Importance of Atherosclerotic Carotid Artery Occlusion

- 10-15% of carotid territory infarcts and TIAs
  - Estimated 61,000 first ever strokes per year (USA)
  - Estimated 19,000 TIAs per year (USA)


Carotid Artery Occlusion

- 10-15% of carotid territory infarcts and TIAs
  - Estimated 61,000 first ever strokes per year (USA)
  - Estimated 19,000 TIAs per year (USA)
Prognosis of Symptomatic Carotid Occlusion on Medical Therapy

The risk of recurrent stroke in patients with symptomatic atherosclerotic carotid artery on medical therapy is:

- 5-7% per year for all stroke
- 2-6% per year for ipsilateral ischemic stroke


Prognosis of Symptomatic Carotid Occlusion
JAMA 1998; 280:1055-1060

IPSILATERAL STROKE

Risk of subsequent stroke is 5-7% per year on medical treatment.

Understanding the mechanism of stroke associated with carotid occlusion is essential for designing more effective treatments.

Revascularization to improve the cerebral circulation is a logical approach only if the risk of recurrent stroke is related to the hemodynamic effect of carotid occlusion.
The Internal Carotid Arteries carry blood from the heart to the brain.

Internal Carotid Endarterectomy for Carotid Stenosis

If the internal carotid artery is only partially blocked in the neck, the risk of stroke can be reduced by surgically removing the plaque.

Internal Carotid Artery Occlusion

Endarterectomy cannot be performed on a completely occluded carotid artery.
Oral Anticoagulation for Secondary Stroke Prevention

- Warfarin has no advantage over aspirin for secondary stroke prevention
- This lack of effect is also evident in the subgroup with large artery disease.

Understanding the mechanism of stroke associated with carotid occlusion is essential for designing more effective treatments.

Causes of Cerebral Ischemia

- Embolic Territorial Infarcts
- Hemodynamic Borderzone Infarcts
...but it’s not so easy
The middle cerebral artery territory is quite variable

Interpretation of Infarction Pattern in 16 Patients With Carotid Occlusion

<table>
<thead>
<tr>
<th>Minimum territory</th>
<th>Maximum territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Territorial Infarction, %</td>
<td>Border-zone Infarction, %</td>
</tr>
<tr>
<td>Wide MCA territory</td>
<td>81</td>
</tr>
<tr>
<td>Small MCA territory</td>
<td>19</td>
</tr>
</tbody>
</table>

Hemodynamic Effects of Internal Carotid Artery Occlusion

Some patients have natural collateral circulatory pathways that provide normal blood flow to the part of the brain usually supplied by the occluded internal carotid artery.

Other patients do not have adequate collateral pathways to provide normal blood flow.

Determining the Hemodynamic Effects of Internal Carotid Artery Occlusion

Simple measurements of regional cerebral blood flow are inadequate to assess the hemodynamic effects of carotid artery occlusion because they do not differentiate between reduced blood supply (ischemia) and reduced metabolic demand.
Cerebral Oxygen Extraction Fraction Reflects the Balance between Oxygen Utilization and Oxygen Delivery

\[ \text{OEF} = \frac{\text{CMRO2}}{\text{CBF} \times \text{CaO2}} \]

OEF = Oxygen Extraction Fraction
CMRO2 = Cerebral Oxygen Metabolism
CBF = Cerebral Blood Flow
CaO2 = Arterial Oxygen Content

When there is a primary reduction in CBF, OEF will increase to maintain CMRO2

In the normal resting state, CBF is regionally matched to CMRO2. OEF is generally uniform throughout the brain.
Measurements of OEF can be used to differentiate between low CBF due to reduced blood supply (ischemia) and low CBF due to reduced metabolic demand.

PET Assessment of Cerebral Hemodynamics in Carotid Occlusion

Measurements of Oxygen Extraction Fraction (OEF) can be used to separate patients with carotid occlusion into two categories:

- **NORMAL OEF**: Good collaterals with normal cerebral hemodynamics
- **INCREASED OEF**: Poor collaterals with reduced CBF relative to oxygen metabolism
St. Louis Carotid Occlusion Study

(JAMA 1998; 280:1055-1060)

HYPOTHESIS

Increased oxygen extraction (OEF) in the cerebral hemisphere distal to symptomatic carotid occlusion is an independent predictor of subsequent stroke in symptomatic, medically treated patients.

