Official Title: A Randomized Pilot Study Comparing Graft-first to Fistula-first Strategies in Older Patients With Incident End-stage Kidney Disease
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Study Title:

A randomized pilot study comparing graft-first to fistula-first strategies in older patients with incident end-stage kidney disease

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Background, Rationale and Context

Each year, more than 600,000 people in the United States receive life-saving hemodialysis (HD) treatments for end-stage kidney disease (ESKD), a third of whom are older adults (age ≥65 years).[1] Timely placement of an arteriovenous (AV) vascular access (native AV fistula [AVF] or prosthetic AV graft [AVG]) is necessary to avoid (or limit) the use of tunneled central venous catheters (TCVC) for HD. Several retrospective studies presented a graded relationship between the type of vascular access placed or used for HD with access complications and patient survival. The lowest access complication rates and longest patient survivals were seen with native, autologous AVF, highest access complication rates and shortest patient survivals with TCVC, and intermediate results with prosthetic arteriovenous grafts (AVG).[2-6] These findings led national committees to promote 'Fistula First Catheter Last' guidelines.[7] A pervasive challenge in any observational study is distinguishing whether the vascular access type *per se* directly affects clinical outcomes or whether there is a selection bias whereby the choice of vascular access approach and access development was a surrogate marker for the severity of comorbidities that themselves affected clinical outcomes. For example, the decision to place an AVF in a patient can reflect a healthier clinical status in ways that are not captured even with sophisticated statistical analyses (e.g., perceived better prognosis, less severe

comorbidities).[8;9] These residual confounders not only can impact achievement of usable, developed AVF, but can also affect patient survival.

The benefits of AVF over AVG are least certain in older adults, as age-related biological changes independently modulate patient outcomes.[10] Nationally representative cohort studies of older adults with incident ESKD have shown similar patient survival between those whose first AV access placed or used was a fistula or a graft.[11;12] Compared with grafts, fistulas fail more often and necessitate longer times and more subsequent procedures to aid development, exposing older patients to time-consuming procedures that may negatively affect upper extremity strength and erode their quality of life.[13-16] Hitherto, the contribution of pre-operative muscle strength to AV access outcomes and the impact of AV access placement on upper extremity strength and self-sufficiency have not been evaluated. We propose a randomized pilot trial in older adults with pre-dialysis advanced chronic kidney disease (CKD) or incident ESKD using a TCVC for HD who had no prior AV access surgery and have upper extremity vasculature suitable for either fistula or graft placement. Participants will be randomized to receive an upper extremity AVF-first or AVG-first access for HD.

Objectives

The primary objective of this study is to prospectively evaluate patient and vascular access outcomes in a randomized intervention and in a patient population in whom fistula-first guidelines have been applied despite the lack of proven benefit and at the detriment of more access failures and procedures. Our hypothesis is that there is a bidirectional relationship between the type of first AV access and patient outcomes as follows: a) the graft-first strategy will confer a more effective transition from TCVC-based to AV access-based HD and will limit upper extremity functional impairment from protracted access development and subsequent access procedures, and b) preoperative muscle strength will impact AVF development.

Methods and Measures

Design

This randomized pilot trial will be parallel-arm in design (Appendix A). We plan to enroll 50 patients of age ≥65 years, with incident ESKD or advanced CKD expected to require HD initiation within 90 days of screening. Screening for potential participants will be performed

in two stages. In the first stage, all patients ≥65 years old receiving chronic HD and use a TCVC will be screened for eligibility. Of these patients, only those who did not have a previous AV access surgery and are considered for AV placement (according to goals of care established by the patient's nephrologist) will be maintained as potential participants and advanced to the second phase of screening pending determination of surgical eligibility for placement of upper extremity AVF and AVG. Ultrasound vascular mapping of both upper extremities to assess vascular anatomy is routinely performed pre-operatively at our institution. Arterial diameter of ≥2 mm and vein diameter of ≥2.5 mm at the site of AV anastomosis indicate suitability for AVF surgical creation.[7] To complete the eligibility criteria, patients must have proper anatomy (in either upper extremity) for placement of AVF (forearm or arm) and AVG (forearm or arm).

