Reflections on the Carotid Artery: 438 BC to 2009 AD
The Karolinska 2008 Award Lecture in Stroke Research

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This essay has 2 objectives. First, it summarizes the publication of the reports that have been scattered through the literature since the largest of the definitive trials have appeared dealing with extracranial carotid stenosis. Second, it discusses the major differences that have been noted between the design and conduct of the large trials.

The carotid arteries, the paired vessels delivering most of the blood to the brain, have been the subject of many observations from Grecian times to the present. The Greeks in 438 BC recognized the importance of these neck vessels. The Parthenon in Athens depicted in marble an attempt by a centaur to kill a soldier by bilateral manual compression of the neck arteries.

The carotid arteries were pictured by Vesalius. They were most elaborately described with their branches and the effects of their occlusion by Thomas Willis of Oxford in 1664 (Figure 1). In 1612, Samuel Champlain, the founder of Canada, was engaged in a battle with hostile Iroquois and a stone-tipped arrow pierced his ear, grazed his face, and entered his neck stopping, as described by his definitive biographer, “just short of his carotid artery.”

Shakespeare’s literary and drinking companion, Christopher Marlowe, died (1593) in a London pub of hemorrhage after a stabbing through the eye into the intracranial site of the carotid artery. All this was recently translated from the Latin in the rediscovered write-up of his postmortem examination3 in 1612. In 1612, Samuel Champlain, the founder of Canada, was engaged in a battle with hostile Iroquois and a stone-tipped arrow pierced his ear, grazed his face, and entered his neck stopping, as described by his definitive biographer, “just short of his carotid artery.”

Egaz Moniz introduced cerebral angiography, in a paper in Revue Neurologique in 1928, a monumental advance. Pathological neck dissections by Hultquist6 in Sweden and then Fisher in Montreal7 verified Moniz’ and Hultquist’s often overlooked observations. The way was paved for the identification of transient ischemic attack, risk profiles, and the important causes of stroke: large artery, cardioembolic, small vessel disease (lacunes), uncertain causes, dissections, and “other” less common but identifiable mechanisms and in time for extensive overuse of anticoagulants for stroke and transient ischemic attack.

Suddenly in 1954, surgery for stroke erupted with Felix Eastcott’s single case report in Lancet (Figure 3). Other writers came forward claiming to have preceded Eastcott. However, in science, the priority belongs to published work in scientific journals. Enthusiasm for carotid endarterectomy (CE) became rampant without guidelines; who will benefit and what are the upper acceptable operative complications of stroke or death? Asymptomatic subjects were referred for CE in increasing numbers. Randomized trials took over the debate launched between 1970 and 1989 and concluding in 2009 (Table 1). Comparisons of the 2 large symptomatic trials indicate important clinical and methodological differences.

Surgeons in the European Carotid Surgery Trial (ECST) were given discretion to randomize only patients they did not “believe” they could help. Records were not kept of those operated on outside the study. A comparison by decades of the relative proportions of patients entered into ECST and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) indicates that patients were omitted from ECST when they were elderly and many went to surgery and not into the trial when they had most severe stenosis. In 2.5 years, NASCET randomized 659 patients with severe stenosis, approximately 22 patients per month. In 12 years, ECST entered 429 patients, approximately 3 “severes” per month. There was no great variation between the 2 studies in the numbers of patients admitted per month with moderate or less stenosis. The presence of the most severe stenosis and the elderly represent highest risk patients and paradoxically the most likely to receive greatest benefit from CE.

Surgeons in NASCET were asked in writing to pledge randomization of all eligible patients. Center coordinators were obliged to report patients who went to CE outside the study to an office at the Mayo Clinic. David Wieber’s conclusion was: “most of those not randomized were excluded by protocol.”

