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Radiocephalic Arteriovenous Fistula Patency and Use

A Post Hoc Analysis of Multicenter Randomized Clinical Trials

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Objective: We sought to confirm and extend the understanding of clinical outcomes following creation of a common distal autogenous access, the radiocephalic arteriovenous fistula (RCAVF).

Background: Interdisciplinary guidelines recommend distal autogenous arteriovenous fistulae as the preferred hemodialysis (HD) access, yet uncertainty about durability and function present barriers to adoption.

Methods: Pooled data from the 2014-2019 multicenter randomized-controlled PATENCY-1 and PATENCY-2 trials were analyzed. New RC-AVFs were created in 914 patients, and outcomes were tracked prospectively for 3-years. Cox proportional hazards and Fine-Gray regression models were constructed to explore patient, anatomic, and procedural associations with access patency and use.

Results: Mean (SD) age was 57 (13) years; 45% were on dialysis at baseline. Kaplan-Meier estimates of 3-year primary, primary-assisted, and secondary patency were 27.6%, 56.4%, and 66.6%, respectively. Cause-specific 1-year cumulative incidence estimates of unassisted and overall RC-AVF use were 46.8% and 66.9%, respectively. Patients with larger baseline cephalic vein diameters had improved primary (per mm, hazard ratio [HR] 0.89, 95% confidence intervals 0.81–0.99), primary-assisted (HR 0.75, 0.64–0.87), and secondary (HR 0.67, 0.57–0.80) patency; and higher rates of unassisted (subdistribution hazard ratio 1.21, 95% confidence intervals 1.02–1.44) and overall RCAVF use (subdistribution hazard ratio 1.26, 1.11–1.45). Similarly, patients not requiring HD at the time of RCAVF creation had better primary, primary-assisted, and secondary patency. Successful RCAVF use occurred at increased rates when accesses were created using regional anesthesia and at higher volume centers.

Conclusions: These insights can inform patient counseling and guide shared decision-making regarding HD access options when developing an individualized end-stage kidney disease life-plan.

Keywords: arteriovenous fistula, Chronic kidney disease, hemodialysis access, maturation, patency, radiocephalic, use

INTRODUCTION

Despite continued advances in medical therapy, kidney disease remained a leading cause of death in the United States in 2020, and its incidence continues to rise.[1,2] Most patients with end-stage kidney disease (ESKD) require hemodialysis (HD), and guidelines recommend distal autogenous arteriovenous fistula (AVF) as the preferred access; however, about 80% of patients initiate HD with a central venous catheter (CVC).[2] The reasons underlying suboptimal utilization of AVFs are complex, but major contributors include inherent difficulties with creation and maintenance of a reliable distal AVF. Radiocephalic AVF (RC-AVF) at the wrist or forearm is a commonly used distal AVF.[3] However, RC-AVFs have a high rate of primary failure, and uncertain long-term durability.[4] An improved understanding of the challenges and opportunities related to RC-AVF creation and maintenance will bring us closer to providing optimal care for the growing number of kidney disease patients in the United States.

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Trial registration: ClinicalTrials.gov; PATENCY-1 (https://clinicaltrials.gov/ct2/show/NCT02110901) and PATENCY-2 (https://clinicaltrials.gov/ct2/show/NCT02414841).

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PH and PY drafted the manuscript text and contributed equally to this work. PH and MAH performed statistical analyses. DMH, SKB, MB, and CKO substantially contributed to data acquisition and study design. All authors contributed to conception and interpretation of the work, manuscript revision, final approval, and attest to the works' accuracy and integrity.

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To help improve patient selection for RC-AVF, several studies have worked to identify preoperative risk factors predictive of failure, but have often been limited by small sample sizes, short follow-up duration, retrospective design, and heterogeneity in inclusion criteria.[5–7] Additionally, improved ESKD management and decreased mortality in conjunction with a steady incidence of ESKD has resulted in a progressively more comorbid dialysis population, making extensions from data collected in prior decades difficult to apply to the current generation of patients with ESKD.[8] The objective of this study was to describe and explore contemporary intermediate-term outcomes of chronic kidney disease patients receiving new RC-AVFs using patient-level data from two large multicenter prospective randomized clinical trials, PATENCY-1 and PATENCY-2.[9,10]

METHODS

Data Source and Study Design

PATENCY-1 (trial registration: ClinicalTrials.gov; no. NCT02110901) and PATENCY-2 (no. NCT02414841) were multicenter, prospective, double-blind, placebo-controlled, randomized trials conducted between 2014 and 2019 across 31 and 39 centers, respectively, in the United States and Canada. Details on the design and results of these studies have been previously published.[9,10] Briefly, 914 patients (311 in PATENCY-1; 603 in PATENCY-2) ultimately received vonapanitase (a recombinant human elastase) or placebo intraoperatively after creation of a new RC-AVF. The trials did not demonstrate an effect of vonapanitase on RC-AVF-related outcomes at 1 year, and further investigation of the drug was ultimately abandoned. Additional details regarding the trials can be found in the Supplemental Methods 1 (http://links.lww.com/AOSO/A164). The original publications of these trials reflected a maximum follow-up duration of 12 months. In the present analysis, data from both trials were pooled and follow up extended to 3 years.

