The Impact of Peripherally-inserted Central Catheters and Vascular Imaging on Hemodialysis Patients

A thesis

Submitted by

Rita L. McGill

In partial fulfillment of the requirements
for the degree of

Master of Science

in

Clinical and Translational Science

May 2016

Advisors:
Thesis Chair: Daniel E. Weiner MD, MS
Project Mentor: Eduardo Lacson Jr. MD, MPH
Statistical Mentor: Robin Ruthazer MPH
Project Mentor: Klemens B. Meyer MD
Project Mentor: Dana C. Miskulin MD, MS

Abstract

Vascular access is a critical determinant of the survival of patients receiving hemodialysis. A working fistula or a graft avoids risks of infection, hospitalization and death that are associated with central venous hemodialysis catheter access.

Adequate blood vessels are required for creation of arteriovenous fistulas and grafts. Little is known about the effect of strategies to manage and preserve veins on the ability to achieve vascular access for hemodialysis. This study defines the epidemiology of two common medical procedures that may influence the likelihood that a patient will transition to a fistula or graft: peripherally inserted central catheters, and vascular imaging procedures. We examined these exposures in Medicare beneficiaries who initiated hemodialysis with central venous catheters, and used proportional hazards models with and without time dependent covariates to determine the associations of these exposures with time to transition to first working arteriovenous fistulas or grafts and patient survival.

We found that one in every eight patients had been exposed to peripherally inserted central catheters, after having initiated hemodialysis or during the two years prior. Pre-dialysis exposure to PICC was associated with a decreased likelihood of achieving a working arteriovenous fistula (HR=0.78, 95% CI=0.71, 0.85) or any fistula or graft (HR=0.85, 95% CI=0.79, 0.91). Post-dialysis exposure to PICC was independently associated with decreased achievement of working arteriovenous fistula (HR=0.81, 95% CI=0.72, 0.90) or any fistula or graft (HR=0.81, 95% CI 0.73, 0.89).

Fewer than 10% of patients had diagnostic vascular imaging prior to initiating hemodialysis, despite exposure to pre-dialysis nephrology care in nearly half. Vascular imaging performed prior to dialysis initiation was associated with increased transition to

arteriovenous fistulas (HR=1.36, 95% CI=1.27, 1.45) and any arteriovenous fistula or graft (HR=1.57, 95% CI=1.49, 1.66). Imaging performed after hemodialysis treatments were initiated was independently associated with increased working fistulas (HR=1.45, 95% CI=1.40, 1.51) and transition to any working fistula or graft (HR=1.63, 95% CI=1.58, 1.69). Approximately 70% of patients who have surgery achieve a fistula or graft, regardless of whether imaging is employed, suggesting that the benefits are mediated by increased performance of surgery in imaged patients.

Our analyses suggest that peripherally inserted central catheters are common and associated with poor outcomes. Vascular imaging is infrequent, but associated with desireable outcomes. Decisions made regarding the use of either of these procedures represent potentially modifiable practice patterns that could influence dialysis outcomes.

Acknowledgements

Thesis Committee:	Daniel E. Weiner MD, MS	Chair
	Robin Ruthazer MPH	Statistical Mentor
	Eduardo Lacson Jr. MD MPH	
	Klemens B. Meyer MD	
	Dana C. Miskulin MD, MS	
Educational mentors:	David Kent MD, MSc	
	Jessica Paulus ScD	
	Farzad Noubary PhD	
	Norma Terrin PhD	
	Angie Mae Rodday PhD	
	Robert J. Goldberg PhD	

The William B. Schwartz Division of Nephrology at Tufts Medical Center

A. Thomas McGill MD, without whose support and sacrifices none of this would have been possible.

Murray Mannos PhD, who gave me the music of mathematics.

Table of Contents

List of Tables

List of Figures **Page**

List of Abbreviations

AV	Arteriovenous
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Center for Medicare & Medicaid Services
CoxPH	Cox Proportional Hazards
CPT	Common Procedural Terminology (coding system)
ESRD	End stage renal disease
GFR	Glomerular filtration rate
IQR	Interquartile range
NIDDK	National Institute of Diabetes, Digestive, and Kidney Diseases
PICC	Peripherally inserted central catheter(s)
Pre-ESRD	Pre-end stage renal disease
SAF	Standard Analytical Files
SAS	Trade-name for Statistical Analysis Software
USRDS	United States Renal Data System
V5	Vascular access modifier for hemodialysis Medicare claims indicating the presence of: central venous catheter
V6	Vascular access modifier for hemodialysis Medicare claims indicating the presence of: arteriovenous graft
V7	Vascular access modifier for hemodialysis Medicare claims indicating the presence of: arteriovenous fistula

Introduction

1.1 Hemodialysis Vascular Access

Before 1960, hemodialysis was an extraordinary measure that temporarily sustained patients with acute kidney injury in the hope that spontaneous renal recovery could occur. Treatment could be sustained only until bloodstream access was exhausted, usually a matter of weeks, and patients with persistent kidney failure would thereafter succumb to uremia. In 1960, the development of surgical techniques to secure durable vascular access allowed hemodialysis to be offered to individuals with irreversible chronic kidney diseases.[1,2] Not surprisingly, hemodialysis patients often refer to their vascular access as their "lifeline."

Fifty-six years later, the dedication and resourcefulness of countless individuals has extended lifesaving kidney treatments to more than 650,000 Americans, of whom approximately 420,000 are treated by maintenance hemodialysis.[3] The lethal entity of terminal uremia was supplanted by a new entity of treated chronic kidney failure, creating a patient population dependent upon life-support administered in the outpatient setting for years or decades.[4] This population gradually evolved from highly selected young patients with favorable prognoses to a population with heavy burdens of comorbid chronic diseases and an average age of 56.9 years.[3] In the United States, the median age of incident dialysis patients is now 62.5 years.[3] With death prevented by the removal of accumulated fluids and small molecules, hemodialysis patients nonetheless contend with complications of chronic kidney disease that evolve over a much longer natural history and also complications directly related to treatment.

Patients with advanced chronic kidney disease (CKD) and those treated with hemodialysis have a high prevalence of comorbid conditions which require complex medical and surgical therapies, ensuring multiple points of contact with the health care system. They receive medical care from many different providers, not all of whom necessarily appreciate the paramount importance of their vascular access needs. The rate of hospitalization in prevalent adult hemodialysis patients is 1.81 admissions per patient year, for a total of 11.1 days per patient year, and one-month readmission rates are approximately 37%.[5] Hospital care represents 40% of total Medicare expenditures for patients on dialysis. [5]

Vascular access remains a critically important a determinant of the outcomes of patients on hemodialysis.[6-9] Most hemodialysis treatments are performed three times a week, and each treatment requires two points of access with the bloodstream: one to move blood from the patient to the dialysis machine, and one to return treated blood to the patient. Blood must be delivered to the machine at 250-500 mL/minute, in order to achieve treatment goals. This requirement, which is higher than needed for most medical procedures, contributes to the importance of vascular access in hemodialysis outcomes.

Hemodialysis vascular access can be classified into three major categories: arteriovenous fistulas, arteriovenous grafts, and central venous catheters.

1. An arteriovenous fistula is created when a vein is surgically connected into a nearby artery. Figure 1 [6] shows an arteriovenous connection at the right wrist, between the radial artery and the cephalic vein, known as a Cimino fistula. The pulsatile high-pressure blood flow in the artery passes through the smaller, thin-walled vein. If

surgery is successful, the vein initially dilates and over the next 1-4 months develops thicker and stronger walls, a process that is known as fistula maturation. Maturation is necessary to permit placement of two large-bore needles for each treatment. A fistula that does not undergo maturation cannot be used for hemodialysis, even if an open connection between the vessels is present. If maturation occurs, AV fistulas are the most durable vascular access, and the least likely to suffer infection or become occluded by clotted blood. Fistulas are subcutaneous structures constructed entirely from a patient's own arteries and veins, which gives them intrinsic resistance to infection.

Figure 1: An AV fistula at the right wrist, connecting the radial artery and cephalic vein.

2. An arteriovenous graft may be constructed in some cases when available veins are not sufficient to create a fistula that can become mature (Figure 2).[6] Grafts differ from fistulas in that artificial materials are used to complete the connection between arteries and veins, and provide a superficial structure into which hemodialysis needles can be placed. Graft surgery is more likely than fistula surgery to be successful, especially when existing veins are small. Grafts can normally be used sooner than fistulas, because the artificial conduit does not have to undergo maturation. However, the functional lifetime of grafts are shortened because the synthetic components are prone to clotting and susceptible to infection. Each

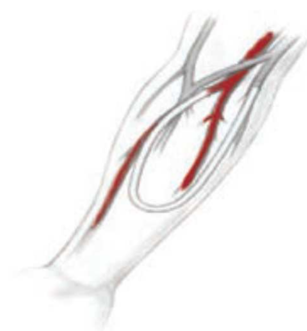


Figure 2: An arteriovenous graft connecting the brachial artery to the cephalic vein, using a U-shaped conduit installed along the forearm.

failed graft causes damage to the vessels to which it was attached, limiting the prospects for the next vascular access site.

3. Hemodialysis can be performed with a two-chambered central venous catheter inserted into a large central vein (Figure 3)[6], which can be used immediately once in place. This makes central venous catheters a convenient and feasible method to initiate hemodialysis in a patient for whom a successful preparatory vascular surgery has not been performed. A dialysis catheter has external ports that can be connected to a dialysis machine, and internal tubing that dwells in the bloodstream. The catheter can therefore introduce bacteria to the bloodstream, and cause catastrophic infections and death. Hemodialysis catheters must have a large diameter to support the blood flows required for effective dialysis. These large devices often damage central veins, which reduces the venous drainage needed to have a fistula without facial or arm edema. Catheter performance depends upon positioning in the central veins, but blood flows are rarely equivalent to those from fistulas or grafts, so inadequate clearance of toxins is more likely with catheter dialysis. For these reasons, catheter use is ideally a temporary measure used while a durable vascular access arteriovenous fistula or graft is sought.

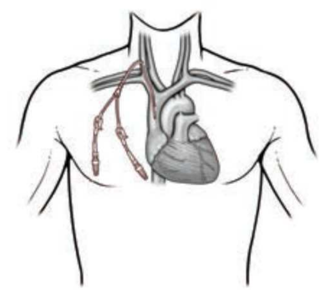


Figure 3: A central venous dialysis catheter in the right internal jugular vein.

The Cimino arteriovenous (AV) fistula, in which an end-to-side anastomosis of the cephalic vein to the radial artery in the forearm is surgically created, was first described in 1966.[10] Alternative sites for construction of primary arteriovenous anastomoses in upper or lower limbs have subsequently been developed.[11-15] AV fistulas have endured for decades as the optimal way to provide ongoing access to the bloodstream for hemodialysis treatments. Use of an AV fistula or even an AV graft, reduces the risks of infection, hospitalization, and mortality in hemodialysis patients, compared to the use of a central venous catheter.[6-9]

Creation of a working AV fistula requires a willing patient with patent blood vessels of adequate caliber and timely referral to a skilled surgeon. Pre-dialysis medical care can promote patient education and timely referral for vascular access surgery.[16,17] Incident hemodialysis patients with no exposure to nephrology care prior to the onset of dialysis are unlikely to initiate dialysis with AV fistulas; prevalent patients have universal exposure to nephrology care. Aside from sex, factors that are known to contribute to the probabilities of vascular access types include: age, race, geography, and whether diabetes was the underlying cause of kidney failure.[18-21]

Achievement of vascular access is low in the US (Table 1)[18]. Most other countries have higher rates of fistula use, and lower rates of central catheter use, in both incident and prevalent patients.[22]

Table 1: Vascular access use in the first year of hemodialysis therapy, by sex

	At initiation		After first year	
	Men	Women	Men	Women
AV fistula (%)	18.8	15.0	71.5	56.9
Avgraft (%)	2.1	3.8	11.0	19.3
Catheter (%)	79.1	81.2	17.5	23.7

Approximately 80% of Americans initiate their hemodialysis treatment using central venous catheters[18], which are frequently complicated by thromboses, bloodstream infections, and stenoses of central veins.[6-9] Before initiating dialysis treatment, only one in four patients beginning hemodialysis with a venous catheter has undergone surgery to create an AV fistula or graft that may potentially mature into a durable vascular access.[18] The most recently published annual statistics of the United States Renal Data System showed that 62.5% of prevalent hemodialysis patients in the United States use AV fistulas,[18] the remainder of prevalent patients were evenly divided between use of AV grafts and central venous catheters,[18] suggesting that more than 75,000 established hemodialysis patients use central venous catheters, despite evidence that failure to transition to an AV fistula strongly predicts poor outcomes and increased costs of care. [23-25]

Table 1 illustrates that central venous catheters are common in both women and men initiating hemodialysis. Over the first year of hemodialysis, the rate of AV fistula use increases from 18.8% to 71.5% in men. Conversion to an AV fistula is less common in women, with only 56.9% using AV fistulas after the first year. While some of this disparity is compensated by the increased use of AV grafts in women, the net result is that after the first year of hemodialysis, central venous catheter use is 23.7% in women and 17.5% in men.[18] These reasons for these disparities in vascular access have not been well-defined. While women are generally considered to have fewer visible superficial veins detectable on physical examination, studies employing ultrasound inspection of blood vessels do not show consistent differences in upper extremity blood vessel caliber between men and women.[26] A meta-analysis of AV fistula outcomes in 62 cohorts revealed intense heterogeneity in the outcomes of women and men, and contradictory effects of sex on fistula outcomes, concluding female sex was associated with more failure of fistulas to mature to usability, but that male sex was associated with more fistula failure over the first year.[27]

The medical care practices that patients encounter before and after initiating hemodialysis are potentially important exposures, and their effects upon hemodialysis patient outcomes have not been closely examined. The central hypothesis of this thesis is that medical care processes experienced by hemodialysis patients contribute to their vascular access outcomes and their survival. This research focuses on two important medical care processes chosen for their likelihood to interact significantly with vascular access prospects: pre-operative vascular imaging and placement of peripherally-inserted central catheters. The associations of these procedures with vascular access outcomes and with patient survival were examined in patients initiating hemodialysis with central venous catheters as their sole vascular access.

1.2 Peripherally inserted central catheters

Peripherally inserted central catheters (PICC) were introduced in 1975 to facilitate parenteral nutrition.[28] Figure 4, PICC are most commonly inserted into cephalic, basilic, or brachial veins, at the level of the antecubital fossa, and advanced to the junction of superior vena cava with the right atrium (Figure 4).