Between the trials, there were striking differences in funding and staffing. NASCET had a budget for full- or part-time center coordinators who were expected to make a 25-page documentation at entry and complete a 20-page documentation of 3-monthly visits, including physical examinations and all details required to identify as closely as
possible the cause of all stroke outcome events. Funding over 11 years was expensive ($40 million US dollars). Money for each entrant was paid only when all completed forms were sent to the central office. Medical and surgical collaborators were assisted by 128 full- and part-time salaried coordinators on 5 continents during the trial’s last 2 years. ECST had funds for a small staff without center coordinators. They were short of funds for detailed cardiac studies and for initial and repeat brain imaging after outcome events.

Despite these organizational differences, the goals of NASCET and ECST were similar. The large staff to garner ongoing detail allowed NASCET to claim a scrupulous trial. By comparison, ECST was useful but more pragmatic.

Results

In the primary analysis of freedom from ipsilateral ischemic stroke at 5 years, or 30-day death in those with severe stenosis (70% to 95%), NASCET showed a clear benefit for CE with an absolute risk reduction (ARR) of 15.9% and a number needed to treat of 6 patients needed to have CE to prevent a stroke within 5 years.12,13

In NASCET’s moderate range (50% to 69%), the benefit was muted with an ARR of only 6% and a number needed to treat of 15 CEs to prevent one stroke occurrence in 5 years. At <50% stenosis, harm was done.13

ECST showed benefit in severe stenosis comparable to and strongly validating NASCET. Their early report found no benefit in patients with moderate stenosis, probably explained by a reported 9% operative 30-day stroke and death rate. In a later report, they said there was slim benefit with an ARR of 5%.10,11

It is conjectural but other than surgical skill variance, some of this interstudy difference may relate to the 14-day average lapse from randomization to CE in the ECST compared with 2 days in NASCET. Still ahead was knowledge of the substantially increased risk facing cerebral ischemic patients in the first 10 to 14 days after the first ever event.16–19

Combined Analyses

Charles Warlow, the Principal Investigator in ECST and I early on in NASCET days, determined that we would validate each individual study result and compare it with data added together, where feasible, from the combination of all basic data from both studies.

The combined analyses required that all ECST angiogram films were to be reread by the NASCET method.
Investigators from ECST devoted several months to NASCET’s database to collate the data that were gathered in common from the 2 large trials and for completeness sake, he included data from the small Veterans Affairs trial. The latter added only 3% to the compilation. These observations were able to validate the beneficial results in the severe patients and to affirm muted benefit only in the 50% to 69% group. Because both studies had detected harm in the face of a stenosis of <50%, it was no surprise that the combination of data affirmed this lack of benefit.

There were too many variables in our protocols and data gathering to make pooling a totally satisfactory strategy. With hindsight, it is my opinion that there are problems in attempting to pool data from protocols that have major differences (as examples, the discretionary randomization rule was only in ECST; bilateral and intracranial vascular images were unique to NASCET, allowing study of collaterals; central office review of all images by a single neuroradiologist was done only in NASCET, the intensive blinded review of every outcome event that was conducted by 2 neurologists, 2 surgeons, and 2 neuroradiologists on a weekly basis was unique to NASCET). If a cardioembolic stroke was called, a senior cardiologist reviewed all the data. Despite efforts to the contrary, there were some disparate definitions (for example, a lacunar stroke in ECST was based on a radiological appearance; in NASCET, a clinicoradiological description was required). Funding in NASCET for repeat brain and cardiac imaging allowed of acceptable decisions about “stroke by cause.”

Subgroup Analyses

Subgroup analyses can be misleading. They are useful and permissible only when conclusions are derived from predetermined protocol inclusions and the probability value bar is set sufficiently higher. Follow-up by subgroup must be meticulous throughout the whole trial. The likelihood of separate future studies in a randomized trial of these important and common subgroups is doubtful.