The goal of the present study was to describe intermediate-term RC-AVF-specific clinical outcomes in a large cohort of patients with newly created RC-AVFs. Additionally, we sought to explore clinical, anatomic, and procedural factors which may be associated with RC-AVF-specific clinical outcomes. All trial participants who received treatment were included in our analyses of RC-AVF patency, and the subgroup with prevalent HD was included in analyses of RC-AVF use (Figure 1). The Mass General Brigham human research committee Institutional Review Board approved the study protocol to use previously collected data without further informed consent.

Outcome Measures: RC-AVF Patency and Use

Outcomes included time from RC-AVF creation to loss of primary, primary-assisted, and secondary patency. Patency definitions used in this study align with established standards for reporting outcomes in HD access (see Supplemental Methods 1, http://links.lww.com/AOSO/A164).[3,11] Median follow up was calculated using the reverse Kaplan-Meier method.

Time from RC-AVF creation to unassisted and overall use was analyzed in trial participants with prevalent HD requirements at the time of RC-AVF creation. The date of successful RC-AVF use was defined as the first day of a consecutive 90-day period where the RC-AVF was successfully used for all prescribed HD sessions. Unassisted use means that no procedural interventions on the access preceded successful use. Censoring occurred with loss-to-follow up, withdrawal, or at study end, and competing risk analysis was used to account for loss of access patency, renal transplantation, and death.

Finally, patients with incident HD requirements were included in an analysis of whether the study RC-AVF could be successfully used within the first 30 days of HD eligibility. The first day of HD eligibility was defined as the earlier of the day of catheter insertion for HD or the day of first attempted RC-AVF use.

Exposures

We examined the following patient-level covariates at baseline: age, sex, non-White race, ongoing tobacco smoking, diabetes, and HD status (on HD at the time of RC-AVF creation). Due to limitations in the trial dataset with low frequency of many race categories, race was dichotomized as white and non-White. Procedural and anatomic factors investigated included the type of anesthesia, the location of RC-AVF, and intraoperative vessel diameter. Vessel measurements were performed by the operating surgeon prior to vein transection and arteriotomy. Finally, we assessed site enrollment volume (divided into terciles). These covariates were strategically selected with a desire for model

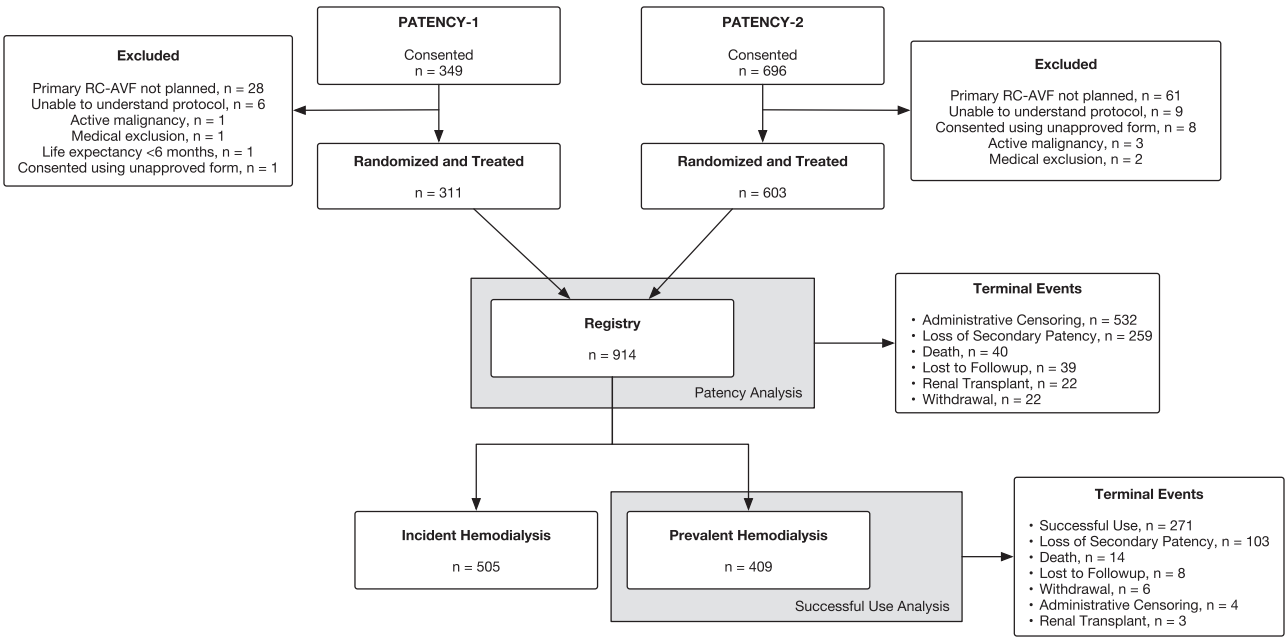

FIGURE 1. Diagram of participant flow through the study.

parsimony, and selection was based on clinical expertise and prior literature identifying them as potential predictors of outcomes after RC-AVF creation.

Statistical Analysis

To identify characteristics associated with loss of patency, we constructed multivariable Cox proportional hazards regression models using the study covariates outlined above. The maximum number of covariates considered for each model was determined by the number of observed events; no fewer than 15 events of interest were observed for each covariate. In addition to the covariates above, a time-dependent covariate was used to adjust for attempted access use (as a proxy for cannulation trauma) in all models for patency. Kaplan-Meier survival curves with at-risk tables were constructed to establish overall estimated primary, primary-assisted, and secondary patency extended to 3 years. Additional Kaplan-Meier survival curves were generated for each patency outcome stratified by intraoperative vein diameter tercile, as well as corresponding adjusted marginal survival curves based on the Cox proportional hazards models.

