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Superior Patency Of Upper Arm Arteriovenous Fistulae In High Risk Patients

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Abstract

Background: Despite an increased propensity to primary failure in forearm arteriovenous fistulae compared to upper arm fistulae, forearm fistulae remain the preferred primary access type for chronic hemodialysis patients. In a high risk patient population with multiple medical comorbidities associated with requirement for intravenous access we compared the rates of access failure in forearm and upper arm fistulae. **Materials and Methods:** The records of all patients having primary native arteriovenous fistulae placed between 2004 and 2009 at the VA Connecticut Healthcare system were reviewed (n=118). Primary and secondary patency of upper arm and forearm fistulae were evaluated using Kaplan-Meier survival analysis. The effects of medical comorbidities on access patency were analyzed with Cox regression. **Results:** The median time to primary failure of the vascular access was 0.288 years in the forearm group compared to 0.940 years in the upper arm group (p=0.028). Secondary patency was 52% at 4.9 years in upper arm fistulae compared to 52% at 1.1 years in the forearm group (p=0.036). There was no significant effect of patient comorbidities on fistula failure; however, there was a trend toward upper arm surgical site as a protective factor for primary fistula patency (Hazard Ratio=0.573, p=0.076). **Conclusions:** In veterans needing hemodialysis, a high risk population with extensive comorbid factors often requiring intravascular access, upper arm fistulae are not only a viable option for primary vascular access, but are likely to be a superior option to classic forearm fistulae.

Keywords: Arteriovenous fistula, radiocephalic fistula, brachiocephalic fistula, hemodialysis, vascular patency, veteran, risk factor.

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End-Stage Renal Disease: Increasing Incidence and Prevalence

The incidence and prevalence of chronic kidney disease (CKD) has increased consistently both worldwide and in the United States over the past decades. Since 1973, enrollment in the Medicare funded end-stage renal disease (ESRD) program has increased dramatically. In 1973, 10,000 patients were enrolled in the ESRD program. By1983, enrollment had reached 86, 354 patients, and has continued to expand, having reached a total of 527, 283 patients as of December 31, 2007 (1, 2). There were an estimated 111,000 incident cases recorded in that same year. In 2010, the projected number of ESRD patients was estimated to be 651,330, which amounts to a total cost of over $28 billion US healthcare dollars(3). These numbers underscore the importance of developing effective and reliable care for this rapidly growing population.

The rising prevalence of CKD is mainly attributable to an increase in the number of patients who undergo renal replacement therapy each year, and to a lesser degree, the somewhat increased survival of ESRD patients (1, 2). But in spite of the resources committed to the ESRD population and improvements in modern dialysis techniques, the population continues to experience substantial morbidity and mortality. ESRD patients are well known to have poor long-term survival in comparison to the population as a whole. In 2007 alone, over 87,800 ESRD patients died (1, 2). Furthermore, dialysis patients have been shown to have a reduced quality of life relative to the general population. As such, the impact of the quality of care these patients receive cannot be overstated (3-5).

Maintaining permanent intravenous access in ESRD patients has proven to be a difficult task, especially as the number of patients with comorbid conditions continues to grow. Approximately 50% of ESRD patients have three or more comorbid medical conditions, and each patient is hospitalized on average 12.6 days per year (1, 2). In fact, vascular access complications and failures are not only a major cause of morbidity and mortality in ESRD patients, but were the most frequent reason for patient hospitalization cited by the National Kidney Foundation in 1997 (1, 6). In total, vascular access accounts for 14% of all ESRD costs, a total of $1 billion United States healthcare dollars yearly (1).

Anatomy of Hemodialysis Access

A major challenge in accommodating the growing ESRD population has been the creation of permanent, reliable vascular access for hemodialysis (HD) delivery. In order to establish durable arteriovenous (AV) access for chronic HD, access blood flow and blood pressure must be sufficient to support modern dialysis flow pumps. Such pumps target access blood flow rates of 300-450 ml/min, and diasylate flow rates of 500-800 ml/min. To meet and maintain these pressure requirements, successful AV access must include a feeding artery that can transfer high pressures to a compliant, distensible venous outflow. Additional sources of resistance to blood flow, such as venous or arterial stenosis, partial or complete thrombosis, and accessory vein outflow can thus compromise the dialysis process. For this reason, an understanding of the vascular anatomy of the upper extremity is essential to creating permanent intravascular access.

In choosing a vein for chronic access creation, a nonsclerotic segment of either a deep or superficial vein that is at least 3 millimeters in diameter is identified, either via physical exam or preoperative venous mapping, to be anastomosed to an artery(7). Selecting an appropriately sized vein is important, as larger veins have been associated with successful fistula maturation. Specifically, the use of veins with diameters greater then 4 mm have been associated with the creation of a functional AV fistula that is able accommodate the high flow rates of dialysis pumps (8). This relationship can be understood logically in terms of Pouseuille's law, which states that blood flow is proportional to the product of the change in pressure gradient and the fourth power of the vessel radius, divided by the viscosity of blood. Though not able to entirely account for the properties of arteries and pulsatile blood flow, Pouseuille's law can in some ways explain the hemodynamics of AV fistulae, specifically why vein diameter, as a major predictor of vessel resistance, has an effect on fistula maturation.

In general, upper arm veins are larger then the venous branches in the forearm (9). In the upper arm, the deep venous system includes the brachial and basilic veins that run parallel to the brachial artery. The basilic vein is the most commonly used deep vein in HD access creation. When creating a transposed basilic vein fistula, the basilic vein is first mobilized at the medial aspect of the upper arm, and then transposed superficially through the deep fascia and anastomosed to the brachial artery. Both the brachial and basilic veins join to form the axillary vein in the upper arm, and later, the subclavian vein from the first rib to the end of the clavicle . The deep brachial vein is rarely used for access (10).

For initial HD access creation, however, the superficial venous system, especially the forearm cephalic vein, is most commonly used. The cephalic vein in the forearm can be used in conjunction with the radial artery to create a radiocephalic fistula at the wrist or snuffbox, while the upper arm segment of the cephalic vein at the elbow can be used for brachiocephalic access with the brachial artery. The distal basilic vein, which courses superficially in the forearm on the ulnar side of the wrist, and the median basilic vein at the elbow, are less commonly used for forearm AV fistula creation. The radial and ulnar veins, which are not generally used for HD access, compose the deep veins of the forearm (10).

History of Hemodialysis Vascular Access

The first hemodialysis treatment in a human was performed by Georg Haas, of Germany, in 1924 and lasted only 15 minutes. Haas used a glass cannula to withdraw arterial blood from the radial artery, which he then returned to the patient's cubital vein. He later modified his vascular access to include a surgical cut-down that cannulated both the artery and an adjacent vein simultaneously. With support from the Rockefeller Foundation, he performed a total of 11 HD treatments by 1929 before losing financial and clinical support. By his death in 1971, he had witnessed the transformation in the care of ESRD that followed the development of modern dialysis techniques (11).

In 1966, Brescia *et al.* published a landmark paper that first described the AV fistula as a type of permanent access for HD patients. A total of 15 surgical fistulae were described in this paper, the first of which was created in February of 1965. In this paper, the group's surgeon, Dr. Appell, described performing a side-to-side anastomosis between the radial artery and the cephalic antebrachial vein at the wrist. He did so by making a 3-5 mm incision over the lateral surfaces of the artery and vein, which were then sutured with arterial silk continuously. Remarkably, of the 14 fistulae included in this study, Brescia and his colleagues reported only 2 primary failures (12). It is worth mentioning that a similar technique was described by Jaboulay and Briau, of France, who published a method of creating an experimental artery-end-to end anastomosis in dogs in 1896 (13). Several years later, Alexis Carrel, also of France, described a three point end-to-end, as well as a side-to-side anastomosis as a means of creating vascular access (14). Carrel went on to receive the Nobel Prize in 1912 for this development (11).

