Hemodialysis Access Surveillance Evaluation (HASE) Study

Protocol Title:
Transonic Hemodialysis Access Surveillance Evaluation (HASE) Study

Objectives
The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) recommends an organized monitoring/surveillance approach with regular assessment of clinical parameters of the arteriovenous access and hemodialysis (HD) adequacy. Data from the clinical assessment and HD adequacy measurements should be collected and maintained for each patient's access and made available to all staff. The data should be tabulated and tracked within each HD center as part of a Quality Assurance (QA)/continuous quality improvement (CQI) program (1).
The evidence from observational studies has emphasized that implementation of a surveillance program is beneficial in regard to access thrombosis, hospitalization and cost burden (see below). However, small sample sizes, randomized studies with suboptimal design and power to detect the difference have questioned the validity of the available information. National debates are beginning to express the futility of the surveillance approach. A well-designed randomized controlled trial that is adequately powered to evaluate multiple variables such as access thrombosis, cumulative access patency, need for tunneled hemodialysis catheters and hospitalizations (all of these parameters can easily be extrapolated to cost) is desperately needed.

Background
Hemodialysis vascular access dysfunction contributes directly to morbidity and mortality and adds to the cost of medical care of dialysis patients (1, 2). While access dysfunction presents several predicaments (prolonged bleeding, edema, high recirculation, low dialysis adequacy or frequently alarming dialysis machine) access thrombosis is the most feared complication. In order to provide an uninterrupted, life-saving dialysis therapy, a clotted access requires an urgent intervention (either thrombectomy or insertion of a tunneled dialysis catheter). Additionally, even after a successful thrombectomy procedure, a thrombotic episode in and of itself can affect the longevity of the access even after a successful thrombectomy procedure.

Vascular access stenosis develops as a result of neointimal hyperplasia and is observed in almost all of the patients with a clotted arteriovenous access (3, 5). It is also the most common cause of hemodialysis vascular access dysfunction. Indeed, a great majority of hemodialysis patients with an arteriovenous access will develop vascular stenosis (4).

While reduction in the blood flow and its subsequent recirculation is relatively a common cause of low Kt/V, the presence of stenosis is the most common cause of reduced blood flow rates. Data have indicated that for every 0.1 decline in Kt/V there is a significant increase in hospitalizations, hospital days and Medicare cost (5). In this context, the detection of the presence of vascular stenosis and its prompt treatment with percutaneous transluminal angioplasty (PTA) is of paramount importance for hemodialysis patients receiving treatment with hemodialysis. Several centers across the Unites States are

performing PTA successfully on an outpatient basis (6). There is evidence that treatment of vascular access stenosis might decrease vascular access thrombosis (7-9).
There are a number of techniques that have been used to measure intra-access blood flow. However, most of these techniques have significant limitations. An ideal surveillance method is the one that can be performed during hemodialysis treatment such as ultrasound dilution technique (UDT) (Transonic) to enable regular periodic measurements and more compliance from patients (no additional appointments are required).

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that access blood flow with ultrasound dilution be performed monthly during the first 1.5 hour of the treatment to eliminate error caused by decrease in cardiac output or blood pressure related to ultrafiltration or hypotension (1). The official KDOQI recommendation indicates that an access flow of less than 600 ml/minute in arteriovenous graft and less than 500 ml / minute in arteriovenous fistula or if the access flow is 1000 ml/minute that has decreased by more than 25% over 4 months, the patient should be referred for hemodialysis access angiogram for further evaluation for the presence of stenotic lesions (1) (Table 1).

Table 1. Indications for referral for arteriovenous access angiogram Based on access blood flow measurement as set by KDOQI guidelines (1)	
Arteriovenous Fistula (AVF)	Arteriovenous Graft (AVG)
access flow rate less than 500 mL/min	access flow rate less than 600 mL/min in grafts
	If access flow is 1000ml/min that has dropped 25% over 4 months
Prospective trend analysis of the test parameter has greater power to detect dysfunction than isolated values alone	
Persistent abnormalities in any of the monitoring or surveillance parameters should prompt referral for access angiogram	

A number of observational studies have found a substantial decrease in the graft thrombosis after implementing a surveillance program (12–16). Based on these data the KDOQI vascular access guidelines have emphasized that hemodialysis units should implement graft surveillance programs and refer patients with suspected graft stenosis for preemptive angioplasty (1). Although there is a paucity of randomized control studies to evaluate hemodialysis access surveillance, the existing controlled trials have raised serious doubts regarding the validity of this approach (17 –25). Serious concerns are expressed regarding surveillance and national debates are beginning to express the futility of this approach. A careful analysis, however, of the available randomized trials points out significant limitations of these studies. Table 2 provides a summary of these trials (11). A brief synopsis of these studies is provided below.

