Research Protocol
Title: The CIS Trial
Principal Investigator: Firas Al-Ali, MD
Other Investigators: John J. Elias, PhD
Andrea Jenkins, RN
Cindy Cole, RN
Georges Markarian, MD
Institutional affiliations: Akron General Medical Center

I. BACKGROUND AND SIGNIFICANCE

A. Treatment for patients who suffer an ischemic stroke typically depends upon a fixed and arbitrary time window. Therapy typically includes intra-venous treatment (IVT) for patients who present within 4.5 hours of beginning of symptoms and intra-arterial treatment (IAT) for patients who arrive within 8 hours of symptomatic onset as the standard of care [1]. During IVT, tissue plasminogen activator (tPA) is injected into a vein in the arm. IAT is an endovascular procedure in which a catheter is inserted into an artery and directed to the site of the blocked blood vessel in the brain. The clot is removed using a mechanical device with or without an injection of tPA directly at the site of the clot. Several types of mechanical devices are approved for clinical use. Not all patients who arrive within this fixed time window receive IVT or IAT, since certain defined subgroups of patients do not improve despite complete revascularization (i.e. opening of the occluded blood vessel) within the accepted time window.

   Patients who should not be treated include those who demonstrate large areas of hypodensity (i.e. dark tissue) on head computerized tomography (CT) scan, those with an intracranial hemorrhage, and those with other stroke mimics such as herpetic encephalitis. [2,3] To further improve the criteria for determining which patients should receive therapy, a group of investigators developed the ASPECT Score, an imaging scale based on head CT. Patients with an ASPECT Score of < 6 will generally not improve with treatment.

B. To further improve patient selection (decrease the number of patients in whom successful revascularization is clinically futile) other noninvasive testing methods have been applied, including CT perfusion, magnetic resonance imaging (MRI) perfusion, and diffusion based images. [4-8] Despite the various forms of noninvasive testing, the good clinical outcome (GCO) rate consistently lags behind the rate of good revascularization, by at least 30-40%.

C. Despite applying the above selection criteria (time from onset of symptoms and findings on CT scan), the percentage of GCO has been consistently lacking behind the recanalization rates which has been steadily improving to up to 80-90%. It is clear that a significant proportion of good revascularizations are futile due to lack of clinical improvement [5-8, 9-12]

The investigators believe that focusing only on time and static noninvasive imaging for selecting patients suitable for IAT ignores critical physiological factors, i.e. differentiating blood-deprived yet viable brain tissue from nonviable tissue. The principal investigator has developed a system referred to as the Capillary Index Score (CIS) that helps differentiate between viable and nonviable tissue. The CIS is obtained during the diagnostic cerebral angiogram (DCA) performed as a necessary step at the time of treatment. The fact that the CIS is obtained just before proceeding with treatment differentiates it from all other currently employed neuroimaging-based patient selection strategies, which are sometime done an hour or more prior to proceeding with the treatment. Tissue in the ischemic area (tissue blocked from its usual primary blood supply), but fed through secondary vessels (pial collaterals) represents tissue that can recover if the clot can be removed. This secondary blood supply is shown by a blush surrounding the capillaries on the DCA. The investigators believe that collateral blood flow graded by this system is more accurate than time to treatment in determining the patients who should be given endovascular treatment. The CIS is a 4 point simple system (0-3). The ischemic territory is divided into 3 sections. If a section exhibits a capillary blush it is given one point. If the three sections of the ischemic territory have a capillary blush the final score is 3. If none exhibit capillary blush the score is zero. Based on the 1/3 hypodensity rule we considered the CIS to be poor (pCIS) if more than 1/3 of the ischemic territory has no capillary blush (CIS=0, 1). A score of 2 or 3 is considered a favorable CIS (fCIS). DCA (injecting the ischemic territory only) is a necessary step performed prior to clot removal. Certain operators inject only the occluded vessel instead of obtaining more complete imaging which assesses the anatomical and physiological status of collateral vessels. It is currently the usual practice of many neurointerventionalists to obtain a complete set of DCA films prior to treatment which assess collateral circulation. This may increase the time of the intervention by 2-5 minutes, which most neurointerventionalists believe carries an extremely low risk and does not affect outcome.

D. The investigators have retrospectively examined the CIS for patients previously treated with IAT for this type of stroke [13-15], initially via large case series analyses and subsequently by blinded application of the CIS to patients in three major prospective randomized placebo- controlled clinical trials. [9-11] The previous studies indicated that patients graded as having a fCIS, indicating good peripheral blood flow, typically have good clinical outcomes following successful revascularization. A good outcome is defined as a slight disability and able to carry out daily activities or better. Good outcome rates have been on the order of 70-90% for patients with a favorable CIS and good revascularization. This proportion of good outcomes far exceeds any published rate of good outcomes using all other peer- review published patient selection methodologies to date. For patients with a pCIS, the maximum rate of good outcomes has been 13% despite good and timely revascularization, which is actually well below the success rate of approximately 20% for patients who are left untreated, without even tPA [7]. These results raise the question if we are not only not helping the patients with pCIS but also actually harming them. Clinical trials focused on IAT have had mixed results, with some trials showing no benefits compared to IVT with tPA alone [5, 8], and more recent trials showing superiority of the IAT plus IVT over IVT alone [3,13-14,16]. The absolute rates