Following Brescia and Cimino's advances, two more methods of creating surgical fistulae were developed. The first of these methods, an end-to-end anastomosis between the radial artery and cephalic vein at the wrist, has been largely abandoned due to high rates of steal syndrome and early failure in the growing elderly and diabetic dialysis population (15). Though not typically used for initial access placement procedures currently, this method is still relied upon in AV fistula revision procedures. A second and more successful method of creating a radiocephalic fistula was described by Lars Rohl in 1968. Rohl's paper detailed the creation of radial-artery-side-to-vein-end-anastomoses in 30 HD patients. The procedure he described involved ligating the radial artery distal to the AV anastomosis, essentially creating a modified end-to-end anastomosis. This technique had the advantage of making laterally located cephalic veins, which had previously been unusable for side-to-side anastomoses, suitable for access creation (16). Later, the distal artery anastomosis was discarded, except for use in patients experiencing post-operative ischemia of the upper extremity. This artery-side-to-vein-end anastomosis remains the standard surgical operation performed today (11).

Perhaps one of the most important modern developments in vascular access was the synthetic AV graft. Still the most frequently used synthetic graft material, polytetrafluoroethylene (PTFE) was used in animals in 1972, and saw its first use in patients by L.D. Baker in 1976 when he published the results of using PTFE grafts as venous prosthesis in 72 HD patients (17, 18). This method was extremely useful in patients for whom native AV fistulae could not be created (18-21). In the 1980s, central venous catheters (CVC) also gained popularity as a means of prolonging temporary HD access (22-24). Overall, these developments led to a reduction in AV fistulae use and an increase in both CVC and synthetic grafts for chronic HD. This, in turn, led to increased cost of ESRD patient care, with upwards of 73% of patients initiating dialysis requiring hospitalization in the early 1990s (6, 25)

The National Kidney Foundation first published the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Vascular Access in 1997 in an effort to improve vascular access outcomes through both evidence and opinion based standards of care (1). Shortly after this, Medicare published clinical performance measures based on K/DOQI, in order to reduce costs and improve patient care. These measures included the proportion of HD patients with AV fistulae access, the proportion of patients with central catheter access, and required frequent monitoring of AV grafts for stenosis (25). Nonetheless, in 2002 the total cost of the ESRD Medicare program had further increased to $17 billion dollars and the number of procedures required to maintain vascular access was four times greater than those needed in 1991 (26).

In 2003, the Centers for Medicare and Medicaid Services and the ESRD network began the Fistula First Initiative (FFI) in an effort to increase AV fistulae usage and decrease the use of CVC for chronic dialysis. Specifically, FFI aimed to achieve K/DOQI guidelines of 50% AV fistula usage in incident, and 40% in prevalent patients. In 2006, this goal was modified to include 65% of prevalent patients in 2006 (25). Though FFI has certainly increased fistula use, it has had several unexpected results, which included the failure of FFI to decrease catheter use to less than 10% of prevalent HD patients; trends following FFI were quite the opposite.

Since FFI began, there has been a progressive increase in CVC use by ESRD patients. The majority of patients in North America continue to start HD with a CVC, in spite of adequate AV fistula planning and placement (27-29). In 2006, of those patients initiating HD, 82% used a CVC for vascular access. Since indwelling dialysis catheters are associated with increased patient mortality as well as an increased risk of sepsis (30-34), these outcomes highlight the need for a shift in current practice paradigms. This would include a shift towards not only increased AV fistula placement, but of improved functionality and durability of those fistulae that are placed.

Modern Vascular Access Patency

Creating and maintaining long-term access for HD remains both a clinical challenge and necessity. In the approach to modern HD access, three principal types of vascular access are used. Among these are autogenous AV fistulae, synthetic AV grafts, and tunneled, cuffed central venous catheters. Arteriovenous (AV) fistulae are the preferred access type for chronic hemodialysis patients, with current practice guidelines choosing radiocephalic forearm fistulae as the preferred initial location for primary vascular access, followed by brachiocephalic and brachiobasilic upper arm fistulae, respectively (35, 36). When placed prior to the initiation of hemodialysis fistulae are preferred as they eliminate the need for indwelling dialysis catheters, which are associated with increased patient mortality as well as an increased risk of sepsis (30-34). Prosthetic AV grafts, while also preferred to central venous catheters, are generally reserved for use in patients with inadequate native vasculature as they have worse long-term patency and increased rates of infection compared to native fistulae (37). Nonetheless, AV fistulae are not without their own complications, including thrombosis, infection, aneurysm, seromas, steal syndrome, heart failure, and bleeding, complicating the placement algorithm.

When monitoring fistula functionality, primary fistula patency is defined as the amount of time that a surgical fistula can reliably support dialysis without requiring additional procedures or interventions to maintain or improve fistula patency. If additional procedures are required to support a particular AV access site, a period of secondary fistula patency begins. These interventions can include angioplasty, thrombectomy, various interventional radiology procedures, accessory vein ligations, and redo surgeries. If such procedures are successful in salvaging a fitsula, a period of cumulative secondary patency can be calculated, which includes the entire duration of fistula functionality from initial surgical creation until ultimate access failure. Access failure is defined as site abandonment necessitating new AV access creation at another anatomical site. For those patients already reliant upon HD, this requires a period of reliance upon CVC while new access is placed.

In a systematic review of 34 modern access patency studies, primary patency rates of upper arm fistulae were approximately 81% and 60%, at 6 and 18 months, respectively, compared to 71% and 49%, in forearm fistulae at 6 and 18 months. Likewise, primary patency rates of upper arm prosthetic grafts were approximately 69% and 49%, at 6 and 18 months, respectively, compared to 51% and 28%, in forearm grafts at 6 and 18 months (37). As such, many patients with AV access require invasive procedures to maintain secondary patency; otherwise the site may need to be abandoned and a new access performed.

Although access failure rates have varied slightly from study to study and across patient populations, forearm fistulae in particular are well documented as failing to mature at rates greater than that of upper arm fistulae (37, 38). In spite of this, forearm fistulae remain the primary vascular access of choice due to relative ease of creation and preservation of proximal vasculature for future access attempts. Although K/DOQI endorses this distal to proximal approach to access creation, there are no randomized control studies to date that have evaluated this classic algorithm.

We evaluated primary and secondary patency rates of upper arm and forearm AV access when placed for primary hemodialysis access in veterans. We have previously shown that veterans often have large numbers of comorbid medical conditions compared to nonveterans, suggesting that this population is at particularly high risk for complications (39, 40). We hypothesized that, since patients with multiple medical comorbidities often require high rates of intravascular (IV) access, high risk patients may have particularly poor rates of forearm access maturation. If veterans have poor rates of access maturation, then upper arm fistulae may be preferred in these patients.

Materials and Methods

The records of all patients who underwent primary AV access creation at the VA Connecticut Healthcare System (West Haven, CT) between April 2004 and December 2009 were reviewed. Patients were identified using the VA Department of Surgery's case list of all vascular procedures performed between April 2004 and December 2009. Once all access creations were identified, follow up data through June 2010 was retrieved from the VA Computerized Patient Record System. IRB approval was obtained from the West Haven VA. Patients were excluded from the study if they had a previous AV fistula or graft placed prior to April 2004. Patients who did not receive autogenous AV fistulae were also excluded for the study. In patients who had two or more access placements during the study period, only data pertaining to the initial operation was collected. Selection for forearm or upper arm fistulae was at the operative surgeon's discretion and included factors such as presence of a palpable vein as well as the venous diameter recorded on preoperative duplex mapping.

