Asymptomatic Carotid Stenosis and Risk of Stroke (The ACSRS Study) Identification of a High Risk Group

Professor A. Nicolaides
Irvine Laboratory for Cardiovascular Investigation and Research
St. Mary's Hospital Medical School
London, U.K.

Rationale for the ACSRS study

Vascular surgeons often think of individuals with a cervical bruit and/or an asymptomatic stenosis of the internal carotid artery as patients with a potentially dangerous carotid bifurcation lesion who are possible candidates for carotid endarterectomy. Yet there is more to be considered in such patients and much that can be done other than carotid endarterectomy to reduce mortality and morbidity.

A prominent message in the consensus statement on the management of patients with asymptomatic carotid stenosis is that the incidence of death from myocardial infarction is three to four times greater than the incidence of stroke (Consensus Group, 1994). Thus, asymptomatic carotid stenosis is a marker for coronary artery disease and is now considered an indication for referring the patient to a cardiologist. When investigated, many such patients without cardiac symptoms are found to have severe three-vessel coronary artery disease and frequently silent myocardial ischaemia. As expressed by Hertzer, for them, this is a “unique opportunity to have their hearts investigated and treated if necessary. Such a moment may never again occur in their life-time” (Chapter 15). The consensus group also stresses the fact that, as arteriopaths, such patients should be scrutinized for the presence of vascular dysfunction in other organs. Another important message is that controlling hypertension is one of the most effective ways for reducing stroke. Although it is not certain that modification of other risk factors such as lowering cholesterol and stopping smoking will prevent stroke it will certainly reduce the incidence of myocardial infarction.

Obviously the broader investigation and management of these patients is beyond the ability and time available to the average vascular surgeon but lies rather in the province of those who have devoted themselves to this, whether angiologist, internist, neurologist or surgeon.
What about the contribution of carotid endarterectomy? Every new operation has to go through a number of stages. Firstly, it must be shown that it can be performed with an acceptably low complication rate. Secondly, it must be shown, not by immediate but also by long-term results that it confers benefit when compared to alternative forms of treatment. The third stage consists of identifying the groups of patients that derive the maximum benefit from the operation and those that derive none. Thus these three stages determine the feasibility of the procedure, provide the scientific backing and formulate the appropriate indications respectively. The fourth stage is that of obsolescence and is often the result of the development of new therapies. Although carotid endarterectomy has been performed for forty years, it has just entered the second stage. During the first stage standards and acceptable limits of morbidity and mortality were defined. Early studies such as the Joint Study of Extracranial Arterial Occlusion (Bauer et al, 1969; Blaisdell et al, 1989) with 8.14% perioperative mortality and the CASANOVA (1991) were performed during this era.

Entry into the second stage was heralded by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (1991) and the European Carotid Surgery Trial (ECST) (1991). These trials have demonstrated that in symptomatic patients with a greater than 70% stenosis, surgery plus best medical therapy, when compared to best medical therapy alone, reduces the incidence of stroke by approximately 50%. Thus, the NASCET and ECST studies have provided the evidence in support of carotid endarterectomy in a subgroup of symptomatic patients (those with a greater than 70% stenosis). It has also been established that if performed in symptomatic patients with a less than 30% internal carotid artery stenosis the effects could be harmful. In the latter category medical therapy alone was associated with less strokes (ECST 1991). We still do not know the effects of carotid endarterectomy in patients with stenosis in the range of 30-70%, presumably because the incidence of stroke in those medically treated is too close to the combined perioperative morbidity and mortality rate.

The Veterans Administration (VA), trial (Hobson et al 1993) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) (1995) both performed in North American in patients with asymptomatic internal carotid stenosis (over 50% in the VA trial and over 60% in the ACAS) have given us new insight into the role of carotid endarterectomy in asymptomatic patients. The results of the VA study and the results of the ACAS study are summarised in figure 38.1.

The annual stroke rate in the medical limb of both the VA and ACAS studies was 2%. In the surgical limb after successful carotid endarterectomy it was 1% in both studies. Stroke as an endpoint alone was not quite statistically
significant in the VA study (p=0.056) but in the ACAS it was (p=0.006). What accounted for the difference in statistical significance were the number of patients randomised (VA: n=444; ACAS: n=1662) and the perioperative combined stroke and death rates (VA: 4.7%; ACAS 2.3%). Thus, the ACAS study has provided the first scientific evidence that under certain circumstances (as defined by the patient and surgeon selection criteria) carotid endarterectomy can reduce the incidence of stroke in patients with asymptomatic carotid stenosis.