NASCET planned ahead. The protocol and investigators’ manuals and all 3-monthly in-person follow-up visits were devised deliberately to keep the data needed for these subgroups in focus. Completion and early submission to the central office gave time to check for completeness and signaled that the patient had not been lost. Analyses of all of these initially identified subgroups have been published in peer-reviewed journals. Much of the work was done by collaborators who came to the database for periods varying from days to months. A summary is presented here for each of these predefined subgroups.

Throughout the grades of stenosis, there is a gradual increase in risk reaching its highest at 80% to 95%, but the benefit increases with the risk (Figure 1 in Inzitari et al21; validating similar observations from ECST as were those of the following 2 groups).

The elderly (>75 years), despite being at greater risk treated medically versus those younger, when free of other organ failure benefit most from CE with a number needed to treat of only 2 for men with severe stenosis and 3 for those with 50% to 69% stenosis. Old age is not a barrier for CE.22

Contralateral occlusion adds to the perioperative stroke and death rate but the long-term outlook significantly favors CE.23 Absent or minor evidence of collateral supply increased the operative risk, but CE proved beneficial in follow-up (intracranial angiographic data were not sought in ECST).

Individual investigators were asked to indicate the cause for each outcome of stroke. Trained nurse-practitioners acting with stroke research fellows in the central office pursued any doubtful or uncertain conclusions; if necessary, the centers were asked to acquire more data (eg, extra history, rhythm monitoring, or echocardiography) so that we were reasonably certain of stroke by cause (large artery, lacunar, cardioembolic, or “other and unknown”). At 5 years, 731 patients experienced 1021 ischemic strokes of which 68.4% were considered large artery, 22.1% uncommon or unknown, 6.9% lacunar, and 2.6% cardioembolic.25 The low number of cardioembolic strokes results from our protocol decree that any one with a potential likelihood of having a cardioembolic stroke was to be excluded. (The ECST did not gather data to allow of diagnosis of stroke outcomes by cause.)

Asymptomatic contralateral stenosis was present in 1820 of the MASCET patients patients; 216 had severe stenosis.21 In them, the 5-year risk of stroke by cause was: large artery 9.9%, lacunar 6%, and cardioembolic 2.1%, thus a ratio of approximately 10:8 of large artery to other than large artery strokes. Enthusiasts for CE in asymptomatic disease must bear in mind that almost half of the strokes that they are hoping to prevent are not of the large artery variety (no validation from ECST, no routine bilateral angiograms).

Patients with “probable” lacunar stroke at randomization showed benefit from CE, although the ARR (giving stroke-
free survival) was only 9.0% at 3 years; it compared with 15.2% with nonlacunar events at entry.\textsuperscript{26} The number of events were too few to be given unequivocal credibility. Unfortunately, NASCET and ECST used dissimilar definitions for lacunar stroke so that our data cannot be aggregated or compared.

Nonprotocol subgroup phenomena arose unexpectedly during the early days of NASCET. They were not conditions with preplanned analyses but were of sufficient interest to warrant post hoc surveillance. Most were drawn to our attention by collaborating centers. The pertinent study of all related outcomes was reported every 3 months to our central database.

Our Tel Aviv collaborator, Jonathan Streifler, had noted the bad effect of widespread white matter changes producing operative complications. The final analyses of patients with widespread leukoaraiosis confirmed higher than acceptable operative complication rates and in long-term follow-up, these individuals had a high risk of lacunar stroke.\textsuperscript{27} (The absence of repeated brain images in ECST denied validation of these observations.)

Collectively, the operative complication rates and the poor long-term outlook strongly suggest that individuals with severe and widespread white matter changes are not rewardable candidates for CE. Recent observations by Palumbo et al report an increased risk of intracerebral hemorrhage if patients with extensive leukoaraiosis are treated for ischemic events with thrombolysins.\textsuperscript{28}

Kappelle, NASCET's Utrecht collaborator, proposed the hypothesis that intracranial stenosis (tandem to the randomizable neck lesion) was not the added risk to CE we had postulated. From our database, he produced the evidence, yet to be validated by other studies, that these individuals with mild to moderate intracranial stenosis benefit from CE at no extra risk.\textsuperscript{29}

