The Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke

(VERiTAS) Study

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1.1 STUDY SUMMARY

Objective
The primary objective of this study is to determine if patients with symptomatic vertebrobasilar stenosis or occlusion with compromised intracranial blood flow as demonstrated by magnetic resonance (MR) imaging are at increased risk for recurrent stroke compared to patients with normal blood flow.

Study Design
This is a multicenter prospective observational study.

Study Population
Patients with symptomatic vertebrobasilar stenosis (≥ 50%) or occlusion.

Study Evaluations
Noninvasive magnetic resonance (MR) imaging consisting of quantitative magnetic resonance angiography (QMRA) and MR perfusion imaging to assess intracranial blood flow.

Number of Participants
80

Number of Clinical Sites
6

Primary Endpoint
- Fatal and nonfatal ischemic stroke in the vertebrobasilar territory within 12 months.

1/21/15 Footnote: *the definition used by the adjudication committee per Dr. Kasner is, "Ischemic stroke is defined as new neurological symptoms or signs lasting at least 24 hours or lasting less than 24 hours but associated with new infarct on CT or MRI".*

Secondary Endpoints
- TIA and fatal and nonfatal ischemic stroke in the vertebrobasilar territory.
- Ischemic stroke in any vascular territory.
- All ischemic stroke and vascular death.
- Aggregate of any ischemic stroke, myocardial infarction and vascular death.
- All stroke (ischemic and hemorrhagic).
- All death (vascular and nonvascular).
- Neurological impairment by NIH Stroke Scale (NIHSS).
- Neurological disability by modified Barthel Index (BI).
- Handicap by modified Rankin Scale (MRS) and modified Glasgow Outcome Score (GOS).

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1.2 OBJECTIVES

Primary Objective:

- To test the hypothesis that among patients with symptomatic vertebrobasilar disease (VBD), those with distal blood flow compromise are at higher risk of subsequent posterior circulation stroke than those with normal flow.

Secondary Objectives:

- To determine the correlation between large vessel flow (QMRA) and tissue level perfusion (MR perfusion) in the posterior circulation, and the predictive value of each modality.
- To determine other predictive factors for stroke in this population.
- To determine the hemodynamic effects of varying degrees of vertebrobasilar stenosis and occlusion.
- To determine changes in hemodynamic status of patients on medical therapy over time.
- To determine the utility of QMRA as a non-invasive screening and monitoring tool in symptomatic vertebrobasilar disease (VBD).

1.3 BACKGROUND AND RATIONALE

Approximately 700,000 strokes occur annually in the U.S. making it the third leading cause of death and the leading cause of permanent disability among adults. Posterior circulation strokes account for 30-40% of all ischemic strokes, resulting in approximately 200,000 cases per year. Atherosclerotic disease of the vertebrobasilar system is an important etiology of posterior circulation stroke[1]. **Symptomatic vertebrobasilar disease (VBD)** carries a high annual risk of stroke, averaging 10-15% per year despite medical therapy. Vertebrobasilar stroke is particularly prone to resulting in devastating consequences due to the concentrated 'eloquence' of brain tissue supplied by the posterior circulation [2]. Consequently, vertebrobasilar stroke can result in high rates of death and disability.

