Medical House Staff IRB Proposal
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Assessment of the procedural etiology of stroke resulting from carotid artery stenting

1. Study Purpose and Rationale:

A. Background

Stroke is the 3rd leading cause of death in the United States and carries an economic burden of $41 billion annually by 2007 estimates. Approximately 87% of strokes are ischemic and of these, approximately one third occur due to emboli from carotid artery stenosis.[1] Carotid endarterectomy (CEA) was established in 1953 and gained popularity thereafter as a safe and efficacious surgical treatment for stroke prevention in symptomatic patients with carotid artery stenosis (North American Symptomatic Carotid Endarterectomy Trial - NASCET[2] and European Carotid Surgery Trial - ECST[3]). For symptomatic patients with a carotid lesion >70% stenosis, CEA reduced the rate of stroke by 17% at 18 months in the NASCET trial and by 12% in the ECST trial. However, over the past fifteen years, carotid angioplasty and stenting (CAS) has emerged as a viable alternative to the fifty-five-year tradition of CEA for stroke prevention in patients with carotid stenosis. CAS is a less invasive procedure that minimizes wound complications and cranial nerve injury associated with CEA, which may translate into shorter hospitalizations and less resource utilization.

In the several randomized controlled trials and carotid stent registry trials comparing CAS with CEA outcomes for the treatment of carotid stenosis, CAS with embolic protection has been found non-inferior to CEA, particularly in high-operative-risk populations (SAPPHIRE).[4] In the most recent and largest prospective randomized trial to date (CREST), the risk of the primary endpoint of stroke, myocardial infarction, or death was not significantly different in the group that underwent CEA and the group that underwent CAS.[5] During the periprocedural period, however, there was a higher risk of stroke with CAS and a higher risk of MI with CEA.

This difference prompts several questions about the safety of CAS in regard to stroke incidence and how the procedure should be applied in different patient populations. Rates of stroke and death in trials comparing CAS with CEA are still debated and mechanisms of stroke complications remain poorly understood. Precise knowledge of the incidence and cause of stroke after CAS will lead to improved devices, techniques, and outcomes.

B. Hypothesis

Review of angiographic studies from strokes occurring in patients after CAS suggests that operator error or patient/lesion selection was the proximate cause of the stroke event.[6] This was extrapolated from two angiographic findings: improper balloon placement and overly aggressive wire removal after carotid stent deployment. Both of these errors can be identified by expert reviewers on angiographic analysis and each are a consequence of operator error and/or unanticipated difficult anatomy. We hypothesize that stroke angiograms from patients in the most recent investigational device studies will reveal evidence of improper balloon placement and/or overly aggressive wire removal after carotid stent deployment when compared with non-stroke angiograms.

2. Study Design and Statistical Procedures:

A. Design

This will be a retrospective study of patients who underwent CAS in the most recent premarket approval (PMA) investigational device exemption (IDE) studies. Of note, stroke rates were even lower than those observed in the CREST trial. Data from 4 studies will be compiled in order to provide an adequate number of events for a comparative analysis. These studies include the ARMOUR (2.7% 30-day major adverse cardiac and cerebrovascular event rate and 0.9% 30-day major stroke rate), EMBOLDEN (study complete, results not yet published), EPIC (3% 30-day stroke, death, MI rate), and EMPiRE (3.7% 30-day stroke, death, MI rate and 2.9% any stroke or death rate) trials. No inter-study comparison will be performed and would be inadequately powered in any event given the limited number (5-12) of strokes per study.

Angiograms of all strokes occurring will be pooled and analyzed independently for possible causes of stroke by an experienced interventionalist. The reader will be blinded to stroke and non-stroke angiograms. The same analysis will be performed on twice the number of non-stroke patients selected at random. Data will be collected into a database that assigns a categorical cause of stroke where one exists: e.g. balloon misplacement and overly aggressive wire removal after stent deployment. Balloon misplacement will be defined by the presence of collateral flow from the superior thyroidal artery. Overly aggressive wire removal will be defined by the presence of the wire snagging the stent during retrieval without appropriate pause and attempt to unsnag it. Other etiologic categories associated with stroke will be recorded from core lab files and include: timing of stroke relative to procedure (intra-procedural, post-procedural, post discharge), sidedness of stroke (ipsilateral, contralateral), balloon sizing, adequacy of embolic protection location (regardless of proximal or distal mechanism), stent placement, lesion characteristics, and aortic arch characteristics (where available).

B. Statistical Procedures

A chi-squared test will be employed to compare the categorical variables designated among our patients with carotid artery stenosis as abnormal angiogram (yes/no) and stroke (yes/no). Based on review of stroke angiograms from the ARCHeR trial, we estimate that at least 50% of stroke angiograms analyzed in our study will have evidence of balloon misplacement and/or aggressive wire removal after stent deployment. In order for this estimate to achieve a power of 80% with an alpha-error rate of 0.05 in our population of 40 stroke and 80-non-stroke patients, we expect the maximum percentage of abnormal angiograms analyzed in the non-stroke population will be 20%.