Setting

Participant recruitment will occur at Wake Forest Baptist Medical Center (WFBMC) Outpatient Nephrology Clinics, WFBMC Inpatient Nephrology Service, Wake Forest Outpatient Dialysis (WFOPD) units or any other Wake Forest affiliated institution (i.e., High Point Regional Medical Center).. After the screening process identifies a potential study candidate, the patient will be approached for study participation. The study coordinator and/or the PI and/or other study member will contact the patient and present an overview of the study. This will be done either in person, by phone, or electronically (e.g., Skype or Facetime). When the patient presents interest in the study after the initial overview, the study coordinator and/or the PI or other study team member will meet in person with the potential study participant to further review the study and the informed consent to patient's and/or patient's family member/representative full understanding, and finalize the enrollment.

Subjects selection criteria

The overall eligibility will be reached as a consensus between the PI and the vascular surgeon.

Inclusion Criteria

1. Age ≥ 65 years

2. Incident ESKD on chronic HD and recovery of kidney function is unlikely or advanced CKD expected to require HD initiation within 90 days of screening and deemed medically necessary by the treating nephrologist to proceed with AV access placement (either AVF or AVG) in preparation for HD initiation
3. TCVC is the sole vascular access used for HD
4. Did not undergo AV access placement in the past
5. Medically eligible to receive AVF or AVG placement as deemed by the treating nephrologist
6. Surgically eligible to receive either an AVF or an AVG
7. HD is the intended long-term modality of treatment for ESKD
8. Planning to remain within Wake Forest provided health care for at least 12 months

Exclusion Criteria

1. Presence of an AVF or AVG
2. Previous attempt(s) for AV vascular access placement
3. Native vasculature not suitable for placement of AV access
4. Imminent transplant planned (within 6 months)
5. Anticipated life expectancy <9 months

This study targets elderly population with advanced CKD and ESKD; therefore, the clinical scenario of when an elderly individual is not able to consent for himself or herself will not be uncommon. Because the study objectives will not be met without including these subjects, this study plans to enroll elderly subjects who are not able to consent for themselves. The foreseeable risks to these subjects in this study are low as is the negative impact. For elderly with impaired mental capacity, permission for study participation will be obtained from the subject's Legally Authorized Representative (LAR).

Sample Size

This pilot trial has the principal aim of testing the feasibility of randomizing initial AV access placement to an upper extremity AVG-first (intervention) or AVF-first (comparator) strategy in patients ≥65 years of age. For this goal, we plan to enroll 50 participants (25 per arm).

Interventions and Interactions

Screening for potential participants will be performed in two stages. In the first stage, all patients ≥65 years old who have pre-dialysis CKD or have ESKD receiving chronic HD will be screened for eligibility. Of these patients, only those who did not have a previous AV access surgery and are considered for AV placement (according to goals of care established by the patient's nephrologist) will be maintained as potential participants and advanced to the second phase of screening pending determination of surgical eligibility for placement of upper extremity AVF and AVG. Ultrasound vascular mapping of both upper extremities to assess vascular anatomy is routinely performed pre-operatively at our institution. Arterial diameter of ≥2 mm and vein diameter of ≥2.5 mm at the site of AV anastomosis indicate suitability for AVF surgical creation.[7] To complete the eligibility criteria, patients must have proper anatomy (in either upper extremity) for placement of AVF (forearm or arm) and AVG (forearm or arm). After written informed consent is obtained, participants will be allocated with equal probability to either a graft-first (intervention) or fistula-first (comparator) strategy. Allocation to AVG or AVF will be done using randomly permuted blocks of varying sizes to maintain balance between the groups.

Demographic and medical data will be collected from all participants, using direct patient interview and electronic medical records. Following randomization, collected data is derived from standard of care and from assessments specifically conducted as part of this study.

Study-specific assessments will include muscle strength (assessed with upper arm grip-strength test in each arm using a hand-held dynamometer)[17], four-meter gait speed (4MGS) [18](HealthMeasures. NIH Toolbox training manualdEnglish version.

Available at: http://www.healthmeasures.net/images/nihtoolbox/

Training-Admin-Scoring_Manuals/NIH_Toolbox_Training_ManualEnglish_9-25-12.pdf.