Risks of stroke in VBD

Several retrospective studies have estimated the risk associated with vertebrobasilar stenosis (50-99%) to be **10-15% per year** [3-5]. These stroke rates approach those seen with symptomatic high grade extracranial carotid stenosis. In a retrospective study of 44 patients with distal vertebral artery (VA) or basilar artery (BA) stenosis of ≥50%, Mouffarij et al. reported a 27% incidence of vertebrobasilar ischemic events, with 5 of 12 events being stroke rather than TIA[3]. An overall 80% stroke free survival at 2 years was evident in this study. A study by Qureshi et al. of 102 patients with symptomatic VBD (>50% stenosis) demonstrated that 14% of patients experienced recurrent stroke, with a stroke free survival of only 72% at two years[5]. Retrospective analysis from the WASID study group[6] examined the risk of stroke in 68 patients with symptomatic intracranial vertebrobasilar 50-99% stenosis treated with aspirin or warfarin over a median follow-up of 13.8 months. Fifteen (22%) of the patients suffered stroke, of which four (27%) were fatal. They reported an overall stroke risk of 13.6 to 15 per 100 patient years for vertebral and basilar artery stenosis respectively, and 7.8 to10.7 per 100 patient years for stroke in the territory of the stenotic artery[4]. Data from the prospective WASID trial comparing use of warfarin versus aspirin in symptomatic intracranial stenosis of 50-99% in 569 patients demonstrated that 15% of patients suffered stroke in the territory of the stenotic artery[7]. The

incidence of stroke at one year was 12%, with stroke rates that were not significantly different between the anterior and posterior circulation[8]. In another recent prospective study of patients with intracranial stenosis ≥ 50%, ischemic events were reported for the 49 patients of the full cohort of 102 patients who harbored symptomatic vertebral or basilar disease. The frequency of recurrent ischemic events (TIA and stroke combined) was found to be 42.8% during a mean follow-up of 23.4 months[9].

The predominant stroke mechanism for patients with VBD appears to be regional hypoperfusion[10]; although thrombotically active plaques are a prominent feature of symptomatic carotid disease, this mechanism appears less prominent as the primary cause of ischemia related to vertebrobasilar stenosis. The posterior circulation vascular anatomy can allow for potential compensations to maintain distal arterial territory flow through collaterals (such as the posterior communicating arteries) in the setting of proximal vessel stenosis or occlusion. The existence and extent of these compensatory blood flow pathways, therefore, may influence the risk of stroke.

Rationale for use of QMRA and MR Perfusion

Various imaging techniques exist for assessing cerebrovascular hemodynamic compromise, including SPECT, PET, Xenon CT and TCD. These modalities are generally aimed at assessing cerebral tissue perfusion, and have proven valuable in assessment of anterior circulation flow compromise. However, these modalities have been less useful in the posterior circulation due to factors such as inadequate spatial resolution for the compact brain territory involved, and bony skull base artifacts. An alternative strategy is therefore desirable. Measurement of large vessel flow in affected and major collateral vessels in the posterior circulation is one such strategy, and can be obtained non-invasively using phase contrast QMRA[11-14]. QMRA imaging can be easily combined with MR perfusion imaging to provide both large vessel and tissue level hemodynamic assessment.

The technique of phase contrast QMRA allows volumetric flow to be measured directly and noninvasively in the craniocervical vasculature, and has been shown to be accurate in both the in vitro and in vivo setting[15-19]. Standardized QMRA software is available as NOVA (Noninvasive Optimal Vessel Analysis), and has been used extensively to assess patients with cerebrovascular disease at the central coordinating site, University of Illinois at Chicago (UIC). A retrospective non-blinded cohort study examining outcomes of patients with symptomatic VBD demonstrated a significantly higher risk of subsequent stroke in patients with hemodynamic impairment as assessed by NOVA QMRA. Furthermore, QMRA may provide an appropriate non-invasive screening and follow-up monitoring tool in patients with known or suspected VBD.

Unlike QMRA which provides information regarding volumetric flow within a given vessel, MR perfusion imaging provides characterization of tissue level perfusion in the brain territory of interest[20]. MR perfusion imaging is readily available on most clinical scanners, and can provide information regarding tissue level hemodynamic compromise. Therefore, tissue perfusion measurements may provide important correlative and predictive data for the conductance flow data from the large vessels obtained using phase contrast QMRA.