Patient demographics were determined via chart review, and included age, race, and gender. Patient charts were evaluated for the preoperative presence or absence of the following comorbidities: hypertension, diabetes mellitus, current smoking, current dialysis, congestive heart failure (CHF), coronary artery disease (CAD), pulmonary disease, stroke, transient ischemic attack (TIA), and cancer. Preoperative laboratory values included albumin and creatinine. Preoperative measures evaluated were body mass index (BMI) and ejection fraction (EF, %). Patient medications were reviewed for the presence or absence of prescribed aspirin (ASA), anti-platelet agents, anticoagulation agents, and statin therapy. Surgical variables included: surgical site (upper arm, i.e.

brachiocephalic or basilic access; forearm, i.e. radiocephalic access), surgical side (right or left), and size of upper arm and forearm veins as recorded on preoperative duplex (cephalic at the distal humerus and cephalic at the wrist, respectively). Postoperative variables recorded included known use of the access for successful hemodialysis. Study data was maintained in a de-identified database.

The primary study outcomes were fistula status (patent versus failed) and duration of fistula patency. Primary patency was calculated as the time period between the date of access placement and the date of either the last follow-up with known fistula patency without failure, or until the date of first fistula failure. Secondary patency was calculated as the time period between the date of access placement and the date of either the last follow-up with known fistula patency without failure, or until the date of absolute fistula failure requiring disuse and site abandonment, i.e. including all secondary procedures to maintain the access. Patients who switched to peritoneal dialysis, received renal transplants, or no longer required HD due to renal recovery were considered to have patent fistulae until the date of dialysis completion. Postoperative survival outcomes included date of death or date of last follow-up in the VA records and patient status (deceased or living). Length of survival was calculated using the date of fistula access as the baseline.

Data analysis was performed on both the entire study population (including all access types) and on only those patients who underwent native AV fistulae creations, excluding patients who receive synthetic AV grafts. Results are reported as mean ± SEM. Statistical analysis was performed with SigmaPlot 11.0 (Systat Software, San Jose, CA). The study population was divided by upper or forearm fistula site and analyzed across these two groups. Categorical variables were analyzed using Chi-square test, and continuous variables were analyzed using the t-test. Primary and secondary patencies were analyzed using Kaplan-Meier statistics, and the difference between the upper and forearm strata were compared using the Gehan-Breslow statistic. Overall survival of the study population was analyzed using Kaplan-Meier statistics. The effect of all independent patient demographic variables collected on primary fistula patency and long-term survival of the study population was analyzed with Cox regression.

Results

Patient Demographics and Comorbidities

A total of 118 patients underwent primary AV fistula placement at the VA Connecticut Healthcare System between April 2004 and December 2009. Of these patients, 44 had upper arm fistulae and 74 had forearm fistulae. There were 11 patients in the upper arm group that underwent basilic transpositions for primary access. The remaining 33 patients received brachiocephalic access. In the forearm strata, 43 patients had radiocephalic access placed. One patient had a radial-interosseus vein fistula placed.

The demographics of the study population are listed in Table 1. There were 116 men and 2 women. The mean age of patients who had upper arm fistulae was 65.8 ± 1.9 years, and the mean age of patients who had forearm fistulae was 65.8 ± 1.4 years; there was no significant difference between these two groups (p= 0.985). All of the patients were either Caucasian (67.8%) or African American (32.2%); patient race did not vary across groups (p= 0.785).

Hypertension was highly prevalent in patients with either upper (97.7%) or forearm fistulae (100%). Diabetes mellitus had a similar prevalence across the two groups, present in 39.8% of the upper arm patients and 35.1% of the forearm patients (p=0.247). 30.5% of patients reported current tobacco use at the time of fistula placement; current tobacco use was more prevalent in the forearm group than the upper arm group (40.5% versus 13.6%; p=0.004). Patients who were receiving dialysis at the time of their operation were evenly distributed across the groups (40.9% upper arm vs. 44.6% forearm; p=0.929). 50% of patients were identified as having heart disease; there was no difference in prevalence across the upper and forearm groups (p=0.792); both

CAD (p=0.997) and CHF (p=0.139) were similarly distributed across the study groups. There was no significant difference between the two groups in prevalence of pulmonary disease (p=0.186). Prior stroke and TIA were identified in 11.4% and 0% of the upper arm patients and 14.9% and 2.7% of the forearm patients, respectively; however this was not statistically significant (stroke, p=0.795; TIA, p=0.717). 17% of patients had a diagnosis of cancer at the time of operation, which was similar between groups (p=.300).

Preoperative Labs, Measures, and Medications

The mean preoperative albumin in the study population was 3.1 ± 0.1 g/dL and did not vary across groups (p=0.157). The mean creatinine was 5.2 ± 0.2 mg/dL; preoperative creatinine also did not vary between the surgical site groups (p=0.304). BMI and EF were similar across the upper and forearm groups (p=0.799 and p=0.903, respectively)

At the preoperative visit 39.8% of patients were taking aspirin, 4.24% were taking an antiplatelet agent, 19.5% of patients were anticoagulated, and 59.3% of patients were taking a statin; these medications did not vary significantly across groups (p=.535-.971).

Surgical and Postoperative Variables

The majority of study patients received left upper extremity fistulae (84.8%, n=100); however the distribution of surgical side did not vary significantly between groups (p=0.344). Preoperative duplex ultrasound vein mapping showed a significant difference between cephalic vein size at the wrist in the upper and forearm groups; patients who received forearm fistulae had a mean cephalic vein width at the wrist of 0.15

± .021 cm compared to a width of 0.08 ± .021 cm in patients who had an upper arm fistula placed (p=.016). The cephalic vein diameter at the distal humerus was similar between the two groups, measuring 0.320 ± .0317 cm in the upper arm group and 0.35 ± .024 cm in the forearm group (p=.405). The number of patients that were successfully dialyzed through their primary AV fistula at least once did not vary across groups (p=0.666).

Access Patency

Cumulative primary patency was reduced in forearm fistulae compared to upper arm fistulae, with forearm fistulae having only 34% primary patency at 1 year compared to 41% at 1 year for upper arm fistulae; the median time to primary failure of the vascular access was 0.288 ± 0.164 years in the forearm group compared to 0.940 ± 0.456 years in the upper arm group (Figure 1A; p=0.028). Similarly, cumulative secondary patency was also reduced in forearm fistulae compared to upper arm fistulae; secondary patency was 52% at 4.9 years in upper arm fistulae compared to 52% at 1.1 years in the forearm group (Figure 1B; p=0.036).

Cox regression analysis of factors affecting primary fistula patency showed no significant effect of patient comorbidities, laboratory values, or medications on fistula failure (Table 2). There was a trend towards upper arm surgical site being a protective factor (hazard ratio=0.573; p=0.076); surgical side did not affect fistula patency (p=0.901).

Patient Survival

There were 35 (29.7%) patient deaths in the study group. Cumulative survival analysis reflected poor survival in this patient population, with 88% survival at 1 year, 62% survival at 3 years, and 58% survival at 5 years after fistula placement (Figure 2). The only preoperative demographic factor that was associated with reduced mortality was use of an anti-platelet agent (Table 3; hazard ratio=4.3; p=0.019). The surgical site, upper arm versus forearm, did not influence patient mortality (hazard ratio=0.956; p=0.919).