Accessed November 16, 2018), satisfaction with the vascular access (using the short-form vascular access questionnaire [SF-VAQ])[19], pain at the AV access site (using the Verbal Descriptor Scale [VDS] or the modified Abbey Pain Scale [mAPS] for people who cannot verbalise)[20;21], level of independence (using activities of daily living [ADL] and independent ADL [IADL] instruments)[22;23], and health-related quality of life (using the Kidney Disease Quality of Life instrument short form [KDQOL-SF] version 1.3. which consists of a generic core (Short Form-36 [SF-36]) and an 11-item kidney disease-specific scale).[24] , participant's

individual study experience (study conduct, intervention outcomes, and intervention decisions) (using the Qualitative Study Interview designed by the PI and safety monitor). The assessment instruments (SF-VAQ, mAPS, ADL, IADL, KDQOL-SF) are summarized in Appendix B. The schedule of assessments is summarized in Appendix C.

Data Collection and Outcome Measure(s)

Data collection at enrollment: sociodemographic characteristics (age, sex, race, marital status, educational level, living arrangement); health behaviors (smoking and alcohol consumption [no, formerly, or yes]); ESKD etiology; date of HD commencement; and pre-dialysis care (first nephrology clinic visit and number of clinic visits prior to the first HD date); Charlson comorbidity index (CCI); medications (lipid lowering drugs, anticoagulants, antiplatelets); upper limb muscle strength assessed with grip-strength test in each arm using an isometric dynamometer; gait speed. The grip-strength test will be performed twice on each hand for each assessment and the mean of the two results will be used for statistical analyses; a cut-off point <16 kg in women and <26 kg in men will define muscle weakness. The four meter gait speed (4MGS) will be assessed on a flat, unobstructed four meter delineated course by trained research staff following a standard operating procedure.

Data regarding arterial and venous diameters on pre-operative ultrasound mapping, AV access date of placement, and location of AV anastomosis will be recorded for each participant. Results of blood work obtained on a monthly basis (per standard care) at the outpatient dialysis units. This includes measurements of dialysis adequacy, anemia management, and bone-mineral metabolism.

Vascular access outcomes.

- The study participants will undergo evaluation of the index vascular access placed as part of the study (AVF or AVG) within 6-8 hours post-operatively; we will document the nature of the vascular access thrill, bruit, pulse, and/or if any signs of ischemia to the upper arm. For participants that have surgery at any other Wake Forest affiliated institution (i.e., High Point Regional Medical Center), we will attempt to obtain the post-operative assessment data from the operation note.

- Three weeks after the index AVG is placed or four weeks after the index AVF is placed, the patients will have the vascular access evaluated at the Dialysis Access Group (DAG) of Wake Forest University; at this evaluation, the development of the vascular access will be assessed, as well as the feasibility of vascular access cannulation for HD (Appendix C, Schedule of Assessments). For participants that have surgery at any other Wake Forest affiliated institution (i.e., High Point Regional Medical Center), we will attempt to obtain the evaluation data from the standard of care one month post-surgery follow up vein duplex performed at their respective institution.
- The outcomes of AVF and AVG that will be continuously monitored during the study are listed in the (AppendixD;) these will include: vascular access procedures (e.g., angioplasty, stent placement, surgical revision, ligation of accessory veins, superficialization of vein), date of successful AV access cannulation, AV access infectious (cellulitis, abscess, bacteremia) and non-infectious (bleeding, stenosis, thrombosis, arterial steal syndrome, nerve injury, seroma, aneurysm, pseudoaneurysm, infiltration) complications, and patency outcomes.[25]

Patient-reported views on AV access outcomes (Appendix B). Pain at the AV access site during access cannulation will be assessed using the VDS or mAPS. Using VDS, pain will be categorized into four intensity levels: absent/no pain, mild pain, moderate pain, and severe pain/pain as bad as could be/extreme pain. Patients' satisfaction with the vascular access will be assessed with the SF-VAQ. Pain at the AV access site will be assessed as acute pain and chronic pain. Acute AV access pain (evaluated with VDS or mAPS) will be assessed as pain experienced during AV access cannulation; the average score obtained at 3 consecutive access cannulation sessions (initial assessment being done with the first cannulation) will be used for analysis. Chronic AV access pain will be assessed as part of the physical symptom domain with SF-VAQ.

TCVC-related outcomes: infectious (e.g., catheter exit site infection, tunnel infection, catheter-related bacteremia) and non-infectious (e.g., catheter malposition, mechanical dysfunction, catheter migration, venous thrombosis, pneumothorax, arterial puncture, hemothorax).

