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Arteriovenous Fistula Use Is Associated with Lower Cardiovascular Mortality Compared with Catheter Use among ESRD Patients

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Abstract

The arteriovenous fistula (AVF) is the recommended form of dialysis vascular access, however, limited studies suggest that AVF creation may result in increased cardiovascular stress and remodeling. To explore the contribution of vascular access type to cardiovascular-related (CV) mortality, we analyzed USRDS Clinical Performance Measures data comprising 4854 patients that initiated dialysis between October 1, 1999–December 31, 2004. CV mortality included death from acute myocardial infarction, atherosclerotic heart disease, cardiomyopathy, arrhythmia, cardiac arrest or stroke. Risk of cardiovascular mortality during a 4-year observation was analyzed by Cox-regression methods with adjustments for demographic and co-morbid conditions. AVF use was strongly associated with lower all-cause and CV mortality. After adjustment for covariates, AVF use 90 days after dialysis initiation remained significantly associated with lower cardiovascular mortality [hazard ratio (HR) 0.69, $p = 0.0004$] compared with catheter use. These findings suggest that vascular access type influences cause-specific mortality beyond that of infection, and support existing guidelines recommending the use of an AVF early in the course of chronic end-stage renal disease therapy.

Cardiovascular disease (CVD) is the primary cause of mortality among end-stage renal disease (ESRD) patients (1). Arteriovenous fistulae (AVF) confer protection against sepsis and all-cause mortality and are the recommended form of vascular access for hemodialysis patients, compared with arteriovenous grafts (AVG) or central venous catheters (CVC) (2-4). However, it is unknown whether an AVF is associated with increased cardiovascular-related (CV) mortality. Limited reports suggest that AVF creation is associated with hemodynamic changes that impose immediate cardiovascular effects which increase cardiac workload, resulting in left ventricular hypertrophy, the progression of which is associated with CV morbidity, mortality, and all-cause death (5-11).

As an increasing proportion of dialysis patients undergo AVF creation, it is critical to better understand the impact of AVF use on CV-related outcomes in order to help guide clinical decision-making prior to dialysis initiation.

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Conflict of Interest

None.

We have previously described predictors of delayed transition to permanent vascular access among incident hemodialysis patients and extend these observations here to focus on the impact of initial and delayed vascular access type on CV-related mortality (12). We hypothesized that AVF use at dialysis initiation would be associated with increased CV-related mortality, and tested this hypothesis in a contemporary, national cohort of incident hemodialysis patients.

Methods

Study Population and Data Collection

Data for this study were obtained from the Centers for Medicare & Medicaid Services' (CMS) ESRD Clinical Performance Measures (CPM) Project (known prior to as the ESRD Core Indicators Project) and from selected U.S. Renal Data System (USRDS) Standard Analytical Files for the years 1999–2005 (data collected during the years 1998–2004). Since 1994, the ESRD CPM Project has annually collected data on a nationally representative random sample of prevalent adult ESRD patients on hemodialysis in the U.S. Information on vascular access at hemodialysis initiation has been collected since study year 1999. Patients are eligible for inclusion in the ESRD CPM Project sample if they are 18 years of age or older on October 1 and alive on December 31 prior to the study year. Data are collected retrospectively for the time period October–December of the year prior to the study year (i.e., October–December 2004 for Study Year 2005).

Demographic and co-morbid characteristics used in our analysis included age (<54.6, 54.6 to <65.8, 65.8 to <74.5, ≥74.5), gender, race (black, white), pre-ESRD albumin (<3.5 mg/dl, ≥3.5 mg/dl), pre-ESRD hemoglobin (<11 g/dl, ≥11 g/dl), pre-ESRD erythropoietin (yes, no), body mass index (BMI, kg/m²) was classified according to the World Health Organization classification system as underweight (BMI <18.5) normal (BMI 18.5 to <25), overweight (BMI 25 to <30), and obese (BMI ≥ 30), tobacco use (yes, no), diabetes (yes, no), hypertension (yes, no), ischemic heart disease (yes, no), myocardial infarction (yes, no), peripheral vascular disease (yes, no), inability to ambulate (yes, no), congestive heart failure (yes, no), cerebrovascular disease (yes, no), pre-ESRD medical coverage (yes, no), and year of incidence (1998–2004).