Table 2. Randomized clinical trials comparing surveillance to monitoring					
Study	Number of patients	Surveillance method	Type of access	Primary outcome	Surveillance (Beneficial or not beneficial)
Sands et al 1999 (23)	103	• Access flow • Static venous pressure	68 AVF 35 AVG	AV access thrombosis	Beneficial
Moist et al 2003 (19)	112	• Access flow • Dynamic venous pressure	AVG	AV access thrombosis or loss	Not beneficial
Ram et al 2003 (17)	101	• Access flow • stenosis	AVG	AV access thrombosis or access survival	Not beneficial
Polkinghorne et al 2006 (24)	137	• Access flow	AVF	Significant stenosis	Not beneficial
Mayer et al 1993 (25)	70	• Duplex Scan (Ultrasound)	AVG	AVG Survival	Beneficial
Malik et al 2005 (21)	192	• Duplex Scan (Ultrasound)	AVG	AVG Patency	Beneficial
Robbin et al 2006 (18)	126	• Duplex Scan (Ultrasound)	AVG	AVG Survival	Not beneficial
Tessitore et al. 2004	79	• Access flow	AVF	Thrombosis	Beneficial

Study Design

Randomized, Prospective Clinical Trial. Patients, PI, funder (Transonic) and statistician blinded (this will be implemented in Velos). Intervention and standard of care are different and cannot be blinded from attending nurses or clinic personnel. If a patient needs to switch schedules, they need to switch to shift that matches their protocol. Otherwise, they will need to switch protocols. No Transonic (funding) personnel will be involved in study design, protocol, analysis, or publication.

Randomization:

Patient is consented, baseline assessment taken, and evaluated for inclusion before randomization (baseline data will be included in analysis to determine representativeness of study patients to clinic patients). Randomization will occur after enrollment period ends.

The intervention and control protocols are significantly different that individual patients in the same dialysis session would be able to identify which arm they are in. Therefore, blocks of patients will be randomized according to dialysis schedule within each clinic.

Because the staffing is similar across shifts, we will do block randomization where all patients in a shift are assigned to the same protocol at each clinic site. For each clinic, the blocks will be given a number based on chronological order (Monday 1st shift = 1, Monday 2nd shift = 2 +, Monday 3rd shift = 3, Tuesday 1st shift = 4, Tuesday 2nd shift = 5, Tuesday 3rd shift = 6). For each clinic site, a coin will be flipped in front of two witnesses: heads = first group treatment; tails = first group control. Then a die will be rolled. The number that is rolled will the first group assigned (based on coin toss). The remaining groups will be allocated in sequence. For instance, if the coin lands on heads and the die lands on 3, Monday 3rd shift is intervention, Tuesday 1st shift is control, Tuesday 2nd shift is intervention, Tuesday 3rd shift if control, Monday 1st shift is intervention and Monday 2nd shift is control. If a patient has to switch dialysis schedules, care must be taken to place them in the same arm.

Inclusion and Exclusion Criteria

Inclusion criteria:

Chronic hemodialysis patients undergoing dialysis therapy via an upper extremity arteriovenous access (arteriovenous fistula or an arteriovenous graft) will be enrolled to have monthly surveillance flow measurement using Transonic system or physical examination of the arteriovenous access by qualified person at least once a month for a period of 2 years.

Exclusion criteria:

- Patients requiring surgical intervention on the arteriovenous access.
- History of access thrombosis (one or more access thrombosis of the current AV access).
- Patients with signs of access infection.
- Patients with a malignancy.
- Patients with life expectancy of less than six months.
- Unable to understand the study.
- Unable to sign the consent form.
- Patients with psychiatric disorder.
- Age less than 18 or greater than 80 years.
- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

Procedures Involved

Chronic hemodialysis patients receiving treatment with an upper extremity arteriovenous access will be enrolled in this 2 year study. End of study starts as last patient from 450 completes follow-up. Patients would be randomly assigned into surveillance or the control group. Randomization will take a cluster pattern per shift. (shift randomization).