To identify characteristics associated with differences in the rates of successful AVF use, we constructed Fine-Gray subdistribution hazard models to account for the competing risk of AVF patency loss. All analyses of successful AVF use were performed in the subset of patients with prevalent HD at the time of access creation to avoid immortal time bias from patients who had their RC-AVF created prior to progression to chronic HD. Outcomes examined were unassisted and overall AVF use, and the competing risks were loss of patency (primary patency for unassisted, secondary patency for overall), renal transplant, and death. We plotted cause-specific Aalen-Johansen cumulative incidence functions for successful RC-AVF use, as well as adjusted cumulative incidence functions estimates from the Fine-Gray subdistribution hazard models stratified by covariates of interest.

Finally, multivariable logistic regression models were constructed to identify characteristics associated with successful RC-AVF use (unassisted and overall) within the first 30 days of HD eligibility for those patients who were not yet requiring HD at the time of RC-AVF creation. The logistic regression models included maturation time prior to attempted RC-AVF use.

All multivariable models were adjusted for vonapanitase administration, the trial drug. After examination of the time-to-event main-effects models, separate models with interaction terms were built to explore effect modification between vein and artery diameter, as well as vein diameter and HD status. A complete-case strategy was used for missing data due to low missingness. All statistical tests were two-sided with an alpha level of 0.05. Analyses were performed using R (version 4.0.5) and the packages *tidyverse*, *survival*, *survminer,* and *cmprsk*.[12]

RESULTS

Patient and Procedural Characteristics

Baseline demographic and clinical characteristics are summarized in Table 1. Median follow-up time was 707 days (25th–75th percentile 447–1066) overall and 638 (450–994) in the subgroup of patients with prevalent HD requirements. Only 0.32% of the overall and 0.48% of the prevalent HD cohorts had any missing covariate data. The mean (standard deviation) intraoperative cephalic vein and radial artery diameters were 3.37 mm (0.82) and 2.75 mm (0.67), respectively. Nearly all radial arteries (97%) measured greater than 2 mm in diameter. Approximately three quarters of RC-AVFs were located at wrist (distal one-third of forearm); 24.1% in the forearm (proximal two-thirds of forearm); and only 2.7% were snuffbox RC-AVF.

Summary of Patency and Use Outcomes

Kaplan-Meier estimates for RC-AVF patency are shown in Figure 2. At 3 years, about one-third of RC-AVFs were estimated to be patent without need for intervention. Two-thirds of RC-AVFs were estimated to have maintained secondary patency at 3 years (66.6%, 95% confidence intervals [CI]: 63.1–70.4). The trial registry stopped following many patients just short of a full 3 years of follow up, and about 89.9% of the risk set present at 2.5 years underwent administrative censoring prior to reaching 3 years. Cause-specific cumulative incidence function estimates for successful unassisted and overall AVF use are shown in Figure 3. By 1 year, 66.9% (62.0–71.3) of accesses were estimated to have been used successfully, and 46.8% (41.8–51.7) of accesses were used without a preceding intervention.

RC-AVF Patency Models

Larger intraoperative vein diameter and incident HD status were most robustly associated with improved primary, primary-assisted, and secondary patency (Table 2). Incident HD status conferred an estimated 38% (adjusted hazard ratio [HR] 0.62, 95% CI: 0.52–0.75), 28% (HR 0.72, 0.55–0.93), and 31% (HR 0.69, 0.52–0.92) reduced hazard for loss of primary, primary-assisted, and secondary patency, respectively. Likewise, each 1mm increase in cephalic vein diameter was associated with an 11% (HR 0.89, 95% CI: 0.81–0.99), 25% (HR 0.75, 0.64–0.87), and 33% (HR 0.67, 0.57–0.80) decrease in the hazard of loss of primary, primary-assisted, and secondary patency, respectively (Figure 4). Female sex was associated with a 24% (HR 1.24, 1.01–1.53) increased hazard of primary patency loss—this association was consistent for primary-assisted (HR 1.24, 0.93–1.64) and secondary patency (HR 1.20, 0.89–1.63), although the range of plausible associations included a very small beneficial association, no effect, or a moderate to large harmful association. Interestingly, each 1 mm increase in artery diameter was associated with a 25% (HR 1.25, 1.05–1.49) increase in the hazard of primary-assisted patency loss, and increased artery diameter appeared to have either no association with or a small negative association with primary and secondary patency. Notably, we did not detect any association between loss of patency and age, smoking status, diabetes, or any other covariates explored.

RC-AVF Use Models

Covariates associated with increased incidence of successful unassisted and overall RC-AVF use were male sex, larger vein diameter, smaller artery diameter, regional anesthesia, and RC-AVF creation at a site in the upper tercile of enrollment volume (Table 3). Diabetes was associated with a 33% decrease in the relative incidence of unassisted RC-AVF use, but did not appear to be associated with a change in the incidence of overall RC-AVF use. Female sex had the largest magnitude of association with the relative incidence of both unassisted (subdistribution hazard ratio [$_{SD}$HR] 0.45, 95% CI: 0.31–0.67) and overall RC-AVF use ($_{SD}$HR 0.55, 95% CI: 0.41–0.75; Supplemental Figure 2, http://links.lww.com/AOSO/A164). When compared to sites enrolling the fewest patients in the trials (≤20 patients), sites enrolling ≥50 patients had an increased relative incidence of successful unassisted ($_{SD}$HR 1.65, 95% CI: 1.14–2.38) and overall ($_{SD}$HR 1.64, 95% CI: 1.21–2.24) RC-AVF use. We did not detect an association between the relative incidence of successful unassisted or overall RC-AVF use and age, non-White race, active smoking, or RC-AVF location. Results of the analyses of

TABLE 1.