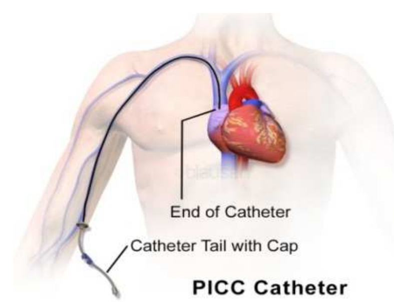


Figure 4: PICC catheter placement. (Illustration from Wikipedia Commons by Blausen Medical Communications. Open Source Ticket #2013061010006654)

PICC are easily placed using portable ultrasound guidance, have lower risks of catheter related blood-stream infections than non-tunneled central venous catheters, and allow home parenteral therapy.[29,30] PICC are convenient for nurses, physicians, and patients. Their use shortens the length of stay in hospitals and nursing facilities, resulting in rapidly increasing utilization over the past 15 years.

However, PICC use is also associated with stenosis, thrombosis, and obliteration of the veins in which they dwell, [31,32] and these complications may have important consequences for the patency of the peripheral and central veins of patients who subsequently require hemodialysis vascular access. Ironically, patients with chronic kidney disease often have multiple comorbid conditions that may increase the chance of PICC exposure,[33] despite the importance of preserving veins for future AV fistula creation. Clinical practice guidelines and position statements that discourage the use of PICC in patients with kidney diseases have received little attention outside of the nephrology community.[34-36]

Few studies have examined PICC exposure in patients receiving hemodialysis or those who will initiate hemodialysis in the near future, or have attempted to define the consequences of their use. We sought to quantify PICC exposure in patients initiating hemodialysis with a central venous catheter as their sole vascular access, a group of patients with indications to preserve blood vessels for creation of dialysis fistulas.

1.3 Vascular imaging for hemodialysis access planning

One of the major barriers to achievement of a working AV fistula is failure of the surgically-created structure to mature into a durable vascular access, a process that requires the development of sufficient blood flow to induce changes in the component blood vessels that result in a durable structure that can withstand repeated cannulation. Even fistulas constructed in advance, using seemingly adequate blood vessels, may experience primary thrombosis or failure to mature.[37-39]

Contrast venography and doppler ultrasound can be used to evaluate blood vessels that cannot be appreciated upon physical examination, but these procedures are costly, time-consuming, and require special expertise. Prior literature on the impact of vascular imaging on the outcomes of hemodialysis vascular access surgery consists almost entirely of single-center experiences.[40,41] Although most studies have demonstrated an increase in the number of fistula and graft surgeries undertaken when preoperative imaging was employed, increased surgery has not consistently translated into more achievement of working fistulas, possibly because of increased failure of the additional procedures.[42-48]

In the absence of evidence for a convincing impact of imaging successful achievement of working fistulas, the performance of imaging is often determined by individual provider preference. We sought to assess how often patients who start hemodialysis using central venous catheters have vascular imaging, and to assess the impact of imaging upon eventual vascular access outcomes and overall patient survival.

1.4 Research Hypotheses

All hypotheses in this research were evaluated with two-sided statistical tests, whether or not a directional hypothesis was specified. The following hypotheses were investigated:

1. PICC exposure may vary by sex. The null hypothesis was that men and women are equally likely to receive PICC. The alternative hypothesis was that women would have greater exposure to PICC than men.
2. PICC insertion may be associated with a reduced likelihood of successful transition from central venous catheter to AV fistula or graft. The null hypothesis was that PICC insertion would have no effect on achievement of arteriovenous vascular access. The alternative hypothesis was that patients with exposure to PICC would have reduced achievement of working AV fistulas and grafts, compared to those who received no PICC.
3. PICC insertion may have associations with survival on hemodialysis. The null hypothesis was that survival would be comparable between patients who received PICC and those who did not. The alternative hypothesis was that patients receiving PICC would have lower survival than those who had no PICC.
4. Vascular imaging may vary by sex. The null hypothesis was that men and women are equally likely to have vascular imaging. The alternative hypothesis was that women would have less exposure to imaging than men.
5. Vascular imaging may have associations with the likelihood of successful transition from central venous catheters to AV fistulas or grafts. The null hypothesis was that achievement of AV fistulas and grafts would not differ between those who received

imaging and those who did not. The alternative hypothesis was that individuals who had imaging would have achievement of working AV fistulas, compared to those who had no imaging.

6. Vascular imaging may have associations with survival on hemodialysis. The null hypothesis was that survival would not differ between patients who had imaging and those who did not. The alternative hypothesis was that patients who had imaging would have increased survival, compared to those who did not have imaging.
7. Vascular imaging may have associations with the frequency of surgery to create fistulas and grafts, as well as associations with the proportions of vascular surgeries that result in durable hemodialysis vascular access.
    a. The null hypothesis was that the rate of surgery would not differ between patients who did or did not have imaging prior to surgery. The alternative hypothesis was that patients who were exposed to imaging would have surgery more often than those who did not.
    b. The null hypothesis was that the proportion of vascular surgeries resulting in durable vascular access would not differ between patients who had imaging prior to surgery and those who did not. The alternative hypothesis was that surgical success, defined as production of a working AV fistula, would more frequent in patients who had preoperative imaging.

Materials and Methods

This study was a retrospective analysis of United States Renal Data System (USRDS) data, in which the associations of two exposures (PICC placement, vascular imaging) with three outcomes (death, conversion to a working AV fistula, and conversion to either a working AV fistula or a working AV graft) were evaluated. Logistic regression was used to evaluate the odds of successful achievement of AV fistulas or grafts in patients who underwent one or more vascular surgeries. Survival analysis and Cox proportional hazards (PH) models were used to evaluate time to event outcomes, starting from the date of hemodialysis initiation. In addition to creating Cox PH models using only information available at the time of initiation of dialysis as covariates, we also constructed Cox PH models using time dependent covariates to accommodate medical care process exposures that occurred after the initiation of hemodialysis.

2.1 Data source

USRDS is the national system that collects, analyzes, and distributes information about end-stage renal disease in the United States. The USRDS is directed by the National Institute of Diabetes and Digestive and Kidney Diseases, and collaborates with the Centers for Medicare and Medicaid Services, the United Network for Organ Sharing, and the national system of ESRD Networks. Mandatory participation of all dialysis facilities is a pre-condition for participation in Medicare, so the USRDS data files contain information on virtually all period prevalent patients being treated for kidney failure in the United States.

Standard Analysis Files provide de-identified patient-specific data from the USRDS database, which are available to researchers via a Data Use Agreement with the

NIDDK. This study was approved by the Institutional Review Board of Tufts Medical Center, with a waiver of the requirement for informed consent. The Core dataset and Medicare payment datasets from 2008 through 2012 were obtained for this research.

The Core dataset includes basic demographic information on all patients being treated for kidney failure, and also provides a longitudinal history of insurance payers (Payer History file), the sequence of treatment modalities (organ transplantation, peritoneal dialysis, and hemodialysis), and residence by zip code. The Medical Evidence files contain mandatory information provided to Medicare on CMS Form 2728 at the time of hemodialysis initiation.

Medicare payment datasets include claims paid before and after the initiation of hemodialysis (pre-ESRD and ESRD claims) for Medicare beneficiaries. Medicare datasets include: Institutional Claims, Institutional Claims Details, Revenue, and Physician/Supplier files.

2.2 Study Population

The study population consisted of adults who initiated hemodialysis for the first time between April 1, 2010 and December 31, 2011, in whom a central venous catheter was the sole vascular access present at the first outpatient hemodialysis treatment. Using the USRDS Payer History file, we restricted our analysis to Medicare beneficiaries $\geq$ 20 years of age who had Medicare coverage 730 days prior to the first hemodialysis treatment, with continuous coverage until the end of 2012 or a censoring event. We included patients for whom Payer History could be verified by the existence of two or more pre-dialysis Medicare claims, at least six months apart, one or more of which occurred > 365 days before the date of the first hemodialysis.

The “prior claims” restriction was designed to identify patients with a high likelihood of having continuous Medicare coverage for the 2 years preceding hemodialysis initiation, allowing us to use claims data to ascertain PICC and vascular imaging events, and generate information on the comorbid conditions of our population. A requirement for longer periods of Medicare coverage before hemodialysis initiation might have enabled the identification of more exposure events, but would entail a trade-off that would further restrict the sample size available for study, and increase the selection bias for an older population. Since Medicare eligibility normally occurs at age 65, the overwhelming majority of new dialysis patients with two years of pre-existing Medicare benefits would be 67 years or older. Two years of pre-hemodialysis Medicare eligibility was selected as an appropriate compromise that would identify a group of patients who were reasonably representative of the hemodialysis population, during a period when most of whom would already have identifiable CKD, with sufficient numbers of exposures and clinical outcomes to detect significant associations.

The vascular access at hemodialysis initiation was determined from the USRDS Medical Evidence form (CMS Form 2728) and verified by examination of hemodialysis treatment claims over the first 6 weeks. Patients were excluded for inconsistent vascular access data if hemodialysis claims showed an AV fistula in use less than 6 weeks or an AV graft in use less than 3 weeks after hemodialysis initiation, in order to exclude patients who already had maturing AV fistulas or grafts at the time of hemodialysis initiation.

2.3 Patient Characteristics

Age, sex, race, body mass index, primary causes of kidney failure, pre-hemodialysis nephrology care, pre-hemodialysis erythropoietin use, inability to ambulate, and pre-enrollment laboratory values (hemoglobin, albumin, and creatinine) were obtained from Medical Evidence enrollment data (CMS Form 2728). Comorbid conditions were determined directly from pre-dialysis Medicare claims, according to the method of Liu et al,[49] with the exception of diabetes, because diabetes was represented as a primary cause of kidney failure as well as a co-morbid condition. We used Medicare service claims for diabetes care to code a separate variable for diabetes as a comorbid condition in patients whose primary kidney failure diagnosis was not diabetic nephropathy, avoiding overlap between diabetes as a comorbid condition and diabetes as a primary cause of kidney failure.

2.4 Exposure Variables

PICC placements, vascular imaging, and surgeries to create AV fistulas and grafts were determined by examining Medicare claims for the two years prior to hemodialysis initiation and during the follow-up time after hemodialysis initiation. Events were identified in the Institutional Details, Physician/Supplier, and Revenue Center Details files using Common Procedural Terminology codes (Table 2).

Table 2: CPT codes for PICC insertions, vascular imaging, and hemodialysis vascular access surgery	
CPT code	Procedure
36569	PICC insertion, without port
36571	PICC insertion, with port
36005	Venous cannulation/ contrast injection
75820	Angiogram of a single arm
75822	Angiogram of both arms
75827	Venogram of superior vena cava
G0365	Vein mapping for dialysis access planning
36818	AV fistula with basilic vein transposition
36819	AV fistula with cephalic vein transposition
36820	AV fistula in forearm with vein transposition
36821	AV fistula, without vein transposition
36825	AV graft, autogenous
36830	AV graft, non-autogenous

Duplicate claims for PICC on the same date on the same individual were counted as a single event. We did not assess imaging procedures for the lower extremities or doppler evaluation of existing AV fistulas (CPT code 93990). We assessed only one imaging event per day on any individual patient. If there were multiple codes for venography, a single venogram was assessed. If venography and vein mapping occurred on the same day, the venogram was the only exposure recorded.

All PICC insertions and vascular imaging events were ascertained, but PICC and imaging events that occurred after transition to a first working AV fistula or first working fistula or graft did not contribute to analyses for these primary endpoints.

2.5 Clinical Outcomes

USRDS Treatment History files were used to ascertain dates of death, transplant, and changes in treatment modality. Patients were followed until: death, transplant, transfer to another dialysis modality or December 31, 2012, whichever came first.

Vascular access outcomes

Vascular surgery to create an AV fistula does not guarantee the production of a working fistula. Even patients with seemingly adequate blood vessels and timely referral to a skillful surgeon may experience primary thrombosis or failure of their fistulas to mature in 23% of surgeries.[27] The interval required for maturation can be highly variable, even among patients who ultimately achieve a working fistula. Since AV grafts require healing of the surgical site, but not maturation, a higher proportion of graft surgery is successful and the interval between surgery and use may be shorter.

The date of surgery does not therefore indicate time of achievement of a working fistula or a graft. The definition of working fistula used by the NIDDK Hemodialysis Fistula Maturation Study required 'use of fistula with 2 needles for 75% of dialysis sessions during a 4-week period with either:

1) 4 consecutive dialysis sessions with mean blood pump speed>=300 or
2) Adequate HD urea clearances (defined as single-pool Kt/V>=1.4 or URR>70)
3) Must be met without any fistula intervention procedures and by the later of 9 months after surgery or 8 weeks after HD initiation[50]

Our dataset lacked information about blood flow rates and urea clearances, but we were able to create a novel endpoint using claims for individual hemodialysis treatments. In 2010, Medicare created a requirement for all facilities providing outpatient HD to include a modifier indicating the vascular access used during treatments. A V5 modifier code attached to a dialysis claim indicates the use of a central venous catheter; a V6 code indicates a graft; a V7 code indicates the use of a fistula. The majority of facilities submitted claims per-treatment. However, it was also possible to submit a monthly claim, in which case a single modifier represented more than one HD treatment. Additionally, if more than one access was used (for example, a single hemodialysis using one needle in a fistula with one port of a catheter, or claims over a month reflecting transition from one access to another, then a single claim could contain more than one modifier.

We formulated our endpoint using these access modifiers, and defined the date of achieving a working access as the first day of the first 30-day period for which all available modifier codes were for AV fistula (or AV graft) with no intervening codes for central venous catheters. In addition to the resemblance to the pre-existing definitions of working fistulas[50,51], 30 days was a clinically plausible interval after which most patients with functioning access would have removal of their hemodialysis catheters.

An example of the raw data in USRDS hemodialysis claims files is provided (Figure 5), showing the vascular access modifier fields.

Catheter modifiers are outlined in red, graft modifiers in blue, and fistulas outlined in green.

Obs	USRDS_ID	mod1	mod2	mod3	mod4	mod5	rev_dt
20011	103303	V5	V9				07JAN11
20012	103342	G4	V6	V9			07JAN11
20013	103345	G5	V9	V7			07JAN11
20014	103359	G4	V7	V9			07JAN11
20015	103443	G5	V7	V9			07JAN11
20016	104344	V6	V9	G5			07JAN11
20017	104484	V7	V9	G5			07JAN11
20018	104504	G4	V9	V6			07JAN11
20019	104633	G5	V9	V5			07JAN11
20020	104888	G3	V5	V9			07JAN11

Figure 5. Representative segment of a USRDS hemodialysis claims file.

These modifier codes were collected and classified in order to create vascular access histories for each patient. Any claim with a V5 (catheter) modifier was considered to represent catheter hemodialysis, even if an additional modifier was present. In this manner, a history of vascular access modifiers could be constructed for each individual in the dataset. A representative segment of a patient history is shown in Figure 6.