Again early in NASCET from our Dallas center, Morgenstern came to enquire about the safety of operating on patients with ≥95% stenosis (severe enough to produce poststenotic narrowing and with marked anastomotic ophthalmic artery flow). The term near occlusion was coined. His temporary conclusion was that CE could be done safely. At the time of our final analyses, Fox identified 137 such patients.\textsuperscript{30} The characteristic radiographic appearances were delineated. The medically treated risk is as low as if they had only moderate stenosis, and combined with the 125 in ECST, the ARR favoring CE is lower, only 7.4%. These figures may be artificially low due to important follow-up differences in protocol. The week after the end of the severe stage of NASCET, the investigators felt compelled to recommend to the physicians of all our “severe” patients that we had shown that they benefited clearly from CE and patients were advised to discuss with their medical advisors the need for them to be considered for CE if they were in the medical arm of the trial. Follow-up without a medical control was lost in approximately half of NASCET’s patients but in only 1% of the ECST group. These differences indicate that combining data is invalid in this subgroup. From our NASCET analyses, we consider near occlusion a legitimate but cautious indication for CE in expert hands.

Women’s benefit after CE was examined by Alamowitch, a Paris collaborator.\textsuperscript{32} With severe stenosis, women receive substantial benefit (ARR, 15.1 versus 17.3 for men). At 50% to 69%, women with stenosis had no real benefit (ARR, 3.0%); men with similar moderate stenosis had an ARR of 10.0%.

With a higher score of 7 risk factors, benefit for women with moderate stenosis emerges as the risk profile accumulates according to the following formula:

1. 3 points for: hemisphere not retinal event, diabetes, prior stroke;
2. for age over 70, stroke not transient ischemic attack; and
3. for severe high blood pressure and a history of myocardial infarction.

At a total score of 8 or more, CE for women gives muted benefit with an ARR of 8.9% and can be recommended.

(No similar observations exist for comparative validation.)

In the medically assigned randomized patients (n = 615) with moderate or severe stenosis in NASCET, 198 had only retinal and 417 had only hemisphere presentations.\textsuperscript{33} Medical therapy in those with amaurosis fugax alone exhibited less than half the risk of stroke compared with patients presenting with recent hemisphere events. CE was only beneficial if male, a history of hemisphere event, intermittent claudication, stenosis 80% to 95%, or no collateral circulation. The risk of stroke increased with an increasing number of these factors and CE is increasingly beneficial.\textsuperscript{34}

Intraluminal thrombus is quite common and ominous. Most often the thrombus lies distal to a severe stenosis. Found in 5.5% of NASCET patients with 85% to 95% stenosis, the 30-day risk of stroke or death was tripled for patients medically treated in the presence of a clot compared with it being absent. The risk for CE was doubled when it was seen. Empirical management could be a delay of CE for 1 month during which heparin followed by warfarin may be given, but the ideal management is untested scientifically, may never be available, and was not mandated. Operating while thrombus is present imposes a high risk of perioperative stroke.

Ultimately, CE is not contraindicated and benefit may be improved if CE is delayed awaiting resolution of the thrombus.\textsuperscript{35}

### Table 2. Asymptomatic Subjects

<table>
<thead>
<tr>
<th>Trial Years</th>
<th>No.</th>
<th>Principal Investigator of Trial (Acronym)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985–1993</td>
<td>444</td>
<td>Hobson (Veterans Affairs)\textsuperscript{38}</td>
<td>Negative: reduced transient ischemic attack, not stroke</td>
</tr>
<tr>
<td>1987–1993</td>
<td>1662</td>
<td>Toole (ACAS)\textsuperscript{39}</td>
<td>Marginal (ARR, 1%); for stroke in all vascular territories, including, ipsilateral, contralateral, and vertebrobasilar stroke</td>
</tr>
<tr>
<td>1993–2003</td>
<td>3120</td>
<td>Halliday, Thomas (ACST)\textsuperscript{40}</td>
<td></td>
</tr>
</tbody>
</table>
Randomized Trials in Asymptomatic Carotid Stenosis

Hobson conducted a Veterans Affairs trial of 444 subjects\textsuperscript{36} published in 1993. No benefit was seen in stroke reduction versus the medical group. Transient ischemic attacks were less in the 211 surgical versus the 233 medical. The trial should not have claimed benefit in the surgical group and speculatively the lack of progression to stroke may have been the result of aspirin in both groups.