Cause of Death Analyses

Previous co-morbidities information was obtained from the USRDS's Patients Standard Analytic File (SAF MEDEVID), which includes information from CMS' 2728 Form. Cardiovascular death was defined as death because of acute myocardial infarction (MI), atherosclerotic heart disease, cardiomyopathy, arrhythmia, cardiac arrest or stroke. Cause and dates of death, obtained from the USRDS PATIENT SAF, were subsequently linked to the clinical information in the ESRD Clinical Performance Measures data file.

Statistical Analysis

Chi-square tests and Mantel-Haenszel odds ratios were used to examine crude associations between patient characteristics and vascular access at initiation of hemodialysis. A *p*-value < 0.05 was considered to be statistically significant. Cox proportional hazards modeling was used to analyze the association between vascular access type and CV-related and all-cause mortality. Patients were considered at risk 90 days after the initiation of ESRD, for ease of interpretation of vascular access exposures and because patients needed to live 90 days to be in the CPM survey, and were censored at the time of non-CV-related death, transplant or the end of the observation period (4 years). A 4-year observation period was chosen because the survival curves for AVG and CVC converged after this time, thereby violating the proportional hazards assumption. Adjustment variables included in the multiple regression model were chosen a priori based on their potential to confound the relationship between vascular access type and

the risk of mortality or based upon their association with time to mortality independent of the predictor of interest.

Results

Study Population

A total of 10,086 incident hemodialysis patients were included in the USRDS Clinical Performance Measures database. After limiting the cohort to black and white patients, 9,100 patients remained. 106 patients were excluded because they were missing co-morbidity, erythropoietin ($n = 119$) or BMI data ($n = 325$), or had a vascular access type other than an AVF, AVG or CVC ($n = 70$). After these exclusions, 8,480 patients remained. Of these, 2,715 did not have albumin or hemoglobin levels either at ESRD initiation or 90 days after dialysis initiation, and 911 did not have vascular access type, leaving 4,854 patients with complete data available for inclusion in the fully adjusted multivariate models.

The baseline characteristics of patients by initial vascular access type are shown in Table 1. Of the 4,854 patients in our cohort, 13.0% used an AVF ($n = 626$), 13.5% used an AVG ($n = 658$) and 73.5% used a CVC ($n = 3570$) at dialysis initiation. Patients with an AVF tended to be younger, were more likely to be male, white and have normal weight (BMI 18.5 to <25). Patients with an AVF were more likely to have normal pre-ESRD serum albumin and hemoglobin levels and more likely to receive pre-ESRD erythropoietin compared with those with an AVG and CVC. Individuals with an incident AVF were more likely to have a history of hypertension, less likely to have diabetes or a history of heart failure compared to those with an AVG or CVC, and as likely to report tobacco use, ischemic heart disease, history of MI, peripheral vascular disease, an inability to ambulate, history of cardiac arrest, and cerebrovascular disease as those with an AVG or CVC (Table 1).

All-Cause Death

As previously reported, all-cause mortality was significantly lower among patients using an AVF. AVF use at 90 days was associated with a 29% reduction in all-cause mortality (CI 0.62, 0.82, $p < 0.0001$) compared with CVC use, while patients using an AVF at dialysis initiation (CI 0.78, 1.13, $p = 0.567$), AVG at dialysis initiation (CI 0.80, 1.06, $p = 0.262$) and AVG use at 90 days (CI 0.82, 1.02, $p = 0.119$) had the same risk of all-cause death as patients using a CVC (data not shown). Fifty-five percent of patients using an AVF 90 days after the start of dialysis survived to the end of the observation period (year 4), while 45.6% and 39.6% with an AVG and CVC, respectively, survived ($p < 0.0001$).

CV-Related Death

Patients who started dialysis with an AVF had a 43% lower risk of CV-related mortality when compared to patients with a CVC (HR = 0.57, CI 0.46, 0.71; $p < 0.001$), while patients with an AVG had a 13% lower CV-related mortality compared to those with a CVC (HR = 0.87, CI 0.74, 1.03; $p = 0.107$) (Model 1, Table 2).