Surveillance group

a. Surveillance group would receive monthly blood flow surveillance by ultrasound dilution technique (using the Transonic system) plus standard care (see below). Patients would be referred for an intervention based on the current KDOQI recommendations i.e. access flow of less than 600 ml/minute for arteriovenous grafts and less than 500 ml/minute for patients with arteriovenous fistulas or if the access flow is 1000 ml/minute that has decreased by more than 25% over 4 months (1). In addition to the detection of access dysfunction, the time interval between the detection of access dysfunction by the Transonic system and the intervention will also be recorded.

b. Patients will be referred for an intervention if clinical indication is met. Clinical indications include prolonged bleeding for more than 30 minutes (cannot be explained by medication), upper extremity edema, difficult cannulation, aspiration of clots during cannulation, aneurysmal formation. Access pressure that prevents normal HD machine operation (such as high venous pressure [>250 mm Hg] on three or more consecutive dialysis treatments, negative arterial pressure [<-250mm hg] on three or more consecutive dialysis treatments). Any Kt/V that cannot be explained by other factors and high recirculation rate of more than 10% would be checked by Transonic Recirculation/flow test prior to referral (rear event).

Control group

Control group will receive standard monitoring (standard care). Standard monitoring is physical examination by a qualified individual (nurse) at each dialysis encounter. Patients will be referred for an intervention if clinical indication is met. Clinical indications include prolonged bleeding for more than 30 minutes, low Kt/v that cannot be explained by other factors, high venous pressure (>250 mm hg) on three or more consecutive dialysis treatments, negative arterial pressure (<-250mm hg) on three or more consecutive dialysis treatments, upper extremity edema, difficulty cannulation, aspiration of clots during cannulation, aneurysmal formation and high recirculation of more than 10%.

Enrollment period

Enrollment period is expected to be 3-6 months.

Transonic measurement protocol:

Access recirculation, access flow would be determined using the ultrasound dilution technique (Transonic system).

1. Within 90 min of the beginning of HD session HD03 sensors are clamped HD tubing lines
2. Recirculation, access flow will be performed according to HD03 Manual.
3. Post intervention evaluation is as per each arm follow up unless other follow up deemed necessary by the interventionalist.

Data Management

Primary Hypothesis:

H_O: Patients screened monthly with Transonic Ultrasound Dilution Technique (UDT) and followed up with proactive intervention (if clinically indicated) will not have a rate of access thrombosis that is different than patients receiving physical examination and reactive intervention (if clinically indicated).

Secondary Hypotheses:

H_{O-1}: Patients screened monthly with UDT and followed up with proactive intervention (if clinically indicated) will not have a time to thrombosis that is different than patients receiving physical examination and reactive intervention (if clinically indicated)

H_{O-2}: Patients screened monthly with UDT and followed up with proactive intervention (if clinically indicated) will not have a number of angioplasty procedures that is different than patients receiving physical examination and reactive intervention (if clinically indicated)

H_{O-3}: Patients screened monthly with UDT and followed up with proactive intervention (if clinically indicated) will not have a number of thrombectomy procedures that is different than patients receiving physical examination and reactive intervention (if clinically indicated)

H_{O-4}: Patients screened monthly with UDT and followed up with proactive intervention (if clinically indicated) will not have a rate of tunneled dialysis catheter (TDC) that is different than patients receiving physical examination and reactive intervention (if clinically indicated)

H_{O-5}: Patients screened monthly with UDT and followed up with proactive intervention (if clinically indicated) will not have a rate of non-tunneled dialysis catheter (non-TDC) that is different than patients receiving physical examination and reactive intervention (if clinically indicated)

Sample Size:

$\alpha = 0.05$, $\beta = 0.80$, 2-sided (testing benefit and harm)

Main predictor: Treatment or control; Main outcome: Thrombosis or no—two-sided therefore chi-square for proportions of dichotomous variables was used for sample size calculations.