3. Study Procedures:

Angiographic analysis will be conducted by an expert interventionalist blinded as described above. A total of 120 angiograms will be reviewed over an estimated period of 1 month. The angiographer will record his/her impression as described above into a database from which statistical analysis will be conducted later.

4. Study Drugs or Devices:

- ARMOUR: Mo.Ma proximal cerebral protection device (Medtronic Invatec, Frauenfeld, Switzerland)
- EMBOLDEN: Embolic protection system for neuroprotection (W.L. Gore)
- EPIC: FiberNet Embolic Protection Ssytem in Carotid Artery Stenting Device (Lumen Biomedical, Inc.)
- EMPiRE: Flow reversal system for neuroprotection (W.L. Gore)

5. Study Questionnaires: N/A

6. Study Subjects:

A. Inclusion Criteria:

General: patients ≥18yo, single lesion carotid artery stenosis using a femoral arterial approach, willing to adhere to follow-up, understands the nature of the procedure and provides informed consent.

Angiographic: target lesion ≥80% stenosis for asymptomatic patients and ≥50% stenosis for symptomatic patients (ipsilateral TIA/stroke within 6 months), target lesion is within the ICA and/or involves the bifurcation of the CCA, ECA diameter where Mo.Ma device (W.L. Gore) will be positioned is 3-6 mm, and CCA diameter where Mo.Ma device will be positioned is 5-13 mm.

Angiograms Included in Present Study: patients who experienced stroke/TIA intra-procedure or within 30 days post-procedure. Patients in whom CAS was aborted, referral for CEA was made, and stroke/TIA occurred during or after CEA within 30-days of the original CAS were also included. We are including this last group because even though stroke/TIA occurred secondary to CEA and not CAS, referral for CEA was made due to stent device failure and/or improper patient selection.

B. Exclusion Criteria:

General: Chronic or PxAfib not treated by Coumadin, prior stenting of ipsilateral carotid artery, life expectancy <12 months, dementia, allergy to ASA or both clopidogrel and ticlopidine, MI within 72 hours prior to indexed procedure, CABG within 30 days of indexed procedure, major residual neurological deficit at pre-procedure neurologic exam, TIA within 48 hrs. of indexed procedure, retinal artery occlusion within 1 month of indexed proceduree, Plt<50K or >700K, WBC<3K, severe chronic renal failure Cr>2.5 mg/dL, cerebral carcinoma or sarcoma, PVD precluding safe femoral artery sheath insertion, and patient unable to undergo insertion of temporary pacemaker.

Angiographic: target carotid artery is completely occluded, CCA ostium has stenosis requiring treatment, multiple ICA stenoses that one stent cannot cover, ipsilateral stenosis that requires

treatment, IC tumor/AVM/aneurysm requiring treatment, inability to position a stiff 0.035'' guidewire in the ECA, contralateral occlusion of the ICA and vertebral arteries, and aortic arch anatomical anomalies that preclude safe placement of the device.

Angiograms Excluded from Present Study: unreadable or incomplete angiograms (including those from patients who experienced stroke/TIA).

7. Recruitment:

Angiograms will be solicited from respective device manufacturers in addition to patient histories, procedure data, and procedure outcome.

8. Confidentiality of Study Data:

Access to all patient data will be restricted to the study investigators. Research assistants for individual trials will de-identify patient names at their respective core labs. A separate encrypted file correlating patient identifiers to their study number will be stored by intermediaries. Blinding will also apply to statisticians performing the analysis. Angiograms and other study materials will be kept in a locked office with password protected computers.

9. Potential Risks:

This is a retrospective study of angiograms and therefore, there is no potential risk to the patients. The only conceivable risk is compromise of patient confidentiality, which is minimized as described above.

10. Potential Benefits:

Benefits gleaned from this retrospective review could inform the medical community as to the causes of stroke in CAS. If balloon placement and aggressive wire removal after stent deployment are found to correlate with stroke occurrence after CAS, devices and techniques could be modified with the goal of further reducing the incidence of stroke as a complication of CAS.

11. Alternatives:

N/A

12. Compensation and/or Costs to Subjects:

None

13. Radiation or Radioactive Substances:

N/A

References:

[1] *American Heart Association*. (n.d.). Retrieved March 30th, 2011, from http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/IschemicClots/Ischemic-Clots_UCM_310939_Article.jsp
[2] North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis (NASCET). N Engl J Med 1991;325:445-453.
[3] European Carotid Surgery Trialists' Collaborative Group. Randomized trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST) Lancet. 1998; 351:1379-1387.
[4] Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients (SAPPHIRE). NEJM 2004. Oct 7;351(15):1493-501.
[5] Brott TG, Hobson RW 2nd, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis (CREST). NEJM 2010. Jul 1;363(1):11-23.
[6] Gray WA, Hopkins LN, Yadav S, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. J Vasc Surg 2006. Aug;44(2):258-68.