Demographics, Comorbidities, Anatomic, and Procedural Summary Statistics

		HD Status	
	Totals*	Prevalent HD*	Incident HD*
Characteristic	**N = 914**	**N = 409**	**N = 505**
Age (yrs)	57 (13)	55 (14)	59 (13)
Sex (female)	203 (22%)	96 (23%)	107 (21%)
Race			
African American	219 (24%)	122 (30%)	97 (19%)
Asian American	36 (3.9%)	17 (4.2%)	19 (3.8%)
Indian Subcontinent	4 (0.4%)	3 (0.7%)	1 (0.2%)
Middle-Eastern	4 (0.4%)	0 (0%)	4 (0.8%)
North American or Alaska Native	5 (0.5%)	0 (0%)	5 (1.0%)
Other	21 (2.3%)	9 (2.2%)	12 (2.4%)
Pacific Islander	6 (0.7%)	2 (0.5%)	4 (0.8%)
White	619 (68%)	256 (63%)	363 (72%)
Hispanic	156 (17%)	85 (21%)	71 (14%)
BMI (kg/m^2)	31 [26, 37]	30 [25, 36]	32 [27, 37]
Smoking status			
Current	131 (14%)	64 (16%)	67 (13%)
Former	403 (44%)	174 (43%)	229 (45%)
Never	380 (42%)	171 (42%)	209 (41%)
Medical history			
Diabetes	580 (63%)	243 (59%)	337 (67%)
Hypertension	885 (97%)	393 (96%)	492 (97%)
Heart failure	252 (28%)	126 (31%)	126 (25%)
Coronary artery disease	260 (28%)	115 (28%)	145 (29%)
Medications			
Any antithrombotic	499 (55%)	213 (52%)	286 (57%)
Aspirin	417 (46%)	181 (44%)	236 (47%)
Statin	499 (55%)	177 (43%)	322 (64%)
Renal disease history			
Prior renal transplant	37 (4.0%)	17 (4.2%)	20 (4.0%)
Prevalent HD	409 (45%)	–	–
Duration of prior HD (mo)	–	9 [5, 19]	–
Current or prior CVC	444 (49%)	401 (98%)	43 (8.5%)
Current or prior ipsilateral CVC	124 (14%)	122 (30%)	2 (0.4%)
Location of AVF			
Wrist	669 (73%)	290 (71%)	379 (75%)
Forearm	220 (24%)	106 (26%)	114 (23%)
Snuffbox	25 (2.7%)	13 (3.2%)	12 (2.4%)
Vein diameter, intraoperative			
≥4.0 mm	282 (31%)	118 (29%)	164 (32%)
3.0–3.9 mm	451 (49%)	198 (48%)	253 (50%)
<3.0 mm	181 (20%)	93 (23%)	88 (17%)
Artery diameter, intraoperative			
≥3.0 mm	433 (48%)	180 (44%)	253 (50%)
2.0–2.9 mm	450 (49%)	210 (52%)	240 (48%)
<2.0 mm	28 (3.1%)	17 (4.2%)	11 (2.2%)
Anesthesia			
General	205 (22%)	96 (23%)	109 (22%)
Regional	216 (24%)	313 (77%)	396 (78%)
Site enrollment volume			
Lower (≤20)	316 (35%)	133 (33%)	183 (36%)
Mid (21–49)	303 (33%)	116 (28%)	187 (37%)
Upper (≥50)	295 (32%)	160 (39%)	135 (27%)

*Mean (SD); n (%); Median [IQR].

Presented as totals, as well as stratified by HD status at time of RC-AVF creation.

AVF indicates autogenous arteriovenous fistula; BMI, body mass index; CVC, central venous catheter; HD, hemodialysis; IQR, interquartile range; RC-AVF, radiocephalic AVF.

both effect modification and RC-AVF use within 30 days of HD eligibility among those with incident HD requirements can be found in Supplemental Digital Content 1 (http://links.lww.com/AOSO/A164) and Supplemental Digital Content 4 (http://links.lww.com/AOSO/A164).

DISCUSSION

In the present study, we report observational findings from an exploratory analysis of high-quality randomized clinical trial data in a large cohort of chronic kidney disease patients undergoing new radiocephalic arteriovenous fistula creation. Our study adds to what is known about autogenous radiocephalic HD access outcomes by extending follow up to 3 years while incorporating granular patient-level detail with a low degree of missingness and high internal validity.