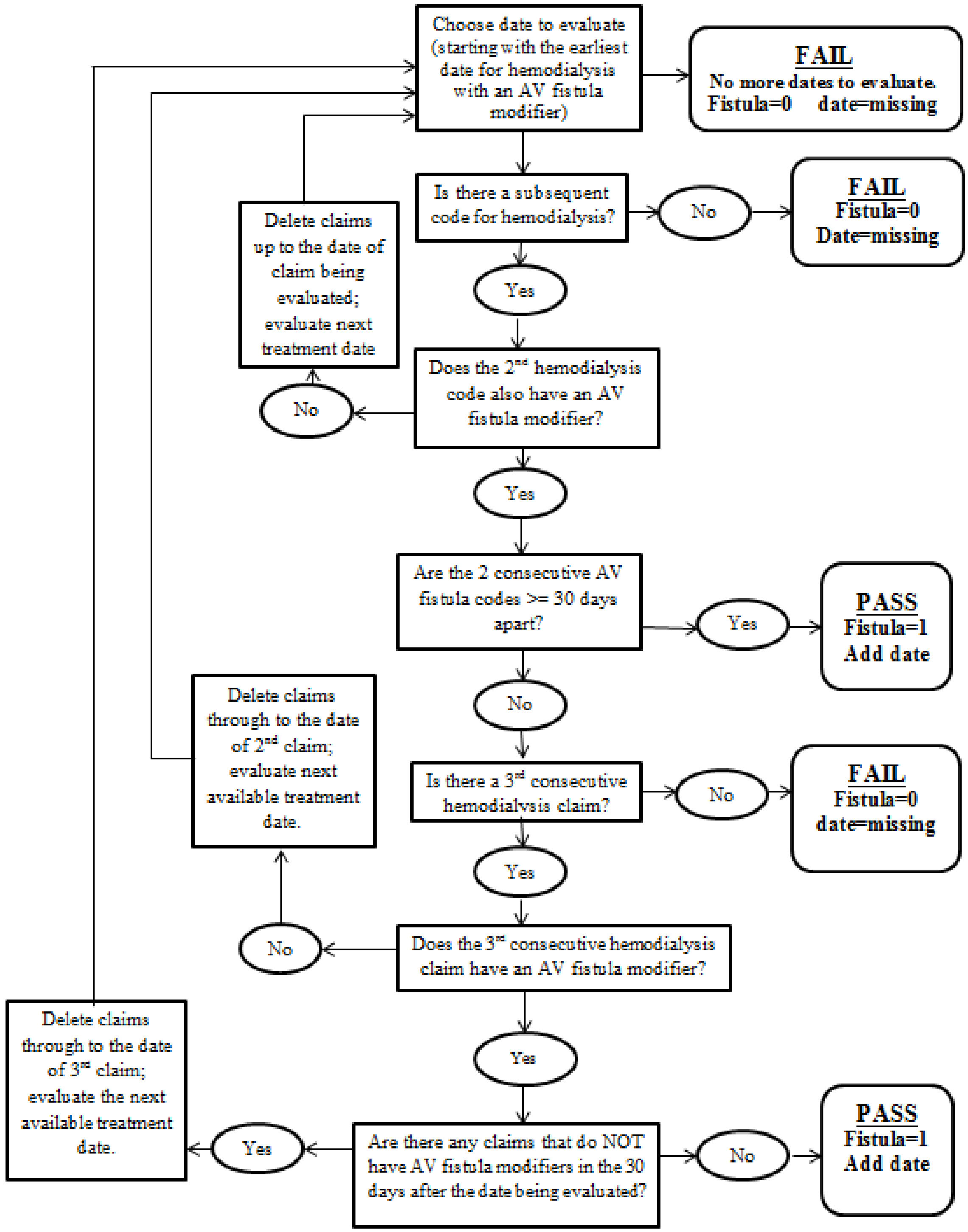
USRDS_ID	rev_dt	DIALDAT	CATH_HD	FISTULA_HD	GRAFT_HD
2213184	29AUG11	03/29/2011	1	0	0
2213184	31AUG11	03/29/2011	1	0	0
2213184	02SEP11	03/29/2011	0	1	0
2213184	05SEP11	03/29/2011	0	1	0
2213184	07SEP11	03/29/2011	0	1	0
2213184	09SEP11	03/29/2011	0	1	0
2213184	12SEP11	03/29/2011	0	1	0
2213184	14SEP11	03/29/2011	1	0	0
2213184	16SEP11	03/29/2011	1	0	0
2213184	19SEP11	03/29/2011	0	1	0
2213184	21SEP11	03/29/2011	0	1	0
2213184	23SEP11	03/29/2011	0	1	0
2213184	26SEP11	03/29/2011	0	1	0
2213184	28SEP11	03/29/2011	0	1	0
2213184	30SEP11	03/29/2011	0	1	0
2213184	03OCT11	03/29/2011	0	1	0
2213184	05OCT11	03/29/2011	0	1	0
2213184	07OCT11	03/29/2011	0	1	0
2213184	10OCT11	03/29/2011	0	1	0
2213184	12OCT11	03/29/2011	0	1	0
2213184	14OCT11	03/29/2011	0	1	0
2213184	17OCT11	03/29/2011	0	1	0
2213184	19OCT11	03/29/2011	0	1	0
2213184	21OCT11	03/29/2011	0	1	0

Figure 6. Example of an individual vascular access history.

In this representative vascular access history, there is a transition from catheter to fistula on September 2nd, but catheter use occurs on September 14th and September 16th. Fistula use resumes on September 19th, and is consistent through October 21st. In this case, September 19th would meet the criteria for achievement of a working AV fistula, but September 2nd would not.

The logic diagram for assigning the date of a transition from the vascular catheter that all patients had at initiation, to a fistula, is shown in Figure 7. A similar algorithm was used to assign the date of transition to a working graft.

Figure 7. The logic diagram for assignment of the date of first AV fistula.



In 333 individuals, a date of first working AV fistula and a date of first working AV graft were both detected. In those patients, the earliest transition date was considered to represent the date of first working non-catheter access. Once vascular access was assigned, visual inspection of a sample of approximately 200 vascular access histories was performed, in which we did not see any deviation from the intention of the algorithm. Moreover, individuals identified as having achieved a working fistula of graft by these algorithms generally had sustained function of the new fistula or graft over time, lending support to our decision to use this novel endpoint.

2.6 Adjustments for relevant covariates

The medical complexity of patients receiving hemodialysis provides potential confounding variables. Analyses were adjusted for age (per 10 years), race, body mass index, primary cause of kidney failure, pre-hemodialysis nephrology care, pre-hemodialysis erythropoietin use, and inability to ambulate, as well as pre-enrollment laboratory values of hemoglobin, albumin, and creatinine, and comorbid medical conditions. Comorbid conditions were determined directly from pre-dialysis Medicare claims, according to the method of Liu et al,[50] including cardiac diseases (further categorized as atherosclerotic heart disease, congestive heart failure, arrhythmia, and other cardiac diseases), diabetes, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, gastrointestinal diseases, liver disease, and cancer. Because diabetes was also captured as a primary cause of kidney failure, we prevented overlap between the two diabetes variable by scoring diabetes as absent in patients whose primary cause of kidney failure was diabetic nephropathy.

Aside from age, we created ordered categories of continuous adjustment variables (BMI, creatinine, albumin, hemoglobin, and pre-dialysis erythropoietin use) to avoid removing patients while still allowing for linear associations to be adjusted for with respect to each outcome. Variables for comorbid conditions, including non-ambulatory status, were dichotomized with referent values for absent (coded as ‘0’). Race, primary diagnosis of kidney failure, pre-dialysis nephrology care, body mass index, and laboratory data were categorized according to clinically relevant values (Table 3).

Table 3: Categorization of adjustment variables			
Variable	**Referent Category**	**Other Categories**	**% missing**
Race	White	Black, All others	0
Primary diagnosis	Primary Glomerulonephritis	diabetes, hypertension, genetic disorders, tubulointerstitial/pyelonephritis, secondary glomerular disease, tumors, miscellaneous	0
Pre dialysis nephrology care	>12 months	6-12 months, 0-6 months, no care, missing	16.5
BMI category	Normal (18.5-24.9)	Underweight(<18.5), overweight(25.0-29.9), obese (>=30), missing	1.4
Creatinine	>6.3 mg/dL	<3.5, 3.5-5.0, 5.1-6.2, missing	0.3
Albumin	>4.0 mg/dL	<3.0, 3.0-3.5, 3.6-4.0, missing	26.5
Hemoglobin	7-10 g/dL	<7, 10.1-12, >12, missing	8.7

The linearity of the continuous age covariate was evaluated by visual inspection of a categorized age variable in Kaplan Meier plots (Figure 8) and log-log plots (Figure 9), and by documenting consistent relationships between the beta coefficients for categories (0.000, 0.217, 0.387, 0.646, and 0.837 for categories 5, 4, 3, 2, and 1) in the patient survival model.

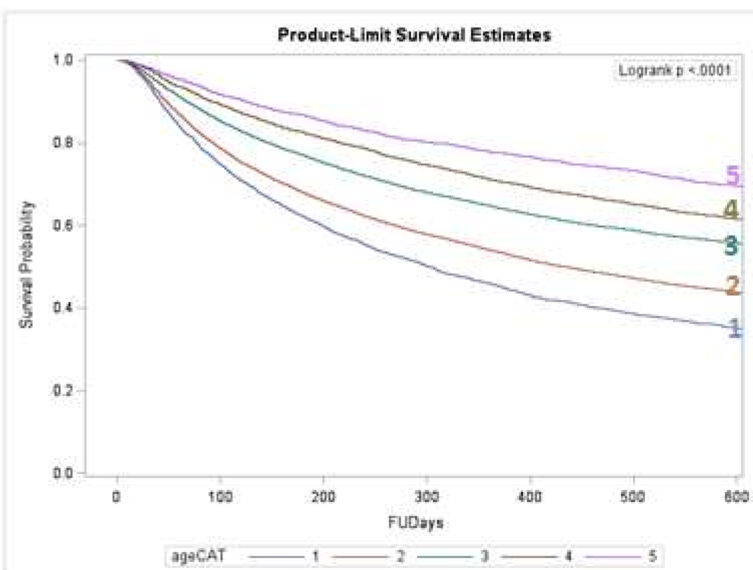


Figure 8:
Kaplan-Meier plot for a categorical age (quartile) variable, demonstrating linearity.
Example shown is for the patient survival model.

Age categories:
5 - <= 55
4 – 55<age<=65
3 – 65<age<=75
2 – 75<age<=85
1 - >85

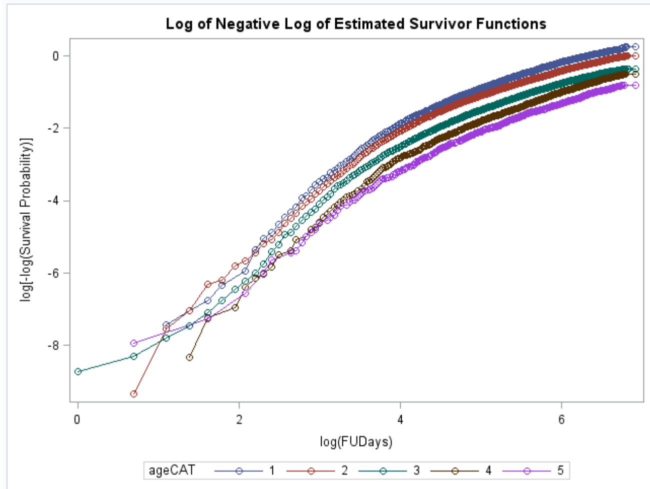


Figure 9. Log-log plot of the categorized age variable, showing parallel linear plots after 60 days, representing the bulk of the data, and minor deviations at earlier time points.

Proportional hazards were assessed with Schoenfeld residuals for each model. A representative smoothed plot of Schoenfeld residuals, for the "underweight" category of body mass index in the model for time to first AV fistula, is shown in Figure 10. The horizontal plot supports the assumption that the hazard ratio is constant over time.

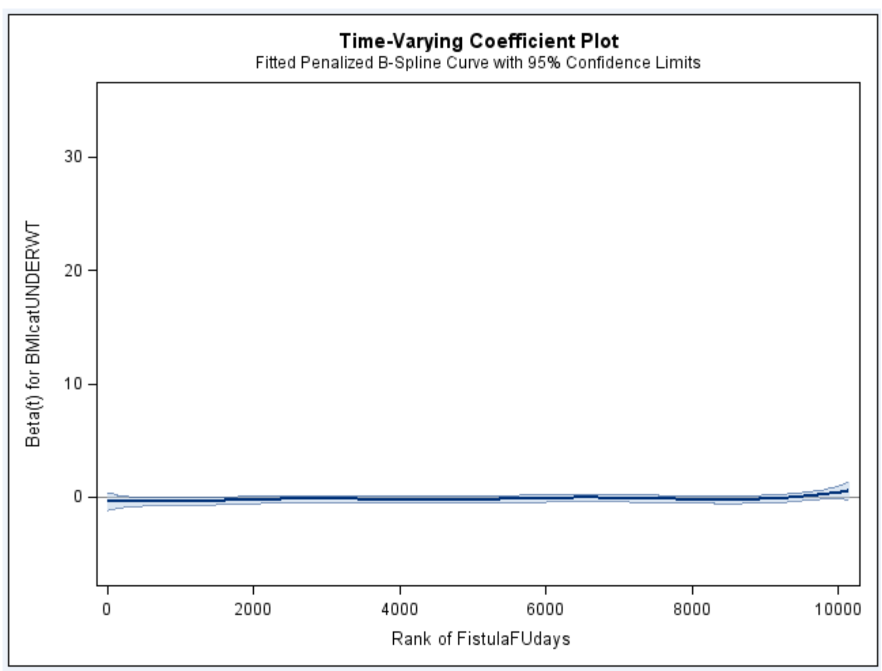


Figure 10: Smoothed plot of Schoenfeld residuals for BMI category "underweight" in the model for time to first AV fistula, supporting the assumption of proportional hazards.

2.7 Primary Statistical Analyses: Overview

Means and medians were used to summarize distributions of normally and non-normally distributed continuous variables respectively, using visual inspection of histograms of the distributions of results. Baseline values were compared between cohorts of interest using t-tests, Wilcoxon rank sum tests and chi-squared tests used as appropriate.

Kaplan-Meier estimation and Cox proportional hazards models were used to evaluate time to outcome events. The HD initiation date was used as time-zero for all survival analyses and proportional hazards models, with exposure events occurring after this date included exclusively as time-dependent covariates.

Logistic regression was used to model the odds of successful transition to AVF, AVG, and AVF/AVG in the subset analysis of patients who underwent one or more vascular surgeries.

