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The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study

Aims and results of quality control

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Aim. **The results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) study have provided the first scientific evidence that in patients with asymptomatic carotid stenosis greater than 60% carotid endarterectomy reduces the risk of stroke from 2% to 1% per year. The implications are that approximately 20 operations need to be performed in order to prevent 1 stroke in 5 years. The aims of the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study are to identify a subgroup or subgroups at a risk for stroke higher than 4% and a group at a risk for stroke less than 1% per year using systemic and local risk factors (plaque characterization) in addition to the degree of stenosis. The aim of this paper is to present the protocol and the results of the quality control.**

Methods. **The ACSRS is a multicentre natural history study of patients with asymptomatic internal carotid diameter stenosis greater than 50% in relation to the bulb. The degree of stenosis is graded using multiple established ultrasonic duplex criteria. In addition, ultrasonic plaque characterization is performed and clinical risk factors and medications are recorded. Training is provided centrally. All carotid ultrasound examinations are recorded on video-tape which together with CT-brain scans and ECG are analysed at the coordinating centre with feedback information to partner centres.**

Results. **The video recordings and analysis of data centrally with feed back information have provided quality control with a significant improvement not only in the completion of data forms but also in the grading of internal carotid stenosis and plaque recordings using ultrasound.**

Conclusion. **The high level of quality of data collected will add credibility to the results of the ACSRS study and may eventually promote the development of international standards of plaque imaging and characterization.**

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Key words: **Atherosclerosis - Carotid stenosis - Cerebrovascular accident.**

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Stroke is the 3rd leading cause of death in the Western World [1] and carotid stenosis is an important etiological factor.[2] However, in individuals with carotid bifurcation disease, only a minority experience warning symptoms, the majority having their stroke from previously asymptomatic lesions.[3] Since morbidity and mortality after acute stroke is unacceptably high, it is very important to recognize and to treat patients with carotid bifurcation disease before they develop symptoms.

The criteria for performing prophylactic carotid endarterectomy in neurologically asymptomatic patients are based on the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS).[4] This was a randomized study of 1 662 patients with asymptomatic carotid stenosis greater than 60%. It demonstrated that the incidence of ipsilateral stroke was reduced by carotid endarterectomy from 2% per year in the medical group to 1% per year in the surgical group (p<0.004). The perioperative stroke and death rate in the ACAS study was 2.3%. One of the implications of the results of the ACAS study is that approximately 20 operations need to be performed in order to prevent 1 stroke in 5 years or 100 operations to prevent 1 stroke in 1 year. The cost of these procedures is a heavy financial burden on the health care of any country.

It has become apparent that what is needed is the identification of a subgroup or subgroups at risk for stroke higher than 4%. This is obvious from the results of the ACAS [4] and Veterans Admin-

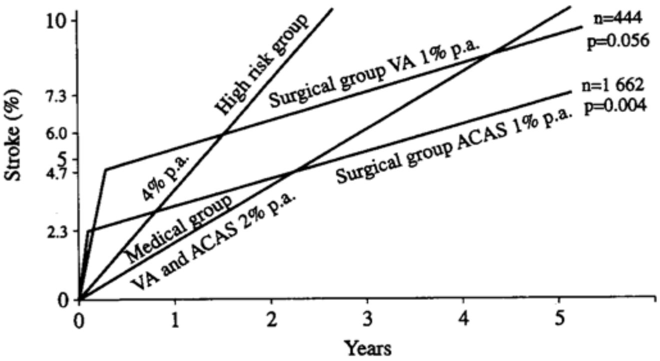

Figure 1.—Diagrammatic representation and summary of the results of the VA and the ACAS studies with stroke as an endpoint. The implications that follow the potential identification of a high-risk group are also shown.

istration (VA) trials [5] (Figure 1). The annual stroke rate in the medical arm of both the VA and ACAS studies was 2% In the surgical arm 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 it was in the ACAS (p=0.006). What accounted for the difference in statistical significance were the number of patients randomized (VA: n=444; ACAS: n=1 662) and the perioperative combined stroke and death rates (VA: 4.7%; ACAS: 2.3%). 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 for stroke but also for cardiac mortality would be minimised. In the VA study the surgeons were also carefully selected but the perioperative combined stroke and death rate (mainly from cardiac complications) of 4.3% suggests that perhaps the patients were at higher risk and not as cautiously chosen as in the ACAS. On the basis of the data shown in Figure 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%. If so, carotid endarterectomy may not confer benefit when applied more widely (Figure 1). Because of these reasons the identification of a high risk group containing the majority of strokes means that the remaining group of patients could have a stroke risk of less than 1% per year. Patients with such a low risk would be spared from an unnecessary operation with a marked financial saving.

A number of clinical risk factors for stroke such as age, hypertension, cardiac disease, diabetes, smoking, raised blood levels of fibrinogen, cholesterol, homocysteine and increased hematocrit have been established for the general population. However, in the group of patients with atherosclerotic carotid disease, these factors have a high, approximately 50%, prevalence, except for diabetes which has a prevalence of the order of 15%, and a low relative risk. Thus, they are unlikely to identify subgroups at high risk for stroke and particularly ipsilateral stroke.