Supported by NS28947

St. Louis Carotid Occlusion Study

STUDY DESIGN

- Prospective
- Blinded
  - Patient
  - Treating physician
  - Endpoint adjudicator
- Endpoints
  - Primary - all stroke
  - Secondary - ipsilateral ischemic stroke, death

81 subjects with symptomatic occlusion of one carotid artery underwent initial evaluation

- Neurological history and examination
  - 17 clinical and epidemiological risk factors
  - arteriographic findings
- PET measurement oxygen extraction fraction (OEF)
- Every six months telephone contact to determine occurrence of stroke or death
- Mean follow-up - 31.5 months
EC/IC Bypass Study
Surg Neurol 1986; 26:227-35

ANALYSIS OF EXTERNAL CAROTID (MAINLY OPHTHALMIC) COLLATERALS IN 808 PATIENTS WITH INTERNAL CAROTID ARTERY OCCLUSION

In medical group, no significant differences in outcome comparing those with large (221), small (183) or trivial/absent (404) filling.

No benefit of surgery compared to medical care in either of the three groups.

St. Louis Carotid Occlusion Study

CONCLUSION

- Patients with symptomatic carotid occlusion and high OEF represent a high risk subgroup who do poorly on medical treatment.
- The ipsilateral stroke rate (26% at 2 years) is comparable to that for medically treated patients with severe (70-99%) symptomatic carotid stenosis.

IMPLICATION

Surgery to improve cerebral hemodynamics is the logical treatment for these patients with high OEF and high stroke risk on medical therapy.
Extracranial-Intracranial Bypass Surgery

A branch of the external carotid artery is used to bypass the occlusion and provide increased blood flow to the brain.

Extracranial-Intracranial Bypass Surgery will return areas of increased OEF to normal in patients with symptomatic carotid artery occlusion.

Pre-Operative

After EC/IC Bypass

Extracranial-intracranial arterial bypass surgery was shown to be NOT effective for preventing stroke in patients with carotid occlusion in a large randomized trial (NEJM 1985; 313:1191-1200).
Could the EC/IC Bypass Study have missed a benefit in the high risk subgroup identified in the St. Louis Carotid Occlusion Study?

2 year stroke risk “Medical Group” = 19%
Stroke risk for all STLCOS patients

2 year stroke risk “Surgical Group” = 21.2%
Low OEF 9% STLCOS stroke risk + 12.2% Peri-op M/M = 21.2%
High OEF 29% STLCOS stroke risk reduced to 9% + 12.2% Peri-op M/M = 21.2%

A randomized, partially blinded, controlled clinical trial to test whether EC/IC bypass surgery, when added to best medical therapy, can reduce by 40% subsequent ipsilateral ischemic stroke at two years in patients with recently symptomatic internal carotid artery occlusion and ipsilateral increased oxygen extraction fraction measured by PET.

Is this a cost-effective approach to health care?
If the COSS hypothesis is proven true, EC/IC bypass surgery will improve outcome and reduce cost:
• 49 QALY/10 yrs/100 patients
• cost savings of $11,000 per patient

Cost Effectiveness of PET Selection for EC/IC Bypass Surgery for Symptomatic Carotid Occlusion
Dordeyn et al, J Nucl Med 2000; 41:800-807
MAJOR INCLUSION CRITERIA

1. **CLINICAL** Ipsilateral hemispheric carotid territory TIA or mild-to-moderate ischemic stroke within 120 days (Barthel index ≥ 12/20).

2. **PET** $^{15}$O/$^{15}$H$_2$O count-based ratio image with ipsilateral-to-contralateral OEF ratio >1.130.

3. **ARTERIOGRAPHIC** Intra-arterial contrast arteriography occlusion of an internal carotid artery with vessels suitable for anastomosis.

---

**COSS Randomization Flow Chart**

---

**SURGERY**

The neurosurgeon(s) at each PCC will *personally* perform the STA-MCA bypass surgery on all subjects randomized to surgery at that site.

All participating neurosurgeons must have submitted operative data to document eligibility and/or attended training course and be approved for participation by the PCC.
ANTITHROMBOTIC TREATMENT

Until the 30-40 day follow-up visit, ASA 81 or 325 mg qd will given to all patients. Following this period, recommendations for anti-thrombotic treatment will be the same as for the non-surgical group.