Primary Analyses: Table 4 lists the multiple primary analyses of this research.

Table 4: Statistical Analyses

Statistical Methods	Exposures	Outcome	Adjustment covariates
Primary Analyses			
Poisson	Sex	PICC	(A), (C)
Poisson, Kaplan-Meier	PICC	Death	
Poisson, Kaplan-Meier	PICC	AV fistula only	
Poisson, Kaplan-Meier	PICC	AV fistula or graft	
Cox PH	PreHD PICC	Death	(B), (C), (D), (E), (i)
Cox PH	PreHD PICC	AV fistula only	(B), (C), (D), (E), (i)
Cox PH	PreHD PICC	AV fistula or graft	(B), (C), (D), (E), (i)
Cox PH, time-dependent	PreHD PICC PostHD PICC	Death	(B), (C), (D), (E), (I)
Cox PH, time-dependent	PreHD PICC PostHD PICC	AV fistula only	(B), (C), (D), (E), (I)
Cox PH, time-dependent	PreHD PICC PostHD PICC	AV fistula or graft	(B), (C), (D), (E), (I)
Poisson	Sex	Vascular Imaging	(A), (C)
Poisson, Kaplan-Meier	Imaging	Death	
Poisson, Kaplan-Meier	Imaging	AV fistula only	
Poisson, Kaplan-Meier	Imaging	AV fistula or graft	
Cox PH	PreHD Imaging	Death	(B), (C), (D), (E), (p)
Cox PH	PreHD Imaging	AV fistula only	(B), (C), (D), (E), (p)
Cox PH	PreHD Imaging	AV fistula or graft	(B), (C), (D), (E), (p)
Cox PH, time-dependent	PreHD Imaging PostHD Imaging	Death	(B), (C), (D), (E), (P)
Cox PH, time-dependent	PreHD Imaging PostHD Imaging	AV fistula only	(B), (C), (D), (E), (P)
Cox PH, time-dependent	PreHD Imaging PostHD Imaging	AV fistula or graft	(B), (C), (D), (E), (P)
Secondary Analyses			
Logistic	Imaging before surgery	AV fistula, AV graft	(B), (C), (D), (E), (p)
Logistic	Imaging before surgery	AV fistula or graft	(B), (C), (D), (E), (p)

Covariate groupings:

- (A) age, race, body mass index
- (B) age, race, body mass index, sex
- (C) Comorbid conditions[49]
- (D) Dialysis variables: pre-HD nephrology care, primary cause of kidney failure, pre-dialysis erythropoietin use
- (E) Laboratory variables: serum creatinine, serum albumin, hemoglobin
- (P) Pre and post PICC (p) PreHD PICC
- (I) Pre and post imaging (i) PreHD imaging

2.8 Sensitivity Analyses:

Multiple sensitivity analyses were performed to evaluate factors that could bias the interrelationships between vascular imaging and conversion of vascular access (Table 5).

Table 5: Sensitivity Analyses for imaging analyses

Condition	Time Dependent?	Exposure(s)	Outcomes	Adjustors*
Exclusion of all censored prior to December 31, 2012	No	PreHD Imaging	Fistula	(A), (p)
Exclusion of all censored prior to December 31, 2012	Yes	PreHD Imaging PostHD Imaging	Fistula or graft	(A), (P)
Exclusion of all who did not survive to day 60	No	Imaging within 60 days of 1st HD	Fistula after day 60	(A), (p)
Exclusion of all who did not survive to day 60	No	Imaging within 60 days of 1st HD	Fistula or graft after day 60	(A), (p)
Exclusion of all who did not survive to day 90	No	Imaging within 90 days of 1st HD	Fistula	(A), (p)
Exclusion of all who did not survive to day 90	No	Imaging within 90 days of 1st HD	Fistula or graft	(A), (p)
Exclusion of all with a primary diagnosis of acute tubular necrosis without recovery	No	PreHD Imaging	Fistula	(A), (p)
Exclusion of all with a primary diagnosis of acute tubular necrosis without recovery	Yes	PreHD Imaging PostHD Imaging	Fistula or graft	(A), (P)
Addition of vascular access as a covariate	Yes	PreHD Imaging PostHD Imaging	Death	(A), (P)
Addition of vascular access as a covariate	Yes	PreHD PICC PostHD PICC	Death	(A), (I)

*All analyses adjusted for (A):
Age, race, body mass index, sex, comorbid conditions[49], pre-HD nephrology care, primary cause of kidney failure, pre-dialysis erythropoietin use, serum creatinine, serum albumin, hemoglobin.
(p) PreHD PICC; (P) PreHD and PostHD PICC
(i) PreHD imaging; (I) PreHD and PostHD imaging

For PICC exposures, a sensitivity analysis was performed in which achievement of AVF or AVG was added as a covariate to the models for death, to ascertain whether effects on survival were mediated by achievement of access.

2.9 PICC and Vascular Imaging as Outcomes

Both PICC insertion and vascular imaging events were classified as pre-hemodialysis or post-hemodialysis, depending upon whether or not the date of insertion preceded the date on which "regular chronic dialysis began," as reported on the CMS Medical Evidence Form.

2.10 PICC and Vascular Imaging as Exposure Variables

For analyses in which PICC was an exposure variable, rather than an outcome, we dichotomized both pre-dialysis and post-dialysis PICC recipients as having received no PICC or at least one PICC. More than 98% of our patients had either zero or one PICC events, either pre-dialysis or post-dialysis, although individual patients had multiple exposures. For post-dialysis PICC recipients, the earliest post-dialysis PICC insertion defined the time of exposure for the time dependent post-hemodialysis PICC variable.

Exposures to either venography or doppler vein mapping were pooled into a single vascular imaging exposure variable. Similar to our treatment of PICC exposure, for analyses in which imaging was an exposure, both pre-dialysis and post-dialysis imaging were dichotomized as no imaging vs. at least one image. More than 98% of our patients had either zero or one pre-dialysis image, and more than 91% had either zero or one post-dialysis image, although occasional individuals had multiple exposures. For post-dialysis imaging, the earliest post-dialysis CPT code defined the time of exposure for the time dependent post-hemodialysis imaging variable.

2.11 Performance of Imaging and Outcomes of Vascular Surgeries

We performed analyses to explore the relationships between the performance of imaging studies and performance of vascular surgeries. The subset of individuals who had undergone at least one vascular surgery was determined by collecting the CPT codes for hemodialysis access creation (Table 2). These individuals were classified according to whether or not a vascular imaging study had been performed on or before the date of the last vascular access surgical procedure that occurred prior to the date of either conversion to an AV graft or fistula, or censoring. A logistic model was constructed to determine the odds ratios for successful conversion of catheter access to AV fistula only, or any AV fistula or graft, adjusting for all covariates in the baseline Cox model.

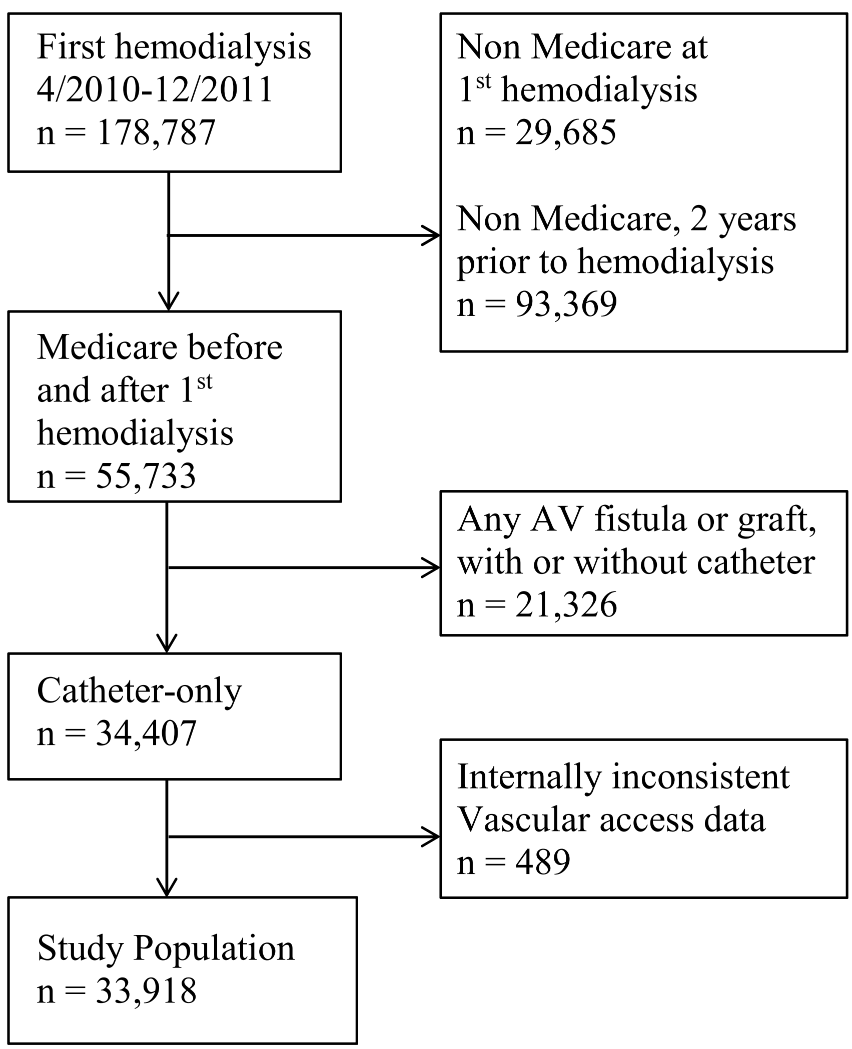
All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) or R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

3.1 Study Population

A total of 33,918 patients satisfied inclusion criteria (Figure 11). The major reason for exclusion was lack of Medicare coverage of sufficient duration in 69% of incident patients, followed by the presence of a working or maturing AV fistula or graft at the first hemodialysis treatment in 12%.

Figure 11. Derivation of the study population



3.2 Baseline Characteristics

The average age of the total study population was 72.6 years, with 47.1% female, 73.2% white, and 22.5% black. Median follow-up after HD initiation was 404 days (interquartile range (IQR), 103-680 days).

Table 6 shows baseline characteristics for the full population and stratified by sex. Compared to men, women were older, had higher BMI, had lower levels of albumin, creatinine and hemoglobin (although the large sample size allowed detection of statistically significant differences that were not clinically meaningful), and more exposure to PICC and imaging. Women had higher rates of diabetes, congestive heart failure, pulmonary disease, stroke, gastrointestinal diseases, and inability to ambulate. Men had more heart disease, arrhythmia, peripheral vascular disease, and cancer.

Table 7 compares baseline characteristics of patients who received any PICC, either before or after starting hemodialysis, to those who had none. PICC recipients were more likely to have each comorbid condition and to be women, and were less likely to have had pre-dialysis nephrology care.

Table 8 compares baseline characteristics of patients who had imaging studies to those who had none. Compared to patients who did not receive imaging studies, individuals who received imaging were more likely to be female and black, to have PICC exposure and pre-dialysis nephrology care, to have kidney failure due to hypertension or diabetes, and to have heart disease, peripheral vascular disease or stroke; they were less likely to be white or non-ambulatory, and had less liver disease and cancer.

Patients with baseline PICC exposure were more likely to have baseline imaging, compared those who had no PICC. Patients with baseline imaging were more likely to have had baseline exposure to PICC, compared to the much larger group who had no baseline imaging. However, among the patients who had received either exposure (n=4,742), there was very little overlap: 2,286 had imaging only, 2,232 had PICC only, and only 224 individuals had received both PICC and imaging.

Table 6: Baseline patient characteristics at hemodialysis initiation, by sex

	All	Men	Women	*P*-values
N	33,918	17,929	15,989	
Age (years), mean (std)	72.6 (11.3)	72.3 (11.4)	73.0 (11.2)	<0.001
Race				<0.001
White	73.2	76.3	69.8	
Black	22.5	19.7	25.5	
Other	4.3	4.0	4.7	
Body Mass Index, mean (std)	28.8 (7.8)	28.0 (6.9)	29.7 (8.6)	<0.001
Pre-ESRD Nephrology care (%)	47.3	47.4	47.3	0.93
Pre-ESRD erythropoietin use (%)	15.2	14.1	16.3	<0.001
Pre-ESRD PICC exposure (%)	7.2	6.3	8.3	<0.004
Pre-ESRD vascular imaging (%)	7.4	7.0	7.8	<0.001
Primary ESRD Diagnosis (%)				<0.001
Diabetes	41.7	40.2	43.5	
Hypertension	32.5	32.5	32.6	
Primary Glomerulonephritis	3.2	3.4	3.0	
Other	22.6	23.9	20.9	
Comorbid conditions (%)				
Atherosclerotic Heart Disease	49.6	52.0	47.0	<0.001
Congestive Heart Failure	45.7	44.6	46.9	<0.001
Other Cardiac Conditions	31.1	29.1	33.3	<0.001
Arrhythmia	29.8	32.0	27.3	<0.001
Peripheral Vascular Disease	28.6	29.6	27.5	<0.001
Pulmonary Disease	26.9	25.7	28.4	<0.001
Diabetes, not cause of ESRD	23.8	23.4	24.2	0.09
Inability to Ambulate	12.5	11.3	13.9	<0.001
Stroke	14.4	13.5	15.6	<0.001
Cancer	11.7	13.9	9.1	0.007
Gastrointestinal Disease	5.3	4.9	5.6	0.004
Liver Disease	4.2	4.3	4.0	0.18
Pre-ESRD labwork, mean (std)				
Serum albumin (mg/dL)	3.0 (0.7)	3.0 (0.7)	3.0 (0.7)	0.03
Serum creatinine (mg/dL)	5.3 (2.7)	5.6 (2.8)	4.9 (2.5)	<0.001
Hemoglobin (g/dL)	9.8 (1.5)	9.8 (1.6)	9.7 (1.4)	<0.001