of good outcomes for these recent trials in the IAT arms have varied widely (52-71%). The investigators believe that a primary factor explaining differences between studies is the portion of people with favorable CIS included in the studies. Interestingly the ratio between the rate of good outcomes in the treatment arm vs. the control arm (no IAT) has been stable across the different positive trials showing the effect of IAT at approximately 1.7 for all of these recent trials, similar to the PROACT II trial more than 15 years ago. [3]. The investigators believe the stagnation of this ratio at 1.7 is evidence that the selection criteria have not improved despite improvement in the rate of revascularization. Based on the existing data, the investigators would like to evaluate the merit of CIS as a primary tool for patient selection in IAT, hoping to prove that the rate of treated to untreated improvement is on the order of 6 to 7. We expect that if we select for patients with fCIS and obtain good revascularization to obtain around 80% GCO in the treated arm. We also expect successful revascularization to be futile for patients with pCIS.

E. The principal investigator believes that the CIS for each patient is determined genetically. In order to explore the genetic link to the CIS, this trial also aims to perform SNP-trait association analysis to identify the genetic loci linked to CIS and stroke outcome in patients suffering from AIS. *Dce1* has recently been found to be responsible for approximately 85% of the variation in collateral extent and it is likely that polymorphisms of *Dce1* are a major determinant of the wide variation in collateral scores in humans. If it is shown that *Dce1* is correlated to CIS and both are predictive outcomes for EVT, then this will further increase confidence in CIS as an assessment of collateral status, strengthen patient stratification of patients to define course of treatment for best outcome and least risk, and suggest the use of genetic testing in clinical decision making.

II. STUDY OBJECTIVE(S); INCLUDING SPECIFIC AIMS AND/OR HYPOTHESES

The hypothesis, or idea being tested, is that as long as patients have a favorable CIS they can be successfully treated with IAT out to 24 hours. For patients with poor CIS, success rates will be relatively low, with no benefit provided by IAT. The long term objective is to:

a. Lengthen the time window of treatment for patients with fCIS from 6 hours to 24 hours. In doing so, we will offer useful treatment to patients who would otherwise be denied treatment under current standards.
b. Encourage focusing on achieving good revascularization rather than limiting time during IAT for patients with fCIS.
c. Improve the percentage of good outcomes in the treated population
d. Save patients with pCIS from complications due to brain edema and intra-cranial hemorrhage that could potentially result from IAT
e. Save the health care system the costs of futile treatment of patients with pCIS.

III. METHODS

A. Study Design:

The current study focuses on patients with acute ischemic stroke due to a blockage of the intracranial internal carotid artery or middle cerebral artery (M1). The study will be performed prospectively in up to 6 stroke centers. Akron General Medical Center is the primary institution for development of the study and data analysis for this multicenter trial. To participate in the study, all centers need to meet certain qualified requirements which include:

- One neurointerventionalist with 6 years' experience in performing IAT with multiple devices.
- Demonstrate coverage of the comprehensive stroke center 24 hours a day.

The proposed study will be carried out over a period of 4 years from the initial approval date. Informed consent will be obtained for each patient, as described in section VIII.

The study will be carried out in 2 phases (Figure 1).

Phase I will compare outcomes between treated patients with fCIS and pCIS. All eligible patients will be assessed by a full diagnostic cerebral angiogram with dye injection of all potential collaterals. DCA will be used to characterize the CIS. Treatment will be identical for both groups. All patients will be treated with the combination of IAT and the normal standard of care for a patient not receiving IAT (which may include IVT, but not always). The sample size will be set to have 60 patients complete the trial. Distribution of fCIS and pCIS patients will not be forced, but the option to balance groups may be employed if the percentage for one group reaches 70%.

In phase II, after confirming the hypothesis that patients with pCIS tend to have poor outcomes as compared to the natural history of the disease, only patients with pCIS will be enrolled. 30 patients will be randomized into treatment including IAT or without IAT plus standard of care based on a simple 1:1 randomization. All otherwise IV tPA eligible patients will be treated with IVT using tPA regardless of the assigned group since this represents current standard of care. Based on previous studies, the results from Phase I should show poor results for pCIS patients, on the order of 15% good outcomes, below the published good outcomes for patients receiving no treatment. This phase will provide preliminary data to determine if IAT provides any benefit in these patients, or is even potentially harmful, which no other clinical trial to date of IAT has formally hypothesized or tested as plausible. Due to the low rate of success the investigators realize this phase will be underpowered to definitively show differences between two groups, but the phase will provide preliminary safety pilot data on a topic not studied to date to develop plans for a larger and adequately powered study.