Clinical outcomes related to hospital admissions observed during the study period will be recorded and will include the main admission diagnosis and length of hospitalization.

All deaths that occur during the study period will be recorded and classified into six categories (Appendix E), and sub-classified as to whether death was access-related. The cause of death will be determined by the patient's primary nephrologist and/or primary doctor according to usual practice.

Analytical Plan

We will begin by examining descriptive statistics (means, standard deviations, minima, quartiles, maxima) and plots of the data (histograms and boxplots) to become familiar with the data and check for outliers. The proportion of people meeting each of the feasibility and protocol adherence endpoints with accompanying 95% confidence intervals (CI) will be calculated using skew-corrected score tests with a continuity correction. The maximum uncorrected error margin associated with the estimation of consent and surgery rates is 0.138, obtained at p=0.5. This suggests that CI around these estimates will tight enough to provide meaningful guideline in the design of the larger trial. We will describe participant characteristics and evaluate reasons for protocol violations. We will calculate rates of dropout and other events, although we expect low numbers. Robust regression and non-parametric methods will be used for comparisons between randomized arms. The associations between pre-operative muscle strength (continuous or binary variable) with AV access primary outcome will be tested using logistic regression. The participants will be followed for a minimum of 12 months following index AV access placement. Participants who undergo AV access placement >90 days after randomization or who experience primary or secondary AV access failure will be analyzed as randomized in the intention-to-treat (ITT) analysis. Missing data will be handled under the missing at random (MAR) assumptions in compliance with an ITT protocol.[26] We will pay close attention to variables with higher rates of missingness, relative to others or display missingness patterns that deviate from the MAR assumptions since they could inform and guide the development of the larger trial. Results from the pilot analyses are likely to have high variability, but will provide valuable insight that will be considered in the design of a larger trial.

Recruitment will be determined as the proportion of people meeting inclusion criteria who ultimately consent to randomization. We aim to consent ≥70% of those eligible. Protocol adherence is based on the ability to undergo a graft or fistula surgery within 90 days of randomization, which we aim to attain in ≥70% of participants. Outcomes of quality of life stratified by the type of first AV-access strategy. Changes in grip strength, pain related to the access (acute and chronic pain), patient's satisfaction with the access, changes in the level of independence (ADLs and IADLs) and HRQoL—will be compared between the two arms, with baseline (preoperative) assessments used as reference.

Subject Recruitment Methods

Clinical records of Wake Forest Nephrology practice, including WFOPD facilities, WFBMC nephrology outpatient clinics, and WFBMC nephrology inpatient service will be reviewed for eligibility. Study participants will be older adults of age ≥65 years with a diagnosis of incident ESKD or have advanced CKD expected to require HD initiation within 90 days of screening who meet the following additional inclusion criteria: (1) use a TCVC for HD, (2) did not undergo surgical creation of an AV access in the past, (3) are medically eligible to undergo surgery for AV access placement, and (4) are surgically eligible to undergo surgical placement of AVF and AVG. Medical eligibility for surgical placement of AV access will be determined as part of standard of care for patients with ESKD. In clinical practice, this aspect takes in consideration patient's clinical prognosis (e.g., unlikely to recover kidney function, medically stable to undergo surgical placement of AV access, anticipated life expectancy ≥9 months) and goals of care (HD is the intended long-term modality of treatment). Surgical suitability for placement of AV access, AVF and AVG, will be determined as part of standard of care by the vascular surgeon. To make this determination, the vascular surgeon will use the results of the ultrasound vascular mapping of both upper extremities. Patients who meet all the eligibility criteria will be approached by the vascular access coordinator, study coordinator, and/or PI for explanation of study participation.