Table 1. Demographics and risk factors of AV Fistulae Patients

Variable	Total (n)	Total (%)	Upper Arm	Upper (%)	Forearm	Forearm (%)	p-value
Total Patients (n)	118		44	37.3%	74	62.7%	
Age (yrs)	65.8±1.1		65.8 ± 1.8		65.8± 1.4		0.985
Race							
Caucasian	80	67.8%	31	75.0%	49	66.2%	0.785
African American	38	32.2%	13	29.5%	25	33.8%	
Gender							
Male	116	98.3%	43	97.7%	73	98.6%	0.717
Female	2	1.7%	1	2.3%	1	1.4%	
Comorbidities							
Hypertension							
Yes	117	99.2%	43	97.7%	74	100.0%	0.792
No	1	0.8%	1	2.3%	0	0.0%	
Diabetes Mellitus							
Yes	47	39.8%	21	47.7%	26	35.1%	0.247
No	71	60.2%	23	52.3%	48	64.9%	
Current Smoker							
Yes	36	30.5%	6	13.6%	30	40.5%	0.004
No	82	69.5%	38	86.4%	44	59.5%	
Current Dialysis							
Yes	51	43.2%	18	40.9%	33	44.6%	0.843
No	67	56.8%	26	59.1%	41	55.4%	
Heart Disease (CAD or CHF)							

Yes	59	50.0%	21	47.7%	38	51.4%	0.792
No	59	50.0%	23	52.3%	36	48.6%	
CAD							
Yes	55	46.6%	21	47.7%	34	45.9%	0.997
No	63	53.4%	23	52.3%	40	54.1%	
CHF							
Yes	23	19.5%	5	11.4%	18	24.3%	0.139
No	95	80.5%	39	88.6%	56	75.7%	
Pulmonary Disease							
Yes	31	26.3%	8	18.2%	23	31.1%	0.186
No	87	73.7%	36	81.8%	51	68.9%	
Stroke							
Yes	16	13.6%	5	11.4%	11	14.9%	0.795
No	102	86.4%	39	88.6%	63	85.1%	
TIA							
Yes	2	1.7%	0	0.0%	2	2.7%	0.717
No	120	98.4%	44	100.0%	72	97.3%	
Cancer							
Yes	20	16.9%	10	22.7%	10	13.5%	0.3
No	98	83.1%	34	77.3%	64	86.5%	
Preoperative Labs							
Albumin (g/dL)	3.1± .1		2.9± .2		3.2± .1		0.157
Creatinine (mg/dL)	5.2± .2		4.9± .3		5.3± .3		0.304
Preoperative Measures							

BMI	28.4± .8		28.2± 1.4		28.2± 1.4		0.799
LVEF (%)	42.7± 2.4		42.3± 4.0		43.0± 3.1		0.903
Medications							
ASA							
Yes	47	39.8%	16	36.4%	31	41.9%	0.69
No	71	60.2%	28	63.6%	43	58.1%	
Anti-platelet							
Yes	5	4.2%	1	2.3%	4	5.4%	0.731
No	113	95.8%	43	97.7%	70	94.6%	
Anticoagulated							
Yes	24	19.7%	9	19.6%	15	19.7%	0.832
No	98	80.3%	37	80.4%	61	80.3%	
Statin							
Yes	70	59.3%	24	54.5%	46	62.2%	0.535
No	48	40.7%	20	45.5%	28	37.8%	
Surgical Variables							
Side							
Right	18	18.0%	9	20.5%	9	12.2%	0.344
Left	100	84.7%	35	79.5%	65	87.8%	
Duplex U/S Vein Mapping							
Cephalic @ Wrist (cm)	.13± .02		.08± .02		.15± .02		0.016
Cephalic @Distal Humerus (cm)	.34± .02		.32± .03		.35± .02		0.405
Postoperative Variables							
AVF Used?							

Yes	50	42.4%	20	45.5%	30	40.5%	0.666
No	63	53.4%	23	52.3%	40	54.1%	
Unknown	5	4.2%	1	2.3%	4	9.1%	

Table 2. Cox Proportional Hazards Analysis of Factors affecting Primary Fistula Patency.

Covariate	Hazard Ratio	95%Conf-L	95%Conf-U	p-value
Age	1.0	1.0	1.0	0.718
Comorbidities				
Hypertension	1.3	0.1	13.1	0.798
Diabetes Mellitus	1.1	0.6	2.0	0.739
Current Smoking	0.9	0.5	1.6	0.669
Current Dialysis	1.1	0.6	2.1	0.718
Heart disease (CHF or CAD)	1.0	0.5	1.8	0.899
Pulmonary Disease	0.9	0.5	1.6	0.656
Cancer	1.1	0.5	2.2	0.859
Preoperative Labs				
Albumin	0.9	0.7	1.1	0.35
Creatinine	1.0	0.8	1.1	0.528
Preoperative Measures				
BMI	1.0	1.0	1.0	0.949
LVEF (%)	1.0	1.0	1.0	0.606
Medications				
ASA	0.9	0.5	1.6	0.775
Antiplatelet	0.5	0.1	2.4	0.419
Anticoagulated	1.0	0.5	2.0	0.941
Statin	1.2	0.6	2.1	0.631
Surgical Variables				
Site-Upper arm	0.6	0.3	1.1	0.076
Side	1.0	0.5	2.0	0.901

Table 3. Cox Proportional Hazards Analysis of Factors Affecting Patient Survival.

Covariate	Hazard Ratio	95%Conf-L	95%Conf-U	p-value
Age	1.027	0.986	1.069	0.201
Comorbidities				
Hypertension	9.34E-08	0	∞	0.998
Diabetes Mellitus	1.881	0.815	4.34	0.139
Current Smoking	0.943	0.39	2.28	0.897
Current Dialysis	1.411	0.559	3.559	0.466
Heart disease (CHF or CAD)	0.649	0.253	1.665	0.368
Pulmonary Disease	1.264	0.505	3.165	0.617
Cancer	1.001	0.351	2.86	0.998
Preoperative Labs				
Albumin	0.864	0.609	1.227	0.415
Creatinine	1.032	0.863	1.234	0.732
Preoperative Measures				
BMI	1	0.952	1.051	0.996
LVEF (%)	1.007	0.992	1.022	0.394
Medications				
ASA	0.711	0.303	1.671	0.434
Antiplatelet	4.314	1.273	14.62	0.019
Anticoagulated	0.78	0.309	1.97	0.599
Statin	1.068	0.45	2.535	0.882
Surgical Variables				
Site-Upper arm	0.956	0.401	2.279	0.919
Side	0.675	0.229	1.987	0.475

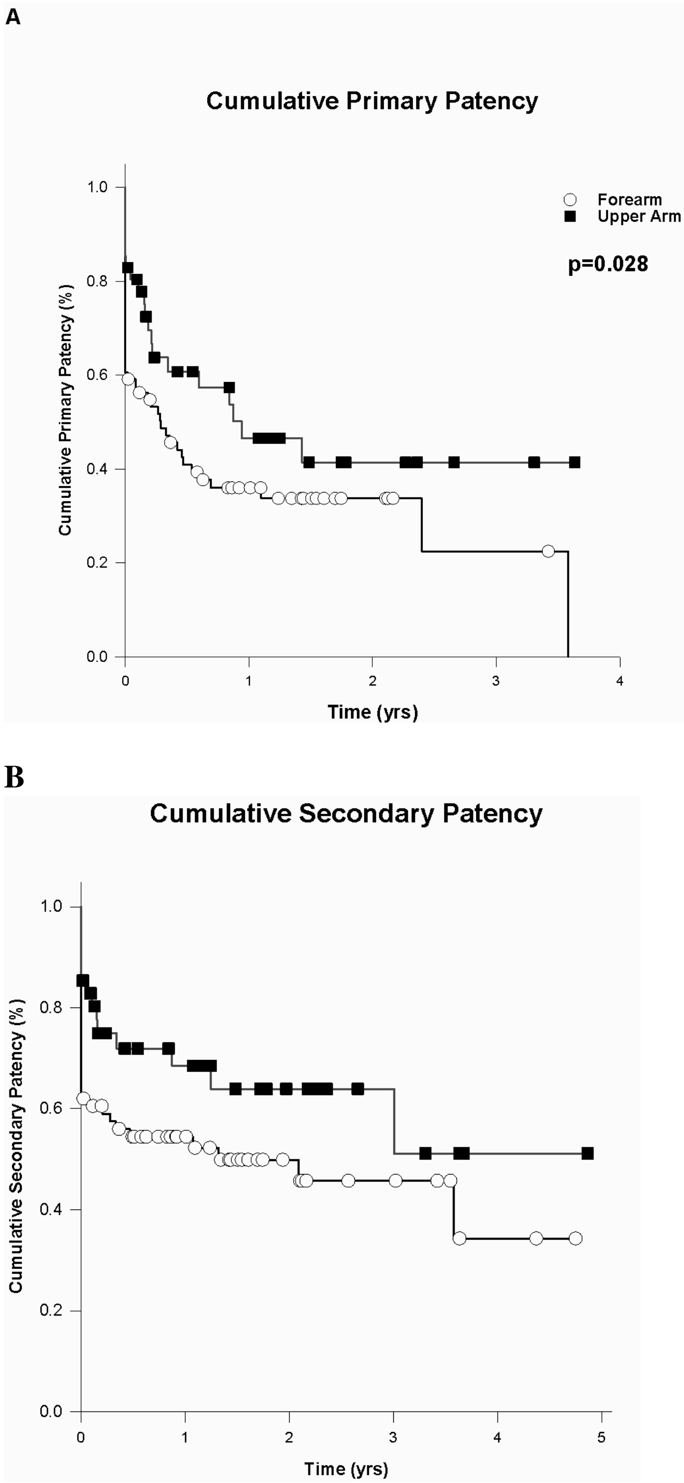

Figure 1. Primary and secondary patency of forearm vs. upper arm fistulae. (A) Kaplan-Meier analysis of primary fistulae patency. (B) Kaplan-Meier analysis of secondary fistulae patency.