There was a suggestion, albeit statistically nonsignificant, that CV-related mortality was lower among patients with an AVF (HR = 0.80, CI 0.61, 1.04; $p = 0.091$), and with an AVG at 90 days after initiation of ESRD therapy (HR = 0.87, CI 0.71, 1.06; $p = 0.160$) compared with patients with a CVC at 90 days (Model 1, Table 2). When we accounted for the initial access type, the vascular access at 90 days after dialysis initiation conferred greater protection from CV-related mortality than did access type at dialysis initiation. Patients with AVF use 90 days after dialysis initiation were 36% (CI 0.52, 0.78, $p < 0.001$) less likely and patients with an AVG equally likely (CI 0.79, 1.08, $p = 0.333$) to experience CV-related mortality compared with patients dialyzed with a CVC at 90 days after dialysis initiation (Model 3, Table 2).

After adjustment for other patient characteristics, AVF use remained associated with a decreased risk of CV-related mortality among patients using an AVF 90 days after ESRD. (HR = 0.69, CI 0.56, 0.84; $p = 0.0004$). In contrast, AVG use neither at dialysis initiation (HR = 0.89, CI 0.73, 1.09, $p = 0.270$), nor at 90 days (HR = 0.95, CI 0.81, 1.13, $p = 0.532$) was associated with increased CV-mortality compared to CVC use after adjusting for patient characteristics (Table 2, Model 4).

The benefit of an AVF was evident across our time series (Fig. 1). CV-related death was ascertained starting 90 days after ESRD initiation to the end of the observation period (year 4). Among patients using an AVF, 78% were free of CV-related death, compared with 68% of patients using an AVG and 65% of patients using a CVC ($p < 0.0001$). Similar patterns persisted after 4 years.

Black patients were 25% less likely to experience CV-related mortality (CI 0.65, 0.87, $p < 0.001$) than white patients, while those reporting the use of pre-ESRD erythropoietin experienced 13% less CV-related mortality than those without pre-ESRD erythropoietin use (CI 0.76, 0.99, $p = 0.036$) (Table 3). Older age was associated with increased CV-related mortality (HR = 1.03; CI 1.02, 1.03; $p < 0.0001$), while individuals with hypoalbuminemia at dialysis initiation were 21% more likely to experience CV-related death (CI 1.05, 1.38, $p = 0.007$), compared to patients with normal serum albumin. Co-morbid diabetes increased the risk of CV-related mortality by 42% (CI 1.25, 1.62, $p < 0.0001$). Further, patients with ischemic heart disease were 35% more likely to experience CV-related death (CI 1.16, 1.56), compared to those without ischemic heart disease, while patients with heart failure were 27% more likely to die of CV-related causes (CI 1.11, 1.44) than those without heart failure. BMI, hemoglobin at dialysis initiation, tobacco use, hypertension, history of MI, peripheral vascular disease, history of CVD and history of cardiac arrest were not associated with CV-related mortality.

Discussion

The principal finding from our study was that AVF use among a nationally representative cohort of incident hemodialysis patients was not associated with either a short- or long-term increase in the risk of CV-related mortality, and therefore, our findings did not support our hypothesis. On the contrary, AVF use 90 days after the initiation of hemodialysis was associated with reduced cardiovascular and all-cause mortality, independent of known risk factors. We observed that while permanent vascular access use at the start of ESRD confers a marginal reduction in CV-related mortality, AVF use 90 days after dialysis initiation confers a 31% reduction in CV-related mortality, when compared with CVC use at 90 days. These findings are interesting, given the higher prevalence of hypertension among patients reporting AVF use at dialysis initiation, and the comparable prevalence of ischemic heart disease, MI, peripheral vascular disease, history of cardiac arrest, and cerebrovascular disease found among AVF, AVG and CVC patients in our patient cohort.