All eligible patients participating in both phase I and phase II will be given the option to donate an additional 8.5 ml blood sample for genetic testing of the *Dce1* gene. Blood samples will be collected in Paxgene DNA tubes. Collection of this sample will occur during regularly scheduled blood work within 48-60 hours of admission. Akron General will store all samples until all patients are enrolled after which the samples will be sent to a biospecimen processing facility to identify polymorphisms of the *Dce1* gene. Results obtained from the genetic testing will be analyzed in conjunction with data from phase I and II.

The primary measure of outcome will be the same for both phases. The outcomes will be measured based on the modified Rankin Scale (see appendix) at least 3 months and again at 1 year following treatment. Patients will be graded according to this scale by an experienced

neurologist or other mRS scale certified health care provider not involved in the treatment and blinded to the treatment for each patient.

B. Study Population:

The population for the study will be patients with anterior circulation acute ischemic stroke due to blockage of the intracranial internal carotid artery or middle cerebral artery (M1) within 8 hours of onset of symptoms. Typically, IAT is only offered to patients up to 6 hours, with no treatment options directly targeting the clot available after that time. Occlusion of one of these vessels will be determined based on CT angiography, magnetic resonance angiography, or DCA. Only patients 18 or over will be considered for the study. Other inclusion criteria include a score of 8 or greater on the National Institute of Health Stroke Scale (NIHSS, see appendix). Exclusion criteria will include contra-indication for IAT found on initial CT, intracranial hemorrhage, stroke mimics (tumor, herpetic encephalitis, etc.), more than 1/3 hypodensity on non-enhanced head CT prior to intervention, ASPECT Score < 6, and pre-existing disability defined as mRS ≥ 2. Pregnant women will also be excluded.