Rationale for the VERiTAS study

VBD represents a potentially treatable high risk source of stroke. Advances in endovascular angioplasty and stenting have created new options for the treatment of VBD, but the interventions themselves carry significant risks[21, 22], and the selection criteria for appropriate candidates remains uncertain. Our preliminary published retrospective data[23] suggests that the

risk of stroke in VBD is affected by the extent to which intracranial blood flow is compromised. Specifically, our analysis has indicated that patients with low intracranial flow as assessed by noninvasive QMRA are at significantly higher risk of stroke than those with normal flow. The objective is now to conduct a prospective longitudinal study of patients with symptomatic VBD to determine if level of blood flow compromise assessed by QMRA and MR perfusion at the baseline examination predicts risk of recurrent ischemic events.

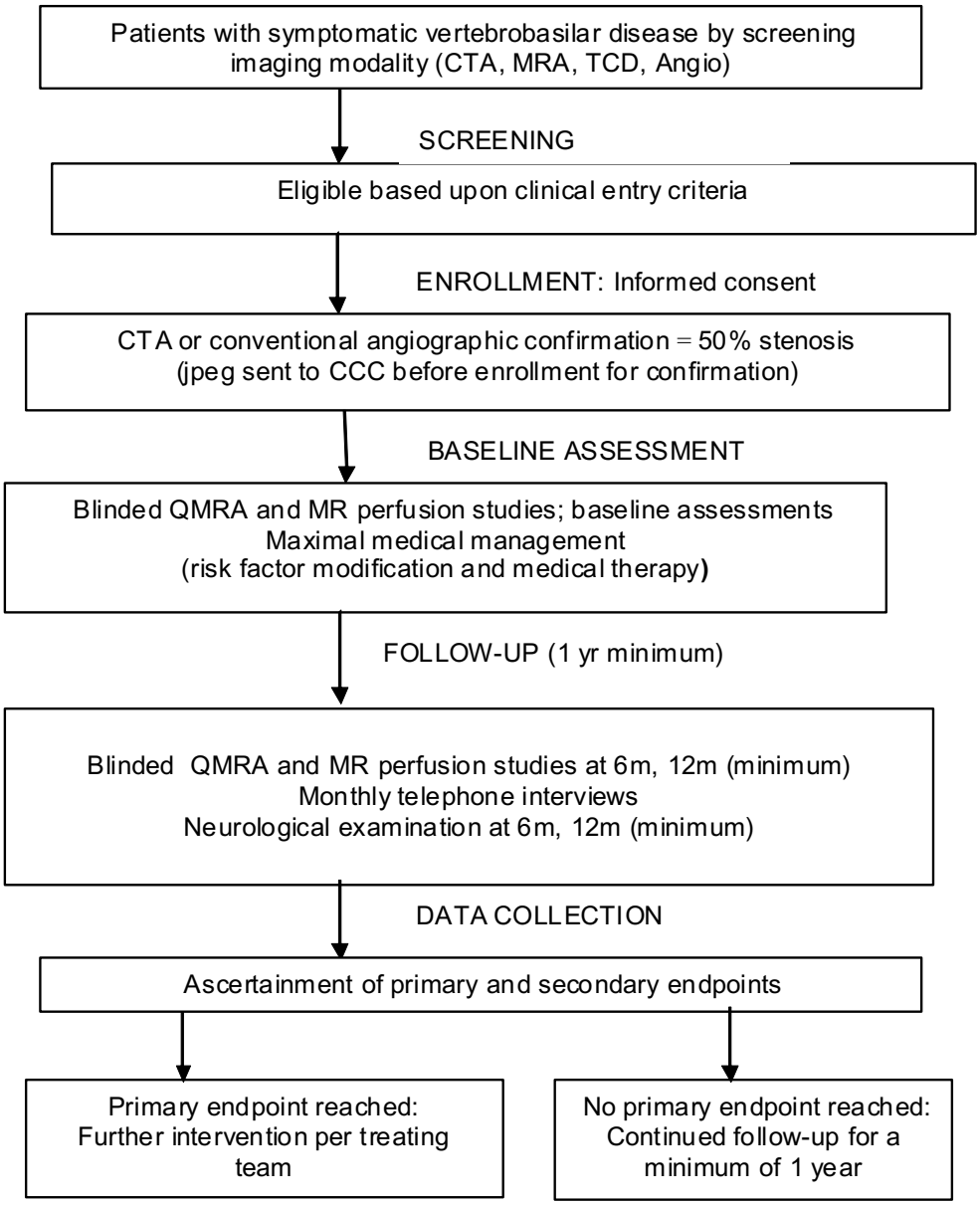
1.4 STUDY DESIGN

The study is a multi-center prospective cohort study. Eligible patients will undergo, in addition to standard assessments, a QMRA imaging study and MR perfusion study to assess their cerebrovascular hemodynamic status, the results of which will be interpreted centrally and kept blinded from the clinicians caring for the patient.

The patients will be prospectively followed for a minimum of one year, and a maximum of two years, on current standard medical regimen to include standard stroke/cardiovascular risk factor modification and medical therapy, and evaluated for recurrent ischemic events.

We anticipate enrollment of a minimum of four patients per year per site over four years with a minimum of one-year of follow-up.

1.5 STUDY SCHEMA



1.6 ELIGIBILITY CRITERIA

Inclusion Criteria:

- Symptomatic patients (TIA or stroke) in the vertebrobasilar territory.
- Conventional angiography or CT angiography (CTA) demonstration of ≥ 50% stenosis or occlusion of extracranial or intracranial vertebrobasilar artery.
    - jpeg sent to CCC for confirmation prior to enrollment.
- Symptoms within 60 days of enrollment.
- Age 18 and above.
- Able to provide informed consent.

Exclusion Criteria:

1. Neurologic criteria:
    - Major disabling stroke prohibiting the ability to return for follow-up assessment.
    - Any neurological disease which would confound follow-up assessment.
2. Medical criteria:
    - Any severe co-morbidity condition with less than 12 month life expectancy.
    - Known cardiac disease associated with cardioembolic risk specifically atrial fibrillation, prosthetic valves, endocarditis, left atrial/ventricular thrombus, cardiomyopathy with EF<25%, cardiac myxoma.
    - Blood dyscrasias, specifically polycythemia vera, essential thrombocytosis, sickle cell disease.
3. Disease criteria:
    - Non-atherosclerotic disease vertebrobasilar disease including dissection, fibromuscular dysplasia, vasculitis, radiation induced vasculopathy.
    - Unilateral vertebral stenosis or occlusion
4. Patient criteria:
    - Unable or unwilling to undergo MRI.
    - Unable to undergo conventional angiography or CT angiography (CTA).
    - Pregnancy.
    - Concurrent participation in an interventional trial for treatment of vertebrobasilar disease.

Renal dysfunction will be exclusionary if it precludes angiography. Renal dysfunction will not be exclusionary if it precludes gadolinium administration as such patients may be enrolled but will not undergo the MR perfusion portion of the study imaging protocol, and thus, will not receive gadolinium. No subjects will be excluded based upon gender, race, ethnic group, religion or socioeconomic status. Children will not be recruited, as atherosclerotic VBD is a condition that affects adults primarily in later life and is not a disease that occurs or is relevant in children.

1.7 PATIENT RECRUITMENT AND ENROLLMENT

Patients presenting with vertebrobasilar distribution TIA or stroke are the source group of patients. Diagnostic evaluation of these patients will be performed at the discretion of the treating physicians at the participating center, but commonly includes one or more of several imaging modalities: magnetic resonance angiography (MRA), computed tomographic angiography (CTA), transcranial Doppler (TCD), or conventional angiography. Those patients who demonstrate evidence of ≥ 50% vertebrobasilar stenosis by any of these diagnostic