Two very important implications have emerged; the first is the importance of selection of patients and surgeons. In the ACAS study the surgeons were carefully selected so as to produce a result in which the perioperative combined stroke and mortality rate would be less than 3%. Patients were also carefully selected so that the perioperative risk, not only of stroke but also of cardiac mortality would be minimised. In the VA study the surgeons were also carefully selected but the perioperative combined stroke and death (mainly from cardiac complications) of 4.3% suggests that perhaps the patients were not as carefully chosen as in the ACAS. On the basis of the data shown in figure 38.1 it can be argued that a post ACAS clinical practice consisting of surgeons and patients more liberally selected may have a perioperative combined stroke and death rate higher than 3%. It is unlikely that it will be higher than 7.3%, this being the figure in the ECST study. If so, carotid endarterectomy may not confer benefit (Fig. 38.1).

The second implication is that of logistics and economics. Based on the ACAS results it has been calculated that in order to prevent one stroke in 5 years, approximately over 20 operations have to be performed or 100 operations to prevent one stroke in 1 year. Thus the cost of actually preventing each stroke could be so high that it would tax the health service of any country.

Where do we go from here? Carotid endarterectomy as an operation needs to enter the third stage. This can be achieved by better defining the type of asymptomatic patients that can derive the maximum benefit and those in whom the operation is likely to be unnecessary or even harmful. In order to achieve this, stratification of patients into risk-of-stroke categories is essential. Such a stratification has not yet been provided by the VA or ACAS studies partly because the necessary technology was not available at the time these studies were organised.

The Asymptomatic Carotid Surgery Trial (ACST 1994; Halliday et al 1995) chapter ?) now in progress has gone some way to remedy this. The ACST is a new European study in which patients with any degree of asymptomatic internal carotid stenosis, based on the individual surgeon’s surgical “grey” area,
are randomised into carotid endarterectomy plus best medical therapy versus medical therapy alone. This is done on the basis of duplex scanning and note is taken not only of the degree of stenosis and the type of plaque (echolucent or echogenic) but also of the presence or absence of ipsilateral cerebral infarcts on CT scanning. This study deserves wide support because it attempts to provide answers beyond those given by the VA and ACAS. It has, however, a number of potential weaknesses. The first stems from the fact that it is performed in what is now becoming the post-ACAS area, when many surgeons may be reluctant to take part, making data collection slow. The second weakness stems from the selection of surgeons and patients which is more liberal than that of the VA and ACAS with possibly higher complication rates. Thirdly, it does not utilise all the local risk factors known to increase the risk of stroke (see below). The information and necessary technology was not available when it was organised. Fourthly, so far there has not been any quality control on the noninvasive tests performed in the different centers.

Two outcome scenarios are possible. The first is that the ACST may fail to show that carotid endarterectomy confers any benefit in terms of stroke prevention. The second is that benefit may be shown, but unless the subgroups in terms of stroke risk are well defined this benefit is likely to be relatively small and similar to the ACAS results. Whatever the result it would be necessary to identify subsequently subgroups at high risk of stroke. Of equal importance would be the identification of a low risk group so that patients in such a group are spared from unnecessary and expensive operations.

A "high risk" group could be arbitrarily defined as a subgroup of patients with asymptomatic internal carotid artery stenosis that has an annual ipsilateral stroke rate of at least 4%, i.e. twice that expected (Fig 38.1). On theoretical grounds the identification of such a subgroup should not be difficult and has become the main aim of the ACSRS study.

**The ACSRS Study**

This is a multicenter study under the auspices of the International Union of Angiology aiming to determine the natural history of patients with advanced asymptomatic carotid stenosis. It is a concerted action funded by the European Commission (Biomed II), the CDER Trust (UK) and other national bodies. The plan of this project is to study a group of patients with asymptomatic internal carotid artery stenosis greater than 50% in diameter with noninvasive tests and to follow them up for five years in order to:

1. Identify a high risk subgroup that has an annual ipsilateral stroke rate greater than 4% using the significant risk factors and findings of the noninvasive tests.
2. Determine the relative value of risk factors and of positive noninvasive investigations in the identification of patients who are at high risk of developing stroke.

3. Determine the strength of associations that may exist between risk factors or findings of the noninvasive investigations.

4. Determine the proportion of all strokes and particularly ipsilateral strokes that will occur in the high risk group.

5. Determine the criteria that will identify a low risk group (ipsilateral stroke less than 1%).

6. Determine the risk factors associated with cardiovascular mortality other than stroke in patients with different grades of internal carotid stenosis.

** Eligibility **

All patients with greater than 50% internal carotid artery stenosis who have not had any ipsilateral hemisphere symptoms. Patients who had hemispheric symptoms more than one year earlier related to the opposite side (some may have had a carotid endarterectomy or may have an occluded internal carotid artery) will also be included, but will be evaluated separately. The ratio of patients with stenosis 50-70% and 71-99% should be 1:2 in order to avoid any bias from centers which may operate on patients with severe stenosis.