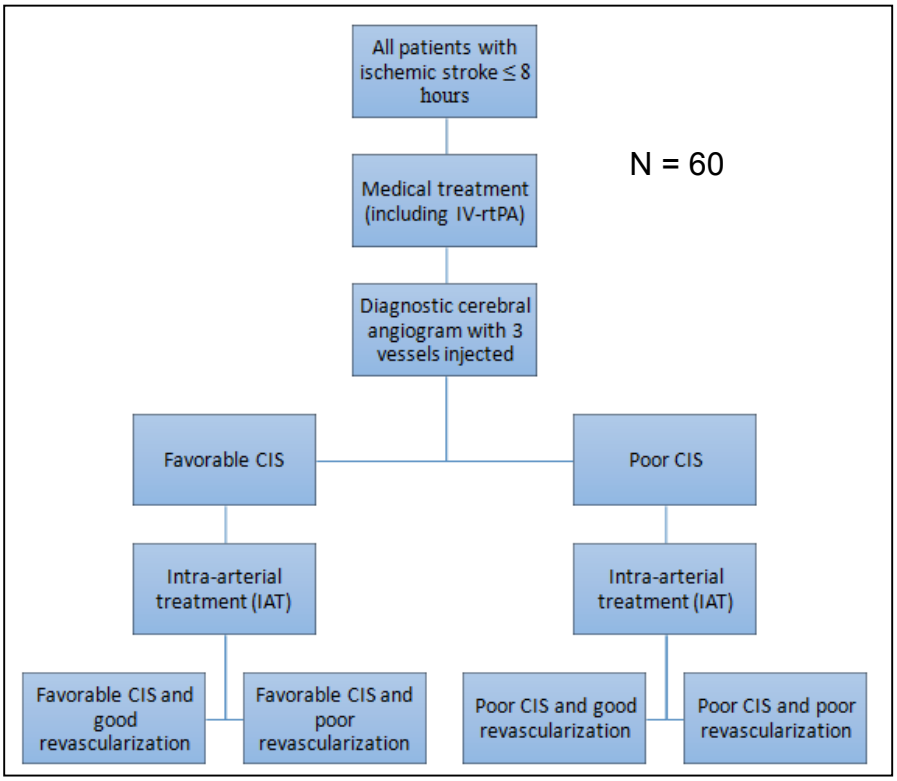

Figure 1: Study design for Phase I

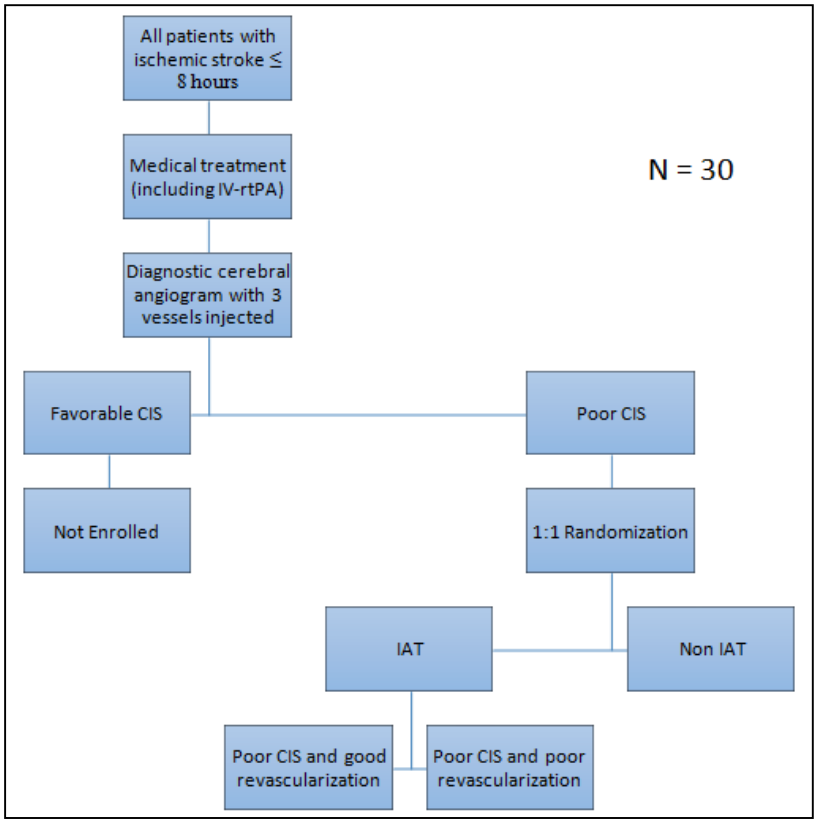

Figure 2: Study design for Phase II

C. Assessment of Resources

The multicenter study will be carried out at up to 6 stroke centers. Each center is expected to have approximately 1 patient per month eligible for the study. Enrollment of patients will be performed at the end of imaging at each institution. At Akron General Medical Center, consent will be obtained within the DCA imaging suite. Consent will be obtained by a person qualified by the local IRB other than the treating physician. At Akron General, consent will be acquired by one of two neurointerventional lab nurses. One of these two nurses is required to be present for treatment of each patient with acute ischemic stroke, regardless of participation in a study. These nurses are familiar with all aspects of the proposed treatment methods and typical outcomes. The nurses will perform documented training on methods for obtaining consent and maintaining confidentiality of data obtained from subjects enrolled in research projects.

D. Study Procedures

Recruitment will occur within the DCA suite or other imaging suite at each site following imaging to determine if patients meet enrollment criteria. Since eligible patients are typically mentally impaired by the stroke, consent will be provided by a designated caregiver or family member as described in section VIII, unless the patient is found to be competent to give informed consent by the treating stroke team neurologist. For all eligible patients, an 8.5 ml blood sample will be collected followed by the DCA to assess the CIS. Sample specimens will be stored at a temperature of 2ºC to 8ºC at each institution for a maximum of 28 days

before being shipped to Akron General. Akron General will store all samples for long-term at temperatures between -70ºC and -80ºC until the samples are sent for genetic analysis.

The initial phase of treatment for patients treated with IAT typically takes 2-3 hours in the angio suite to try to remove the clot from the blood vessel. To remove the clot, Trevo stent retriever (Stryker Neurovascular) will be used as the first pass. Patients are then transferred to the neuroscience intensive care unit (routine). The length of stay in the unit varies from patient to patient and will be determined by the local treating team. Patients can be discharged to home care or to a rehabilitation facility depending on their condition, based on the current standard of care. All medications and rehabilitation techniques prescribed for patients following the procedure will be based on the normal standard of care for the treating physician, regardless of the treatment group or classification of the CIS.

For follow-up, patients will be seen by the participating neurologist at intervals typical of the standard of care. The primary outcome measure will be acquired at the 90 day follow up. At this appointment, a mRS score will be ascribed for the patient by a modified Rankin Scale certified health care provider blinded to the CIS categorization (phase I) or the treatment (phase II). Assessment based on the mRS is standard for follow up appointments, regardless of inclusion in the study. A standard follow up visit typically takes 15-30 minutes. For patients who cannot make it to the neurologist for a follow-up visit due to persistent significant handicap or limited access to transportation, mRS will be categorized over the phone by discussing the condition of the patient with a caregiver or nurse at the home or rehabilitation facility and the patient.

A secondary follow-up, patients will be seen by the participating neurologist at intervals typical of the standard of care. The primary outcome measure will be acquired at the 1 year follow up. At this appointment, a mRS score will be ascribed for the patient by a modified Rankin Scale certified health care provider blinded to the CIS categorization (phase I) or the treatment (phase II). Assessment based on the mRS is standard for follow up appointments, regardless of inclusion in the study. A standard follow up visit typically takes 15-30 minutes. For patients who cannot make it to the neurologist for a follow-up visit due to persistent significant handicap or limited access to transportation, mRS will be categorized over the phone by discussing the condition of the patient with a caregiver or nurse at the home or rehabilitation facility and the patient.

