are given as mean (SD) unless otherwise specified. *P* values for categorical variables are obtained from χ^2 tests (or Fisher exact tests in low cell count settings); *P* values for continuous variables are obtained from analysis of vsriance when mean (SD) is reported and from Kruskal-Wallis rank sum test when median [IQR] is reported. Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; creatinine in mg/dL to μmol/L, ×88.4; phosphorus in mg/dL to mmol/L, ×0.3229.
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; CVC, central venous catheter; ESKD, end-stage kidney disease; HD, hemodialysis; IQR, interquartile range; PRA, panel-reactive antibody; SD, standard deviation; WBC, white blood cell.
[a]Suppressed cell count; per federal research regulations, cell counts less than 10 must not be reported.
[b]Corticosteroids include prednisone, methylprednisolone, and dexamethasone.

Outcomes

Patients were followed up from the date of kidney transplantation until the following outcomes: (1) all-cause mortality; (2) allograft loss from all causes as indicated by return to dialysis, retransplantation, or death; and (3) allograft loss from cause other than death (return to dialysis or retransplantation). All analyses censored patient follow-up at the end of the study period (December 31, 2011). Determination of all outcomes and censoring events was made through standard data fields from the "Patient" file in the USRDS.

Statistical Analyses

We used standard descriptive statistics to characterize the 3 exposure groups by the last known dialysis access before the kidney transplantation. Continuous variables are presented as median with interquartile range or mean (standard deviation), and categorical variables, as count (percentage). Any differences among the vascular access groups were identified using analysis of variance or Kruskal-Wallis tests for continuous variables and Pearson χ^2 or Fisher exact tests for categorical variables. We used cause-specific Cox-proportional hazards regression to challenge the null hypotheses of no differences in study outcomes among the categories of last dialysis access used before kidney transplantation. All models were stratified by calendar year of the transplantation. The adjusted models included demographic characteristics, comorbid conditions, transplant-related variables, and laboratory results. Each of these variable categories was added in incremental adjustment steps with the final model simultaneously accounting for all the factors. For allograft loss from causes other than death, we conducted analyses in 2 ways: (1) using death as a competing risk, and (2) using death as a censoring event. The ensuing results were essentially identical; hence, we only presented results that censored for death. In regression analyses, missing data were addressed with multiple imputation by chained equation using the MICE package in R.[11] A total of 27.4% of patients had at least 1 variable missing, with the percentage of missing ranging from <0.01% (race) to 15.6% (recipient peak panel-reactive antibody). There was no reason to believe that the data would be related to unobserved characteristics, Therefore, we assumed the data to be missing at random and performed multiple imputation by

chain equations using the MICE package in R to impute 32 data sets. Imputations were performed separately for each outcome and the imputation model included all variables in the final model, including a Nelson-Aalen estimate of the hazard and the event indicator. Analysis models were applied to each data set separately and results were combined using Rubin's rules. Schoenfeld residuals plots were used to identify any deviations from the proportionality assumption; no such deviations were detected. We conducted statistical analyses using SAS software, version 9.3 (SAS Institute) and R, version 3.1 (R Project for Statistical Computing).

RESULTS

We identified 9,291 patients who received a first kidney transplant between 2006 and 2011 and who had at least 30 days of hemodialysis at a facility of the large dialysis organization. The flow diagram of cohort selection is shown in Figure 1. Two-thirds of patients were reported to have used an AVF (65.3%) during their most recent outpatient hemodialysis treatment, one-fifth (20.4%) used an AVG, and the rest (14.3%) used a CVC. The 3 vascular access groups differed on a number of characteristics, and the details for all measured characteristics can be found in Table 1. Patients with a CVC were the youngest (50 years) and patients using an AVG were the oldest (54 years) median age. Although sex was almost evenly distributed in the AVG and CVC groups, 69% of patients with an AVF were men. Black patients constituted 34% of patients in the AVF and CVC groups, but more than half in the AVG group. There were also substantial differences in comorbid conditions; the AVG group appeared systematically sicker and had had ESKD longer compared with the other groups. More patients with CVCs received their kidney from a living donor (34.4%) compared with the other 2 groups (10.9% in the AVG group and 17.5% in the AVF group).