Table 7: Baseline patient characteristics at hemodialysis initiation, by PICC status				
	All	**Any PICC**	**No PICC**	***P*-values**
N	33,918	4,257	29,661	
Age (years), mean (std)	72.6 (11.3)	71.2 (11.9)	72.8 (11.2)	<0.001
Female (%)	47.1	51.8	46.5	<0.001
Race				<0.001
White	73.2	71.5	73.5	
Black	22.5	25.4	22.1	
Other	4.3	3.1	4.4	
Body Mass Index, mean (std)	28.8 (7.8)	29.8 (8.3)	28.7 (7.7)	<0.001
Pre-ESRD Vascular Imaging (%)	7.4	9.1	7.3	<0.001
Pre-ESRD Nephrology care (%)	47.3	41.2	48.2	<0.001
Pre-ESRD erythropoietin use (%)	15.2	14.3	15.3	0.002
Primary ESRD Diagnosis (%)				<0.001
Diabetes	41.7	42.7	41.6	
Hypertension	32.5	29.6	32.9	
Primary Glomerulonephritis	3.2	2.3	3.3	
Other	22.6	25.4	22.2	
Comorbid conditions (%)				
Atherosclerotic Heart Disease	49.6	59.4	48.2	<0.001
Congestive Heart Failure	45.7	55.7	44.3	<0.001
Other Cardiac Conditions	31.1	40.7	29.7	<0.001
Arrhythmia	29.8	37.8	28.6	<0.001
Peripheral Vascular Disease	28.6	38.5	27.2	<0.001
Pulmonary Disease	26.9	35.3	25.7	<0.001
Diabetes, not cause of ESRD	23.8	27.8	23.2	<0.001
Inability to Ambulate	12.5	19.1	11.6	<0.001
Stroke	14.4	17.5	14.0	<0.001
Cancer	11.7	12.9	11.5	0.007
Gastrointestinal Disease	5.3	8.9	4.7	<0.001
Liver Disease	4.2	6.3	3.9	<0.001
Pre-ESRD labwork, mean (std)				
Serum albumin (mg/dL)	3.0 (0.7)	2.9 (0.7)	3.0 (0.7)	<0.001
Serum creatinine (mg/dL)	5.3 (2.7)	4.8 (2.5)	5.4 (2.7)	<0.001
Hemoglobin (g/dL)	9.8 (1.5)	9.7 (1.5)	9.8 (1.5)	0.004

Table 8: Baseline patient characteristics at hemodialysis initiation, by imaging status				
	All	**Any Image***	**No Image**	***P*-values**
N	33,918	13,267 (39.1%)	20,651 (60.9%)	
Age (years), mean (std)	72.6 (11.3)	72.1 (11.3)	72.9 (11.3)	<0.001
Female (%)	47.1	49.1	45.9	<0.001
Race, (%)				<0.001
White	73.2	69.7	75.5	
Black	22.5	26.0	20.2	
Other	4.3	4.3	4.3	
Body Mass Index, mean (std)	28.8 (7.8)	29.2 (7.9)	28.6 (7.7)	<0.001
Pre-ESRD PICC exposure (%)	7.4	8.9	7.1	<0.001
Pre-ESRD Nephrology care (%)	47.3	49.9	45.7	<0.001
Pre-ESRD erythropoietin use (%)	15.2	15.7	14.8	0.10
Primary ESRD Diagnosis				<0.001
Diabetes	41.7	44.8	39.8	
Hypertension	32.5	33.5	31.9	
Primary Glomerulonephritis	3.2	3.0	3.3	
Other	22.6	18.7	25.0	
Comorbid conditions (%)				
Atherosclerotic Heart Disease	49.6	51.1	48.7	<0.001
Congestive Heart Failure	45.7	48.1	44.1	<0.001
Other Cardiac Conditions	31.1	32.4	30.2	<0.001
Arrhythmia	29.8	30.3	29.5	0.11
Peripheral Vascular Disease	28.6	29.7	27.9	<0.001
Pulmonary Disease	26.9	27.3	26.7	0.27
Diabetes, not cause of ESRD	23.8	23.3	24.1	0.10
Inability to Ambulate	12.5	10.9	13.6	<0.001
Stroke	14.4	15.0	14.1	0.02
Cancer	11.7	11.2	11.9	0.04
Gastrointestinal Disease	5.3	5.4	5.2	0.46
Liver Disease	4.2	3.8	4.4	0.006
Pre-ESRD labwork, mean (std)				
Serum albumin (mg/dL)	3.0 (0.7)	3.0 (0.7)	3.0 (0.7)	0.14
Serum creatinine (mg/dL)	5.3 (2.7)	5.3 (2.7)	5.3 (2.7)	0.12
Hemoglobin (g/dL)	9.8 (1.5)	9.8(1.5)	9.8 (1.5)	0.06

*Any Image includes all patients receiving any venogram or any doppler vein mapping, either before or after hemodialysis initiation, or both.

3.3 Exposures to PICC and Imaging

There was at least one exposure to PICC before or after HD initiation in 4,257 (12.6%) patients. A total of 6,487 PICC were placed, 53% in the 2 years preceding dialysis initiation. Among patients receiving PICC, 46% had pre-dialysis PICC only, 42% had post-dialysis PICC only, and 11% had both. More than one PICC was placed in 30% of these patients and more than five PICC were placed in 2.5% of patients (maximum, 14 PICC). The distribution of PICC events per patient, before and after hemodialysis initiation, is shown in Table 9.

Table 9: Total numbers of PICC placements per patient, before and after HD initiation

PreHD PICC	PostHD PICC										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**12**	**13**	**Total**
0	29661	1460	237	69	25	4	1	2	2	0	1	31462
1	1530	233	56	20	8	5	1	0	0	0	0	1853
2	300	68	7	6	0	0	1	0	0	1	0	383
3	99	25	8	1	2	2	1	0	1	0	0	139
4	28	11	4	0	0	0	0	0	0	0	0	47
5	6	2	1	0	0	0	0	1	0	0	0	10
6	6	3	1	1	0	0	1	0	0	0	0	13
7	1	4	3	0	0	0	0	0	0	0	0	38
9	2	0	0	1	0	0	0	0	0	0	0	3
Total	31633	1806	317	98	40	11	5	3	3	1	1	33918

Vascular imaging was performed in 13,267 patients (39.1%) while 20,651 patients (60.9%) had no imaging performed. Among the patients who had imaging, 50.3% had doppler vein mapping only, 37.4% had venography only, and 12.3% had both. Only 2,510 patients (7.4%) had imaging performed prior to HD initiation. Imaged patients received 9,757 doppler vein mapping studies and 9,267 venograms. Among 19,024 images, 85.7% were performed after HD initiation. Although several individual patients had large numbers of studies, 96.5% of patients had two or fewer imaging studies performed.

Table 10 shows the per-patient distributions of pre-dialysis and post-dialysis imaging studies.

Table 10: Total numbers of imaging studies per patient, before and after HD initiation

PreHD Images	PostHD Images											
	0	1	2	3	4	5	6	7	8	9	10^+	Total
0	20651	8068	1831	512	182	86	36	16	10	6	10	31408
1	1616	468	144	53	29	8	4	1	1	1	3	2328
2	100	39	14	4	3	0	0	0	0	0	1	151
3	11	3	0	1	0	1	0	0	0	0	1	17
4	0	1	1	0	1	0	0	0	0	0	0	3
6	0	1	1	0	0	0	0	0	0	0	0	1
Total	22378	8579	1991	570	215	95	40	17	11	7	15	33918

3.4 Procedural exposures in Women and Men

There were 593,586 months at risk for PICC and imaging in 15,989 women, compared to 649,821 months at risk in 17,929 men. During this time 3,515 PICC were placed in 2,204 women, and 2,972 PICC were placed in 2,053 men, for a total of 6,487 PICC in 4,257 patients. No exposure to PICC was noted in 88.5% of men and 86.2% of women. During the same period, 6,508 women received 9,600 images (4,758 venograms and 4,842 dopplers) and 6,759 men received 9,424 images (4,509 venograms and 4,915 dopplers).

In the Poisson regression models using the total numbers of PICC exposures (or total number of images) as the outcome and including time at risk as an offset term, women had increased exposure to both PICC and vascular imaging compared to men. For PICC, the unadjusted incidence rate ratio for women was 1.29 (95% CI=1.23, 1.36), which increased to 1.31 (95% CI= 1.25, 1.38) after adjustment for all covariates. For vascular imaging, the unadjusted incidence ratio was 1.12 (95% CI=1.08, 1.15), which decreased to 1.09 (95% CI=1.06, 1.12) after adjustment for all covariates.

3.5 Associations of PICC with Vascular Access and Mortality Outcomes

Among patients exposed to PICC, the frequencies of achieving either fistulas or grafts were significantly lower than among those who did not receive PICC. Transition to a working AV fistula occurred in 1,052 (24.7%) of patients who received PICC, versus 9,088 (30.6%) of those who did not (Figure 2).

Transition to a working AV graft occurred in 489 (11.5%) of patients who received PICC versus 3,130 (10.6%) of those who did not. The overall probability of achieving any permanent vascular access was reduced for patients exposed to PICC (36.2% vs. 41.2%, *P*<0.001). Overall, 20,159 patients never transitioned from CVC to any other working access. Among 13,759 patients who achieved a working AV fistula or graft, PICC was associated with longer catheter exposure before the first working vascular access (218 days vs. 197 days, *P*<0.001). A representative Kaplan-Meier plot showing increase time to AVF/AVG in patients with PICC shown in Figure 12.

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
PrePICCyes	1	1	-0.34917	0.03622	92.9574	<.0001	0.705	PrePICCyes 1

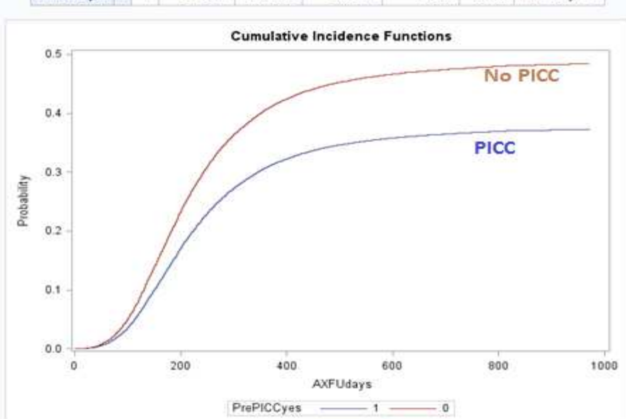


Figure 12. Kaplan-Meier plot of time to first AV fistula or graft, by PICC exposure (Log-rank *P*<0.001) , taking death into account as a competing risk

Among 33,918 patients, 15,686 (46.2%) died; death was more frequent in those who had exposure to PICC (56.4% vs 44.8%, *P*<0.001). Among those achieving AVF or AVG, 30.4% with PICC exposure vs 22.5% without PICC exposure died (*P*<0.001), while among those who did not transition from CVC, 71.2% with PICC exposure vs 60.4% without PICC exposure died (*P*<0.001).

In adjusted Cox models (Table 11) comparing patients with and without pre-dialysis PICC exposure, patients who received PICC had a 23% lower likelihood of achieving an AVF, a 15% lower likelihood of any AV fistula or graft and a 15% higher likelihood of death. When post-HD PICC was added as a time dependent covariate, further reductions in the likelihoods of achieving an AV fistula, or any AV fistula or graft were observed; these reductions were independent of the effects of PICC placement before HD initiation. The adjusted hazard ratio (HR) for death was 1.05 (95% confidence interval (CI) = 0.99, 1.11) for PICC placed prior to HD initiation, and 2.26 (95% CI = 2.13, 2.39) for PICC placed thereafter. The association between post-HD PICC and death remained significant in an exploratory post-hoc analysis in which achievement of vascular access was included as a covariate in the time dependent model for death (HR=2.19, 95% CI = 2.07, 2.32).

Table 11: Relationships of PICC with first working AV fistula, first working AV fistula or graft, and death

	1st AV fistula	**1st AV fistula or graft**	**Death**
Baseline Cox Model			
Pre-hemodialysis PICC	**0.77**	**0.85**	**1.15**
(95% CI)	(0.71, 0.85)	(0.79, 0.92)	(1.09, 1.21)
Time dependent Cox Models			
Pre-hemodialysis PICC	**0.78**	**0.85**	**1.05**
(95% CI)	(0.71, 0.85)	(0.79, 0.91)	(0.99, 1.11)
Post-hemodialysis PICC	**0.81**	**0.81**	**2.26**
(95% CI)	(0.72, 0.90)	(0.73, 0.89)	(2.13, 2.39)

*Adjusted for: age, sex, race, pre-dialysis Nephrology care, pre-dialysis erythropoietin, primary diagnosis for kidney failure, body mass index, hemoglobin, albumin, creatinine, and all comorbid conditions

Sensitivity Analyses: PICC:

An exploratory post-hoc analysis added achievement of vascular access as a covariate to the time dependent model for death. The association between post-hemodialysis PICC and death remained significant (HR=2.19, 95% CI 2.07, 2.32). Although women received PICC more often, interaction terms between sex and PICC placement were not significant for the vascular access outcomes. For pre-dialysis PICC, *P*= 0.40 for fistula and *P*=0.54 for any vascular access. For post-dialysis PICC, *P*=0.40 for fistula and *P*=0.71 for any vascular access.

3.6 Associations of Vascular Imaging with Vascular Access and Mortality

Among 33,918 patients, 30% achieved a working AVF, 10.7% achieved a working AVG, 59.4% had persistent use of CVC throughout the observation period, and 46.2% died. Compared to patients who were never imaged, patients who had imaging had more fistulas and grafts and lower proportions of death and persistent CVC use (Table 12).

Table 12: Vascular Access and Mortality Outcomes, by Imaging Status

	Total	**Imaged**	**Never imaged**	***P*-value***
N	33,918	13,267	20,651	
Vascular Access				<0.001
CVC, n(%)	20,159 (59.4)	5,502 (41.5)	14,657 (71.0)	
AV fistula, n(%)	9,899 (29.2)	5,441 (41.0)	4,458 (21.6)	
AV graft, n(%)	3,860 (11.4)	2,324 (17.5)	1,536 (7.4)	
Death, n(%)	15,686 (46.2)	5,231 (39.4)	10,455 (50.6)	<0.001

**P*-value for independent proportions between imaged and never imaged groups
Abbreviations: CVC(central venous catheter), AV(arteriovenous)

Consistent with longer expected fistula maturation times, the median number of catheter days was 210 (IQR, 151-296) in patients who received fistulas compared to 164

(IQR, 108-262) in those who received grafts (P<0.001). An unadjusted survival plot shows earlier and more frequent achievement of AVF/AVG in Figure 13.