Pre-operative condition and patients outcomes will be assessed using standardized and validated measures. The primary endpoint of a mRS score will be obtained at least 90 days following treatment and again at 1 year following treatment. NIHSS score will be obtained in the emergency room before the treatment, within 24 h of treatment, and before discharge. The person who will obtain the NIHSS will be certified to obtain it. Adequacy of revascularization will be assessed at the end of treatment by the treating physician according the modified thrombolysis in cerebral infarction (mTICI) scale (see Appendix). All of these measures are standards for care and trials of acute ischemic stroke. [8-10] All case report forms will be maintained by the primary investigator at the local site, and stored within locked cabinets. The personal identifying information on the case report forms will be de-identified and assigned a code before being transferred to Akron General Medical Center for transfer of the data to a de-identified database which will be used for analysis.

IV. DATA COLLECTION

A. How and what data will be collected

Data related to patient demographics, stroke risk factors, condition prior to treatment, time of treatment, and outcomes will be collected for each patient. Data on demographics will include sex, age, and race. Data on stroke risk factors will include history of hypertension, blood pressure, prior heart attack, arrhythmias, diabetes, glucose (sugar) level at admission, and obesity. Data on condition prior to treatment will include NIHSS score determined in the emergency room. Data on time of treatment will include time from symptoms to arrival at emergency room, time to start of DCA, and time to end of the procedure. Data on outcomes will include mRS at 3 months, mRS at 1 year, NIHSS score within 24 hours and at discharge, and complications brain edema and intra-cranial hemorrhage. Other parameters within these categories could be acquired as deemed necessary for analysis of the data.

V. DATA ANALYSIS

A. Sample Size Considerations

Phase I

A power analysis has been performed based on the previous retrospective analyses of the relationship between outcomes and the CIS for phase I. The sample size was calculated for the influence of the combination of CIS and revascularization on good outcomes (mRS ≤ 2) based on the following assumptions.

- The percentage of patients with fCIS will be 60%
- The percentage of patients with good revascularization will be 50%
- The rate of good outcomes for the combination of fCIS and good revascularization is assumed to be 70%
- The rate of good outcomes for the combination of fCIS and poor revascularization is assumed to be 20%
- The rate of good outcomes for the combination of pCIS and good revascularization is assumed to be 20%
- The rate of good outcomes for the combination of pCIS and poor revascularization is assumed to be 10%

The assumptions provide the following power analysis:

- $\alpha = 0.05$ for overall analysis and set to 0.025 for subgroup analysis comparing fCIS and good revascularization to all other groups due to multiple comparisons
- power = 0.90
- Needed Sample size = 54 patients
- An additional 6 patients completing the trial are budgeted due to risk of errors in estimated outcomes. An additional 15-20 patients are expected to be enrolled due to patients lost to the 90 day follow up and/or deviations from the protocol.

Phase II

Phase II will be an exploratory study evaluating the rates for good outcomes for patients with pCIS treated with IVT plus IAT vs. IVT (or other standard of care) only. The rate of good outcomes is expected to be approximately 13% for the IAT group with revascularization. The investigators have no prior data on expected rates of good outcomes for patients with pCIS treated with IVT only. The best possible outcome rate would be on

the order of 25% noted previously for untreated acute ischemic stroke. Due to the low levels of good outcomes, the investigators acknowledge the study will be underpowered to detect a difference between the two treatment groups for a total sample size of 30. Phase II will serve as a pilot study to initially establish estimates of rates of good outcomes for pCIS patients treated with IVT only for design of a larger prospective study.

Genetic Analysis

Genetic analysis will be performed based on the following:

- Genetic and expression analysis for the two groups based on their collateral score
- Adjust groups for cardiovascular/stroke risk factor presence and other known confounding conditions
- High density SNP array analysis will be performed for common and rare alleles against known collateral-related genes that have been identified in mice. These include human RABEP2 and its isoform RABEP1 and related gene pathways; VEGFA, FLK1 and their related gene pathways; NOTCH, DLL4, ADAM10, ADAM17, CNX37 and their related gene pathways.
- Subgroup analysis will be performed for ethnicities.
- Taqman assays and/or exome sequencing of significantly associated SNPs and/or genes.
- Pending results, a future validation study will follow this discovery study by increasing the sample size.

B. Statistical Methodology

Data for the proposed study will be analyzed using comparison of proportions and multivariable logistic regression. Analysis of proportions based on Fisher exact tests will be used to compare rates of good outcomes between the fCIS and pCIS groups as the primary end point for phase I. The influence of successful revascularization on outcomes for patients with fCIS or pCIS will also be analyzed using Fisher exact tests as the secondary end point.

Binary and/or ordinal multiple logistic regression analyses will be used to evaluate the influence of multiple parameters on the likelihood of a good outcome. These parameters will include CIS, mTICI score, NIHSS score, time to revascularization, age, sex, history of diabetes mellitus, history of high blood pressure, history of coronary artery disease. The same analyses will be performed for phase II, instead focusing on the treatment groups rather than the CIS classification.