Kaplan-Meier incidences of mortality and all-cause allograft loss, by vascular access type, are shown in Figure 2. Using unadjusted Cox proportional hazards regression, we found that patients with an AVG had 33% higher all-cause mortality (hazard ratio [HR], 1.33; 95% confidence interval [CI], 1.15-1.54) compared with those using an AVF (Table 2). However, the association was attenuated and no longer present in a model adjusted for demographics, comorbid conditions, transplant variables, and laboratory results (HR, 1.13; 95% CI, 0.97-1.33). CVC use was not associated with all-cause mortality compared with AVF use in either unadjusted or adjusted models.

Similar findings were obtained from analyses of the outcome of allograft loss from all causes (Table 3). Patients with AVGs had a 31% higher unadjusted rate of allograft loss from all causes compared with those with AVFs (HR, 1.31; 95% CI, 1.17-1.48), but the association was attenuated and no longer significant in the fully adjusted model (HR, 1.13; 95% CI, 1.00-1.28). Patients with CVCs had rates of all-cause allograft loss that were no different from those with AVFs in unadjusted or adjusted models.

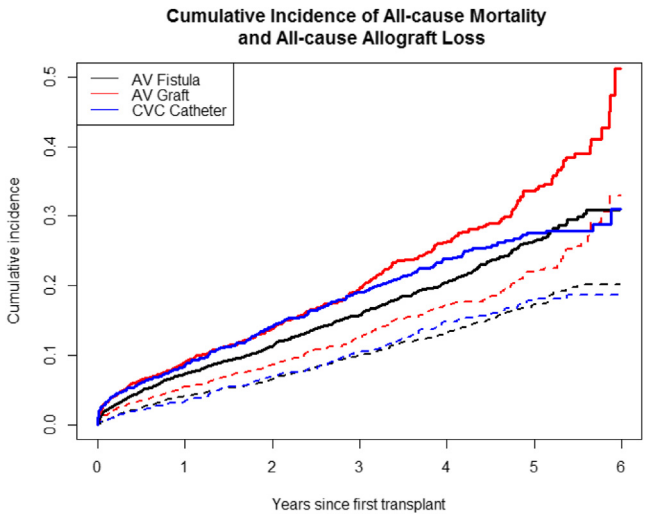

Figure 2. Actuarial cumulative incidence of all-cause mortality and all-cause allograft loss. Solid lines: all-cause allograft loss; dotted lines: mortality. Abbreviations: AV, arteriovenous; CVC, central venous catheter.

Last, we studied the association between the last vascular access used pretransplantation and allograft loss from causes other than death (Table 4). AVG use was associated with a 30% higher rate of allograft loss (HR, 1.30; 95% CI, 1.10-1.53), and CVC use was associated with a 22% higher rate of allograft loss (HR, 1.22; 95% CI, 1.01-1.47), both compared with AVFs in the unadjusted model. The associations were maintained, albeit attenuated, after adjustment for demographic, comorbid condition, and transplant variables. However, adjustment for laboratory values once again rendered both associations null.

Table 2. Association Between Last Vascular Access Used Pretransplantation and All-Cause Mortality

	HR	95% L	95% U	*P*
Unadjusted				
AVG vs AVF	1.33	1.15	1.54	<0.01
CVC vs AVF	0.99	0.83	1.18	0.91
Demographics-adjusted				
AVG vs AVF	1.27	1.09	1.48	<0.01
CVC vs AVF	1.07	0.89	1.28	0.48
+ Comorbid conditions added				
AVG vs AVF	1.13	0.97	1.33	0.11
CVC vs AVF	1.05	0.88	1.26	0.60
+ Transplant variables added				
AVG vs AVF	1.16	0.99	1.36	0.06
CVC vs AVF	1.10	0.92	1.32	0.31
+ Laboratory results added				
AVG vs AVF	1.13	0.97	1.33	0.12
CVC vs AVF	1.00	0.83	1.21	0.99

Note: HRs estimated using Cox proportional hazards regression models stratified for calendar year of transplantation; results shown are based on multiply imputed data (N = 9,291; m = 32 sets).
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter; HR, hazard ratio; L, lower 95% confidence limit; U, upper 95% confidence limit.