imaging are potentially eligible for the study, and will be reported to the study site coordinator or any key research personnel who will assist in consenting. Patients will be identified through the Neurosurgery, Neuroendovascular and Neurology services at the participating centers. No study procedures will take place prior to subject consenting.
At sites where conventional angiography or CTA is not standard of care, subjects will be asked to undergo the informed consent process and sign the consent form prior to determination of final eligibility (the consent form will include consent for angiography to determine final eligibility). Subjects who meet angiographic inclusion criteria will continue with the study procedures; subjects who do not meet angiographic criteria will be withdrawn from the study. This will be outlined in the consent form. At sites where conventional angiography or CTA is routine, subjects will be consented based on presence of inclusive angiographic criteria. Patients with angiographically confirmed $\geq$ 50% vertebrobasilar stenosis who meet the clinical entry criteria and sign the consent form will be enrolled.

Enrollment
Eligible patients who agree to participate in the study will sign written informed consent documents, and will be considered enrolled into the study. As part of the process of informed consent the patient will be told the purpose of the study, and that the study entails undergoing MR scans, and clinical follow-up to assess for occurrence of stroke and TIA. Consent will be documented by signing a consent form approved by the participating site Institutional Review Board (IRB). At the time of the enrollment, patients will fall into two categories:
1. Patients who have undergone or are scheduled to undergo conventional catheter angiography or CTA performed as part of standard work-up.
2. Patients for whom conventional catheter angiography or CTA is not considered to be part of the standard work-up: the participant is informed of the protocol requirement for catheter angiography or CTA at the time of informed consent, and single or bilateral vertebral vessel injection conventional angiography, or head and neck CTA, will be performed as part of the study. Any patients not meeting the angiographic criteria of ≥ 50% vertebrobasilar stenosis will not continue as participants in the study and will not undergo the study procedures described below.

1.8 STUDY PROCEDURES

Baseline Evaluations
Clinical Evaluation:
Following enrollment and confirmation of angiographic stenosis ≥ 50%, baseline assessments by the participating study coordinator and study physician are performed. This will consist of a thorough clinical and neurological evaluation including review of recent hospital records, and imaging studies. Clinical information including the nature and frequency of cerebral ischemic events will be gathered. Medications at the time of enrollment will be recorded. Data regarding standard stroke risk factors will be specifically recorded including the following baseline history: age, gender, race, hypertension, diabetes mellitus, lipid disorder, coronary disease, smoking, alcohol consumption, and parental death from stroke. A neurological evaluation will be performed. The NIHSS will be recorded and functional status will be measured using the Barthel Index, modified Rankin Scales and modified Glasgow Outcome Score. The data will be recorded on web-based standardized case report forms.

MR imaging:
An MR imaging protocol consisting of QMRA and MR perfusion will be performed at time of enrollment. The study is performed based upon a pre-specified protocol utilizing standardized

NOVA software. The NOVA portions of the study will be transferred via secure internet based transfer to the clinical coordinating site at UIC for central review by a certified NOVA interpreter. The MR perfusion portion of the study will be sent via sFTP transfer or CD to the clinical coordinating center at UIC for central review by a specified neuroradiologist. The results of the study will remain blinded to the patient and participating site personnel including the evaluating study physician.

The imaging protocol will be performed with the use of NOVA software installed on Siemens, G.E. or Phillips 3.0 Tesla MR scanners. The protocol will involve an approximately 60 minute MR scan consisting of initial time of flight (TOF) imaging of the cranial and cervical vasculature to include 15 vessels. A 3-D image of the vessels will be created, based upon which sites for blood flow measurement will be marked. Phase contrast MRA imaging will then be performed in the plane perpendicular to the identified sites to obtain blood flow measurement at those sites. MR perfusion will be performed using the dynamic susceptibility contrast (DSC) technique.

Standard management

Risk factor modifications

Patients will be placed on a standard medical regimen to include antithrombotic agents and standard stroke/cardiovascular risk factor medical therapy as managed by the participating center study physician in conjunction with the patient's primary care physician.