VI. DATA AND SAFETY MONITORING PLAN

A. Describe any provisions for monitoring the data for safety

A safety committee will monitor the data. The safety committee will be composed of at least 3 voting members. At least two members will be neurologists, neuroradiologists or neurointerventionalists with experience treating acute ischemic stroke who are not investigators at any of the sites. These members will not be affiliated with the institution of the principal investigator, any sub- investigator, or Akron General Medical Center. At least one member with a background in biostatistics who is not an investigator or affiliated with Akron General Medical Center will also be on the committee.

For phase I, the only deviations in normal standards of care are:

1- the extra few minutes for full DCA for some centers as opposed to injecting only the occluded vessel
2- Adding IAT to treatment of patients seen between 6 and 24 hours of onset of symptoms.

The safety committee will be looking at known potential complications for IAT in both fCIS and pCIS groups. These include:

A. parenchymal hemorrhage type 2 symptomatic or asymptomatic hemorrhagic transformation within the vascular territory of the index ischemic stroke within 24 hours of treatment
B. Any neurological worsening (NIHSS increase of 4 points or more) within 24 hours of treatment.

The rate of complications will be assessed by the safety committee after evaluation of 20, 30 and 40 patients. The trial will be stopped for safety if the rate of brain edema and intra-cranial hemorrhage is significantly larger for the pCIS group than the fCIS group.

The safety committee will meet at the end of phase I and give its recommendation to launch phase two or not depending on their review. The primary reason not to launch phase II would be higher than expected good outcomes for the pCIS patients treated with EVT plus standard of care, giving the indication that IAT should not be withheld from patients during phase II. During phase II, the safety committee will review the data on complications as noted above and percentage of good outcomes after 10 and 20 subjects are evaluated for comparisons between the two treatment groups.

VII. STUDY LIMITATIONS

A. Potential Limitations of Procedures

The primary limitation for phase II is the small sample size. Due to the expected relatively low rates of good outcomes for pCIS patients regardless of type of treatment, the power will not be sufficient to establish whether or not treatment with IAT is beneficial for patients with pCIS. The study will, however, provide the preliminary data needed to plan for a future, larger prospective clinical trial. Potential limitations for the genetic component of this study include DNA damage due to improper handling or storage of blood samples. The Paxgene DNA tubes are designed to stabilize DNA in the blood. However, the tubes will only function properly if the instructions for inverting the tube multiple times and prompt shipment for storage at Akron General are followed.

VIII. ETHICAL CONSIDERATIONS

A. Informed Consent

Enrollment of patients will be performed in an imaging suite at each institution. Once eligibility is determined by the treating physician based on imaging, the consent process will be initiated by a study research coordinator or study nurse. These investigators are familiar with all aspects of the proposed treatment methods and typical outcomes and maintaining confidentiality of data obtained from subjects enrolled in research projects.

Consent will be obtained using IRB-approved consent forms. The consent process will emphasize oral presentation with brief summaries of the relevant information due to the time

sensitive nature of treatment of stroke. The consent process will include visual illustrations and simple consent forms. The presentation will include an explanation of the diagnosis/proposed treatment with a focus on risks, benefits and alternative treatments. Best available rates on outcomes for the proposed treatment methods will be provided.

Due to the influence of stroke on mental function, a capacity assessment will be performed for each eligible subject. The capacity assessment will include the following elements:

- Indication that the patient is being asked to make a treatment choice and the patient's ability to assess current health situation and make the choice is being evaluated
- Inquiries into the patient's self-assessed ability to make a treatment choice and assessment of the patient's ability to paraphrase disclosed information
- Ability of the patients to express a stable choice, with treatment decision expressed immediately after disclosure and at the close of the interview
- Careful documentation of the encounter

Alternative measures of consent will be employed for patients who do not demonstrate acceptable mental capacity. The alternative process will include:

- Attempting to establish whether patient has drafted an advance directive (i.e. living will, power of attorney)
- In the absence of an advance directive, seeking substituted judgment of a proxy authorized by state law

For the cases with patients who do not demonstrate acceptable mental capacity and whose proxy (i.e. power of attorney, family member) is not immediately present, telephone consent will be used. A study research coordinator or study nurse will fully explain the diagnosis and proposed treatment, with a focus on risks, benefits and alternative treatments in the same manner as the normal consent process. The telephone consent process will include the following steps:

- Two witnesses will listen to the statements made by the person authorized to give consent on the phone.
- One of those witnesses will indicate, "Phone consent by," print the consenting individual's name followed by their own initials.
- Both persons will date and sign the consent form as witnesses.
- The proxy will provide written consent, using the normal trial consent forms, upon arrival at the hospital.