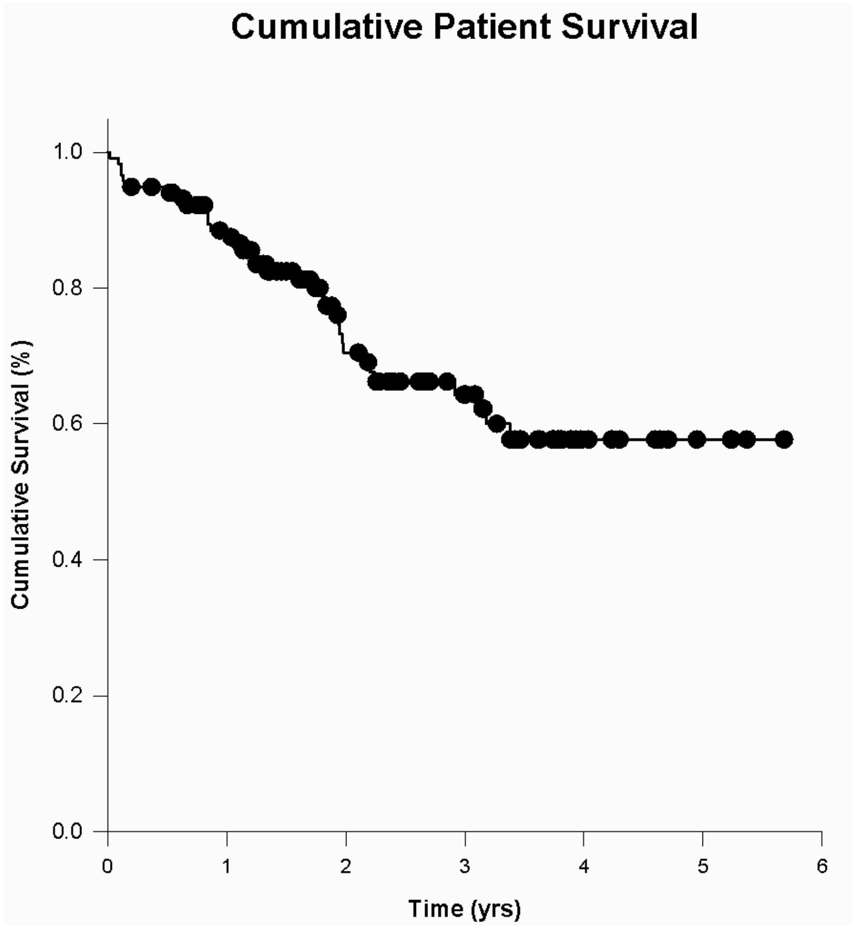

Figure 2. Kaplan-Meier analysis of post-operative survival

Discussion

Forearm fistulae have long been the gold standard for primary hemodialysis access. Our results, however, argue that forearm fistulae are far from a simple solution for hemodialysis access in veterans with end stage renal disease (ESRD). In a patient population with reduced life expectancy, we found superior primary and secondary patency of upper arm access in comparison to forearm access. We conclude that upper arm AV fistula are not only a viable option for primary vascular access, but are likely to be a superior option to classic forearm fistulae in these high-risk patients.

Historically, the radiocephalic fistula, which has been used for hemodialysis access since the mid 1960s, has been the preferred initial access site, as the wrist is easily accessible for the surgeon and use of this site preserves more proximal access sites for future placement once the wrist site fails. Although this mode of access is appropriate for many patients, it is important to recognize the varying needs of the growing ESRD population. In 1966, when Brescia and Cimino (12) first introduced the radiocephalic fistula, their patients' demographics were remarkably different than the majority of those patients needing dialysis today. In their study, the average patient age was 43 years, and almost all of the patients required HD as a result of chronic glomerulonephritis. At that time, successful HD required blood flows of 250-300 ml/min, as compared 350-450 ml/min in modern dialysis blood pumps.

As hemodialysis became more prevalent in patients with diabetes in the 1970s, it was noticed that diabetic patients had increased rates of failure of radiocephalic fistulae due to both early thrombosis and low AVF blood flow (41). These observations led to the suggestion that upper arm fistulae be considered for initial access in complicated access patients, especially those with diabetes, hypertension, stroke, peripheral vascular disease, and prior amputation (41). It was also suggested that preoperative evaluations of such patients include blood pressure in both arms, a meticulous search for a suitable vein, thorough evaluation of arterial pulses, phlebography in obese patients, x-rays to detect arterial calcifications, and ultrasound evaluation of both arterial and venous blood flow in the upper extremity (41).

In a prospective study of 204 access patients, Dixon *et al*. found that primary and cumulative patency of upper arm native access were significantly longer than that of forearm access (42). In their study 1-, 3-, and 5-year cumulative secondary patency of upper arm AVF were 69%, 53%, and 53%, respectively, compared to 52%, 43%, and 34% for lower arm access. Primary patency of upper arm access was also superior to that of forearm access. In a larger, systematic review of 34 studies, Huber et. al. also reported significantly greater primary patency of upper arm native access compared to forearm access (60% vs. 49% at 18 mo.) (37). As such, our results are consistent with a number of studies in the literature that suggest that forearm fistulae are not the best option in many patients.

Interestingly, we found no significant effect of patient comorbidities on access failure. Access patency relies upon the presence of vasculature that can support high flow rates. Several patient risk factors have been previously identified as significant predictors of access patency, likely as a result of microvascular and macrovascular changes related to various comorbid conditions. These risk factors include diabetes, age greater than 65 years, white race, peripheral vascular disease, and coronary artery disease (43). Huijbregts et al. reported peripheral vascular disease and diabetes to be significant predictors of fistula failure (44). Although our study did not identify these factors as predictive of access patency, our study was limited by a relatively small sample size, high prevalence of comorbid conditions, and homogeneity of the veteran population in this single center study. Nevertheless, we were able to identify a trend towards the upper arm surgical site being a protective factor for primary fistula patency (Table 2), which agrees with the results of our cumulative patency analysis (Figure 1).

Overall survival in the ESRD population is poor, with 5-year survival estimated to be 30-50% in nondiabetics, and 25% in diabetics (45). Our results were consistent with these reports, with 58% survival at 5 years in our study population (Figure 2). In addition, we found preoperative use of anti-platelet agents, as a proxy of underlying disease, to be associated with patient mortality. Mortality is typically higher in hemodialysis patients requiring central venous catheters and AV grafts for access compared to mortality patients using native access. Using data from the U.S. Renal Data System Dialysis Morbidity and Mortality Study Wave 1, the relative risk of death patients with diabetes was shown to be greater than that of patients with native fistulae (AVG, relative risk=1.41, $p<0.003$; CVC, relative risk=1.54, $p<0.002$). Similarly, in non-diabetic patients, CVC remained associated with greater risk of mortality (relative risk=1.70, $p<0.001$), with the vast majority of complications due to infection in both diabetic and non-diabetic patients. In addition, in spite of the historical association of AV fistulae with shunting and cardiac failure, the risk of cardiac death was greater in patients using CVC (diabetic relative risk=1.47, $p<0.05$; non-diabetic relative risk= 1.34, $p<0.005$) (30, 46). In one report, non-fistula access was the most important risk factor for infection ($p=0.02$), with the majority of infections occurring in patients with temporary vascular access such as CVC (38, 47). As such, our findings of poor survival in these patients with fistulae may underestimate mortality in comparison to other ESRD populations that include patients with AV grafts and CVC.