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
PreIMAGEyes	1	1	0.50008	0.02885	300.5520	<.0001	1.649	PreIMAGEyes 1

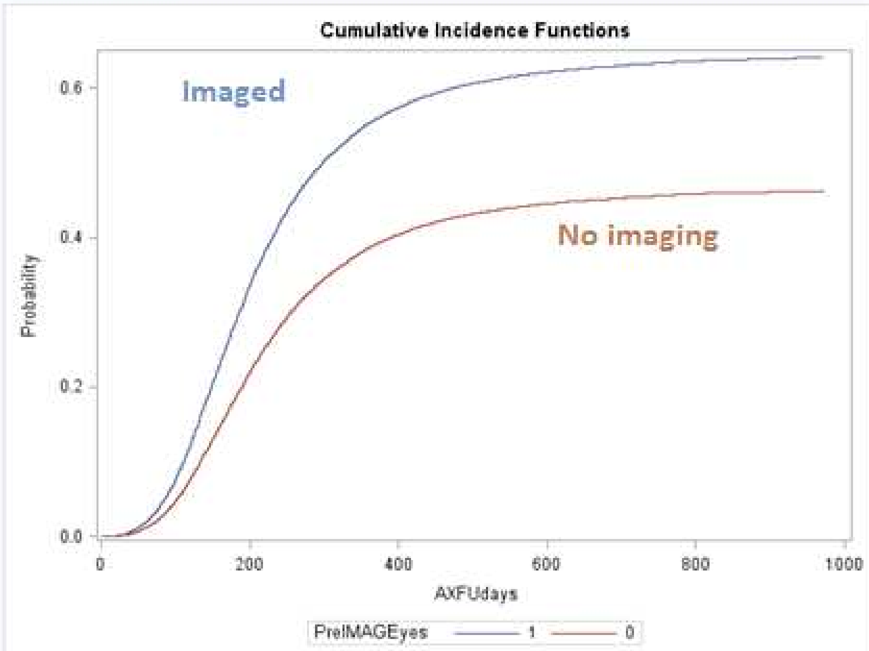


Figure 13. Kaplan-Meier plot of time to first working AV fistula or graft, in individuals who did and did not have vascular imaging prior to hemodialysis initiation. (Logrank P <0.001)

In multivariable adjusted baseline Cox models, patients with imaging prior to HD initiation were 33% more likely to achieve a working fistula, 55% more likely to achieve a working fistula or graft, and 12% less likely to die during follow-up than those who did not have pre-dialysis imaging (Table 13).

Table 13: Relationships of imaging to first working AV fistula, first working AV fistula or graft, and death			
	1st AV fistula	**1st AV fistula or graft**	**Death**
Baseline Cox Models			
Pre-hemodialysis Imaging	**1.33**	**1.55**	**0.88**
	(1.25, 1.43)	(1.47, 1.64)	(0.83, 0.94)
Time dependent Cox Models			
Pre-hemodialysis Imaging	**1.36**	**1.57**	**0.88**
	(1.27, 1.45)	(1.49, 1.66)	(0.82, 0.93)
Post-hemodialysis Imaging	**1.45**	**1.63**	**0.85**
	(1.40, 1.51)	(1.58, 1.69)	(0.82, 0.88)
*All models adjusted for: age, sex, race, pre-dialysis Nephrology care, pre-dialysis erythropoietin, primary diagnosis for kidney failure, body mass index, hemoglobin, albumin, creatinine, PICC placement, and all comorbid conditions.			

These associations were maintained with the addition of post-dialysis imaging studies as a time-dependent covariate. Moreover, post-dialysis imaging had strong independent associations with all three outcomes. Individuals who had imaging after hemodialysis initiation were 45% more likely to achieve a working fistula, 63% more likely to achieve any working fistula or graft, and 15% less likely to die, compared to those who had no imaging after hemodialysis initiation.

Sensitivity Analyses

The decision making in the management of hemodialysis patients is complicated, and takes place over an extended period during which accumulating consequences of past decisions may affect both subsequent decisions and outcomes. When observational cohort data is examined in this complex environment, there are many potential biases. We therefore undertook many different types of sensitivity analyses in order to evaluate potential biases, the results of which are presented in Table 14.

Table 14: Hazard Ratios for Imaging: Primary models and sensitivity analyses					
	Exposure		**Outcome**		
	Time-dependent?	**Timing of imaging**	**DEATH**	**Any Access**	**FistulaOnly**
Primary Analyses					
Baseline	No	Pre-HD	**0.88** (0.83, 0.94)	**1.55** (1.47, 1.64)	**1.33** (1.25, 1.43)
Time-dependent	Yes	Pre-HD	**0.88** (0.82, 0.93)	**1.57** (1.49, 1.66)	**1.36** (1.27, 1.45)
	Yes	Post-HD	**0.85** (0.82, 0.88)	**1.63** (1.58, 1.69)	**1.45** (1.40, 1.51)
Sensitivity Analyses					
Excluding acute kidney injury as the primary cause of kidney failure	No	Pre-HD	**0.89** (0.83, 0.95)	**1.55** (1.46, 1.64)	**1.33** (1.24, 1.42)
	Yes	Pre-HD	**0.89** (0.83, 0.94)	**1.57** (1.48, 1.66)	**1.35** (1.26, 1.44)
		Post-HD	**0.86** (0.82, 0.89)	**1.62** (1.56, 1.67)	**1.43** (1.38, 1.49)
Restricted to imaging performed within first 60 days after HD initiation*	No	Pre-60 days	**0.88** (0.84, 0.92)	**1.75** (1.68, 1.81)	**1.54** (1.48, 1.61)
Restrict to imaging performed within first 90 days after HD initiation**	No	Pre-90 days	**0.92** (0.88, 0.96)	**1.71** (1.65, 1.77)	**1.52** (1.46, 1.58)
Excluding all patients censored prior to December 31, 2012 for any reason	No	Pre-HD		**1.45** (1.36, 1.55)	**1.21** (1.12, 1.31)
	Yes	Pre-HD		**1.47** (1.38, 1.57)	**1.23** (1.15, 1.34)
		Post-HD		**1.58** (1.52, 1.65)	**1.41** (1.34, 1.47)
Model for death, using achievement of any access as a covariate	Yes	Pre-HD	**0.93** (0.87, 0.99)		
		Post-HD	**0.88** (0.85, 0.91)		

*In this analysis, only imaging performed on or before the 60th day after HD initiation was an exposure; time to first successful AVF and/or AVG after day 60 were the outcomes.

**In this analysis, only imaging performed on or before the 90th day after HD initiation was an exposure; for any AVF or AVG created prior to day 90, the date of outcome was recoded to day 91. Time to first successful AVF and/or AVG after day 90 were the outcomes

The most important factor was the high mortality, especially the high early mortality in our population, who were selected for having incurred the additional risks of central venous catheters, added to the high mortality of dialysis patients in general. In many of our primary analyses, the probability of both exposures and outcomes were affected by whether or not patients survived. Sensitivity analyses conditioned upon survival for 60 days or 90 days were similar in direction to the main analyses, with slightly larger hazard ratios.

An additional analysis was conditioned upon remaining in the dataset until the end of the follow up period, removing both non-survivors and those whose lack of access reflected a good prognosis, such as transplant recipients and peritoneal dialysis patients. This analysis, which implicitly conditioned for 365 days or more on hemodialysis, was weakened by the exclusion of 60.2% of our population. In this sensitivity analysis, the effects of pre-dialysis imaging were attenuated but still significant in both baseline and time-dependent models; the effects of post-dialysis imaging in the time-dependent model were preserved.

Exclusion of patients whose entry into hemodialysis was due to acute kidney injury (7%) showed hazard ratios nearly identical to the cohort as a whole, suggesting that inclusion of these patients was not changing the overall outcomes of the population.

Time dependent models for death that included achievement of a fistula or graft as a covariate did not attenuate the effects imaging, suggesting that associations with survival were not directly mediated by effects of vascular access.

Although the incidence of imaging was higher in women, interaction terms between vascular imaging and sex were not significant for any of the three outcomes.

3.7 Vascular Imaging and Vascular Surgery

We identified 32,341 vascular access surgeries in 18,883 patients. Table 4 shows that surgery was performed in a higher proportion of imaged patients than non-imaged patients (70.9% vs. 45.9%, *P*=0.002). Among 18,883 patients who underwent at least one surgery, 49.8% had an imaging study performed by the date of surgery. The number of surgical procedures per patient was higher in imaged patients compared to non-imaged patients (1.8 vs. 1.6, *P*<0.001).

Among the patients who had surgery, a working AVF/AVG was achieved in 71.3% of imaged patients and 69.7% of non imaged patients (*P*=0.02). After adjustment for all baseline covariates, the odds ratio (OR) for having any AVF/AVG was 1.09 (95% CI=1.02, 1.16), favoring imaged patients. Corresponding models for AVF only and AVG only were not significant (OR 1.03, 95% CI=1.02, 1.16 for AVF; OR 1.07, 95% CI=0.97, 1.18 for AVG).

Discussion

In this study, the epidemiology of PICC placement and vascular imaging in patients receiving hemodialysis with central venous catheters was assessed, and associations to crucial clinical outcomes were evaluated.

4.1 Procedural Exposures of Women and Men

Our data show that women treated with hemodialysis have 31% more exposure to PICC placement and 9% more exposure to vascular imaging for access planning than men. These findings were statistically significant, and robust to adjustment for a wide variety of potential confounders. However, PICC exposure exceeded 10% in both women and men.

Vascular imaging was employed slightly more often in women, and therefore cannot explain the lower achievement of AV fistulas and grafts in women. Overall employment of vascular imaging was low in both women and men, and only 7.0% of men and 7.8% of women had any imaging prior to the initiation of hemodialysis.

Taken together, PICC and imaging exposures were more strongly associated with all three outcomes than sex, and tests for interactions between both exposures and sex did not reveal significant changes in the effect of either exposure upon any of the three outcomes.

Although the initial research hypothesis was sex differences in exposure to PICC, this hypothesis was subsumed into the larger question of the effects of specific exposures, adjusting for sex and evaluating for interactions of exposures with sex.

4.2 PICC placement and the hemodialysis patient

One in every eight patients who initiated HD with a CVC in the United States was exposed to PICC while receiving HD or within the two years prior to HD initiation. PICC placement before or after HD initiation was strongly associated with failure to transition to a working fistula, and transition to any permanent access was reduced despite a small increase in the percentage of AV grafts. PICC placed after HD initiation was associated with a higher risk of death, which remained significant despite adjustment for baseline comorbid conditions, case-mix factors, and achievement of vascular access.

Our findings confirm the very limited previous published observations about PICC use in dialysis patients. In a case-control study of 282 patients receiving outpatient HD, 44% of patients dialyzing via HD catheters had a history of PICC use, compared to <20% of those with working AV fistulas.[52] The pre-dialysis PICC exposure in that study, which assessed events occurring up to 14 years prior to HD, was higher than we observed; we examined claims for only the two years preceding dialysis. A recent cross-sectional study reported that hospitalized patients with GFR below 45 ml/min/1.73m^2 were 30% more likely to receive PICC than the overall hospital population.[33] In both of these prior studies, 30-50% of PICC were placed for non-specific indications such as “difficult vascular access.”[33,52] PICC placement enables blood sampling and continuous vascular access without frequent venipunctures or direct cannulation of central veins, and these conveniences contribute to their expanding popularity.[53,54] As PICC use has increased, potential concerns about bloodstream infections, thromboses, and stenoses of central and peripheral veins have emerged.[30-32,55,56]

Our study expands the available findings to a large national sample of dialysis patients with CVC and provides further evidence of the potential adverse consequences of PICC. We found that PICC exposure was common, and associated with poorer vascular access outcomes. The association of PICC placement after HD initiation with death was not explained by baseline comorbid conditions nor by adjustment for achievement of vascular access, suggesting that this association may represent reverse causation, in which PICC placement is a marker for severity of illness and subsequent higher likelihood of death. Therefore PICC placement in a catheter-dependent HD patient may indicate clinical situations in which the short-term risk of death is particularly high.

HD patients are a vulnerable population. The central importance of durable dialysis vascular access alters the usual balance between the risks and benefits of PICC. Premature exhaustion of veins needed for fistula construction may lead to prolonged or permanent use of HD catheters, which increases risks for bacteremia, endocarditis, metastatic infection, hospitalization, and death. In an observational study of 79,545 patients, conversion from CVC access to a working fistula or graft was associated with 30% decreases in both hospitalization and mortality.[23,25] In a meta-analysis of 545,441 patients, CVC use was associated with 53% higher risk of death and more than twice as many fatal infections, compared to working AV fistulas.[57] Our findings also show a very high proportion of death among patients who fail to transition from CVC. PICC placement may precede the diagnosis of CKD, but our data suggest that frequent placement does not abate after recognition of either CKD or even ESRD.

We found extended pre-dialysis nephrology care to be one of the few modifiable variables associated with decreased PICC exposure. Nephrologists are familiar with the consequences that occur when patients begin HD with depleted vascular access, and need to accept responsibility for protecting veins for AV fistulas and grafts before and after HD initiation. However, vein protection strategies can and should be practiced by all clinicians who provide care to patients with CKD. Individual programs have created successful vein protection protocols that employ alternatives to PICC. In our center, nurses responsible for PICC placement prompt clinicians to consult interventional radiologists to place small bore cuffed tunneled central catheters in the internal or external jugular veins. These small catheters are unlikely to injure large central veins, and the potential loss of an external or internal jugular is less problematic than the loss of a vein needed for an AV fistula. These alternatives require additional resources and expertise, making it important to provide convincing non-anecdotal evidence that the downstream risks of failed HD vascular access justify the additional efforts required to protect veins.

4.3 Vascular Imaging and the Hemodialysis Patient

In a cohort of catheter-dependent HD patients, vascular imaging performed before or after HD initiation was strongly associated with increases in both AV fistulas and grafts and better patient survival, even after adjustment for baseline comorbid conditions and other relevant confounders. However, among the subset of patients who underwent surgery, we could demonstrate only minimal differences in surgical outcomes.

Fewer than 40% of patients had any vascular imaging, suggesting that clinicians are ambivalent about performing these studies. This may reflect an ambiguous literature, consisting primarily of single-center studies that have focused upon short-term surgical outcomes rather than fistula maturation or usability.[40,46,47] This study evaluated clinically meaningful endpoints, defined by the vascular access utilized during dialysis treatments, in a large national sample.

Our data expand upon a recent systematic review that suggested that the evidence was insufficient to conclude that imaging improved fistula outcomes, which included only two single-center trials that examined fistula maturation. [40] One study showed that imaging prior to fistula surgery was associated with lower early failure and better assisted patency, but no difference in one-year fistula survival. [58] The other selected HD patients with visible superficial veins, and concluded that imaging did not improve surgical success in this group.[59] Our large sample size allowed us to demonstrate a small but significant increase in the odds of working AVF/AVG among patients who had surgery if imaging was performed. Our findings contrast with those of a retrospective analysis of 256 procedures, in which the fistula maturation rate decreased after implementation of a preoperative imaging protocol, resulting in a hypothesis that imaging promoted unsuccessful vascular surgery by detecting marginal blood vessels that would otherwise have been left untouched.[48] In our cohort, if any vascular access surgery was attempted, the proportion of patients in this cohort who achieved any AVF/AVG was approximately 70% whether or not imaging was performed. The increased achievement of working AVF/AVG in imaged patients was therefore predominantly due to surgery being attempted upon a much higher proportion of the imaged patients than non-imaged patients.