Our study is one of few to specifically estimate the association between AVF use and CV-related mortality. In the USRDS Morbidity and Mortality Study Wave 1, Dhingra et al. found that prevalent diabetic ESRD patients with a CVC were 47% more likely to experience a CV-related death than diabetic patients using an AVF, while nondiabetic patients using a CVC had a 38% greater risk of CV-related death compared with AVF patients (3). Dhingra's report lacked predialysis quality of care indicators, such as pre-ESRD serum albumin and hemoglobin, and limited follow-up time to 24 months, while ours extends follow-up to 48 months. Furthermore, cohort characteristics differ between the present study and that of Dhingra et al. Incident patients reporting AVF use in our study had a similar burden of co-morbid conditions compared with patients using a CVC, while Dhingra's 1993 report found that patients using an AVF had a lower prevalence of diabetes, peripheral vascular disease, coronary artery disease and

congestive heart failure (3). Despite cohort differences between the two studies, our findings are comparable. The burden of disease shared among patients with different vascular access types in our more contemporary patient cohort may reflect the increasing number of co-morbid conditions found among the incident U.S. hemodialysis population (13). It is less likely to be accounted for by the current national efforts at increasing the prevalence of AVFs, and consequent reduction in selecting only healthy patients, as the distribution of a subgroup of incident dialysis patients reporting AVF use by Dhingra is similar to the current patient cohort (15% vs. 12%), respectively.

In a USRDS Wave II study, the association of AVF use and heart disease were examined among elderly ESRD patients, however, unlike our findings, no significant association was found between CV-related survival and vascular access type (14). This study had a limited sample size and included only Medicare-eligible patients, resulting in an older patient cohort than the present study.

Our study further delineates patient characteristics associated with CV-related mortality. Decreased CV-related and all-cause death was associated with black race, younger age, and pre-ESRD erythropoietin use, while patients with low pre-ESRD serum albumin, diabetes, ischemic heart disease, and congestive heart failure had a greater risk of CV-related and all-cause death. These findings are similar to previous reports in which black ESRD patients were less likely to experience cardiac death compared with white patients, and younger age and pre-ESRD erythropoietin were associated with lower CV-related death (1,15-19).

Multiple possible explanations exist for the association between AVF use and decreased risk of CV-related death. These may include greater delivered dose of dialysis because of better blood flow rates among patients with AVF use, reduced risk of infection, and lower levels of inflammatory factors which may be responsible for CV-mediated disease (4,20-24). Limited, short-term studies have examined the association of AVF creation with cardiovascular performance, and report an increase in volume load and left ventricular hypertrophy within three months of AVF creation, and persistently reduced myocardial oxygen supply over a 6-month study period, suggesting that patients with AVF use may be more likely to experience CV-related death (5,7,8). However, our findings suggest that these detrimental cardiovascular changes may attenuate over time. This concept is supported by Mahmoud et al. who observed that left ventricular performance was improved, and ATP depletion and cardiac infarct size were significantly lower following ischemia and reperfusion injury 8 weeks after AVF creation in a canine model, compared with a sham-operated group. This observation was thought to occur, in part, by the development of coronary collaterals, which may serve to protect the myocardium during cardiac stress (25).

The significant reduction in CV-related death was observed only among patients reporting AVF use 90 days after dialysis initiation. This finding is likely attributable to death within the first 120 days of dialysis initiation, when a majority of first-year deaths occur, and when CVC use increases the risk of early mortality (26,27).

Several limitations to our observations should be noted. First, the study design is observational, and may reflect selection bias. While our patients in the different vascular access categories had a similar distribution of many co-morbid conditions, we attempted to address the issue of bias by controlling for co-morbidities that could influence vascular access type. While differences were seen between vascular access types and the proportion of patients with hypoalbuminemia, anemia, diabetes, hypertension, and history of MI, these co-morbidities were not found to be significantly associated with vascular access type among incident hemodialysis patients (12). Further, data from the DOPPS does not support the belief that AVF creation is more likely to occur amongst the healthiest patients. Pisoni et al. reported that AVF

use in the U.S was low even among patients who lack diabetes, CAD and peripheral vascular disease, and these co-morbidities were not associated with vascular access use among prevalent patients in the DOPPS study (28).