Broadly, we report acceptable secondary patency at three years (66.6%, 95% CI: 63.1–70.4; Figure 2) and successful use at one year (66.9%, 62.0–71.3; Figure 3). Our estimates of secondary patency appear higher than historical estimates (69.5% vs. 53–58% at 2 years), but in the context of lower primary patency (37.7% vs. 55–63% at 1 year).[4,13,14] Although we are

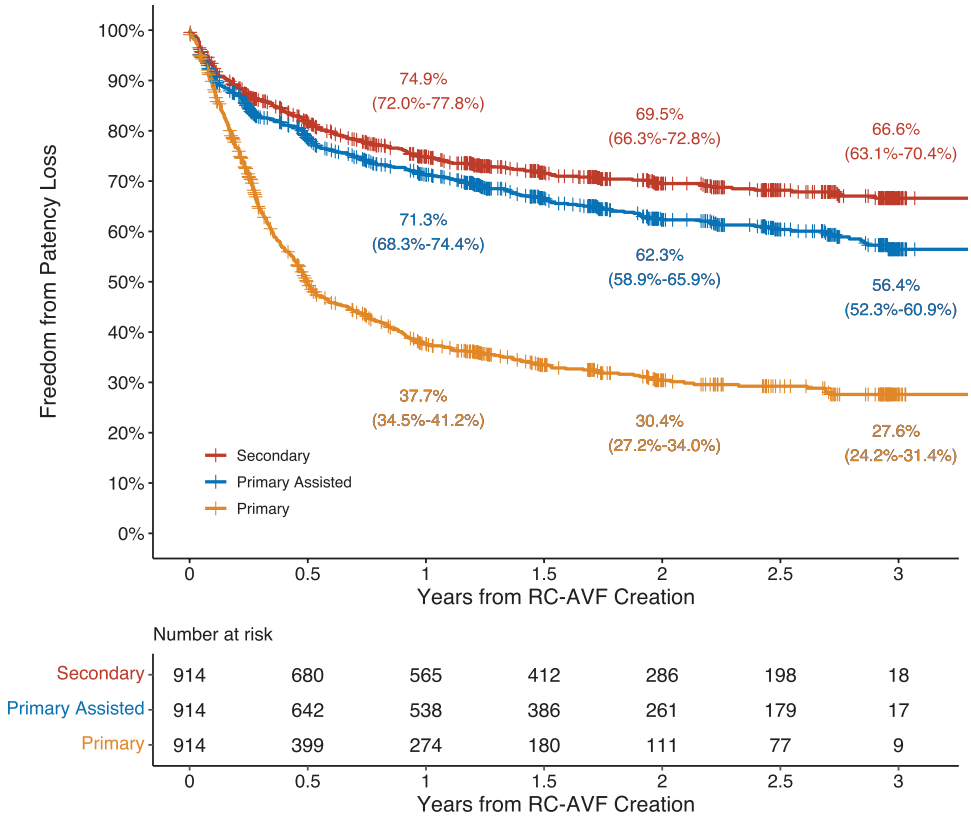

FIGURE 2. Kaplan-Meier survival estimates and corresponding at-risk table for primary, primary-assisted, and secondary patency. Ticks represent censoring events. Patency estimates with 95% confidence intervals at 1-, 2-, and 3 years are labeled explicitly.

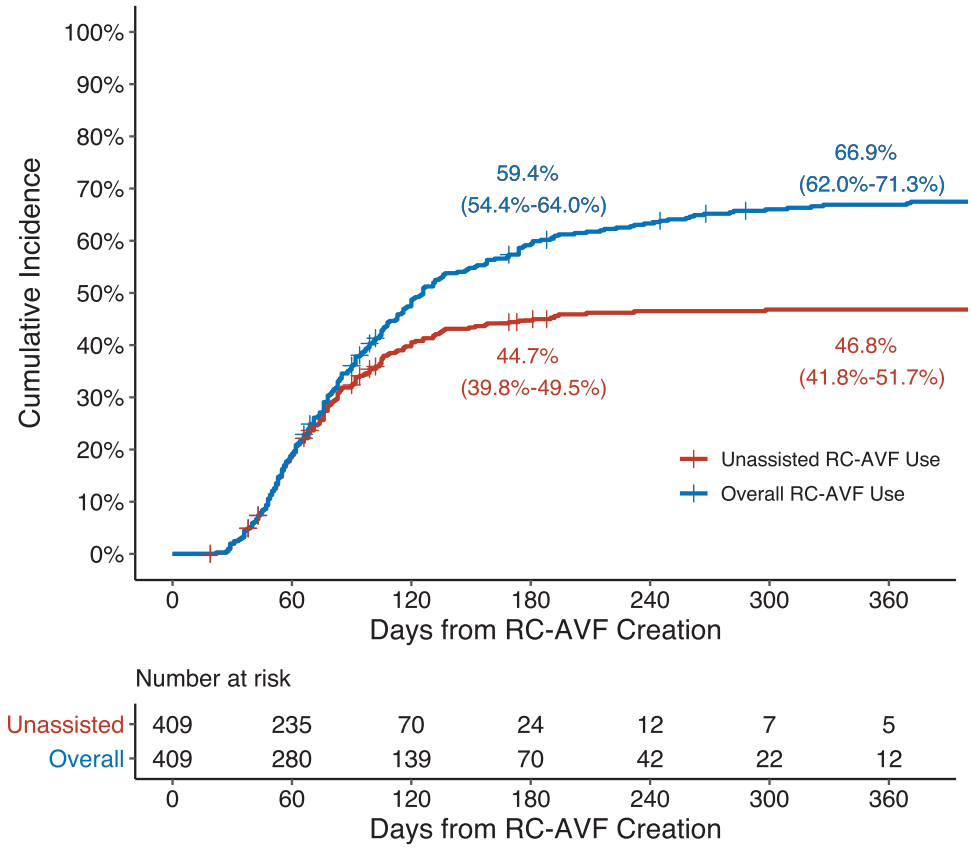

FIGURE 3. Cause-specific cumulative incidence functions and corresponding at-risk table for successful radiocephalic AVF use in patients with prevalent hemodialysis at the time of AVF creation. Ticks represent censoring events. Curves for competing risks not displayed. Cumulative incidence estimates with 95% confidence intervals at 6 months and 1 year are labeled explicitly. AVF, arteriovenous fistula.