Antithrombotic treatment will follow the recommendations for anti-platelet treatment of the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association (Stroke 1999; 30:2502-2511).

RISK FACTOR INTERVENTION

Risk factor intervention will be monitored by:
- Smoking: Question
- Hypertension: Cuff blood pressure
- Hyperlipidemia: Blood measurements
- Diabetes mellitus: Hemoglobin A1C levels

POST-RANDOMIZATION SURGICAL TREATMENT

Unless patients have reached a primary endpoint, no additional cerebrovascular surgery is permitted after randomization in either group. This includes contralateral internal or common carotid endarterectomy or angioplasty, ipsilateral external carotid artery endarterectomy or angioplasty, vertebral or basilar artery angioplasty, any arterial grafting procedures to the carotid or vertebral arteries. The only exception to this is development of contralateral carotid stenosis of greater than 60%, which in the judgment of the local investigators, requires surgery.
Non-surgical patients who have an ipsilateral TIA HAVE NOT EXPERIENCED A PRIMARY ENDPOINT and must continue adherence to the protocol.

The EC/IC Bypass Trial showed no benefit for EC/IC bypass surgery in patients with carotid occlusion who had recurrent symptoms after the occlusion was documented.

Thus, performance of EC/IC bypass for recurrent TIAs distal to the carotid occlusion in the non-surgical group is not indicated based on the best currently available information.

POST-RANDOMIZATION
IPSILATERAL TRANSIENT ISCHEMIC ATTACKS

Surgical group: Combination of all stroke and death from randomization to 30 days post-operatively plus subsequent ipsilateral ischemic stroke within two years of randomization.

Non-surgical group: Combination of all stroke and death from randomization to equivalent of 30 days post-operatively plus subsequent ipsilateral ischemic stroke within two years of randomization.

SECONDARY ENDPOINTS

All stroke, disabling stroke, fatal stroke, death, NIHSS, Rankin Scale, Barthel Index and SSQoL

Disabling stroke will be defined as a Barthel Index of <60 at the first scheduled return visit more than 4 months after the stroke occurred. All stroke endpoints determined by the adjudication committee will be classified into stroke subtypes by the TOAST criteria.
ENDPOINT ADJUDICATION

Final adjudication of stroke and death endpoints (ipsilateral stroke, non-ipsilateral stroke, fatal stroke, death) will be by a 3-person blinded Adjudication Committee supplied with the information from the DMC that has been sanitized to remove all information regarding treatment assignment. Information regarding each possible endpoint will be sent to 2 adjudicators.

St. Louis Carotid Occlusion Study
Post hoc identification of Highest Risk Sub-Group

2-YEAR IPSILATERAL STROKE RATE

<table>
<thead>
<tr>
<th></th>
<th>High OEF</th>
<th>Normal OEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (81)</td>
<td>38%</td>
<td>8%</td>
</tr>
<tr>
<td>Clinically High Risk (45)</td>
<td>50%</td>
<td>12%</td>
</tr>
</tbody>
</table>

1 Count-based OEF ratio cut-off of 1.16 based on ROC curve analysis
2 Hemispheric symptoms within 120 days

Six Steps to Randomization

- Step 1 Recruitment
- Step 2 Screen patients with carotid occlusion
- Step 3 Enroll eligible patients
- Step 4 PET measurement of OEF
- Step 5 Arteriography (if needed)
- Step 6 Randomize
STEP 2 Screen Patients with Carotid Occlusion

SCREENING

All initially identified patients with carotid occlusion by vascular imaging will be screened for eligibility.

All screened patients will be registered in the COSS database.

Satellite Clinical Centers

- High volume
- Neurologist and coordinator
- Identified with single PCC
- Screen Doppler and angios for eligible subjects
- Refer eligible subjects to PCC
  - final eligibility determination by neurosurgeon
  - Baseline evaluation
  - PET
  - Surgery
- Perform all follow-ups beginning with 30/40 day

COSS Randomization Flow Chart
Carotid Occlusion Surgery Study

Initial Clinical Inclusion Criteria: 1

Vascular imaging demonstrating occlusion of an internal carotid artery

May be demonstrated by any vascular imaging modality (e.g. Doppler ultrasound, magnetic resonance angiography, CT angiography or intra-arterial catheter arteriography).