Initially, we completed an analysis of all vascular access creations, which included both synthetic grafts and autogenous AV fistulae at our study site. The AV graft data was removed from the final analysis for several reasons, the most important of which was maintaining homogeneity of the study comparison. In addition, only four synthetic grafts were included in the initial analysis, which greatly limited our ability to determine the full effect of synthetic grafts on access patency in this particular group of patients. In the future, inclusion of additional study sites would expand our ability to draw conclusions from both AV graft and fistulae patients. It is worth noting, however, that both datasets were quite similar. Regardless of inclusion or exclusion of synthetic AV grafts from the study, both primary and secondary patency of upper arm access was significantly greater than that of forearm access. Furthermore, cox regression analysis of the AV fistulae and AV graft population also did not show a relationship between patient comorbidities and access patency. Again, we were able to note a trend towards upper arm as protective factor in maintaining access patency. Patient survival was slightly decreased in the access population as a whole in comparison to the AV fistula population, potentially due to poorer overall survival of those patients who are not appropriate candidates for native fistulae (Appendix).

We suggest that in choosing a site for primary vascular access, the predicted long-term survival of the patient be considered, choosing a more definitive solution for HD access in patients with an overall poor predicted survival. In such poor risk patients, we believe that preservation of proximal access becomes less important than establishing reliable, long-term access that will probably be durable for the remainder of the patient's lifetime. Although the standard algorithm for site selection starts with the wrist and forearm sites, our data suggests that the use of the larger upper arm veins are more likely to provide flow rates amenable to hemodialysis and are less likely to fail to mature, serving as a suitable initial access. Preferential use of upper arm sites may thus avoid the need for temporary CVC usage, as well as reduce patient morbidity and redo surgery, improving patient satisfaction with care.

The results of this study are limited by its retrospective design, its small size, and its analysis of only a single center. In particular, as a result of the studies retrospective nature, we could not control for surgical site, nor for the vein used in our population. Additionally, there are there are multiple vascular surgeons at the VA in West Haven, CT and we therefore could not control for surgical technique. Also, while the computerized patient record system at the VA gave us excellent follow-up information on those patients dialyzed or followed by nephrology within the VA system, patient follow-up was somewhat limited for those patients dialyzed elsewhere to early postoperative time points. As such, we chose to use the Gehan-Breslow statistic to compare our access patency curves in the current study. Though the log-rank method of comparing stratified Kaplan-Meier plots is often used in vascular research, the Gehan-Breslow statistic emphasizes early data points on survival analyses, where our follow-up was most consistent, as opposed to the log-rank method which places more emphasis on late data points.

In young patients with few medical comorbidities and a reasonable predicted lifespan, we believe that, all other factors being equal, distal access remains a reasonable first choice option for permanent access. Such patients will likely require the use of more proximal sites within their lifespan, as no fistula can yet provide infinite hemodialysis access. In this study, veterans requiring hemodialysis form a high risk population with poor survival and need for immediate access. Additional studies are needed to define the impact of particular risk factors, especially in more heterogeneous ESRD populations. Nonetheless, commitment to maintaining hemodialysis access for this difficult group of patients may require abandoning the historical dogma of creating a distal hemodialysis access site first under all circumstances.

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Appendix

AV Fistula and Graft Analysis

(Includes 4 AV grafts which are not included in the final analysis)

Patient Demographics and Comorbidities

A total of 122 patients underwent primary AV access creations, either native fistulae or synthetic grafts, at the VA Connecticut Healthcare System (West Haven Veterans Affairs Hospital) between April 2004 and December 2009. A total of 46 patients had upper arm fistula creations and 76 had forearm fistula creations.

The demographics of the study population as a whole are listed in Table 1-1. The mean age of patients who underwent upper arm access creations was 65.2 ± 1.8, and the mean age of patients who underwent forearm access creations was 65.6 ± 1.3; age did not vary significantly between the two groups (p= 0.868). All of the patients were either Caucasian (66.4%) or African American (33.6%); patient race was similar across groups (p= 0.704). The study population consisted of 120 males and 2 females.

Hypertension was highly prevalent in both the upper (95.7%) and forearm access (100%) groups preoperatively. Diabetes mellitus was also highly prevalent, and had a similar prevalence (p=0.44) across the two groups, present in 54.4% of the upper arm patients and 36.8% of the forearm patients. There were a total of 37 patients (30.3%) who reported current tobacco use at the time of access creation; current tobacco use was more prevalent in the forearm group than the upper arm group (40.8% versus 13.0%, p=0.002). Patients who had already initiated dialysis at the time of their operation were evenly distributed across the groups (43.5% upper versus 46.1% forearm, p=.929). A total of 61 patients (50.0%) were identified as having heart disease; there was no difference in prevalence across the upper and forearm groups ($p=0.575$). CAD and CHF were also similarly distributed across the study groups ($p=0.998$ for CAD; $p=0.069$ for CHF). There was no significant difference between the two groups in the prevalence of pulmonary disease ($P=0.13$). Prior stroke and TIA were identified in 13.1% and 10.9% of the upper arm patients and 10.9% and 0% of the forearm patients, respectively; this did not vary significantly across groups ($p=0.768$ for stroke and $p=0.709$ for TIA). A total of twenty patients (16.4%) had a diagnosis of cancer at the time of operation, 10 of these patients were in the upper arm group, and 10 were in the forearm group ($p=.323$).

Preoperative Labs, Measures, and Medications

The mean preoperative albumin of the study population was 3.1 ± 0.1 and did not vary between the upper and forearm groups ($P=0.179$). The mean creatinine was $5.2\pm .2$; preoperative creatinine did not vary between study groups ($p=0.31$). BMI and EF were similar in the upper and forearm groups ($p=0.606$ and $p=0.744$, respectively)

At the preoperative visit 38.5% of patient were taking aspirin, 4.1% were taking an antiplatelet agent, 19.7% of patients were anticoagulated and 58.2% of patients were taking a statin medications did not vary significantly across groups.

Surgical and Postoperative Variables

A total of 4 AV grafts were included in the study. The remaining 118 patients received native AV fistulas. AV grafts were evenly distributed across the upper and forearm groups ($p=.993$). The majority of patients received left upper extremity fistulas (85.3%, $n=104$); the distribution of surgical side did not vary significantly between groups (p=0.367). Preoperative duplex ultrasound vein mapping showed a significant difference between cephalic vein size at the wrist in the upper and forearm groups. Those who received forearm fistulas had a mean cephalic vein width at the wrist of .317 ± .020 cm versus .240 ± .0257 cm in those patients who ultimately received primary upper arm fistulas (p=.036). Duplex ultrasound vein mapping of cephalic vein measurements at the distal humerus was similar between the two groups (p=.488). A total of 53 patients were known to have successfully received hemodialysis via their primary AV fistula at least once to date in June of 2010; this did not vary across groups (p=0.879).

Access Patency

Kaplan-Meier survival analysis showed the median time to primary failure to be 0.288 years in the forearm fistula group versus .940 years in the upper arm group. Using the Gehan-Breslow statistic, the difference between the fistula survival curves (Figure 1-1A) was significant (p=0.018). When including secondary patency via additional invasive procedures for fistula repair, the Kaplan-Meier curves (Figure 1-1B) remained significantly different (p=0.04). The median time to absolute fistula failure was 1.323 years versus 3.491 years in the forearm and upper arm groups, respectively.