Second, we are unable to specifically address the pathophysiology by which AVFs may be associated with lower CV-related mortality. Our findings have implications for outcomes research, and raise etiologic questions that would incorporate literature suggesting that AVF creation leads to an increase in flow-mediated CV stress, but that additional factors exist which are protective (7,8,14). Although this study has limitations, it examines a nationally representative cohort of incident hemodialysis patients, and is generalizable to the U.S. adult hemodialysis population.

In conclusion, we found that incident hemodialysis patients who have delayed AVF use 90 days after initiation of ESRD therapy experience a significant reduction in CV-related and all-cause mortality compared with ESRD patients who report CVC use. This decreased risk of mortality was independent of the effects of other known risk factors. Our findings suggest that vascular access type influences cause-specific mortality beyond that of infection, and support existing guidelines recommending the use of an AVF early in the course of chronic ESRD therapy.

Acknowledgments

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Cardiovascular death

Fig. 1. Survival curve for cardiovascular death by vascular access type starting 90 days after dialysis initiation. Observations used in the Cox proportional hazards model were censored at 4 years.

TABLE 1
Characteristics of study cohort at baseline by vascular access type

Characteristic	Total cohort n = 4854	AVF cohort n = 626	AVG cohort n = 658	CVC cohort n = 3570	Chi-square p-value
Age	63.3 ± 15.1	62.2 ± 14.5	64.9 ± 13.6	63.2 ± 15.5	0.005
Sex					
Female	2239 (46.1)	199 (31.8)	363 (55.2)	1677 (47.0)	<0.001
Male	2615 (53.9)	427 (68.2)	295 (44.8)	1893 (53.0)	
Race					
Black	1613 (33.2)	164 (26.2)	257 (39.1)	1192 (33.4)	<0.001
White	3241 (66.8)	462 (73.8)	401 (60.9)	2378 (66.6)	
Serum albumin (g/dl)					
Low (<3.5)	3246 (66.9)	300 (47.9)	383 (58.2)	2563 (71.8)	<0.001
Normal (≥3.5)	1608 (33.1)	326 (52.1)	275 (41.8)	1007 (28.2)	
Hemoglobin (g/dl)					
Low (<11)	3717 (76.6)	430 (68.7)	494 (75.1)	2793 (78.2)	<0.001
Normal (≥11)	1137 (23.4)	196 (31.3)	164 (24.9)	777 (21.8)	
Pre-ESRD EPO					
Yes	1525 (31.4)	280 (44.7)	248 (37.7)	997 (27.9)	<0.001
No	3329 (68.6)	346 (55.3)	410 (62.3)	2573 (72.1)	
BMI class					
Under (<18.5)	261 (5.4)	29 (4.6)	31 (4.7)	201 (5.6)	0.001
Normal (18.5 to <25)	1413 (29.1)	211 (33.7)	173 (26.3)	1029 (28.8)	
Over (25 to <30)	1433 (29.5)	171 (27.3)	237 (36.0)	1025 (28.7)	
Obese (≥30)	1747 (36.0)	215 (34.4)	217 (33.0)	1315 (36.8)	
Smoke					
Yes	297 (6.1)	47 (7.5)	31 (4.7)	219 (6.1)	0.112
No	4557 (93.9)	579 (92.5)	627 (95.3)	3351 (93.9)	
Diabetes					
Yes	2477 (51.0)	299 (47.8)	376 (57.1)	1802 (50.5)	0.002
No	2377 (49.0)	327 (52.2)	282 (42.9)	1768 (49.5)	
Hypertension					
Yes	3917 (80.7)	530 (84.7)	533 (81.0)	2854 (79.9)	0.022