** Eligibility Of Centers **

Participating centres should have an active noninvasive vascular laboratory with colour duplex facility and experience in the investigation of patients with extracranial cerebrovascular disease, a neurologist, a vascular physician or surgeon, and a radiologist. Also they should be able to identify 15 to 30 individuals or patients with asymptomatic atherosclerotic carotid bifurcation disease that can be entered into the study.

** Materials And Methods **

The presence of the following clinical risk factors and their severity will be recorded for each patient: age, hypertension, cardiac status, diabetes, smoking, blood fibrinogen, serum cholesterol and its lipoprotein fractions, serum triglyceride, haematocrit, white blood cell count, presence and severity of peripheral arterial disease as well as any previous surgery and the current medication.

The following noninvasive tests will be performed:
1. Grading of the internal carotid artery stenosis using duplex scanning.
2. Grading of the degree of stenosis of the opposite internal carotid artery.
3. Carotid plaque characterisation. Plaques will be classified into the following types:

   - **Type I**: Uniformly echolucent
   - **Type II**: Predominantly echogenic with less than 50% echolucent areas.
   - **Type III**: Predominantly echogenic with less than 50% echolucent areas.
   - **Type IV**: Uniformly echogenic
   - **Type V**: Plaques which cannot be classified due to heavy calcification causing acoustic shadowing

   In addition, computerised carotid plaque characterisation will be performed on plaque images supplied by different centres thus providing an observer-independent evaluation of the carotid plaques. Software is provided to individual partner centres that wish to perform computer analysis of plaques locally.

4. Plaque ulceration. The presence of plaque ulceration if visible on duplex is noted and the ulcer size (maximum width and depth in mm) is documented.

5. Maximum plaque thickness in mm.

6. Intima-media thickness of the common carotid artery. Maximum thickness in mm 2 cm proximal to the bifurcation on each side.

7. Vessel diameter at the site of the plaque in mm.

8. Residual lumen in mm.

9. Cerebral reactivity to hypercapnia (optional test)

   Those teams who have a transcranial Doppler facility will also measure the change in middle cerebral artery velocity in response to CO₂ inhalation, or diamox test.

10. The presence and type of silent cerebral infarction on computer tomography in the corresponding middle cerebral artery territory will be recorded.

   All these risk factors are known to increase the relative risk of stroke (Table 38.1). Although each risk factor has been investigated individual studies there is no natural history study that has included several of these factors (Nicolaides et al, 1993).
Follow-up

Six monthly visits of the patients to the hospital for a follow-up carotid duplex examination to evaluate any progression of the stenosis and changes in plaque morphology.

End points

1. Ipsilateral stroke (including fatal)
2. Any stroke (including fatal)
3. Death from cardiovascular causes other than stroke
4. All other deaths
5. Neurovascular events including transient ischaemic attacks and amaurosis fugax

Sample size

The aim is to recruit 1500 patients from over 100 participating centres (15 patients from each). Patients with varying degree of stenosis should be included and as a working guideline for each centre, two thirds of patients should have greater than 75% internal carotid stenosis in order to carry out a stratified analysis.

Analysis Of Results

1. The prevalence, sensitivity and specificity of each test will be analysed.
2. Stroke free survival will be determined using life table analysis
3. The relationship between the noninvasive tests will be determined. This will demonstrate which tests are independent of each other.
4. Multivariate analysis will be performed to determine the value of each test and the combination of tests in identifying the high risk group in terms of stroke.
5. Other multivariate analysis will be performed in order to determine the value of each risk factor and noninvasive test singly and in combination, in identifying those at risk of cardiovascular death other than stroke.
6. Proportional hazards models will be used to explore the relationship between stroke free survival and different combinations of noninvasive tests.

This study has been launched to determine the natural history of asymptomatic carotid stenosis and to answer the question “Does a high risk subgroup exist?”

The identification of a high risk subgroup will provide patients who would have the potential maximum benefit from carotid endarterectomy.
have to be proven subsequently by a randomised prospective study. On the other hand, the identification of a low risk group may spare such patients from unwarranted surgery.

Equally important is the quality control inherent to the design of the study. Data collected by partner centres on forms and videotapes are being sent to the coordinating centre. The results are being checked and feed-back information is sent back to the partner centres. Centres will be visited by the coordinating team and there is provision for training of technologists from partner centres in London. One of the added values of this study is that not only will criteria emerge for the identification of groups of patients at high risk or low risk of stroke but also international standards for these criteria.
References


7. European Carotid Surgery Trialists Collaborative Group. MRC European Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 337:1235, 1991