Table 3. Association Between Last Vascular Access Used Pretransplantation and Allograft Loss From All Causes

	HR	95% L	95% U	*P*
Unadjusted				
AVG vs AVF	1.31	1.17	1.48	<0.01
CVC vs AVF	1.09	0.95	1.25	0.23
Demographics-adjusted				
AVG vs AVF	1.23	1.09	1.39	<0.01
CVC vs AVF	1.12	0.97	1.29	0.11
+ Comorbid conditions added				
AVG vs AVF	1.13	1.00	1.28	0.05
CVC vs AVF	1.11	0.97	1.28	0.13
+ Transplant variables added				
AVG vs AVF	1.15	1.02	1.31	0.02
CVC vs AVF	1.19	1.03	1.37	0.02
+ Laboratory results added				
AVG vs AVF	1.13	1.00	1.28	0.06
CVC vs AVF	1.12	0.96	1.29	0.14

Note: HRs were estimated using Cox proportional hazards regression models stratified for calendar year of transplantation; results shown are based on multiply imputed data (N = 9,291; m = 32 sets).
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter; HR, hazard ratio; L, lower 95% confidence limit; U, upper 95% confidence limit.

Table 4. Association Between Last Vascular Access Used Pretransplantation and Allograft Loss From Causes Other Than Death

	HR	95% L	95% U	*P*
Unadjusted				
AVG vs AVF	1.30	1.10	1.53	<0.01
CVC vs AVF	1.22	1.01	1.47	0.04
Demographics-adjusted				
AVG vs AVF	1.24	1.04	1.47	0.01
CVC vs AVF	1.20	0.99	1.45	0.06
+ Comorbid conditions added				
AVG vs AVF	1.17	0.98	1.39	0.08
CVC vs AVF	1.21	1.00	1.46	0.05
+ Transplant variables added				
AVG vs AVF	1.19	1.00	1.42	0.04
CVC vs AVF	1.34	1.10	1.62	<0.01
+ Laboratory results added				
AVG vs AVF	1.17	0.98	1.39	0.08
CVC vs AVF	1.30	1.06	1.57	0.01

Note: HRs were estimated using Cox proportional hazards regression models stratified for calendar year of transplantation; death was treated as a competing risk; analyses censoring for death yielded almost identical results. Results shown are based on multiply imputed data (N = 9,291; m = 32 sets).
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter; HR, hazard ratio; L, lower 95% confidence limit; U, upper 95% confidence limit.

DISCUSSION

Using a large cohort of first-time kidney transplant recipients who had previously received hemodialysis, we examined whether outcomes differed by type of vascular access used for hemodialysis. We did not find any compelling evidence that all-cause mortality or allograft survival differed among the 3 groups of hemodialysis vascular access after we accounted for differences in patient characteristics.

This study was motivated by established evidence on differences in outcomes across access types in patients undergoing hemodialysis. The associations of type of vascular access used in hemodialysis patients with important patient outcomes are well established.[7,12-18] Several studies have shown higher mortality and worse cardiovascular outcomes in patients with CVCs and AVGs compared with those with AVFs.[14,19,20] Similar evidence for any differences in the outcomes of new kidney transplant recipients was unavailable. Patients undergoing kidney transplantation usually retain their peripheral vascular access (CVCs are usually removed after the transplant is considered functional) and these remain patent for variable periods and may induce chronic inflammation or impose long-term cardiovascular burden in these recipients.

Our main a priori hypothesis was that kidney transplant recipients with AVGs would have worse outcomes than otherwise similar patients who had AVFs. This expectation was based partly on the established association of grafts versus fistulas in the hemodialysis population,[7-9,12,16,17,21] but more importantly on studies demonstrating that the presence of AVGs was associated with markers of systemic inflammation.[22]

A study by Wasse et al[8] of 91 patients undergoing hemodialysis showed that patients with retained AVGs had higher concentrations of inflammatory markers, namely C-reactive protein, interleukin 6, and tumor necrosis factor. These patients lacked clinical evidence of previous infection or inflammation and hence retained AVGs were considered to be the source of the inflammatory markers in these patients. Additionally, the study also reported an association between elevated C-reactive protein levels and erythropoietin resistance ($P = 0.003$), which associates with cardiovascular morbidity in these patients.

Other studies have found similar results.[9,14,21,23,24] Banerjee et al[9] analyzed participants in the CHOICE (Choices of Healthy Outcomes in Caring for End-Stage Renal Disease) prospective cohort study and found that the presence of an AVG was associated with a significant 30% increase in C-reactive protein levels. Thus, a similar phenomenon was hypothesized to occur post-transplantation when an AVG left in place could possibly lead to elevated inflammation and contribute to worse outcomes in these patients.