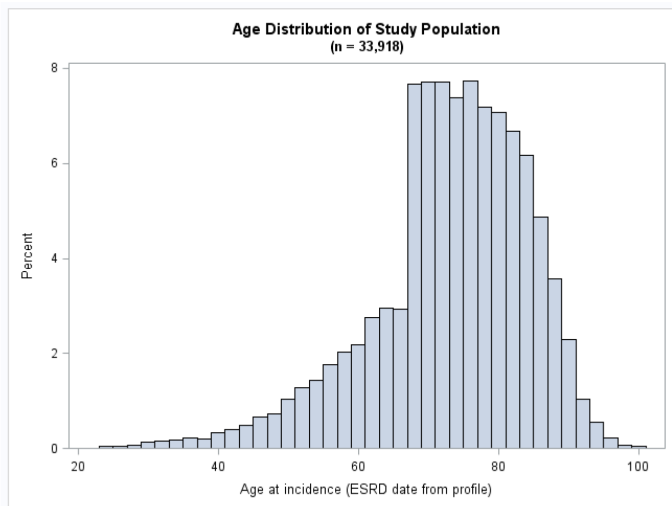
Working AVF and AVG were both achieved more frequently in imaged patients, despite the imaged group having more comorbid conditions and less favorable demographics. The proportion of AVGs in imaged patients was higher in imaged patients than in non-imaged patients. These findings support the notion that imaging was more selectively performed in more complex clinical scenarios where the vasculature was not ideal. Much has been written about prolonged catheter use as an unintended consequence of the pursuit of AVF in patients with insufficient vasculature.[48,60-63] Our data suggest that accurate assessment of vessel quality may guide surgeons to appropriate, patient-centered choices of procedures that minimize catheter days. Taken together, the increased probability of surgery and more appropriate choice of procedure suggests that imaging may be a marker for clinical engagement and quality of care, hypotheses that would be best assessed using a prospective study design.

4.4 Strengths and Limitations of these Analyses

A major strength of this research is the large population, in which the frequencies of pre-dialysis and post-dialysis PICC and imaging could be ascertained, providing insight into national practice. Our data provided large numbers of fistulas, grafts and deaths, allowing us to uncover robust associations that are potentially generalizable to large numbers of patients. The following considerations were important to our study design.

1. Our study was limited to individuals who had Medicare coverage two years prior to the day of the first hemodialysis treatment, selecting for an older group than the overall US hemodialysis population. While these patients comprise the majority of the dialysis population, our findings are potentially limited to this large subset and may not apply to younger patients who do not have Medicare coverage prior to dialysis initiation. This nonetheless is clinically relevant to our questions, as older patients have fewer intact blood vessels and more difficulty obtaining vascular access. We did include any adult with Medicare coverage, regardless of age, achieving some representation for younger patients.

   There are few entitlements for Medicare prior to age 65, aside from end-stage kidney disease and disability. Since our population definition included first-time initiation of hemodialysis, the only way a younger patient would enter this dataset was if Medicare benefits were being received due to another pre-existing diabling condition. Therefore, the younger population had more disability and chronic illness than the overall population of young HD patients. The full population of young HD patients also includes patients with isolated kidney disease and better overall health, who may have private insurance or have public assistance. These individuals would not enter our dataset due to their lack of Medicare pre-coverage. Our case definition excludes most of these healthy younger patients, which can be seen when the age histogram of the overall catheter-only HD population is compared to the subset with Medicare coverage (Figure 14).



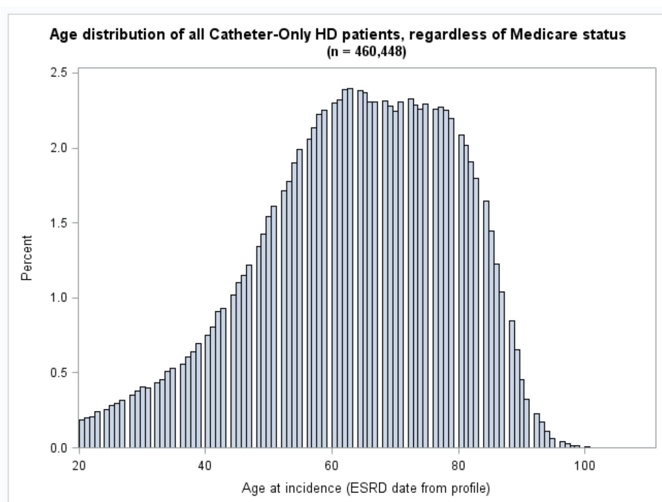


Figure 14: Comparison of the age distribution of the entire US hemodialysis population with the study population, showing the missing segment of patients age<67.

In both of our papers we acknowledge that the requirement for Medicare benefits reduces the generalizability of our findings – and in the imaging paper we specifically point out that selecting for older and sicker patients creates a selection bias for patients with potentially fewer viable blood vessels apparent on physical examination – a bias that could accentuate the usefulness of imaging.

That said, the missing subset [of high-functioning younger patients with few comorbid conditions] does not contribute heavily to the problem of HD catheter-related sepsis and death that motivates our studies. It has already been established that imaging is not beneficial in patients who have favorable vascular anatomy (Nursal) we hope to demonstrate that imaging has a role in improving outcomes in those for whom the surgical approach cannot be determined by physical inspection alone.

To evaluate this uncertainty, we analyzed the subgroup of patients who were < 67 years old (Table 15) and compared this to the subgroup of patients who were > 67 years old (Table 16), in the baseline Cox model and found that the overall direction and size of effects was extremely consistent, and that inclusion of the younger group was not altering the results of the population.

Table 15: Baseline Cox Models for the subgroup < 67 years old

	Fistula Only	Any AVF/AVG	Death
PrePICC	0.81 (0.69, 0.95)	0.91 (0.80, 1.04)*	1.23 (1.09, 1.40)
PreIMAGE	1.20 (1.05, 1.37)	1.45 (1.30, 1.62)	0.78 (0.67, 0.91)

*P>0.05

Table 16: Baseline Cox Models restricted for the subgroup >= 67 years old

	Fistula Only	Any AVF/AVG	Death
PrePICC	0.75 (0.68, 0.84)	0.82 (0.75, 0.90)	1.13 (1.06, 1.21)
PreIMAGE	1.38 (1.28, 1.49)	1.59 (1.50, 1.69)	0.90 (0.84, 0.97)

2. The general form of the relationships in this research is expressed in Figure 15 (below), with hypotheses represented by dashed lines.

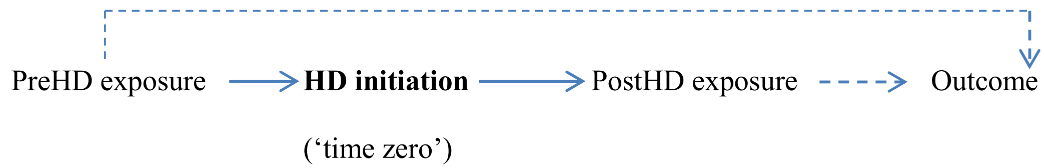


Figure 15. General directed acyclic graph for associations of exposures and outcomes

In these studies, PICC and vascular imaging are exposures, and outcomes are first AV fistula, first AV fistula or graft, and death. We used time-to-event analyses, with time being measured from the initiation of hemodialysis, when patients began to accrue the risks associated with use of central venous dialysis catheters. Roughly 50% of PICC exposures and 85% of imaging exposures occurred after hemodialysis was initiated. If we had ignored the timing of these post-HD exposures and considered these patients to have been exposed from the time of HD initiation onward, we would have biased our estimates of the impacts of their post-dialysis exposures. In order to consider post-HD exposures without allocating immortal person time, we created time dependent variables for PICC and imaging that occurred after HD initiation (HD initiation was the time of cohort entry and considered as time 0 in base models). This allowed individuals to be unexposed up until the time of exposure, and only afterwards accrue time in the exposed group. Immortal time was not an issue in the pre-dialysis exposures, which were uniformly classified as present or absent upon cohort entry.

3. Our ability to ascertain pre-dialysis PICC placement was limited to the two year period prior to hemodialysis initiation, raising the possibility that patients for whom PICC exposure occurred earlier may have been misclassified as unexposed to PICC. Such misclassification would have led us to underestimate the associations of PICC with reduced transition to AV access, which were nonetheless significant. Ascertaining exposures earlier than two years before HD initiation would have increased the requirements for duration of Medicare benefits prior to dialysis initiation and caused selection of a smaller, older, and less representative cohort. Our exposure ascertainment also depended upon the accuracy and completeness of Medicare claims coding. Failure to ascertain PICC procedures would also have caused us to underestimate overall exposure, which was nonetheless surprisingly high. Exposure misclassification due to underascertainment would be expected to bias our results to the null, in which case the true associations of PICC with vascular access outcomes could have been stronger than we reported. Similarly, detection of imaging procedures from coding data could potentially underestimate imaging exposure. Failure to code for imaging procedures was less likely for imaging than PICC, because the high reimbursements for imaging procedure codes presented an incentive to capture these claims more completely. There are no other national measurements of imaging that can serve as 'gold standards' for exposure ascertainment, so this is the best information available at this time.
4. The clinical motivations for decisions on whether or not to place PICC could not be assessed in this administrative dataset. We observed a surprisingly strong

association between post-dialysis PICC and death, which persisted despite adjustment for baseline comorbid conditions and even for the achievement of vascular access. Because there is not a plausible mechanism for PICC to cause a marked increase in short-term death, we hypothesized that the association was more likely to have been driven by reverse-causation, when situations in which short-term death is likely are associated with hospitalization, need for vascular access, and placement of PICC. Placement of a PICC after hemodialysis initiation may be a marker for periods of elevated mortality risk.

5. When observational cohort data is examined in a complex medical environment, there are ample opportunities for bias. We therefore undertook many different types of sensitivity analyses in order to evaluate potential biases in the strong associations between imaging exposures and the achievement of vascular access.
    5a. Patients dying early would have less opportunity to have imaging or surgery, so high early death rates could potentially inflate the effects of imaging. Similar to most hemodialysis populations, our study population had high early mortality. We therefore performed sensitivity analyses for the vascular access outcomes, using the subset that survived until day 60 (84.9% of patients) and also the subset that survived until day 90 (77.5% of total). Analogous models for PICC exposure were not deemed appropriate, because there was no plausible corresponding disadvantage in achieving vascular access due to having had less opportunity to receive a PICC.

5b. We performed additional analyses excluding all patients censored prior to December 31, 2012, to collectively eliminate death, kidney transplantation, transfer to peritoneal dialysis, and recovery of kidney function. This condition eliminated 60.1% of the study population, reducing generalizability. The remaining subset was immortal from the date of dialysis initiation until administrative censoring, guaranteeing at least 12 months of follow-up time. With death eliminated, only vascular access outcomes could be assessed and concordant results in this subset would further support our primary findings. Although outside of the scope of this thesis project, we are evaluating the possibility of further analyses that incorporate competing outcomes within a time-dependent Cox proportional hazards model.

5c. Among our study population, 7.4% had 'acute tubular necrosis without recovery' entered as the primary cause of kidney failure on their enrollment forms. Patients with acute kidney injury (AKI) may have spontaneous recovery, in which case they would have left the dataset early without having had either imaging or vascular access surgery. Early departure from the dataset biases the associations of imaging with access by giving the group without imaging less achievement of vascular access. Also, patients with acute kidney injury often have underlying comorbid diagnoses that may result in the need to spend time in skilled nursing facilities, where progress towards hemodialysis vascular access may be systematically impeded by competing clinical priorities. Confounding by

AKI would inflate the effect of imaging because the group that wasn't exposed to imaging would be enriched in acute kidney patients who were less likely to have successful vascular access outcomes (Figure 16.)

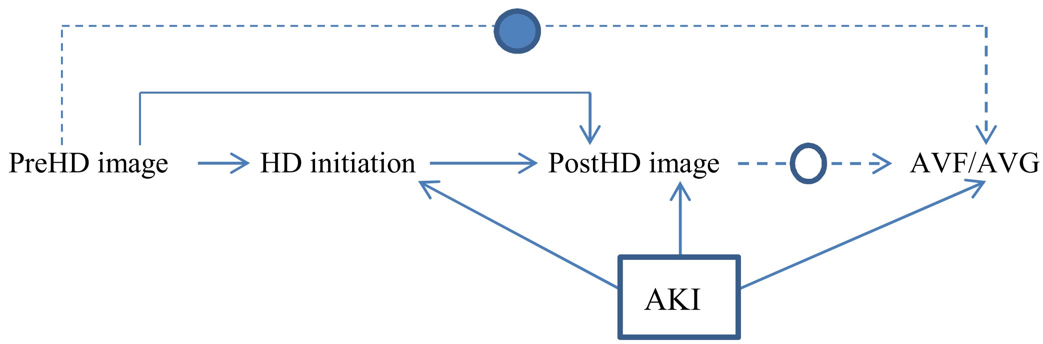


Figure 16. Confounding by acute kidney injury (AKI)

Hypothesis 1: PreHD imaging affects achievement of access.

Hypothesis 2: PostHD imaging affects achievement of access.

We therefore undertook sensitivity analyses of our data, with these patients excluded, represented in the directed acyclic graph by the box around AKI.

6. To assess whether the associations of PICC and imaging with survival were mediated primarily by the achievement of vascular access, we conducted sensitivity analyses adding achievement of AV fistula or graft to time-dependent models for death, in which PICC and imaging were the primary exposures. A significant association between PICC and death risk independent of attainment of vascular access supports the potential for alternative pathway(s) or explanation(s) for this association.
7. As part of the original thesis proposal, which sought to evaluate care process differences between men and women, we hypothesized interactions between PICC

and sex, and imaging and sex. However, these pre-specified interactions were not statistically significant for either exposure, either pre or post dialysis initiation (*P*-values ranged from 0.17-0.7).

8. An important limitation of our surgical claims analysis arises from the observational nature of this data, in which we are unable to assess the physical examination findings, imaging results, and the motivations for clinical decision-making, which could potentially confound the relationship between performance of imaging and performance of surgery. Surgeons may prefer to create vascular access using vessels that they can visualize and palpate, and imaging may be less likely to be obtained when vessels are obvious. Therefore the non-imaged group would contain more patients with large visible veins for whom surgical outcomes were likely to be good, and the imaged group would be more likely to have patients with unfavorable venous anatomy. Alternatively, the non-imaged group could be enriched in patients for whom the pursuit of vascular access was deferred due to poor prognosis.

Potentially important variables that were not available in our dataset included physical examination findings, assessment of 'overall health,' and the motivation for ordering imaging. Lacking these variables, we could not construct the ideal counterfactual: 'What would the outcomes of the exposed patients had they not been exposed?,' a limitation which becomes especially problematic for analyzing the effects of vascular imaging, in which these unmeasured variables could bias our associations in either direction. We could not evaluate the possibility that vascular imaging was a surrogate for physician engagement and effort. Future studies will need to employ other designs to address the causal relationships that may underlie these associations. We endeavored to address as many of these uncertainties as possible, by performing many different sensitivity analyses, and found that our findings were quite robust. Moreover, our effect sizes were fairly large, so cumulative unmeasured confounding would have needed to have been both prevalent and strong in order to entirely eliminate these associations.