TABLE 2.

Cox Proportional Hazards Model Summaries for Time-to-loss of Primary, Primary-assisted, and Secondary Patency After Radiocephalic AVF Creation

	Primary			Primary Assisted			Secondary		
Covariates	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (yrs)	0.99	0.99–1.00	0.094	1.00	0.99–1.01	0.4	1.00	0.99–1.01	0.5
Sex (female)	1.24	1.01–1.53	0.041	1.24	0.93–1.64	0.14	1.20	0.89–1.63	0.2
Race (Non-White)	0.98	0.82–1.17	0.8	1.07	0.85–1.35	0.6	0.96	0.74–1.25	0.8
Current smoker	0.90	0.71–1.14	0.4	1.03	0.76–1.40	0.8	0.96	0.67–1.35	0.8
Diabetes	1.20	1.00–1.46	0.054	1.06	0.83–1.36	0.7	1.02	0.78–1.34	0.9
Coronary artery disease	1.14	0.94–1.37	0.2	0.88	0.67–1.16	0.4	0.80	0.59–1.08	0.2
Daily antithrombotic	0.92	0.77–1.11	0.4	0.82	0.64–1.06	0.13	0.93	0.71–1.23	0.6
Daily statin	1.19	0.99–1.44	0.065	1.14	0.88–1.47	0.3	1.03	0.78–1.37	0.8
Incident HD*	0.62	0.52–0.75	<0.001	0.72	0.55–0.93	0.011	0.69	0.52–0.92	0.011
AVF location									
Wrist/Snuffbox	–	–		–	–		–	–	
Forearm	0.96	0.78–1.19	0.7	1.00	0.75–1.32	>0.9	1.00	0.73–1.37	>0.9
Vein diameter (mm)	0.89	0.81–0.99	0.036	0.75	0.64–0.87	<0.001	0.67	0.57–0.80	<0.001
Artery diameter (mm)	1.15	1.00–1.32	0.058	1.25	1.05–1.49	0.011	1.18	0.97–1.44	0.092
Anesthesia (regional)†	0.93	0.76–1.14	0.5	0.79	0.61–1.02	0.069	0.77	0.58–1.03	0.075
Site enrollment volume									
Lower (≤20)	–	–		–	–		–	–	
Mid (21–49)	1.03	0.84–1.25	0.8	0.77	0.59–1.02	0.067	0.74	0.54–1.01	0.059
Upper (≥50)	0.94	0.76–1.17	0.6	0.82	0.62–1.09	0.2	0.76	0.56–1.03	0.073

Interpretation note: HR < 1 indicates longer time until loss of patency. All models additionally adjusted for vonapanitase (trial drug) administration. A time-dependent covariate for first attempted cannulation was used to adjust for cannulation trauma.

*No chronic intermittent HD requirement at time of AVF creation, reference = prevalent HD

†Reference level: General anesthesia

AVF indicates arteriovenous fistula; CI = confidence interval; HD, hemodialysis; HR = hazard ratio.

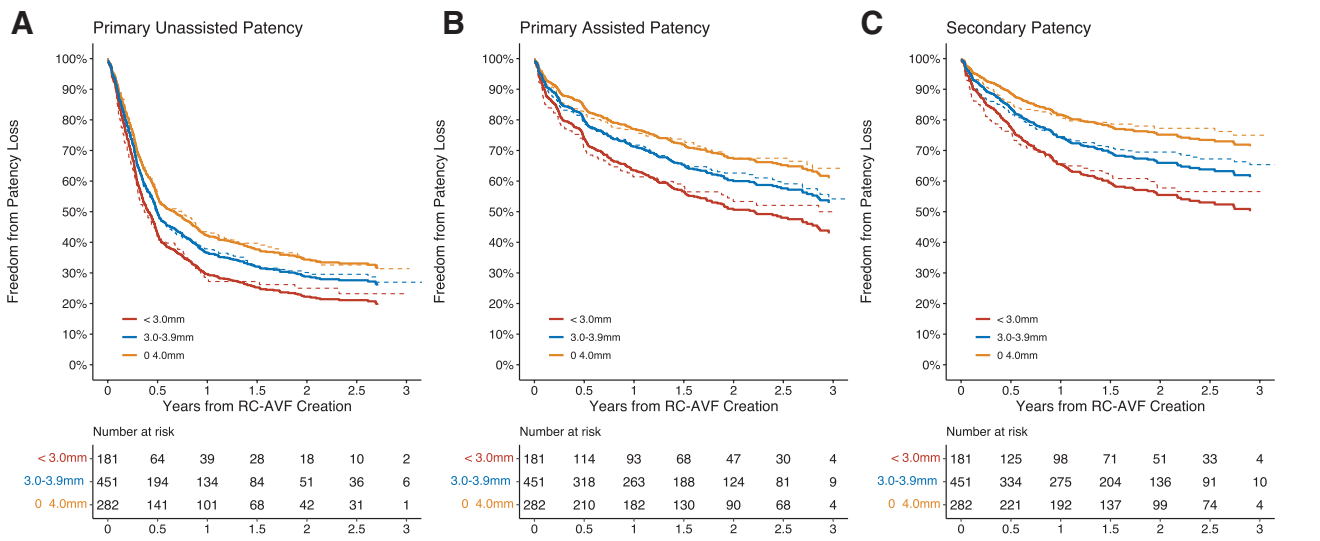

FIGURE 4. Kaplan-Meier (dotted lines) with corresponding at-risk tables and Cox adjusted marginal survival estimates (solid lines) for primary (A), primary-assisted (B), and secondary (C) patency stratified by intraoperative cephalic vein diameter.