Treatment versus control estimates of thrombosis (based on Tessitore 2004; Scaffaro 2009, Moist 2003, Robbin 2006, Sands 1999, Ram 2003, Tessitore 2008): 34% in control; 24% in treatment (effect size 30%); 342 per group; loss to f/u (move, transplant, different clinic) 5% = 1/(1-.5)=1.05=359 (low estimate); loss to mortality 10% a year = 1.11 2x (per Dr. Salman) = 443

Variables to be collected at baseline:

age, sex, race (white, black, Asian/Pacific Islander, American Indian/Alaskan Native), ethnicity (Hispanic or not), insurance type (private, Medicaid, Medicare,

Veterans/Military, uninsured), length of time in dialysis (weeks); diabetic (y/d), CAD, PVD, HTN, how long access has been in place (weeks), location (Right/Left, arm/forearm), type of access (AVF or AVG), other clinical variables, button hole, history previous access (Y/N), history of previous catheter (Y/N), length of catheter placement/use (Days)

Variables to be collected monthly:
Monthly questionnaire.

Statistical Analysis:

- **Step 1:** Descriptive analysis to assess similarity of patients between trial arms and to assess representativeness of study participants to hemodialysis patients (generalizability).
- **Step 2:** Descriptive analysis for primary outcome (chi-square) and secondary outcomes (t-test or non-parametric equivalent)
- **Step 3:** Kaplan-Meier Survival Curve (unadjusted)
- **Step 4:** Survival Time Analysis Cox proportional hazards model (adjusted)
- **Step 5:** Multilevel regression with random effects in a mixed regression model to adjust for potential group-level RN, center, city effects. Primary analysis is a dichotomous variable (y/n). Secondary analysis outcomes continuous but may be treated as categorical variables

Covariates for evaluation in the models: individual-level predictors: age, race, sex, insurance, length of time in dialysis (weeks), diabetes (y/n), CVD (y/n), how long access has been in place (weeks), access location, type of access, location of access , length of time in study before thrombosis or mortality (weeks); other significant clinical variables group-level predictors: RN, dialysis center, city

Cross-overs: intervention participants who do not get clinically indicated treatment will be analyzed in two ways--included in treatment arm (intention-to-treat) and excluded (per protocol)

Statistical monitoring: analysis will be conducted 6 months; 12 months; 18 months; and 24 months. If a clear benefit is identified early or if the intervention is unexpectedly harmful, the study will be stopped early.

Risks to Subjects

Risk from Ultrasound Dilution Technique: UDT is a non-invasive procedure that generates no risk to patients undergoing hemodialysis. We do not anticipate any problems as a result of patients undergoing this procedure.

Risk to Privacy: There may be breach of confidentiality regarding protected health information. To minimize the potential risk to privacy all data are de-identified with use of study specific ID numbers only. To ensure that participants' confidentiality is

maintained each participant will be assigned a unique study identification number and will be tracked through the study by this number. Only the PI and authorized study personnel will maintain the code linking study identification numbers to specific participants. When data generated from any study is shared, only de-identified information will be exchanged. No protected health information will be sent to any collaborators or be used in any publications of the findings.

Potential Benefits to Subjects

No direct benefit can be promised to subjects from participation in this research study.

Setting

Study subjects will be recruited at four dialysis centers. They count with the study populations that will make the research possible. These centers also possess the resources necessary to carry out study procedures safely and effectively. The centers are as follows:

1. Dialysis Clinic Inc.

   176 Washington Avenue Extension,

   Albany, NY 12203
2. DCI Rubin Troy

   1850 Peoples Ave,

   Troy NY 12180
3. DCI Rubin Clifton Park

   21b the Crossings Blvd,

   Clifton Park, NY 12065
4. DCI Rubin Saratoga Springs

   59c Myrtle St,

   Saratoga Springs, NY 12866

Resources Available

- **Loay Salman, MD MBA:**
  I am an American Board of Internal Medicine (ABIM) certified in Internal Medicine and Nephrology. I am specialist in Hypertension. I am also certified by the American Society of Diagnostic and Interventional Nephrology (ASDIN) to do interventional Nephrology procedures. I am currently Chief: Division of Nephrology and Hypertension and The Thomas Ordway Distinguished Professor of Medicine at the Albany Medical College. I have been practicing Interventional Nephrology for seven years. I have published around forty articles mostly in the field of hemodialysis vascular access. I had established a basic research track at the University of Miami with focus on vascular access prior to my current

position. In my previous position I created a very well organized data base for this research. University of Miami vascular lab was rewarded with RO1 grant from the National Institute of Health (NIH). As a principal Investigator I will bring my knowledge and expertise on vascular access to the research team at Albany Medical College.