Follow-up evaluations

Monthly telephone follow-up assessment

The participating site study coordinator will contact patients monthly by telephone until 12 months for determination of new events. If a potential endpoint is identified treating physician will be notified, and the participating site arranges for the patient to be evaluated by the blinded study physician within 72 hours. If a stroke is clinically suspected, brain imaging with CT or MR will be performed in accordance with standard clinical management. The data from the telephone interviews will be recorded using standardized web-based case report forms.

Clinical visit follow-up assessment

In person follow-up will be performed at the participating site at 6 months (m), and 12m as a minimum, and every 6m thereafter up until completion of the study or 2 years maximum. A detailed neurological evaluation and assessment for new symptoms or signs will be performed at these visits. Interval occurrence of any symptoms of cerebrovascular disease or other medical problems will be determined. Clinical evaluations will be performed by the blinded study physician unfamiliar with the results of the study MR imaging. The patient's medication regimen and NIHSS Score will be recorded. The data will be recorded using standardized web based data forms.

MR imaging follow-up assessment

The MR imaging protocol will be repeated at 6m and 12m, at a minimum, and at 24 months if prior to the completion of the study. Results will be centrally reviewed and the results will remain blinded from the participating center.

Time course of assessments and follow-ups

MONTHS	0	1*	2*	3*	4*	5*	6*	7*	8*	9*	10*	11*	12*	18	24
Demographics	x														
Baseline Evaluation	x														
Angiogram/CTA	x														
MR imaging	x						x						x		x
Telephone interview		x	x	x	x	x	x	x	x	x	x	x	x		
Clinical Follow-up Evaluation	x						x						x	x	x
NIHSS, BI, MRS, GOS	x						x						x	x	x

**Minimum follow-up for all recruited patients (12m). Maximum is 24m.*

1.9 STUDY ENDPOINTS

Primary endpoint:

- Stroke (fatal and nonfatal ischemic stroke) in the vertebrobasilar territory at 12 months.

Secondary endpoints:

- TIA and fatal and nonfatal ischemic stroke in the vertebrobasilar territory.
- Ischemic stroke in any vascular territory.
- All ischemic stroke and vascular death.
- The aggregate of ischemic stroke, myocardial infarction and vascular death.
- All stroke (ischemic and hemorrhagic).
- All death (vascular and nonvascular).
- Neurological impairment as determined by the NIH Stroke Scale.
- Neurological disability as determined by the modified Barthel Index.
- Handicap as determined by the modified Rankin Scale and Glasgow Outcome Score.

Ischemic stroke is defined as new neurological symptoms or signs lasting at least 24 hours or lasting less than 24 hours but associated with new infarct on CT or MRI. TIA is defined as new neurological symptoms or signs lasting less than 24 hours without radiographic correlate of infarct. Vascular death is defined as a death of known vascular etiology or sudden death that could not be explained by a known nonvascular process.
Initial determination of endpoints will be defined by the participating site study physician but will be ultimately be independently determined by a central adjudication committee.

1.10 DATA ANALYSIS

A dedicated Biostatistician and Director of the Data Management Center for the Center for Stroke Research at the UIC Department of Neurology and Rehabilitation, UIC will oversee all statistical analysis of the study.

Analysis
Analysis of the primary endpoint (ischemic stroke in the vertebrobasilar territory) will consist of time-to-endpoint comparison using the log-rank test between patients designated as ‘low flow’ versus ‘normal flow’. The designation of flow status will be based upon the patient’s initial enrollment QMRA study, using parameters defined in the preliminary studies. Adjusted analysis will be performed using multivariate logistic and proportional hazard regression models to examine stroke incidence adjusted for key confounders. Post-hoc sensitivity analysis will be

performed to examine alternative cut-points for designation of low or normal flow status, and to examine the predictive value of each MR imaging modalities (QMRA and MR perfusion) and whether the combination of the two modalities provides a better indicator of stroke risk than either alone. Patients will be censored from analysis at the time of any crossovers to interventional procedures.