Cox regression analysis of primary fistula patency (Table 2-1) in the study population as a whole showed no significant effect of patient comorbidities on fistula failure (p=0.685-0.988). Preoperative labs, measures, and medications also did not significantly contribute to fistula failure (p=0.445-0.881). There was a trend toward upper arm surgical site as a protective factor (hazard ratio=0.578, p=0.079). Surgical side did not affect fistula patency (hazard ratio=0.915, p=0.814).

Patient Survival

Kaplan-Meier survival (Figure 2-1) of the study population was shown to be 87% at 1.11 years, 64% at 3.14 years, and 47.8% at 5.011 years. There were 36 patient deaths in the study group that occurred from the time of operation to June of 2010. Cox regression analysis of long-term survival in the study population (Table 3) showed a trend toward diabetes mellitus as a risk factor for patient mortality (hazard ratio=0.74, p=0.075). Antiplatelet therapy, as a proxy of underlying disease, also contributed to patient mortality (hazard ratio=1.465, P=0.018). Surgical site, upper versus forearm, did not influence patient mortality (hazard ratio=-0.0824, p=0.852).

Table 1-1. Demographics and risk factors of AV Access Patients.

Variable	Total #	Total (%)	Upper	Upper (%)	Forearm	Forearm (%)	p-value
Total Patients (n)	122		46		76		
Age (yrs)	65.4± 1.1		65.2 ± 1.8		65.6 ± 1.3		0.868
Race							
Caucasian	81	66.4%	32	69.6%	49	64.5%	0.704
African American	41	33.6%	14	30.4%	27	35.5%	
Gender							
Male	120	98.4%	45	97.8%	75	98.7%	0.709
Female	2	1.6%	1	2.2%	1	1.3%	
Comorbidities							
Hypertension							
Yes	120	98.4%	44	95.7%	76	100.0%	0.273
No	2	1.6%	2	4.4%	0	0.0%	
Diabetes Mellitus							
Yes	73	59.8%	25	54.4%	48	63.2%	
No	49	40.2%	21	45.7%	28	36.8%	0.44
Current Smoker							
Yes	37	30.3%	6	13.0%	31	40.8%	0.002
No	85	69.7%	40	87.0%	45	59.2%	
Current Dialysis							

Yes	55	45.1%	20	43.5%	35	46.1%	0.929
No	67	54.9%	26	56.5%	41	54.0%	
Heart Disease (CAD or CHF)							
Yes	61	50.0%	21	45.7%	40	52.6%	0.575
No	61	50.0%	25	54.4%	36	47.4%	
CAD							
Yes	57	46.7%	21	45.7%	36	47.4%	0.998
No	65	53.3%	25	54.4%	40	52.6%	
CHF							
Yes	25	20.5%	5	10.9%	20	26.3%	0.069
No	97	79.5%	41	89.1%	56	73.7%	
Pulmonary Disease							
Yes	32	26.2%	8	17.4%	24	31.6%	0.13
No	90	73.8%	38	82.6%	52	68.4%	
Stroke							
Yes	16	13.1%	5	10.9%	11	14.5%	0.768
No	106	86.9%	41	89.1%	65	85.5%	
TIA							
Yes	2	1.6%	0	0.0%	2	2.6%	0.709
No	120	98.4%	46	100.0%	74	97.4%	
Cancer							
Yes	20	16.4%	10	21.7%	10	13.2%	0.323

No	102	83.6%	36	78.3%	66	86.8%	
Preoperative Labs							
Albumin	3.1 ± .1		3.0 ± .2		3.2 ± .1		0.179
Creatinine	5.2 ± .2		4.9 ± .3		5.4 ± .3		0.31
Preoperative Measures							
BMI	28.2 ± .8		27.5± 1.5		28.6 ± .9		0.606
LVEF (%)	49.9 ± 2.4		41.9 ± 4.0		43.5 ± 3.0		0.744
Medications							
ASA							
Yes	47	38.5%	16	34.8%	31	40.8%	0.639
No	75	61.5%	30	65.2%	45	59.2%	
Anti-platelet							
Yes	5	4.1%	1	2.2%	4	5.3%	0.717
No	117	95.9%	45	97.8%	72	94.7%	
Anticoagulated							
Yes	24	19.7%	9	19.6%	15	19.7%	0.832
No	98	80.3%	37	80.4%	61	80.3%	
Statin							
Yes	71	58.2%	24	52.2%	47	61.8%	0.39
No	51	41.8%	22	47.8%	29	38.2%	
Surgical Variables							
AVF or AVG							

AVF	118	96.7%	44	95.7%	74	97.4%	0.993
AVG	4	3.3%	2	4.4%	2	2.6%	
Side							
Right	18	14.8%	9	19.6%	9	11.8%	0.367
Left	104	85.3%	37	80.4%	67	88.2%	
Duplex U/S Vein Mapping							
Cephalic @ Wrist (cm)	.30 ± .02		.24 ± .03		.317 ± .02		0.036
Cephalic @ Distal Humerus (cm)	.39 ± .02		.37 ± .02		.4 ± .02		0.488
Postoperative Variables							
AVF/AVG Used?							
Yes	53	43.4%	21	45.7%	32	46.1%	0.879
No	63	51.6%	23	50.0%	40	54.0%	
Unknown	6	4.9%	2	4.4%	4	5.3%	

Table 2-1. Cox Proportional Hazards Analysis of Factors Affecting Primary Access Patency

Covariate	**Hazard Ratio**	**95%Conf-L**	**95%Conf-U**	**p- value**
Age	1	0.975	1.027	0.921
Comorbidities				
Hypertension	1.086	0.215	5.469	0.984
Diabetes Mellitus	1.118	0.652	1.919	0.685
Current Smoking	0.897	0.504	1.595	0.71
Current Dialysis	0.897	0.48	1.675	0.733
Heart disease (CHF or CAD)	1.074	0.587	1.962	0.818
Pulmonary Disease	0.906	0.501	1.637	0.744
Cancer	1.005	0.491	2.057	0.988
Preoperative Labs				
Albumin	0.916	0.731	1.148	0.445
Creatinine	0.956	0.83	1.101	0.528
Preoperative Measures				
BMI	0.997	0.961	1.033	0.849
LVEF (%)	0.998	0.988	1.009	0.751
Medications				
ASA	0.901	0.515	1.577	0.715
Antiplatelet	0.524	0.12	2.278	0.389

Anticoagulated	0.952	0.499	1.815	0.881
Statin	1.204	0.667	2.173	0.537
Surgical Variables				
Site-Upper arm	0.578	0.314	1.065	0.079
Side	0.915	0.437	1.917	0.814

Table 3-1. Cox Proportional Hazards Analysis of Factors Affecting AV Access Patient Survival.