Characteristic	Total cohort n = 4854	AVF cohort n = 626	AVG cohort n = 658	CVC cohort n = 3570	Chi-square p-value
No	937 (19.3)	96 (15.3)	125 (19.0)	716 (20.1)	
Ischemic heart disease					
Yes	1232 (25.4)	150 (24.0)	147 (22.3)	935 (26.2)	0.078
No	3622 (74.6)	476 (76.0)	511 (77.7)	2635 (73.8)	
MI					
Yes	451 (9.3)	67 (10.7)	47 (7.1)	337 (9.4)	0.075
No	4403 (90.7)	559 (89.3)	611 (92.9)	3233 (90.6)	
Peripheral vascular disease					
Yes	703 (14.5)	83 (13.3)	85 (12.9)	535 (15.0)	0.248
No	4151 (85.5)	543 (86.7)	573 (87.1)	3035 (85.0)	
Inability to ambulate					
Yes	167 (3.4)	14 (2.2)	19 (2.9)	134 (3.8)	0.111
No	4687 (96.6)	612 (97.8)	639 (97.1)	3436 (96.3)	
Cardiac arrest					
Yes	42 (0.9)	7 (1.1)	2 (0.3)	33 (0.9)	0.220
No	4812 (99.1)	619 (98.9)	656 (99.7)	3537 (99.1)	
Heart failure					
Yes	1595 (32.9)	164 (26.2)	207 (31.5)	1224 (34.3)	<0.001
No	3259 (67.1)	462 (73.8)	451 (68.5)	2346 (65.7)	
Cerebrovascular disease					
Yes	436 (9.0)	53 (8.5)	71 (10.8)	312 (8.7)	0.213
No	4418 (91.9)	573 (91.5)	587 (89.2)	3258 (91.3)	
Insurance coverage					
Yes	4444 (91.6)	583 (93.1)	616 (93.6)	3245 (90.9)	0.022
No	410 (8.4)	43 (6.9)	42 (6.4)	325 (9.1)	

Values are expressed as mean $\pm$ SD or n (%).

To convert albumin and hemoglobin in g/dl to g/l, multiply by 10.

TABLE 2

Risk of CV-related mortality by vascular access type

Vascular access type	Model 1 unadjusted HR (95% CI) ^a	Model 2 unadjusted HR (95% CI) ^b	Model 3 unadjusted HR (95% CI) ^c	Model 4 adjusted HR (95% CI) ^d
Vascular access at initiation				
AVF vs. CVC	0.57 (0.46, 0.71) *	0.58 (0.49, 0.68) *	0.80 (0.61, 1.04)	0.85 (0.65, 1.11)
AVG vs. CVC	0.87 (0.74, 1.03)	0.87 (0.76, 1.00)	0.87 (0.71, 1.06)	0.89 (0.73, 1.09)
Vascular access at 90 days				
AVF vs. CVC			0.64 (0.52, 0.78) *	0.69 (0.56, 0.84) *
AVG vs. CVC			0.93 (0.79, 1.08)	0.95 (0.81, 1.11)

^aExposure is access at ESRD initiation.^bExposure is access at 90 days.^cExposures are access at initiation and 90 days.^dExposures are access at initiation and 90 days, adjusted for age, sex, race, and co-morbidities.* Indicates *p*-value < 0.05.

TABLE 3Adjusted risk of CV-related mortality by patient characteristic^a

Patient characteristics	CV mortality	
	HR (95% CI)	P-value
Female vs. male	1.01 (0.88, 1.14)	0.929
Black vs. white	0.75 (0.65, 0.87)	<0.0001
Age (for 1 year increase)	1.03 (1.02, 1.03)	<0.001
BMI		
Under vs. normal	1.27 (0.98, 1.65)	0.071
Overweight vs. normal	0.98 (0.84, 1.13)	0.744
Obese vs. normal	0.93 (0.79, 1.09)	0.382
Serum Albumin		
Low vs. normal	1.21 (1.05, 1.38)	0.007
Hemoglobin		
Low vs. normal	1.16 (1.0, 1.34)	0.053
Smoke use	1.28 (1.00, 1.64)	0.049
Pre-ESRD erythropoietin	0.87 (0.76, 0.99)	0.036
Diabetes	1.42 (1.25, 1.62)	<0.0001
Hypertension	0.88 (0.76, 1.03)	0.103
Ischemic heart disease	1.35 (1.16, 1.56)	<0.0001
Myocardial infarction	1.12 (0.92, 1.35)	0.259
Peripheral vascular disease	1.13 (0.96, 1.33)	0.148
Cerebrovascular disease	1.02 (0.84, 1.24)	0.853
Cardiac arrest	1.16 (0.64, 2.10)	0.635
Congestive heart failure	1.27 (1.11, 1.44)	0.0004

^a Adjusted for age, sex, race, and co-morbidities.