- **Shari Meola (Senior Manager, Research Support)**
  Shari Meola brings over 20 years' experience to the current study. She has the experience and skills to ensure timely completion of all the project milestones, organize communications among investigators, ensure regulatory and IRB compliance, overs study and effectively multi-task the various administrative duties associated with large complex studies. She also contributes to manuscripts for publication and data presentations at scientific meetings.
- **Nicolle Bateman RN (AMC Study Coordinator and Dialysis Center staff)**
  Nicolle Bateman has over 16 years' experience in dialysis access and hemodialysis therapy. She is CITI certified and is highly skilled at recruiting, enrolling and retaining participant's in previous studies. She has demonstrated that she can efficiently and effectively coordinate the flow of participants during their study visits to the CRC, reinforce compliance with study interventions, collect and retain data in a well-organized manner, and maintain updated regulatory documentation and case report forms.

Recruitment Methods

Study staff will identify potential subjects from dialysis centers mentioned above. Subjects will be approached for a brief conversation to establish if there is interest in hearing about the study. If the patient is interested, the study coordinator will then present a detailed explanation of the study.

Subjects who meet all of the inclusion criteria ascertained at the screening visit will be enrolled in the study. In order to reach the goal of 450 subjects who complete the protocol, we will screen up to 900 subjects with CKD, allowing for a screening to enrollment ratio of 2:1. Once the target enrollment is complete we will discontinue screening irrespective of whether we have yet to reach 900 subjects.

Study team members who approach patients at centers will be very careful of explaining to potential subjects that research participation is completely voluntary and that their decision whether to participate or not, will have no impact in their medical care. Also, participants will receive a full explanation of the extent of their participation in the study prior to signing the informed consent form.

Number of Subjects
450 Patients.

Confidentiality
Patients' identifying information will be stored in a password-protected, firewall enabled database, only available to approved study staff. The database will be kept for the duration of the study.

All subjects will be assigned a unique study number, and a Master Key spreadsheet linking the subject's name and medical record number to the study number will be kept by the principal investigator in a password-protected and firewall enabled file. Only personnel specifically involved in the conduct of the study, including the PI and research coordinators, will have access to the spreadsheet linking the unique study number to identifiable patient information. All data and questionnaires obtained from subjects will be labeled with their unique study numbers, and only study personnel will have access to the database than can link data with subject identifiable information. All hard copies of data such as questionnaires will include only the subject's unique study number to protect subject privacy and will be stored by the research coordinator in locked offices at the Dialysis Clinic Inc. located at 176 Washington Avenue Extension, Albany, NY 12203 while the study is active. Only the research coordinator will have access to the records. The offices are monitored by security personnel and require electronic keys to be accessed. Once the study is completed all study documents will be archived by the PI at Albany Medical College.

Study personnel will receive training to secure understanding of the importance of protecting subject privacy and the appropriate handling of subject protected health information. At a minimum, this will include all mandatory training required by the Albany Medical College and the Subjects Human Research Office.

Provisions to Protect the Privacy Interests of Subjects
As was mentioned before, study team members who approach patients at centers will be very careful of explaining to potential subjects that research participation is completely voluntary and that their decision whether to participate or not, will have no impact in their medical care. Also, participants will receive a full explanation of the extent of their participation in the study prior to signing the informed consent form. They will be explained that if they want to stop participation at any time, they may do so without any consequences.

Patients will be given ample opportunity to voice any particular limitations or objections they have to participation previous to signing the informed consent form and their requests will be taken into consideration at the moment of decision to include them in the study.

Consent Process

Written, informed consent to participate in the study will be obtained by a qualified, authorized member of the study team as determined by the IRB and the Principal Investigator; a process that will take place prior to carrying out any study procedures.