

Evidence Based Medicine

How should physicians practically approach symptomatic and asymptomatic carotid stenosis?

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The North American Symptomatic Carotid Endarterectomy Trial-NASCET AND Asymptomatic Carotid Atherosclerosis Study-ACAS:

Why are these studies important and noteworthy?

Carotid endarterectomy was first introduced in North America in 1954 and since then surgeons were performing this procedure for stroke prevention without much evidence of its efficacy. In 1988 the NASCET investigators set out to determine if CE was beneficial in patients with carotid stenosis and TIA or partial stroke, in other words symptomatic patients.

The same questions applied to patients who had no prior history of TIA or infarction. Therefore in 1987, the ACAS investigators designed a study to find out whether the addition of CE to aspirin plus risk factor modifications will affect the incidence of TIA or infarctions in patients with asymptomatic but haemodynamically significant carotid stenosis in at least one artery.

In the Pakistani perspective, it is important to know what kind of benefits can be expected from such an invasive procedure, and what should be the acceptable risk while undertaking them.

Who were the participants?

NASCET was conducted at 50 centers across USA and Canada for severe disease and patients with moderate disease were recruited from 106 centers. The selection of these centers was based on very stringent criteria. Each center had a rate of <6% for stroke and death occurring within 30 days of operation for at least 50 consecutive CE performed within the previous 24 months. Six hundred and sixty two patients with high-grade stenosis were enrolled between January 1, 1988 and February 21, 1991. At this point, randomization of patients with high grade stenosis was terminated due to evidence of treatment efficacy with CE. These were patients who had experienced within the past 120 days, one or more TIA or minor stroke, and had ipsilateral stenosis of more than 30% and less than 100%. Patients who were 80 years of age or more and who had risk factors for cardioembolic strokes were excluded. For the moderate stenosis group, patients were eligible if they had symptoms of focal cerebral ischaemia ipsilateral to a stenosis of 50-70

percent in the ICA, within 180 days, as shown on selective angiography. Octagenarians were not excluded from this part. Of the 2226 patients with moderate stenosis, 1118 were assigned to medical therapy and 1108 got surgical therapy. There were 858 eligible patients with 50-69% stenosis, and 1368 had <50% stenosis.

ACAS was carried out at 39 centers across the USA. Candidates were eligible who were between the ages of 40 and 79 years and who had unilateral or bilateral surgically accessible stenosis of the region of the bifurcation of the common or internal carotid artery of at least 60%. Those who had history of TIA or stroke were excluded. During the 6 years of the study, more than 42,000 patients were screened and 1662 patients were randomized, 825 to the surgical arm and 834 to the medical arm.

What was the intervention?

In NASCET participating physicians applied the best available medical therapy to all treatable risk factors in all patients: Antiplatelet with 1300mg Aspirin per day or a lower dose if necessitated by side effects and antihypertensive, anti lipid and anti diabetic therapy for all requiring it. Those in the surgical arm also underwent CE, the procedure of which was left to the surgeon's discretion.

In ACAS, All patients received 325 mg of regular or enteric-coated aspirin daily. Stroke risk factors and their modification were reviewed with all patients at the time of randomization and again during subsequent interviews and telephone follow-ups. This included discussion of diastolic and systolic hypertension, diabetes mellitus, abnormal lipid levels, excessive consumption of ethanol, and tobacco use. In addition, patients randomized to the surgical arm received the normal evaluation and care of a surgical patient. They were scheduled to undergo CEA within 2 weeks of randomization.

What was the outcome?

In NASCET, 69% of the patients were males, more than 90% were whites and 69% had TIA as the entry event. Hypertension was the predominant risk factor being present in around 60% whereas diabetes was only there in less than 20% of the patients. The risk of any fatal or non fatal ipsilateral stroke by 24 months after randomization was 26% for the medical patients and only 9% for the surgical patients,

translating to an absolute risk reduction of 17% and a relative risk reduction of 64% with surgery. The surgical patients had an early disadvantage, because of the risk of perioperative stroke and death which was 1.2% but this was offset by an absolute risk reduction of 10.6% of any major stroke or death over the next two years. A secondary analysis showed that finer divisions of the degree of high-grade stenosis correlated with the degrees of risk reduction after surgery.

For the primary analysis of any fatal or nonfatal ipsilateral stroke, in the moderate stenosis group of NASCET, the five-year failure rate for patients with 50 to 69 percent stenosis was 22.2 percent for medically treated patients and 15.7 percent for surgically treated patients ($P=0.045$). This meant an absolute risk reduction of 6.5% and a relative risk reduction of 29%. Also 15 patients would need to be treated by endarterectomy to prevent one ipsilateral stroke at five years. For patients with stenosis of less than 50 percent, the corresponding five-year failure rates were 18.7 percent for medically treated patients and 14.9 percent for surgically treated patients ($P=0.16$).

In ACAS as well, more than 80% of the patients were above 60, 66% were males, and more than 90% were white. Hypertension was again the commonest risk factor, with DM present in only 20% of the patients. For the surgical group, the risk in the perioperative period was 2.3% (95% CI, 1.28% to 3.32%), whereas for the medical group it was 0.4% (95% CI, 0.0% to 0.8%). All patients randomized to the surgical group were required to have arteriography. Of the 414 patients who underwent arteriography prior to CEA, five experienced a cerebral infarction, for an arteriographic complication rate of 1.2%. The study achieved its significance after a median of 2.7 years of follow-up. The estimated 5-year risk of ipsilateral stroke and any perioperative stroke or death was 11.0% for the medical group and 5.1% for the surgical group. The reduction in 5-year ipsilateral stroke risk in the surgical group was 53% of the estimated 5-year risk in the medical group ($p=0.004$). Although not statistically significant, men had a better outcome with surgery than women with fewer operative complications.

What were the conclusions?

NASCET and ACAS were two large trials carried out

in patients with carotid stenosis. The NASCET shows that symptomatic patients with carotid stenosis of >70% derive substantial benefit from CE that persists for more than 5 years. Those with stenosis between 50-70% benefit less, and those with stenosis <50% derive no advantage from surgery.

ACAS evaluated asymptomatic patients and showed that those with greater than 60% stenosis benefit from CE, with evidence of benefit being more robust in men than in women.

How does this impact our clinical practice?

Before NASCET and ACAS, carotid endarterectomies were being performed without much evidence of their long term benefits. These two trials not just provided this evidence but also laid down standards for perioperative care in CE.

In Pakistan, carotid disease is not such a major risk factor. But in those who have the disease, surgery is definitely advisable for symptomatic individuals with greater than 70% stenosis, and perhaps also in those with moderate stenosis. For asymptomatic individuals again, it can be considered in men with greater than 60% stenosis. However, what must be kept in mind is that the benefit will only be realized at a center offering an angiography complication rate in the range of 1.2% and a carotid endarterectomy complication rate in the range of 2.1%. With higher rates of complications, the benefit will diminish. Also NASCET showed that if they have no recurring symptoms, patients have little to gain from endarterectomy after two to three years of the initial event.

We should offer this procedure to patients in centers where the perioperative complications are regularly audited.

Recommended Reading

1. The North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; 325: 445-53.
2. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG et al. *N Engl J Med* 1998; 339: 1415-25.
3. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995; 273: 1421-8.
4. Wasay M, Azeemuddin M, Masroor I, Sajjad Z, Ahmed R, Khealani BA, Malik MA, Afridi MB, Kamal A. Frequency and outcome of carotid atherosclerotic disease in patients with stroke in Pakistan. *Stroke*. 2009; 40: 708-12.