unable to draw definitive causal conclusions from these results, one interpretation of these findings could be that regular protocolized follow up with HD access experts leads to more procedural intervention (and lower primary patency), but also less frequent access abandonment.

Successful overall RC-AVF use aligned closely with unassisted use for about 3 months postoperatively (Figure 3). After 3 months, the curves separate substantially and by 1 year, the estimates for overall and unassisted use were 66.9% (62.0–71.3) and 46.8% (41.8–51.7), respectively. This pattern may reflect eagerness by clinicians to promote maturation with interventions if the access still does not appear ready for use by 3 months, and the gap between the curves can be interpreted as the result of assisted maturation (Supplemental Figure 5, http://links.lww.com/AOSO/A164). Beyond 1 year, nearly all accesses had either been used successfully or abandoned. Our estimates for successful use align with those of the Dialysis Outcomes and Practice Patterns Study (DOPPS) and the Hemodialysis Fistula Maturation (HFM) study at 71% at 7 months (n = 319, forearm only) and 76% at 1 year (n = 353, forearm and upper arm), respectively.[15,16]

Regarding the predictors of access patency, we found that patients undergoing RC-AVF creation before dialysis initiation and those with larger baseline cephalic vein diameters had improved fistula durability. Both findings align with previously described phenomena and have mechanistic plausibility.

Anticipatory creation of an AVF prior to progression to ESKD may be associated with improved access patency due to

TABLE 3.

Fine-Gray Subdistribution Hazard Model Summaries for Time to Successful Unassisted and Overall Radiocephalic AVF Use (≥90 Consecutive Days of Use for All Prescribed HD) From Day of AVF Creation

	Summary	Unassisted			Overall		
Covariates	**N = 409***	**$_{SD}$HR**	**95% CI**	***P***	**$_{SD}$HR**	**95% CI**	***P***
Age (yrs)	55 (14)	1.00	0.99–1.01	0.4	1.00	0.99–1.01	0.8
Sex (female)	96 (23%)	0.45	0.31–0.67	<0.001	0.55	0.41–0.75	<0.001
Race (non-White)	153 (37%)	0.85	0.62–1.15	0.3	0.87	0.68–1.12	0.3
Current smoker	64 (16%)	1.27	0.89–1.80	0.2	1.23	0.92–1.65	0.15
Diabetes	243 (59%)	0.67	0.50–0.92	0.012	0.92	0.71–1.19	0.5
AVF location							
Wrist/Snuffbox	303 (74%)	–	–		–	–	
Forearm	106 (26%)	1.06	0.75–1.51	0.7	1.23	0.91–1.65	0.2
Vein diameter (mm)	3.00 [3.00, 4.00]	1.21	1.02–1.44	0.026	1.26	1.11–1.45	<0.001
Artery diameter (mm)	2.50 [2.20, 3.00]	0.63	0.49–0.83	<0.001	0.76	0.62–0.94	0.010
Anesthesia (regional)†	313 (77%)	1.59	1.08–2.33	0.020	1.42	1.04–1.94	0.026
Site enrollment volume							
Lower (≤20)	133 (33%)	–	–		–	–	
Mid (21–49)	116 (28%)	1.44	0.96–2.16	0.082	1.29	0.94–1.79	0.12
Upper (≥50)	160 (39%)	1.65	1.14–2.38	0.008	1.64	1.21–2.24	0.002

*Statistics presented at N (%) or median [IQR]. All participants with prevalent HD at time of AVF creation included.

†Reference level: General anesthesia.

Interpretation note: HR < 1 indicates decreased rate of successful use.

95% CI indicates 95% confidence interval; AVF, arteriovenous fistula; $_{SD}$HR, subdistribution hazard ratio.

(1) a guaranteed period of access maturation prior to attempted cannulation, (2) a less inflammatory and hypercoagulable milieu, and (3) limited impetus for attempts at procedurally assisted maturation.[17–19] Cannulation trauma is known to influence patency, and therefore our models adjusted for attempted RC-AVF cannulation.[20,21] Our interpretation is that regardless of the specific underlying biology, autogenous access creation prior to ESKD may provide the best chance for longitudinal patency. However, access creation is not without risks, and these findings motivate further research into the optimal timing of pre-ESKD access creation.[22,23]