Covariate	**Hazard Ratio**	**95%Conf-L**	**95%Conf-U**	**p-value**
Age	0.0294	-0.00917	0.0679	0.135
Comorbidities				
Hypertension	-17.016	-13787.583	13753.552	0.998
Diabetes Mellitus	0.74	-0.0739	1.553	0.075
Current Smoking	-0.0593	-0.948	0.83	0.896
Current Dialysis	0.32	-0.609	1.248	0.5
Heart disease (CHF or CAD)	-0.347	-1.274	0.581	0.464
Pulmonary Disease	0.186	-0.719	1.092	0.687
Cancer	-0.0238	-1.073	1.026	0.965
Preoperative Labs				
Albumin	-0.118	-0.464	0.229	0.505
Creatinine	0.0215	-0.158	0.201	0.814

Preoperative Measures				
BMI	-0.00443	-0.0473	0.0385	0.84
LVEF (%)	0.00733	-0.00736	0.022	0.328
Medications				
ASA	-0.304	-1.156	0.547	0.484
Antiplatelet	1.465	0.249	2.682	0.018
Anticoagulated	-0.249	-1.181	0.683	0.6
Statin	0.072	-0.793	0.937	0.871
Surgical Variables				
Site-Upper arm	-0.0824	-0.946	0.782	0.852
Side	-0.342	-1.418	0.734	0.533

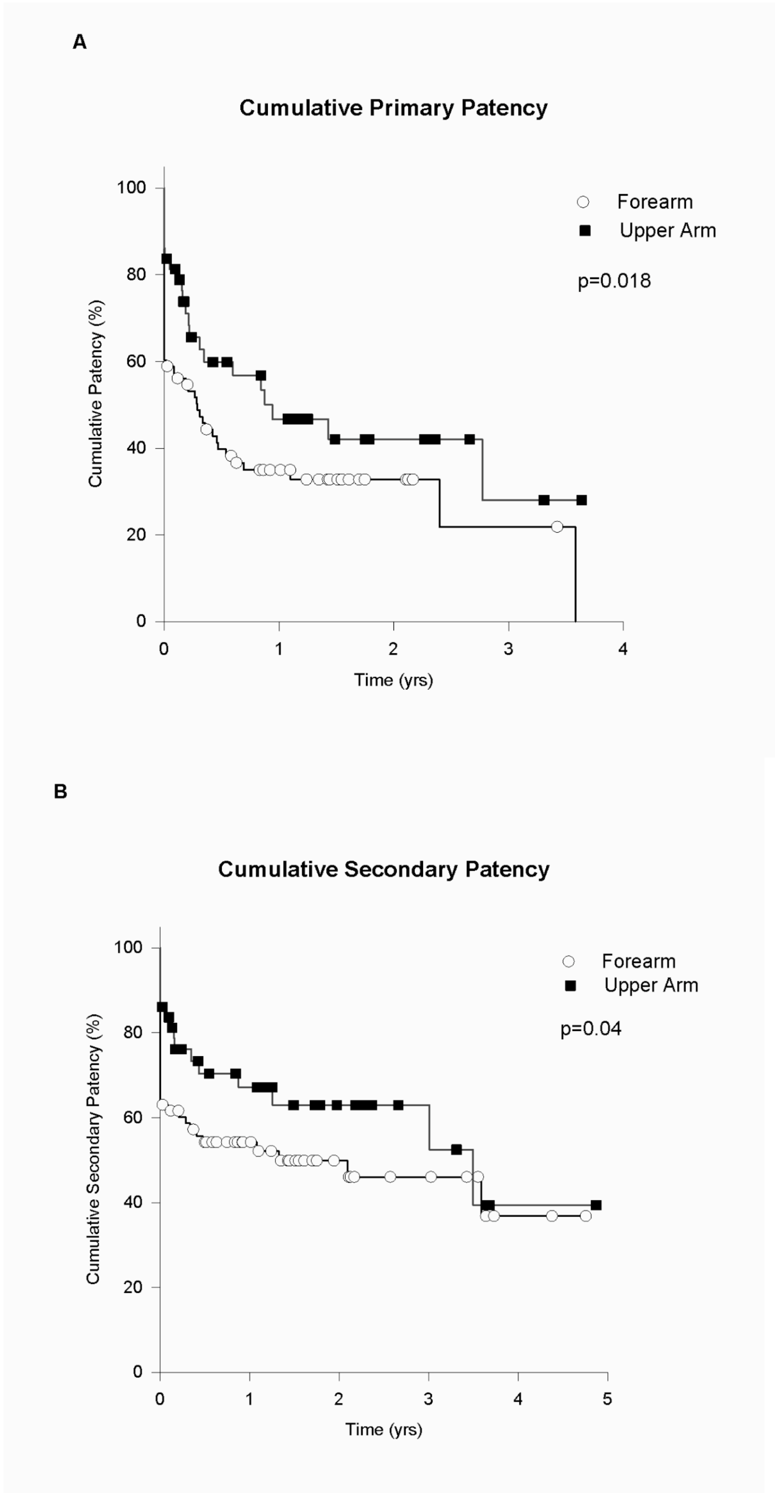

Figure 1-1. Primary and secondary patency of forearm vs. upper arm access. (A) Kaplan-Meier analysis of primary access patency. (B) Kaplan-Meier analysis of secondary access patency.

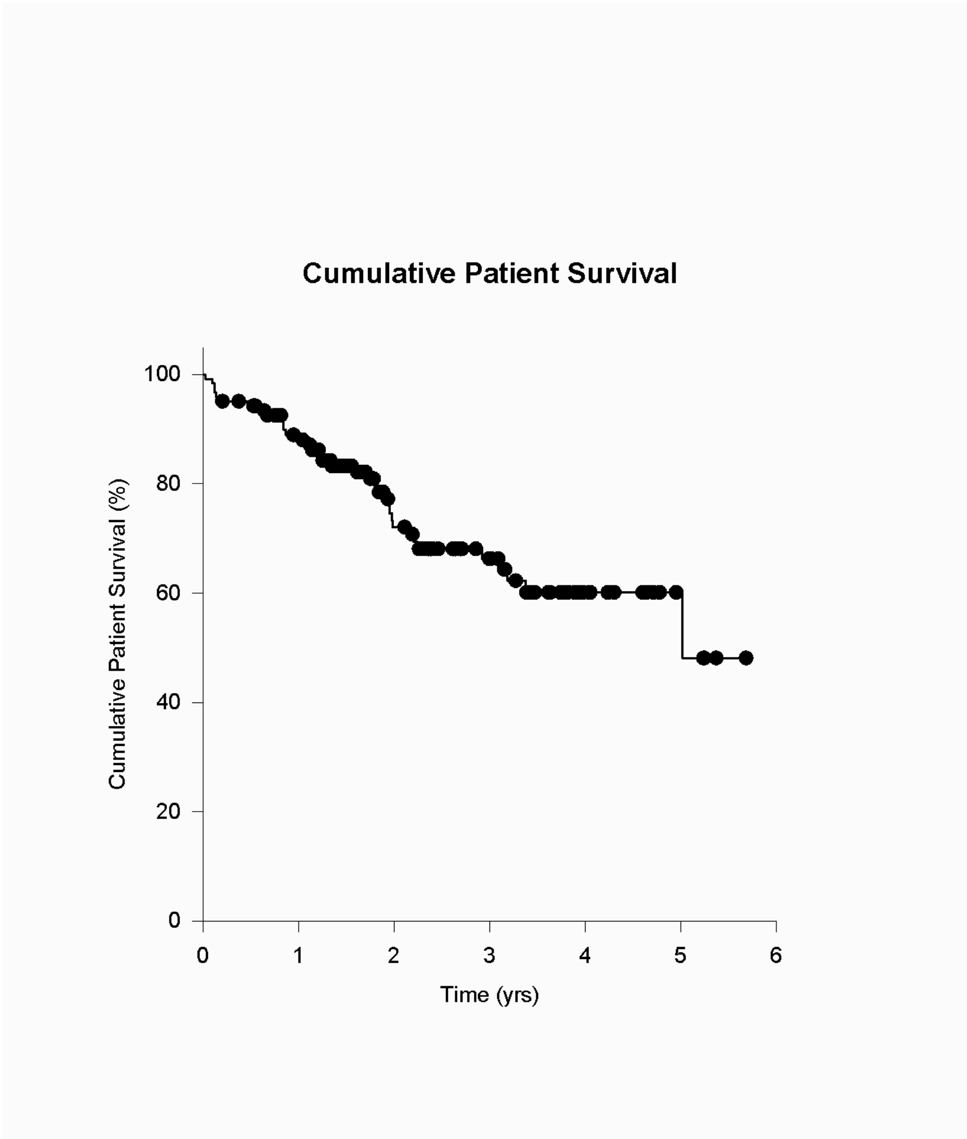

Figure 2-1. Kaplan-Meier analysis of post-operative survival (Native and synthetic fistulae).