Human Subjects Protection

This study poses **moderate risks** to the study participants. The potential participants for this study have already been determined to need an AV access for chronic HD. This study plans to randomize the participants into two groups; each group will undergo surgical placement of one of the two types of AV access, fistula (forearm or arm) or AVG (forearm or arm), respectively. All interventions, procedures and complications will be treated and followed by their nephrologist as standard of care. Postoperative evaluation of AV access development will follow according to usual clinical practice for each individual. The patients are examined at the outpatient dialysis unit on a regular basis by the nephrologist, physician assistant, and nurses with experience in vascular access assessment. Timing of AV access cannulation and TCVC removal/reinsertion will be determined by patient's nephrologist. Any abnormalities that relate to the AV access including changes on physical examination (such as extremity edema; collateral veins; alterations in the pulse, thrill, or bruit of the fistula or graft; signs and symptoms indicative of limb ischemia) or problems noted during the dialysis session (such as inability to maintain prescribed blood flow rates, abnormal venous and/or arterial access pressures, prolonged bleeding at the end of dialysis, unexplained decrease in dialysis clearance) will be addressed as directed by patient's nephrologist according to standard practice. Vascular access procedures that may be performed on the AV access following surgical placement (such as fistulogram, thrombectomy, angioplasty, stent placement, ligation of collateral veins, access ligation, fistula superficialization) will also be directed by the patient's nephrologist and vascular surgeon according to standard practice.

All the assessments of upper arm muscle strength, AV access pain, level of independence, and patient reported views on vascular access and quality of life will be gathered either at participant's dialysis session or at regular physician office visit. Evaluation of acute AV access pain will be performed at the beginning of dialysis session. There will be no medical visits and no blood collections done exclusively for this study.

Informed Consent

Signed informed consent will be obtained from each subject by the study coordinator, a study team member, the vascular access coordinator, or the PI. The participant will have

sufficient time to read the Informed Consent and to have all questions answered. The vascular access coordinator and study coordinator involved in this study have good knowledge on the medical aspects of both types of AV accesses: fistulas and grafts. Patients will be informed on both types of AV access and the expected course of each type of AV access. The assessments involved in the study and the chances of being assigned randomly to one of two groups will be explained to each potential participant. We will provide adequate opportunity for the subject to consider all options, and respond to the patient's questions to ensure the information was comprehended. Informed consent will be obtained in the dialysis centers, outpatient nephrology clinics, or inpatient service. Patients will be made aware of their right to withdraw from the study at any time without adverse effects on their clinical care.

Confidentiality and Privacy

Taking part in this research study may involve collection of information that is considered confidential or private. Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. Complications related to placement of an arteriovenous graft for hemodialysis, such as graft thrombosis and graft infection with/without systemic infection, will be closely tracked. All vascular access-related clinical events will be adjudicated (based on standards of care) by the patient's nephrologist and treating physicians. Events will be recorded electronically and reported to the principal investigator monthly. An independent Safety Officer, unblinded to treatment assignments, will review the following vascular access-related events on a quarterly basis: primary access failure, access infection (local and systemic), access thrombosis, and arterial steal syndrome. All concerns regarding the frequency of arteriovenous graft-related complications will be reported to the Wake Forest IRB. In addition, the principal investigator, Safety Officer, and members of the research group will carefully consider amendments (including halting the trial if necessary).

Reporting of Unanticipated Problems, Adverse Events or Deviations (Appendix E)

The principal investigator along with the research staff will be responsible for periodic evaluation of clinical trial data to ensure continued participant safety, protocol compliance, data collection as well as scientific validity. Adverse events are not anticipated, but any occurring will be documented and reported according to WFSM IRB policies and procedures. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review. Protocol violations and expected procedure-related events (i.e., having a potentially causal relationship to the strategy) occurring within 7 days of an access intervention will be collected.

All deaths occurring during the trial period will be collected. The cause of death will be determined by the patient's nephrologist and/or primary team according to standard practice. Deaths will be classified into one of six categories: cardiovascular, infectious, malignancy-related, elective withdrawal from dialysis, sudden death at home, or other). After deaths are classified into these categories, they will be further classified as to whether the death was access-

related. Deaths will be considered access-related if resulted from a direct complication of the access or an access-related procedure (e.g. complications of catheter-related bacteremia leading to death). Access-related deaths will be further sub-classified as index fistula-related, index graft-related or catheter-related deaths. All vascular access-related clinical events will be adjudicated (based on standards of care) by the patient's nephrologist and treating physicians. Events will be recorded electronically and reported to the PI monthly. An independent Medical Safety Officer (Dr. Todd W. Robinson), unblinded to treatment assignments, will review the following vascular access-related events on a quarterly basis: primary access failure (i.e., permanent access failure before hemodialysis suitability), access infection (local and systemic), secondary access failure (i.e., permanent access failure after was used for hemodialysis), and arterial steal syndrome. Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the PI or designated member of the research team to the IRB and the NIA government agency as appropriate.