B. Risks and Side Effects

Acute anterior circulation large vessel occlusion ischemic stroke is a serious and potentially fatal condition. Severe disability and death can result regardless of the type of treatment performed. For the proposed study, risk is minimized by treating all patients in phase I with the combination of IAT and standard of care. Randomization of treatment between IAT plus standard of care or standard of care alone is only used for the patients with pCIS in phase II, after establishing a poor rate of good outcomes (< 15%) for those patients with pCIS treated with the combination of IAT and IVT. Patients not enrolled in the study will be treated with the normal standard of care for the participating institution. At Akron General Medical Center the normal standard of care is supportive treatment. The investigators believe there is a risk to treating patients with pCIS with IAT. Opening

up the blood supply to ischemic tissue could potentially increase the risk of vasogenic edema and/or hemorrhagic transformation, as well as possible herniation.

It is theoretically possible that results from the genetic analysis could be used to obtain information that could lead to patient discrimination by possible employers and insurance providers. However, given the de-identification at the contributing institution followed by off-site genetic analysis on the de-identified samples, coupled with the genetic data for any individual not being returned to the contributing site, the risk is felt to be negligible.

No compensation to patients for poor outcomes is available for participating in this study. Akron General Medical Center will continue to provide standard care to all enrolled subjects following the initial stroke care, and submit charges for all usual care to the patient's insurance. The patient will be responsible for any charges not covered by insurance. In case of emergency following treatment, patients should follow standard practices to seek urgent medical treatment. Adverse events should also be reported to the principal investigator (Dr. Al-Ali) at 330-780-3406.

C. Adverse events

Adverse events may include:

1. New clot formation due to placement of guiding catheter
2. Intra-cranial hemorrhage due to perforation of the treated vessel
3. Symptomatic intra-parenchymal hemorrhage
4. Extension of clot to a previously patent vessel
5. Interval developing of significant vasogenic edema causing herniation and/or other sign of mass effect
6. Arterial access complications such as retroperitoneal hematoma, rectus muscle hematoma, or large groin hematoma more than 25 cm
7. Arterial venous fistula in the groin confirmed by ultrasound
8. Allergic reaction to dye

Each complication will be treated following the standard of care. Since the complications above are reported with these types of intervention, but there is no firm data to determine the accepted rate per operator, any center that has two or more events will be scrutinized and their technique will be evaluated by the principal investigator and safety committee. If a shortcoming is identified, guidelines will be provided for the center specific to the complications or the center could be dropped.

D. Benefits to Subjects

For phase I, patients who can be treated between 6 and 24 hours following onset of symptoms for acute ischemic stroke will be treated with IAT plus standard of care. Currently those patients are not offered IAT due to the belief that too much time has passed to restore tissue that has been deprived of the primary source of circulation. However, the new Extend IA trial proved that these patients could be treated. [4] The investigators believe that successful treatment beyond 6 hours with IAT is possible for patients with fCIS. In doing so we are offering a potentially useful treatment to patients who would otherwise not have the option.

E. Costs to Subject

Costs to the subjects will be standard costs for the treatment performed for acute ischemic stroke. Usual, customary, and reasonable treatment costs will be initially billed to the patients insurance, if applicable, with the patient responsible for any portion not paid by insurance in accordance with usual institutional policies. The protocol is based on standard techniques for treating acute ischemic stroke that can be applied to an individual patient based on the discretion of the treating physician.

F. Compensation to Subject

All patients who participate in the 90 day follow up visit will be compensated for parking and mileage expense up to a maximum of $25. All patients who participate in the 1 year follow up visit will be compensated for parking and mileage expense up to a maximum of $25.

F. Provisions for vulnerable subjects

Vulnerable subjects, children, pregnant women, and prisoners, will not be enrolled in the study.

G. Subject Privacy and Data Confidentiality

Measures will be taken to protect the privacy of the subjects and confidentiality of their personal information from the enrolled subjects. The enrollment process will take place within the imaging suite or emergency department, in a manner to maximize the probability that only the caregivers will be aware that a subject is eligible for a trial. The only other person at each site who will be aware that a subject is enrolled will be a research coordinator at each site tasked with collecting data and reviewing procedures.

The protected health information will be collected for each enrolled subject at each site. The paper files will be stored within locked filing cabinets within the office of the primary investigator or research coordinator. The data will be de-identified before being provided to the primary institution for analysis (honest broker). Patients will be identified based on a code including an identifier for the site and the patient number at the site. Any electronic files relating the patient name to the code will be kept at the home institution. The files will be password protected and stored on a single desktop computer. The files may be backed up on a password-protected portable drive. When data is used for presentations at professional organizations or submissions to journals, no patient identifiers will be disclosed. All data will be maintained at each site for a minimum of 3 years. After the principal investigator has determined that the data has been fully analyzed and presented, the paper data from individual patients will be shredded, while electronic data will be deleted and overwritten.

IX. PLANS FOR DISSEMINATION OF FINDINGS

Data acquired for the study will be prepared for publication in journals focused on treatment of acute ischemic stroke. The study will also be registered on clinicaltrials.gov to allow the general public to access the results of the study.