The first large trial of asymptomatic subjects was The Asymptomatic Carotid Atherosclerosis Study (ACAS).\textsuperscript{37} The result, with an acceptably low postoperative complication rate, was significant favoring CE, but the ARR was merely 1% per year in a condition known to have an annual risk rate medically treated of 2% per year. The number needed to treat was unacceptably high: >65 CE procedures were needed to prevent a stroke in 2 years. Discouraged by these marginal benefits, a second larger trial was conducted in Europe (Asymptomatic Carotid Surgery Trial [ACST]). Similar annual benefit was obtained and it was reported to add strength to the ACAS conclusions “that if the perioperative risk of stroke and death does not exceed 3% CE is worthy of recommendation.”\textsuperscript{38}

It was suggested in a British Medical Journal editorial by Toole that populations should now be screened to find asymptomatic subjects with carotid stenosis \( \geq 60\% \) by ultrasound.\textsuperscript{39} Committees of the American College of Physicians\textsuperscript{40} and of the American Academy of Neurology\textsuperscript{41} and many neurologists have spoken against this suggestion. Vascular surgeons have been enthusiastic to continue the custom of performing CE in asymptomatic subjects. The ACAS Trial and the European Carotid Surgery Trial have many things in common, but there are compelling differences disallowing aggregating or pooling the results of the 2 trials. First of all, the European trialists strayed from the custom of all the other large carotid trials wherein the primary analysis focused on freedom of stroke in the territory of the stenosis and the CE. In the European trial, the primary analysis counted stroke in any vascular territory. The leap of faith required here was that strokes in any of the arterial territories supplying the brain could benefit from a single artery procedure. This is an improbable postulate. The ACST investigators have been invited to report comparative Kaplan-Meier survival curves for ipsilateral strokes. This is still awaited. This trial also gave surgeons discretion to select out from the trial all subjects whom they “felt” or “believed” would benefit by CE rather than being randomized.

The trials are not comparable. Neither have anything to report about a higher risk group. Neither of them identified an increasing risk based on increasing degree of stenosis. There is now some reason to be hopeful that there is an identifiable small group at increased risk. From a longitudinal followed large group of asymptomatic subjects, Spence has identified “hits” in transcranial Doppler in patients who prove to be at higher risk of stroke than those without this suggestive evidence of embolization from the stenosing plaque.\textsuperscript{42} Their outlook for stroke is substantially higher than those without this suggestive evidence. A randomized trial of these individuals to affirm that they will do better with CE has yet to be done. Because of the low numbers of events in a low-risk group of patients, it may never be done. The use of CE for asymptomatic subjects remains dubious, but risk profile management is strongly indicated.

Recent Medicare surveys have exposed the distressing fact that approximately 60% of US vascular surgeons are operating on these subjects with a complication rate greater than 3%.\textsuperscript{43} The subjects would have been better off left alone with vigorous and prolonged risk profile treatment.

Physicians should refrain from referring patients to surgeons and centers where the operative complication rate has not been obtained by ongoing independent audit and the results readily available. Subjects who are being advised to have CE for asymptomatic lesions should be apprised of the likelihood that the strokes they are facing are going to be strokes not from the stenosed artery, but from other causes in a ratio of 8 to 10.

Disclosures

None.

References


Key Words: carotid artery | carotid endarterectomy | carotid stenosis | prevention
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