Appendices

Appendix A: Study Flow Diagram

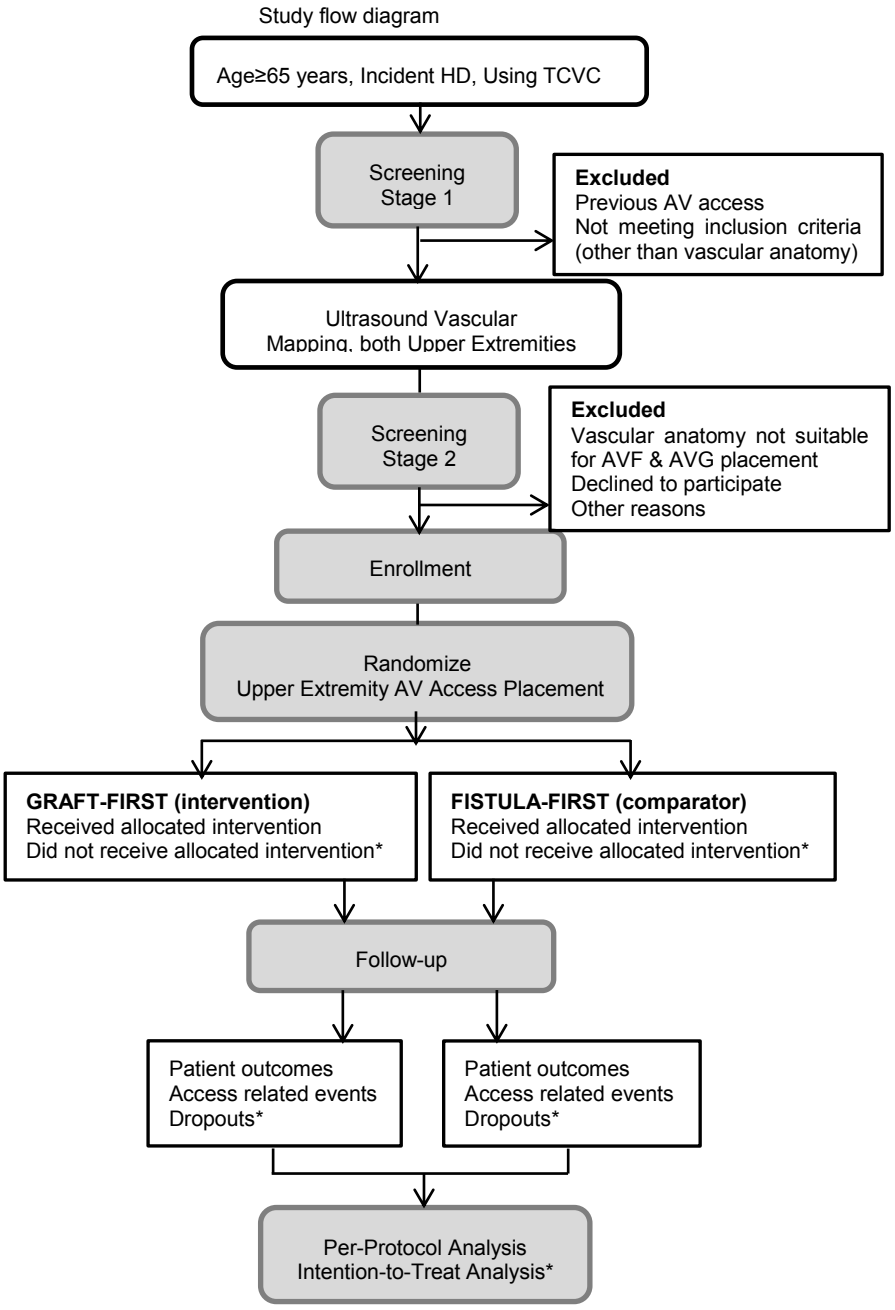
Appendix B : Assessment Instruments

Appendix C : Schedule of Assessments

Appendix D: Vascular access outcomes

Appendix E: Protocol Violation, Expected Events, Cause of Death

Appendix A: Study Flow Diagram



Appendix B: Assessment Instruments

1) **Grip Strength Test**: a muscle strength test that uses a hand-held dynameter to assess the upper arm grip-strength in each arm. Study participant will squeeze the dynameter as hard as possible two separate times for each arm.
2) The four meter gait speed (4MGS) will be assessed on a flat, unobstructed four meter delineated course by trained research staff following a standard operating procedure. Participants will be asked to walk at their usual pace from a standing start. Two trials will be completed. The arithmetic mean of the two trials will be used for analysis. Participants will be allowed to use their usual walking aids and ambulatory oxygen, with the cylinder carried by an assistant and these factors will be kept constant within person measurements on repeated walk tests. To express gait speed in ms-1, distance walked (i.e. 4 meters) will be divided by time expressed in seconds.
3) **Short Form Vascular Access Questionnaire (SF-VAQ):** a questionnaire that the study participant will complete that measures the participant's satisfaction with their vascular access. Participant will circle a number on the scale that indicates their level of agreement with each statement regarding physical symptoms, social functioning, complications and overall satisfaction.
4) **Verbal Descriptor Scale (VDS):** a scale the study participant will complete that measures their pain at the AV access site. The participant will rate their pain as either absent/no pain, mild pain, moderate pain, or severe pain/pain as bad as could be/extreme pain.
5) **modified Abbey Pain Scale (mAPS)** : a scale used for people who cannot verbalize that measures their pain at the AV access site. The study staff will score the scale by observing the participant's vocalization, facial expression, and body language.