Initial Clinical Inclusion Criteria: 2-5

Clinical diagnosis of TIA or ischemic stroke in the hemispheric territory of the occluded carotid artery

Neuroimaging confirmation not required

Retina only ineligible

No brainstem/cerebellar symptoms/signs

Previous CEA eligible unless asymptomatic post-op occlusion

Within 120 days prior to projected performance date of PET

Modified Barthel Index ≥ 12/20

Language comprehension intact, motor aphasia mild or absent

This must be determined by a physician investigator

Initial Clinical Inclusion Criteria: 6-9

Age 18-85 inclusive

Competent to give informed consent

Legally an adult

Accessible and reliable for follow-up
Carotid Occlusion Surgery Study

Initial Clinical Exclusion Criteria: 1

Non-atherosclerotic carotid vascular disease
The intent is to include only atherosclerotic carotid occlusion. All other non-atherosclerotic conditions (for example, moyamoya disease, fibromuscular dysplasia, carotid dissection, arteritis, radiation-induced vasculopathy such as that following irradiation for neck cancer) are excluded. These entities are given as examples, not as an all-inclusive list.

This must be determined by a physician investigator.

Carotid Occlusion Surgery Study

Initial Clinical Exclusion Criteria: 2

Blood dyscrasias, ONLY
P. vera, essential thrombocytosis, sickle cell (SS, SC)

NOT EXCLUSIONS: anticardiolipin antibodies, lupus anticoagulant, protein S, C, or antithrombin III deficiency, Factor V Leiden or other causes of activated protein C resistance, prothrombin gene mutations)

Carotid Occlusion Surgery Study

Initial Clinical Exclusion Criteria: 4-8

4. Other non-atherosclerotic condition likely to cause focal cerebral
5. [Deleted]
6. Any condition likely to lead to death within 2 years
7. Other neurological disease that would confound follow-up assessment
8. Pregnancy
Carotid Occlusion Surgery Study

Initial Clinical Exclusion Criteria: 9

Subsequent cerebrovascular surgery planned which might alter cerebral hemodynamics or stroke risk

This includes contralateral internal or common carotid endarterectomy or angioplasty, ipsilateral external carotid artery endarterectomy or angioplasty, carotid stump closure, vertebral or basilar artery angioplasty, any arterial grafting procedures to the carotid or vertebral arteries.

Carotid Occlusion Surgery Study

Initial Clinical Exclusion Criteria: 10-12

10. Any condition which in the participating surgeon’s judgment makes the patient an unsuitable surgical candidate
11. Concurrent participation in any other experimental treatment trial
12. Participation within the previous 12 months in any experimental study that included exposure to ionizing radiation

Carotid Occlusion Surgery Study

Initial Clinical Exclusion Criteria: 13-14

13. Acute, progressing or unstable neurological deficit
   Neurological deficit must stable for 72 hours prior to the performance of PET
14. If supplemental arteriography is required, allergy to iodine or x-ray contrast media, serum creatinine > 3.0 mg/dl or other contraindication to arteriography.
Carotid Occlusion Surgery Study

Initial Clinical Exclusion Criteria: 15-16

15. Allergy or contraindication to aspirin if aspirin is to be used in the peri-operative period

16. Medical indication for treatment with anticoagulant drugs, ticlopidine, clopidogrel or other antithrombotic medications such that these medications cannot be replaced with aspirin in the perioperative period as deemed necessary by the COSS neurosurgeon if the participant is randomized to surgical treatment.

Remediable medical conditions: Patients with the following conditions can become eligible if the exclusion criterion no longer applies within any time 120 days of onset of the most recent qualifying event:

17. Uncontrolled diabetes mellitus (FBS > 300 mg%/16.7 mmol/L),
18. Uncontrolled hypertension (systolic BP>180, diastolic BP >110),
19. Uncontrolled hypotension (diastolic<65)
20. Unstable angina

COSS Randomization Flow Chart

Screen

Initial Clinical and Vascular Imaging Criteria

ENROLL

PET DEF Criteria

PET DEF Criteria

Arteriographic Criteria

Randomized

Surgery

No Surgery
Carotid Occlusion Surgery Study

SUPPLEMENTAL ARTERIOGRAPHY

Intra-arterial catheter arteriography is required prior to randomization to document carotid occlusion and both extracranial and intracranial arteries suitable for anastomosis. At the time of enrollment, a decision will be made by the surgeon whether supplemental catheter arteriography will be necessary either because it has not been performed or because the existing study is inadequate to provide the necessary information.