Consideration of candidate access vessel diameter has long been a focus of surgeons tasked with determining the best access for a given patient. Our findings confirm those of previous studies that suggesting baseline vein diameter should be an important consideration in access creation.[5,6,24–26] However, our findings regarding artery diameter are somewhat counterintuitive and perplexing. Any discussion of artery diameter must be framed by the consideration that nearly all arteries (97%) were ≥2 mm in diameter, which is consistent with society guidelines.[3] We demonstrated that larger arteries had decreased rates of successful access use, and also detected a weak association between larger artery diameter and decreased patency. A possible explanation for this finding is that physicians increased the acceptable artery size threshold when considering access candidates with poor vessel quality, such as underlying vessel calcification, atherosclerosis, or connective tissue disease—unfortunately, these data are not available. Another possible explanation is that larger arteries produce perturbations in flow patterns such as more turbulent flow, higher flow volumes, and more shear stress on the vein wall. Although shear stress is important for the maturation process, it seems plausible that excessive stress may lead to maladaptive vessel remodeling.[27–30] In attempting to explain this finding, we performed additional analyses investigating whether a size mismatch between the artery and vein could be underlying our observation (Supplemental Table 4, http://links.lww.com/AOSO/A164). None of our interaction models detected effect modification, but the possibility of size mismatch playing some role remains - effect modification is quite difficult to detect without a large effect size or effective sample size.

We found interesting associations with improved RC-AVF use and both site enrollment volume and anesthesia modality. Although we do not have volume information beyond the number of enrolled patients, it seems reasonable to use enrollment volume as a proxy for overall HD access creation volume. One could conclude that sites with more experience creating and maintaining HD access also have better outcomes, whether as a result of improved patient selection when considering factors beyond those investigated in the present study, or simply due to increased surgeon technical skill and familiarity with the nuances of access surgery. Positive volume-outcomes relationships have been demonstrated in numerous other surgical procedures, although causality is controversial and difficult to assess.[31–36] The use of regional anesthesia has been previously shown to improve HD access creation through anesthetic-induced peripheral vasodilation, facilitating the technical aspects of RC-AVF creation and improving perioperative access flow volume.[37–39] Additionally, regional anesthesia may be a proxy for centers with expertise in access surgery and established relationships between access surgeons and anesthesiologists.

Although our study was not explicitly designed to address questions of healthcare disparities, we detected worse RC-AVF use and patency in female patients despite adjusting for numerous other factors. Female patients used their RC-AVFs at about half the rate of male counterparts (Supplemental Figure 6, http://links.lww.com/AOSO/A164). Sex-based disparities have been reported in many aspects of vascular surgery, including aortic disease, peripheral artery disease, and HD access.[5,6,40–44] The underlying reasons for these disparities are certainly complex, and likely represent an amalgamation of differences in vascular anatomy and physiology, access to healthcare, underlying renal disease biology, and societal factors including sexism. Improvement in the equity of HD access outcomes will require ongoing work to discover and address the underlying etiologies observed disparities. Acknowledgement of sex disparities is an important step toward their elimination.

The present study must be interpreted carefully in the context of its design. Although the data were collected prospectively as part of a well-designed randomized clinical trial, and therefore have a low degree of missingness and good ascertainment of outcomes, post hoc analysis of these data are subject to the inherent limitations of observational cohort studies. The exploratory nature of this work must be acknowledged—although all models were built thoughtfully, conclusions about causality

can be fraught without a well-defined prespecified hypothesis and development of a causal framework aimed at eliminating confounding. Although PATENCY-1 showed some promising results, the larger follow-up study PATENCY-2 did not show any drug effect, and the drug's influence on the results reported here is likely minimal. In addition, all models were adjusted for randomization to either the drug or placebo group, so the point estimates and the adjusted marginal survival curves can be interpreted as agnostic to the trial drug. However, no amount of confounding adjustment can eliminate the potential for limited generalizability present in any clinical trial dataset—the study sample may not represent the overall population of interest. By design, all patients in our analysis were cared for at centers participating in a clinical trial, and therefore may be inherently distinct from other practice environments. Data from observational cohorts like HFM and DOPPS, or less granular national datasets like the USRDS, benefit from increased generalizability but have challenges with outcome ascertainment and sample heterogeneity.[15,40,45,46] Patients in the PATENCY trials were chosen for entry based on their suitability for RC-AVF as determined by the treating surgeon, and therefore these results do not apply to patients who are not candidates for RC-AVF, Additionally, the patients in this study may be different from the general HD access population of interest in that they consented to be enrolled in a randomized trial.

Several strengths of this study are important to highlight. The follow up was quite long given the granularity of the data. The 3-year time scale is highly relevant to understanding HD access outcomes, where autogenous access longevity is the primary goal in preventing access-related morbidity and mortality. Because the data were collected prospectively under detailed and nearly identical study protocols, the potential for misclassification bias is low. Misclassification is one of the key systematic biases present in most observational datasets, which can lead to spurious conclusions with difficulty predicting the direction or magnitude of the bias. Another strength of our work lies in the accounting of competing risks. Competing risks are common in the HD population, where terminal events like death, renal transplant, and loss of access patency preclude the occurrence of the outcomes of interest. Particularly in the case of estimating successful AVF use, where the competing terminal events are nearly as common as the event of interest, dramatic overestimation of the rates of successful AVF use will inevitably occur without accounting for competing risks.[47]

To conclude, our findings can inform shared decision-making regarding HD access options when considering the best access for a patient as part of the individualized ESKD life-plan. Future work is needed to better understand the causal pathways underlying the observed associations and to link clinical outcomes with the biologic mechanisms at play. Finally, our findings highlight the need for studies to determine the optimal timing of access creation in patients with chronic kidney disease not yet requiring HD.

DISCLOSURES

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