6) **Activities of Daily Living (ADL)** and **Instrumental Activities of Daily Living (IADL):** these two scales measure the level of independence of the study participant. For the ADL scale, study staff will ask participants how well they can perform various daily activities such as bathing, grooming, dressing, eating, etc.

For the IADL scale, study staff will ask participants how well they can perform various daily activities such as housekeeping, food preparation, shopping, etc.

7) **Kidney Disease Quality of Life instrument short form (KDQOL-SF) version 1.3**: this survey consists of a generic core (Short Form-36 [SF-36]) and an 11-item kidney disease-specific scale. This survey will be completed by the study participant and asks a wide variety of questions about their health and quality of life.
8) **Qualitative Study Interview:** this interview will consists of questions regarding the participant's study experience (study conduct, intervention outcomes, and intervention decisions).

Appendix C: Schedule of Assessments

	Schedule of assessments					
Assessment	Enrollment	Week 1 or 2 after AV access placement	Week 3 after AVG placed or Week 4 after AVF placed	Week 5 or 6 after first AV access cannulation	Week 24 or 25 of AV access use	Week 24 or 25 after AV access placement *if* primary AV access failure
Grip strength	√	√	Evaluation at DAG to assess AV access development and suitability for cannulation	√	√	√
4MGS	√			√	√	√
VDS or mAPS		√		√	√	√
SF-VAQ		√		√	√	√
ADLs and IADLs	√				√	√
KDQOL-SF 1.3.	√				√	√
Qualitative Study Interview						

AV, arteriovenous; 4MGS, four meter gait speed; VDS, Verbal Descriptor Scale; mAPS, Modified Abbey Pain Scale; SF-VAQ, Short-form vascular access questionnaire; ADLs, Activities of daily living; IADLs, Instrumental ADLs; KDQOL-SF, Kidney Disease Quality of Life Short-form. The Qualitative Study Interview will be performed on a maximum number of 10 subjects who have been enrolled in study >6 months and have had AV access surgery and are still currently enrolled in study either during a study visit or before the subject's dialysis treatment at their respective dialysis center.