Supplemental catheter arteriography will be performed as part of COSS only if the PET study meets criteria for increased OEF.

Carotid Occlusion Surgery Study

BASELINE EVALUATION PRIOR TO PET

A baseline clinical evaluation by a neurological physician prior to PET

NIH Stroke Scale, modified Barthel Index, and modified Rankin scale, Stroke Specific Quality of Life assessment

Baseline laboratory studies

COSS Randomization Flow Chart

Screen

Initial Clinical and Vascular Imaging Criteria

Enroll

PET OEF Criteria

OUT

Arteriographic Criteria

OUT

Randomized

Surgery No Surgery

OUT

No OUT

OUT

No OUT

OUT
Carotid Occlusion Surgery Study

STEP 4 PET Measurements of OEF

As soon as possible after enrollment, all subjects will undergo positron emission tomography measurements of cerebral oxygen extraction fraction.

Patients who have previously undergone cerebrovascular surgery prior to enrollment (including carotid endarterectomy or angioplasty/stenting of the contralateral internal carotid artery, ipsilateral external carotid artery or vertebral arteries) must wait 7 days before PET.

PET will be done at least 72 hours after acute stroke to avoid the transient increase in OEF that occurs with acute ischemic stroke.

Carotid Occlusion Surgery Study

POSITRON EMISSION TOMOGRAPHY

At the time that PET is scheduled, surgeons will reserve time on the operating room schedule so that surgery may be performed as soon as possible after final eligibility determination and randomization.
Carotid Occlusion Surgery Study

**POSITRON EMISSION TOMOGRAPHY**

- 100 mCi O-15 Oxygen Inhalation
- 75 mCi O-15 Water Injection

Either scan may be repeated

**Count-based PET Method for Determination of OEF Asymmetry**
Comparison of PET OEF Methods for Prediction of Stroke Risk
(Derdeyn et al: J Nucl Med 2001; 1195-1197)

Carotid Occlusion Surgery Study

POSITRON EMISSION TOMOGRAPHY

PET carries essentially no risk other than the radiation exposure.

Carotid Occlusion Surgery Study

POSITRON EMISSION TOMOGRAPHY

The maximum radiation exposure from COSS (PET and arteriography) is equivalent to one-half of the allowable annual dose to radiation workers (for example, x-ray technicians). The risk from the radiation exposure in this study is too small to be measured and is small when compared with other everyday risks such as accidents on the road, at home or on the job.
**Carotid Occlusion Surgery Study**

**STEP 5 Supplemental Arteriography**

Supplemental catheter arteriography will be performed as part of COSS only if the PET study meets criteria for increased OEF.

On the day following the arteriogram, each subject will be contacted by telephone to determine the occurrence of any adverse effects.

---

**Carotid Occlusion Surgery Study**

**ARTERIOGRAPHIC ELIGIBILITY**

Intra-arterial catheter arteriography is required prior to randomization to document carotid occlusion and both extracranial and intracranial arteries suitable for anastomosis.

Arteriographic eligibility will be decided by the surgeon.

---

**COSS Randomization Flow Chart**

- Screen
- Initial Clinical and Vascular Imaging Criteria
  - No OUT
  - Enroll
  - PET OEF Criteria
    - No OUT
    - Arteriographic Criteria
      - No OUT
      - Randomize
        - Surgery
        - No Surgery

---
Carotid Occlusion Surgery Study

STEP 6 Randomization

Once a local investigator has received notification of PET eligibility and has entered the information from the SCREENING, INITIAL ELIGIBILITY and ARTERIOGRAPHY (if applicable) forms, he or she may log onto the system to receive treatment assignment for that patient.

The patient is defined as randomized when the treatment is assigned. Every patient who is assigned a treatment must be included in the final analysis.

POST-RANDOMIZATION MEDICAL THERAPY

At the time of randomization, participants randomized to medical therapy will remain on the anti-thrombotic treatment preferred by their physicians. Anti-thrombotic treatment for participants randomized to surgical treatment will be determined by the COSS neurosurgeon as necessary for surgical hemostasis. Those participants taking oral anticoagulants will need to replace this medication with aspirin for a period before and after surgery and those taking ticlopidine or clopidogrel may need to as well.