4.5 Conclusions

Our data show that one in eight patients who have started dialysis with central venous catheters as their sole vascular access have had exposure to PICC, either before and after dialysis initiation, or both. PICC exposure was associated with longer time to conversion from a central venous catheter to a working AV fistula or graft and shorter survival on dialysis. Placement of PICC in a patient dialyzing with a CVC may indicate a period in which mortality risk is high and short term prognosis is poor.

Clinicians should be mindful of the potential serious long-term consequences of PICC use in patients with CKD, and consider when the future risks outweigh the short-term benefits and convenience of these devices. Effective protection of veins should be practiced by everyone taking care of patients with CKD.

Only 40% of patients who initiated HD with CVC as their sole vascular access had vascular imaging studies performed. Patients who were imaged were much more likely to undergo vascular surgery, with achievement of an AVF/AVG in approximately 70% of patients who had surgery, whether imaging was performed or not. Imaging had strong positive associations with future achievement of working AV fistulas and grafts and better survival, despite similar surgical outcomes. Prospective studies are needed to disentangle the effects of imaging from those of active clinician engagement.

New hemodialysis patients are a vulnerable group of patients with complex medical needs that ensure that they will have multiple points of contact with the health care system. The medical care that these patients experience has profound effects upon the natural history of treated kidney failure. Clinicians caring for patients receiving hemodialysis, and patients with advanced CKD who may require dialysis in the future, should be mindful of everyday medical care decisions that may have important consequences. Increasing appropriate use of vascular imaging and decreasing PICC exposure in patients with kidney disease merit exploration as ways to improve the survival and quality of outcomes in US hemodialysis patients.

References

1. Quinton W, Dillard D, Scribner BH. Cannulation of blood vessels for prolonged hemodialysis. *Transactions - American Society for Artificial Internal Organs.* 1960;6:104-113.
2. Scribner BH, Buri R, Caner JE, Hegstrom R, Burnell JM. The treatment of chronic uremia by means of intermittent hemodialysis: a preliminary report. 1960. *Journal of the American Society of Nephrology : JASN.* 1998;9(4):719-726; discussion 719-726.
3. United States Renal Data System. Chapter 1: Incidence, prevalence, patient characteristics, and treatment modalities. *2015 Annual Data Report: Epidemiology of kidney disease in the United States* 2015, 2016.
4. Murray JS, Tu WH, Albers JB, Burnell JM, Scribner BH. A community hemodialysis center for the treatment of chronic uremia. *Transactions - American Society for Artificial Internal Organs.* 1962;8:315-320.
5. United States Renal Data System. Chapter 5: Hospitalization. . *2015 Annual Data Report: Epidemiology of kidney disease in the United States* 2015, 2016.
6. National Kidney Foundation. Hemodialysis Vascular Access: what you need to know. 2016; https://www.kidney.org/sites/default/files.11-50-0216_va.pdf. Accessed February 2, 2016.
7. Lok CE, Foley R. Vascular access morbidity and mortality: trends of the last decade. *Clinical journal of the American Society of Nephrology : CJASN.* 2013;8(7):1213-1219.
8. Xue H, Ix JH, Wang W, et al. Hemodialysis access usage patterns in the incident dialysis year and associated catheter-related complications. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2013;61(1):123-130.
9. Banerjee T, Kim SJ, Astor B, Shafi T, Coresh J, Powe NR. Vascular access type, inflammatory markers, and mortality in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2014;64(6):954-961.
10. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *The New England journal of medicine.* 1966;275(20):1089-1092.
11. Spergel LM, Ravani P, Asif A, Roy-Chaudhury P, Besarab A. Autogenous arteriovenous fistula options. *Journal of nephrology.* 2007;20(3):288-298.
12. Rose DA, Sonaike E, Hughes K. Hemodialysis access. *The Surgical clinics of North America.* 2013;93(4):997-1012, x.
13. Baktiroglu S, Yanar F, Ozturk A. Brachiocephalic and basilic fistula. *The journal of vascular access.* 2015;16 Suppl 9:S29-33.
14. Kim JJ, Gifford E, Nguyen V, et al. Increased use of brachiocephalic arteriovenous fistulas improves functional primary patency. *Journal of vascular surgery.* 2015;62(2):442-447.
15. McGrogan D, Al Shakarchi J, Khawaja A, et al. Arteriovenous fistula outcomes in the elderly. *Journal of vascular surgery.* 2015;62(6):1652-1657.
16. Ishani A, Gilbertson DT, Kim D, Bradbury BD, Collins AJ. Predialysis care and dialysis outcomes in hemodialysis patients with a functioning fistula. *American journal of nephrology.* 2014;39(3):238-247.
17. Zarkowsky DS, Hicks CW, Arhuidese I, et al. Quality Improvement Targets for Regional Variation in Surgical End-Stage Renal Disease Care. *JAMA surgery.* 2015;150(8):764-770.
18. United States Renal Data System. Chapter 4: Vascular Access. *2015 Annual Data Report: Epidemiology of kidney disease in the United States* 2015, 2016.

19. Hopson S, Frankenfield D, Rocco M, McClellan W. Variability in reasons for hemodialysis catheter use by race, sex, and geography: findings from the ESRD Clinical Performance Measures Project. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2008;52(4):753-760.
20. Patibandla BK, Narra A, Desilva R, et al. Disparities in arteriovenous fistula placement in older hemodialysis patients. *Hemodialysis international. International Symposium on Home Hemodialysis.* 2014;18(1):118-126.
21. Goldfarb-Rumyantzev AS, Syed W, Patibandla BK, et al. Geographic disparities in arteriovenous fistula placement in patients approaching hemodialysis in the United States. *Hemodialysis international. International Symposium on Home Hemodialysis.* 2014;18(3):686-694.
22. Pisoni RL, Zepel L, Port FK, Robinson BM. Trends in US Vascular Access Use, Patient Preferences, and Related Practices: An Update From the US DOPPS Practice Monitor With International Comparisons. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2015;65(6):905-915.
23. Lacson E, Jr., Wang W, Lazarus JM, Hakim RM. Change in vascular access and mortality in maintenance hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2009;54(5):912-921.
24. Bradbury BD, Chen F, Furniss A, et al. Conversion of vascular access type among incident hemodialysis patients: description and association with mortality. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2009;53(5):804-814.
25. Lacson E, Jr., Wang W, Lazarus JM, Hakim RM. Change in vascular access and hospitalization risk in long-term hemodialysis patients. *Clinical journal of the American Society of Nephrology : CJASN.* 2010;5(11):1996-2003.
26. Caplin N, Sedlacek M, Teodorescu V, Falk A, Uribarri J. Venous access: women are equal. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2003;41(2):429-432.
27. Al-Jaishi AA, Oliver MJ, Thomas SM, et al. Patency rates of the arteriovenous fistula for hemodialysis: a systematic review and meta-analysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2014;63(3):464-478.
28. Hoshal VL, Jr. Total intravenous nutrition with peripherally inserted silicone elastomer central venous catheters. *Archives of surgery (Chicago, Ill. : 1960).* 1975;110(5):644-646.
29. Al Raiy B, Fakih MG, Bryan-Nomides N, et al. Peripherally inserted central venous catheters in the acute care setting: A safe alternative to high-risk short-term central venous catheters. *American journal of infection control.* 2010;38(2):149-153.
30. Chopra V, O'Horo JC, Rogers MA, Maki DG, Safdar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. *Infection control and hospital epidemiology.* 2013;34(9):908-918.
31. Fallouh N, McGuirk HM, Flanders SA, Chopra V. Peripherally Inserted Central Catheter-associated Deep Vein Thrombosis: A Narrative Review. *The American journal of medicine.* 2015;128(7):722-738.
32. Gonsalves CF, Eschelman DJ, Sullivan KL, DuBois N, Bonn J. Incidence of central vein stenosis and occlusion following upper extremity PICC and port placement. *Cardiovascular and interventional radiology.* 2003;26(2):123-127.
33. McGill RL, Tsukahara T, Bhardwaj R, Kapetanos AT, Marcus RJ. Inpatient venous access practices: PICC culture and the kidney patient. *The journal of vascular access.* 2015;16(3):206-210.

34. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: hemodialysis adequacy and vascular access. . *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2006;48(Supplement 1):S1-S322.
35. Hoggard J, Saad T, Schon D, Vesely TM, Royer T. Guidelines for venous access in patients with chronic kidney disease. A Position Statement from the American Society of Diagnostic and Interventional Nephrology, Clinical Practice Committee and the Association for Vascular Access. *Seminars in dialysis.* 2008;21(2):186-191.
36. Williams AW, Dwyer AC, Eddy AA, et al. Critical and honest conversations: the evidence behind the "Choosing Wisely" campaign recommendations by the American Society of Nephrology. *Clinical journal of the American Society of Nephrology : CJASN.* 2012;7(10):1664-1672.
37. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney international.* 2002;62(4):1109-1124.
38. Peterson WJ, Barker J, Allon M. Disparities in fistula maturation persist despite preoperative vascular mapping. *Clinical journal of the American Society of Nephrology : CJASN.* 2008;3(2):437-441.
39. Voormolen EH, Jahrome AK, Bartels LW, Moll FL, Mali WP, Blankestijn PJ. Nonmaturation of arm arteriovenous fistulas for hemodialysis access: A systematic review of risk factors and results of early treatment. *Journal of vascular surgery.* 2009;49(5):1325-1336.
40. Kosa SD, Al-Jaishi AA, Moist L, Lok CE. Preoperative vascular access evaluation for haemodialysis patients. *The Cochrane database of systematic reviews.* 2015;9:Cd007013.
41. Wong CS, McNicholas N, Healy D, et al. A systematic review of preoperative duplex ultrasonography and arteriovenous fistula formation. *Journal of vascular surgery.* 2013;57(4):1129-1133.
42. Silva MB, Jr., Hobson RW, 2nd, Pappas PJ, et al. A strategy for increasing use of autogenous hemodialysis access procedures: impact of preoperative noninvasive evaluation. *Journal of vascular surgery.* 1998;27(2):302-307; discussion 307-308.
43. Allon M, Lockhart ME, Lilly RZ, et al. Effect of preoperative sonographic mapping on vascular access outcomes in hemodialysis patients. *Kidney international.* 2001;60(5):2013-2020.
44. Malovrh M. Native arteriovenous fistula: preoperative evaluation. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2002;39(6):1218-1225.
45. Lok CE, Oliver MJ. Overcoming barriers to arteriovenous fistula creation and use. *Seminars in dialysis.* 2003;16(3):189-196.
46. Niyyar VD, Wasse H. Vascular mapping: does it help to maximize fistulae placement? *Advances in chronic kidney disease.* 2009;16(5):316-320.
47. Vachharajani TJ. Pre-Access Creation Evaluation--Is Vein Mapping Enough? *Advances in chronic kidney disease.* 2015;22(6):420-424.
48. Patel ST, Hughes J, Mills JL, Sr. Failure of arteriovenous fistula maturation: an unintended consequence of exceeding dialysis outcome quality Initiative guidelines for hemodialysis access. *Journal of vascular surgery.* 2003;38(3):439-445; discussion 445.
49. Liu J, Huang Z, Gilbertson DT, Foley RN, Collins AJ. An improved comorbidity index for outcome analyses among dialysis patients. *Kidney international.* 2010;77(2):141-151.
50. Dember LM, Imrey PB, Beck GJ, et al. Objectives and design of the hemodialysis fistula maturation study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2014;63(1):104-112.
51. Lee T, Mokrzycki M, Moist L, Maya I, Vazquez M, Lok CE. Standardized definitions for hemodialysis vascular access. *Seminars in dialysis.* 2011;24(5):515-524.

52. El Ters M, Schears GJ, Taler SJ, et al. Association between prior peripherally inserted central catheters and lack of functioning arteriovenous fistulas: a case-control study in hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2012;60(4):601-608.
53. Chopra V, Flanders SA, Saint S, et al. The Michigan Appropriateness Guide for Intravenous Catheters (MAGIC): Results From a Multispecialty Panel Using the RAND/UCLA Appropriateness Method. *Annals of internal medicine.* 2015;163(6 Suppl):S1-40.
54. Alexandrou E, Ray-Barruel G, Carr PJ, et al. International prevalence of the use of peripheral intravenous catheters. *Journal of hospital medicine.* 2015;10(8):530-533.
55. Chopra V, Kuhn L, Coffey CE, Jr., et al. Hospitalist experiences, practice, opinions, and knowledge regarding peripherally inserted central catheters: a Michigan survey. *Journal of hospital medicine.* 2013;8(6):309-314.
56. Rhee Y, Heung M, Chen B, Chenoweth CE. Central line-associated bloodstream infections in non-ICU inpatient wards: a 2-year analysis. *Infection control and hospital epidemiology.* 2015;36(4):424-430.
57. Ravani P, Palmer SC, Oliver MJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *Journal of the American Society of Nephrology : JASN.* 2013;24(3):465-473.
58. Ferring M, Claridge M, Smith SA, Wilmink T. Routine preoperative vascular ultrasound improves patency and use of arteriovenous fistulas for hemodialysis: a randomized trial. *Clinical journal of the American Society of Nephrology : CJASN.* 2010;5(12):2236-2244.
59. Nursal TZ, Oguzkurt L, Tercan F, et al. Is routine preoperative ultrasonographic mapping for arteriovenous fistula creation necessary in patients with favorable physical examination findings? Results of a randomized controlled trial. *World journal of surgery.* 2006;30(6):1100-1107.
60. Gomes A, Schmidt R, Wish J. Re-envisioning Fistula First in a patient-centered culture. *Clinical journal of the American Society of Nephrology : CJASN.* 2013;8(10):1791-1797.
61. Drew DA, Lok CE, Cohen JT, Wagner M, Tangri N, Weiner DE. Vascular access choice in incident hemodialysis patients: a decision analysis. *Journal of the American Society of Nephrology : JASN.* 2015;26(1):183-191.
62. Moist LM, Lok CE, Vachharajani TJ, et al. Optimal hemodialysis vascular access in the elderly patient. *Seminars in dialysis.* 2012;25(6):640-648.
63. Vachharajani TJ, Moossavi S, Jordan JR, Vachharajani V, Freedman BI, Burkart JM. Re-evaluating the Fistula First Initiative in Octogenarians on Hemodialysis. *Clinical journal of the American Society of Nephrology : CJASN.* 2011;6(7):1663-1667.