Appendix D. Vascular access outcomes

Vascular access outcomes (according to the recommendations of the Committee on Reporting Standards for Arteriovenous Accesses, Society for Vascular Surgery and American Association for Vascular Surgery	
AV access outcome	***Definition***
Primary access failure	Permanent failure of the fistula or graft before hemodialysis suitability. This includes inadequate maturation, thrombosis, failure of first and subsequent cannulations, and other complications leading to nonfunctional fistula or graft.
Successful cannulation	The arteriovenous access became the primary vascular access for hemodialysis (the fistula or graft access has been cannulated with two 16- or 15-gauge needles for ≥3 consecutive dialysis sessions and the TCVC was removed).
Suitability for hemodialysis	Fistula or graft use with two needles and maintenance of blood flow ≥300ml/min for ≥75% of dialysis sessions over a continuous 4-week. The maturation criteria can be satisfied at any time within 6 months of fistula or graft creation surgery.
Unassisted access maturation	Criteria for fistula or graft suitable for hemodialysis (based on the above criteria) are met before any endovascular or secondary surgical procedure to facilitate maturation.
Assisted access maturation	Satisfaction of the criteria for fistula or graft suitability for hemodialysis after a procedure to facilitate maturation (e.g., angioplasty, stent placement, surgical revision, ligation of accessory veins).
Primary access patency	Intervention-free access survival defined as the time from fistula or graft creation to any intervention to maintain patency.
Secondary access failure	Permanent failure after the fistula or graft met dialysis suitability criteria with subsequent abandonment.
Noninfectious complications	Stenosis, thrombosis, hand ischemia, aneurysm, pseudoaneurysm, infiltration.
Infectious complications	Fistula or graft cellulitis, abscess, bacteremia.
Access procedures	Angioplasty, stent placement, surgical revision, ligation of accessory veins, superficialization of vein.
Other clinical outcomes	TCVC placement, new AV access surgical creation, AV access–related hospitalization or death.
Limb ischemia following AV access placement	
Symptoms	Paresthesia, pain, hand stiffness, ulceration and tissue loss in the limb with arteriovenous access.
Physical examination	Diminished or absent radial pulse, pallor, diminished sensation, and, in advanced stages or severe cases, ulceration and gangrene.
Grade 1, mild	Cool extremity with few symptoms but steal demonstrable by flow augmentation with access occlusion.
Grade 2, moderate	Intermittent ischemia only during dialysis/claudication.
Grade 3, severe	Ischemic pain at rest/tissue loss.
TCVC access outcome	***Examples***

Infectious complications	Catheter exit site infection, tunnel infection, bacteremia.
Non-infectious complications	Catheter malposition, mechanical dysfunction, catheter migration, venous thrombosis, pneumothorax, heamothorax, arterial puncture.

Appendix E. Protocol Violation, Expected Events, Cause of Death

A. Protocol violations	
Dropouts and their causes (e.g., withdrawal of consent, transfer to another center, refusal to undergo study-specific assessments)	
B. Expected procedure-related events	
Local events	**Systemic events**
Bleeding from access site requiring intervention	Allergic reaction to local anesthetic
Nerve injury	Allergic reaction to generalized anesthetic
Ischemia (to nerves or distal extremity)	Heart failure (high output congestive heart failure)
Arterial steal syndrome requiring intervention	Myocardial infarct
Seroma	Pulmonary embolism
	Aspiration pneumonia
	Nosocomial infection
	Sudden death
C. Classification of causes of death	
1. *Cardiovascular* Acute coronary syndromes and related complications Heart failure Cardiac dysrhythmias Valvular disorders Myocardial disorders Pericardial disorders Complications of cardiac or vascular surgery Complications of cardiac or vascular procedures Cardiac perforation following hemodialysis catheter insertion Cardiac arrest during placement of a dialysis catheter in radiology suite Acute stroke syndromes and complications (ischemic and hemorrhagic) Complications of peripheral vascular disease (examples: ischemic gut, ischemia of the extremities) Complications of aortic dissection and aortic aneurysm Complications of congenital heart disease	
2. *Sudden death at home* without antecedent illness or procedure that could have contributed to the death.	
3. *Infectious* Bacteremia/sepsis from any source, including complications of vascular access. Examples of sources of sepsis: pneumonia, urinary tract, infective endocarditis, intra-abdominal abscess, colitis, septic joint, soft tissue ulcer, dialysis vascular access related bacteremia, dialysis vascular access related sepsis and infective endocarditis, dialysis vascular access related sepsis and osteomyelitis, dialysis vascular access related sepsis and ectopic abscess, infective endocarditis of mechanical valve from infectious complication of dialysis vascular access, etc.	
4. *Malignancy-related* Complications of any malignancy leading to death. This includes metastatic disease leading to withdrawal of care or palliation.	
5. *Elective withdrawal from dialysis* Elective discontinuation of dialysis therapy, in the absence of an acute, antecedent precipitant such as	

an acute medical illness.
6. *Other:* Any other condition that did not fall into one of the 5 preceding categories. Examples: admission for failure to thrive with sudden death in the hospital and no clear precipitant, admission for bowel perforation and died in hospital from complications, air embolism related to placement of hemodialysis catheter, intravascular clot and embolism from dialysis catheter, etc.

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