Another explanation for the possibility of worse outcomes in patients with AVGs relates to the presence of subclinical vascular graft infections in these patients post-transplantation. This has been reported in prospective studies and case series of hemodialysis patients and kidney transplant recipients[25,26] and is particularly concerning in immunocompromised patients after kidney transplantation. We did not study episodes of unexplained infections in our cohort and were unable to study inflammatory markers other than those routinely measured in hemodialysis clinics, namely, white blood cell count, platelet count, and albumin and ferritin levels. Among the

limited markers available, there was no difference in white blood cell counts or the acute-phase protein ferritin.

Observational studies on clinical outcomes by vascular access type are prone to selection bias. In patients undergoing hemodialysis, it has been shown that patients with AVFs are relatively less sick compared with those with AVGs. It has been shown throughout these studies that patients with CVCs and, to a lesser degree, AVGs have a higher burden of comorbid conditions, and adjusted associations were usually attenuated compared with unadjusted findings. Thus, one must assume that the well-described associations in the hemodialysis population are only partly causal and that there is (perhaps considerable) residual confounding present by the inability to perfectly measure, quantitatively and qualitatively, all relevant comorbidities and conditions. In kidney transplant recipients, for whom eligibility for this procedure serves as an "equalizer" and restricts the range of comorbid conditions acceptable, one would expect less confounding by comorbid conditions. However, our findings illustrate that there were still considerable differences in comorbidity burden across vascular access groups, with patients in the AVG group generally being sicker than patients in the other 2 groups. The average time since ESKD was also longer in patients with AVGs (5.1 years) compared with those with AVFs (4.2 years), which makes sense given that patients are more likely to use up their native vessel options as duration of hemodialysis treatment increases. The impact of these differences is illustrated in the sequentially adjusted models, in which most of the confounding for the comparison of AVGs versus AVFs was driven by adjustment for comorbid conditions, with almost no changes after adjustment for transplant-related factors and laboratory measurements.

Interestingly, patients using CVCs had the shortest time since ESKD incidence, 3.7 years. It is possible that patients who expect to receive a transplant quickly, for example, from a living donor, opt to have a more temporary access solution rather than to have a surgically created fistula or graft. Some might also have run out of options for vascular access, prompting them to actively look out for live kidney donors. The proportion of living donors was much greater in patients using a hemodialysis CVC (34.4%) than in AVF or AVG users (17.5% and 10.9%, respectively). Patients using CVCs pretransplantation had similar rates of all-cause mortality compared with patients with AVFs, an expected outcome because patients' CVCs are usually removed soon after kidney transplantation, typically within a week, after graft function is recovered. By contrast, our study identified an association of CVC use with increased risk for allograft loss from causes other than death compared with patients using AVFs. This finding was unexpected and cannot easily be explained. It is possible that this association is spurious or by chance. Future research needs to refute or corroborate this specific association.

Certain limitations of our study require discussion. In this retrospective analysis of routinely collected data from mandated reporting to the Centers for Medicare & Medicaid Services and the electronic health records of a national dialysis provider, the associations identified may be residually confounded. Patients were not randomly assigned to different access types and so confounding by indication, information bias, and ascertainment bias are possible due to the nature of data collection. We have accounted for the potential confounders in the statistical model, though residual confounding by unobserved characteristics, or imperfectly measured characteristics, could still be present. Because laboratory parameters measured pretransplantation could be a downstream consequence of vascular access choice, it would have been possible that adjustment for these laboratory markers as potential mediators would lead to potential overadjustment. However, the absence of any major changes in estimated associations indicates that laboratory factors did not confound the associations of interest. We also lacked more specific data for inflammatory markers, such as C-reactive protein and interleukin 6, which were used in the prior studies. Finally, the generalizability of our findings to other countries with different vascular access and transplantation practices is also uncertain.

In conclusion, contrary to studies in the hemodialysis population in which type of vascular access has been shown to be associated with important health outcomes, the present study does not provide convincing support for the hypothesis that type of vascular access pretransplantation is a strong determinant of post-transplantation outcomes.

ARTICLE INFORMATION

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