X. REFERENCES

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XI. APPENDICES

MODIFIED RANKING SCORE

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Modified thrombolysis in cerebral infarction (mTICI) scale

0: No perfusion
1: Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion
2a: Perfusion of less than half of the vascular distribution of the occluded artery
2b: Perfusion of half or greater of the vascular distribution of the occluded artery
3: Full perfusion with filling of all distal branches

Integrated Acute Stroke Flowsheet

National Institutes of Health Stroke Scale

Complete a full assessment TID during the first 72 hours after admission for stroke, with any decline in neurological status, and when the patient is received from ER, ICU, or PACU into 6NW or 6 Observation. After the 72 hour period, a full assessment should be completed with any changes in neurological status, and prior to discharge.
Complete a modified assessment (the shaded sections, and any other area of concern) when the neurological assessment is required more often than TID.
Administer NIHSS in order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Scores should reflect what the patient does, and not what the clinician thinks the patient can do. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

CATEGORY	Description	Score	Date/Time	Date/Time	Date/Time	Date/Time
1a. Level of consciousness ***(Patients who score 2 or 3 on this item, should be assessed using the Glasgow Coma Scale)	**Alert, keenly responsive** **Not alert** (arousable by minor stimulation to obey, answer, or respond) **Not alert** (responds to repeated or painful stimulation) Only reflex motor, autonomic effects, or totally **unresponsive**	**0** **1** **2** **3**				
1b. LOC, questions (month, age)	**Answers both questions correctly** **Answers one question correctly** **Answers neither question correctly**	**0** **1** **2**				
1c. LOC, commands (Open/close eyes, make fist, release fist) Pantomime may be used	**Performs both tasks correctly** **Performs one task correctly** **Performs neither task correctly**	**0** **1** **2**				
2. Best gaze (Patient follows examiner's finger or face through full horizontal field)	**Normal** **Partial gaze palsy** **Forced deviation** (deviation not overcome by oculocephalic maneuver)	**0** **1** **2**				
3. Visual (Introduce visual stimulus/threat to patient's field quadrants)	**No visual loss** **Partial hemianopia** (sector or quadrant field deficit) **Complete hemianopia** (dense field loss, such as half of visual field) **Bilateral hemianopia** (blind)	**0** **1** **2** **3**				
4. Facial palsy (Show teeth, raise eyebrows, squeeze eyes shut) Pantomime may be used	**Normal** **Minor paralysis** (mild asymmetry on smiling) **Partial paralysis** (paralysis of lower face) **Complete** (one or both sides: paralysis of upper and lower face)	**0** **1** **2** **3**				
5a. Motor arm - Left (**Test each limb independently**: Palm Down: Elevate arm to 90° if pt sitting, 45° if pt supine and score drift/movement over 10 seconds)	**No drift** (limb holds for full 10 seconds) **Drift** (limb drifts downward but does not fall to rest on a support) **Some effort against gravity** (drifts to fall on support) **No effort against gravity** (trace movement, limb falls immediately)	**0** **1** **2** **3**				
5b. Motor arm – Right (As above)	**No voluntary movement** **Amputation, joint fusion etc**	**4** **X**				
6a. Motor leg - Left (**Test each limb independently**: With pt supine, elevate extremity to 30° and score drift/movement over 5 seconds)	**No drift** (limb holds for full 5 seconds) **Drift** (limb drifts downward but does not fall to rest on a support) **Some effort against gravity** (drifts to fall on support) **No effort against gravity** (trace movement, limb falls immediately)	**0** **1** **2** **3**				
6b. Motor leg - Right (**As above**)	**No voluntary movement** **Amputation, joint fusion etc**	**4** **X**				
7. Limb ataxia (Finger-nose, heel down shin)	**Absent** **Present in one limb** **Present in two limbs**	**0** **1** **2**				
8. Sensory (Pin prick to face, arm, trunk, and leg – compare side to side) Look at grimace in aphasic patient	**Normal** **Mild to moderate sensory loss** (less sharp/dullness) **Severe or total sensory loss** (not aware of touch)	**0** **1** **2**				
9. Best language (Name item, describe a picture and read sentences)	**No aphasia** **Mild to moderate aphasia** (reduced fluency or comprehension) **Severe aphasia** (communication exchange very limited) **Mute, global aphasia**	**0** **1** **2** **3**				
10. Dysarthria (Evaluate speech clarity by having patient read or repeat listed words)	**Normal articulation** **Mild to moderate dysarthria** (can be understood) **Severe dysarthria** (unintelligible or worse) **Intubated** or other physical barrier	**0** **1** **2** **X**				
11. Extinction and Inattention (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	**No abnormality** (no neglect) **Visual, tactile, auditory, spatial, or personal inattention**, or extinction to bilateral stimulation **in one of the sensory modalities**) **Profound: more than one modality** affected	**0** **1** **2**				
		TOTAL SCORE				
PUPILS • • • • • • • ● ● **Sizes: 1mm 2mm 3mm 4mm 5mm 6mm 7mm 8mm 9mm** **Reaction: + normal S sluggish - absent**		**Left Size/Reaction** **Right Size/Reaction**				
	Signature on back side of page. **Initials of examiner**					