Sample size calculations

Sample size estimates are based upon stroke rates from published preliminary data[23], which indicate a 71% and 100% one year stroke free survival in the 'low flow' and 'normal flow' groups, respectively, translating into annual event rates of 0.29 and 0.0. Although our data indicated a 0 stroke rate in the 'normal' flow group, there was a 0.04 rate of TIA, which can occur on a clinical spectrum with stroke. As a result the sample size calculations were based on a conservative estimate of 0.02 event rate in the normal flow group. Sample sizes were calculated for a range of possible event rates in the low flow group from 0.18 to 0.28. A 10% attrition rate was included in the calculations. Based upon these estimates, a total sample size of 80 patients will achieve approximately 80% power in detecting a significant difference between the groups with an annual event rate of 0.22 in the low flow group. Exploration for risk factors and adjustment for covariates will be performed with Cox proportional hazards analysis.

1.11 RISKS

Potential Risks to Subjects:

For patients who would not have undergone conventional cerebral angiogram or CTA as part of their standard work-up, the risk of conventional cerebral angiography or CTA are introduced by participation in the study. In the current era, conventional cerebral angiography poses a minimal risk of adverse events, with stroke risk of <1% [24], and these risks will be included in the informed consent process. CTA, as an alternative to conventional angiography, also poses minimal risk of adverse events. As part of the study assessments, patients will be undergoing MR imaging including MR perfusion with gadolinium contrast. Patients with contraindication to undergoing MRI will be excluded from the study; patients with contraindication to administration of gadolinium will not undergo the MR perfusion portion of the imaging protocol, and will not receive gadolinium. Therefore the risks related to undergoing MRI are minimal. There is also a potential risk for loss of confidentiality of protected health information (PHI).

Conventional Angiogram:

The risks associated with angiography are discomfort and bruising in the groin where the catheter is inserted into the artery. The major risk of angiogram is stroke. Some strokes are minor and some can lead to death or permanent loss of the ability to see, speak, or move. The risk of stroke associated with angiogram is 1%. Other less serious risks include bleeding, or infection at site of insertion and allergic reaction or kidney damage from the contrast media utilized.

CTA:

The risks include slight risk of bruising or infection where IV is inserted for administration of contrast dye, and allergic reaction or kidney damage from the contrast dye utilized.

MRI:

Some subjects may experience claustrophobia as a result of being put into the MRI machine. Subjects who have history of claustrophobia will be informed of description of the procedure. MRI is also contraindicated for subjects with metal fragments in the body, pacemakers and

aneurysms clips. All subjects will be screened prior to procedure to ensure there are no contraindications.

Risks involved in contrast dye administration are the potential risks of allergic reaction to contrast dye, nausea, headache, hot flashes, heart palpitations, rash, hives, slight risk of infection where IV is inserted, discomfort at the injection site, difficulty breathing, and in extreme cases, death.

Protection Against Risks

Due to fact that the majority of the procedures to be performed are routinely employed standard procedures, the procedural risks will be controlled by performing all procedures according to standard of care guidelines. Protection against the loss of confidentiality will be controlled by the use of a secure web based data entry system that is CFR 21 compliant. Data forms will be coded to exclude any patient identifiers. A master list of subjects linking them to their study number will be kept in locked office of the research personnel in a locked cabinet. Subjects will be thoroughly screened to minimize risk of angiography and MRI.

Data and Safety Monitoring

This study does not include any specified intervention or incorporate any experimental treatment. Given there is no proposed intervention or proposed management beyond standard clinical care as defined by the physicians caring for the patient, a Data Safety and Monitoring Board is not indicated. The principal investigator will be responsible for monitoring any adverse events related to obtaining angiograms or MRA scans obtained primarily for the purposes of the study.

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