Carotid Occlusion Surgery Study

SURGERY

Subsequent STA-MCA anastomosis will be performed as quickly as possible in the judgment of the participating surgeon.

For subjects who were receiving antithrombotic drugs other than aspirin prior to randomization, surgery will be performed as soon as the participating neurosurgeon considers the bleeding risk to be acceptable.
Superficial Temporal Artery-Middle Cerebral Artery Bypass


Carotid Occlusion Surgery Study

FOLLOW-UP SCHEDULE

Monthly Telephone Calls

30-35 days post randomization

Additional Visit 30-35 days post operative if surgery is delayed > 5 days

Every three months post-randomization for the duration of the trial

Carotid Occlusion Surgery Study

FOLLOW-UP

All surgical patients will undergo repeat PET at the first follow-up visit to document reversal of hemodynamic abnormalities

At each follow-up visit:
- Neurological history and exam to identify new stroke performed by a physician investigator who was not the operating surgeon
- NIHSS, Rankin Scale, Barthel Index and SSQoL
- Monitor antithrombotic treatment and risk factors
- Doppler studies to assess graft patency in surgical patients.
Antithrombotic treatment will follow the recommendations for anti-platelet treatment of the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association (Stroke 1999; 30:2502-2511).

<table>
<thead>
<tr>
<th>Event</th>
<th>Recommended Therapy</th>
<th>Therapeutic Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA (atherothrombotic)</td>
<td>ASA 50–325 mg/d</td>
<td>ER-DP 200 mg+ASA 25 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clopidogrel 75 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ticlopidine 250 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASA 50–1300 mg/d</td>
</tr>
<tr>
<td>TIA (atherothrombotic) and aspirin-intolerant</td>
<td>Clopidogrel 75 mg/d</td>
<td>Ticlopidine 250 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin (INR 2–3)</td>
</tr>
<tr>
<td>TIA (atherothrombotic) recurrence during ASA therapy*</td>
<td>ER-DP 200 mg+ASA 25 mg BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clopidogrel 75 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ticlopidine 250 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin (INR 2–3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASA 50–1300 mg/d</td>
</tr>
</tbody>
</table>

Warfarin is not recommended based on the results of the Warfarin–Aspirin Recurrent Stroke Study (N Engl J Med 2001; 345:1444-1451).

*The recommended antithrombotic agents have not been specifically tested in patients who have experienced a TIA during ASA therapy.

Risk factor intervention will be monitored by:
- Smoking: Question
- Hypertension: Cuff blood pressure
- Hyperlipidemia: Blood measurements
- Diabetes mellitus: Hemoglobin A1C levels
Carotid Occlusion Surgery Study

Primary Endpoint

Surgical group: Combination of all stroke and death from randomization to 30 days post-operatively plus subsequent ipsilateral ischemic stroke within two years of randomization.

Non-surgical group: Combination of all stroke and death from randomization to equivalent of 30 days post-operatively plus subsequent ipsilateral ischemic stroke within two years of randomization.

COSS Primary Endpoints

Surgical Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>30 Days Post-op</td>
<td></td>
</tr>
<tr>
<td>2 yrs</td>
<td></td>
</tr>
</tbody>
</table>

Non-Surgical Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td></td>
</tr>
<tr>
<td>30 Days Post Randomization</td>
<td></td>
</tr>
<tr>
<td>Mean Randomization - Surgery Delay</td>
<td>2 yrs</td>
</tr>
</tbody>
</table>

Carotid Occlusion Surgery Study

Secondary Endpoints

All stroke, disabling stroke, fatal stroke, death, NIHSS, Rankin Scale, Barthel Index and Stroke Specific Quality of Life scale

Disabling stroke will be defined as a Barthel Index of <12/20 at the first scheduled return visit more than 3 months after the stroke occurred.

All stroke endpoints determined by the adjudication committee will be classified into stroke subtypes by the TOAST criteria
Safety Monitoring

- Two Levels of Monitoring
  - In-House Safety Committee
  - NINDS PSMB

Questions?
Contact Information:
  Donna Auer
  734-615-3276
  Fax 734-936-9294