The degree of internal carotid stenosis is the only well established measurement that is used to assess risk.[4] Indeed, it is currently the main criterion used to decide whether carotid endarterectomy is indicated or not, although a number of other findings related to carotid bifurcation disease and cerebral circulation (local factors) have been suggested as being associated with an increased risk for ipsilateral stroke. They consist of plaque echolucency,[6-8] plaque ulceration,[9-11] occluded contralateral internal carotid artery,[12] silent cerebral infarction on CT-brain scans [12, 13] and rapid progression of the degree of stenosis.[14]

Recent studies have demonstrated that hypoechoic plaques (echolucent) are associated with a stroke rate 2.8 times higher than isoechoic or hyperechoic plaques in relation to the surrounding tissues.[15] The ability to digitize and normalize images using linear scaling with blood and adventitia as 2 reference points by assigning grey levels of 0 and 190 to them respectively has provided the means of obtaining reproducible measurements of plaque echodensity.[16-18] Using this methodology the Tromsø study [19] has shown echolucent plaques to be associated with an adjusted relative risk for all cerebrovascular events of 4.6 (95% C1 1.1 to 18.9) independent of the degree of stenosis. In this study there was also a significant linear trend for higher risk with increased plaque echolucency.

Although the significance of individual ultrasonic measurements (*e.g.* type of plaque, gray scale median, presence of ulceration) and silent infarcts on CT-brain scans related to carotid bifurcation disease (local risk factors) in terms of increased risk has been demonstrated, there have not been any large prospective studies to assess whether a combination of some or all of these noninvasive findings can identify a high risk group for stroke.

The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study has been designed to test the hypothesis that a combination of local and systemic risk factors would be able to identify high and low risk groups for cerebrovascular events, including stroke, and cardiovascular death.

Aims of ACSRS study

The ACSRS is an international multicentre natural history study under the auspices of the International Union of Angiology aiming to determine the natural history of patients with asymptomatic internal carotid artery stenosis. It is a concerted action initially funded by the European Commission (Biomed II) and subsequently by the Cardiovascular Disease Educational and Research Trust (UK). The plan of this project is to study a group of patients with asymptomatic internal carotid artery stenosis of 50-99% in relation to the diameter of the bulb (ECST method) with noninvasive tests and to follow them up for 5 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 conventional risk factors and of positive noninvasive investigations in the identification of patients who are at high risk for stroke.
3. Determine the proportion of all strokes and particularly ipsilateral strokes that will occur in the high risk group.
4. Determine the criteria that will identify a low risk group (ipsilateral stroke rate less than 1%).
5. Determine the risk factors associated with cardiovascular mortality other than from stroke in patients with different grades of internal carotid stenosis.

Materials and methods

Eligibility of centers

Participating centers have an active noninvasive vascular laboratory with color duplex facility, a volume of patients of at least 500 per year and staff which is experienced 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 on average 15 individuals or patients with asymptomatic atherosclerotic carotid bifurcation disease that can be recruited to the study from new attendees to their practice.

Admission to the study: patient's inclusion criteria

Patients with greater than 50% internal carotid artery stenosis (ECST) on duplex scanning who have not had any ipsilateral hemispheric or retinal symptoms and are truly asymptomatic on neurological examination are eligible for admission to the study. Patients who had hemispheric symptoms related to the contralateral side may also be included provided they have been asymptomatic for the last 6 months. The ratio of patients with stenosis 50-69% and 70-99% referred from any centre should be 1:2. This is to avoid any selection bias towards lower degrees of stenosis from centers which have a policy to operate on patients with severe stenosis.

Risk factors and noninvasive investigations

The presence or absence of the following clinical risk factors and their severity is recorded for each patient: age, gender, hypertension, cardiac status (old MI or angina), diabetes, smoking, plasma fibrinogen, blood cholesterol, HDL, LDL, triglycerides, creatinine, hematocrit, weight and height. The presence of relevant family history, presence and severity of symptomatic peripheral arterial disease other than cerebrovascular, previous operations and medications are recorded also.

Grading of internal carotid artery stenosis is performed using duplex scanning on admission to the study and subsequently every 6 months. This follow-up will ensure that the patient is seen by the team including a neurologist and will provide clinical information and documentation on the rate of progression of the degree of carotid stenosis. The velocity criteria for grading the degree of internal carotid stenosis are summarized in Table I.[20-27] The centres have been encouraged and trained to use a combination of absolute velocity measurements and velocity ratios.[21-28] This is because absolute velocity measurements may result in underestimation (*e.g.* in the presence of cardiac arrhythmia) or overestimation of a stenosis (*e.g.*

TABLE I.—*Duplex velocity criteria selected for highest accuracy* (From Nicolaides* et al. *1996).*[20]

Angiographic diameter stenosis		Duplex velocity criteria				
N %	E %	20, 21 PSVIC	20-22 EDVIC	23-25 PSVIC/PSVCC	26 PSVIC/EDVCC	27 EDVIC/EDVCC
		<120	<40	<1.5	<7	
11	50					
	60					<2.6
47	70	120-150	40-80	1.5-2	7-10	
60	77		80-130	2-3.2		
65	80	150-250				
70	83		>130	3.2-4	10-20	2.6-5.5
82	90	<250		<4	20-30	
90	94				>30	>5.5
99	99			Trickle flow		

* Minimum false positive and false negative tests.
N=NASCET; E=ECST; PSV=peak systolic velocity; EDV=end-diastolic velocity; IC=internal carotid; CC=common carotid.

in the presence of contralateral severe stenosis). Table I and Figure 2 allow partner centers to express the degree of stenosis in relation to the distal internal carotid diameter (NASCET) or the bulb (ECST). In addition, the residual lumen (percent diameter reduction) is also determined in transverse section (B-mode and colour mode) provided acoustic shadowing due to calcification is absent.[29-31] The characteristics of vertebral artery flow whether cephalad, reversed or absent are also recorded. The entire duplex examination including still images of plaques is recorded on video tape.

A high frequency linear array transducer (*e.g.* 7-4 MHz) is used and the following technical ultrasound settings are observed to ensure optimum image quality for plaque type classification and texture analyses.

1. Maximum dynamic range is used which ensures the greatest possible display of gray scale values.
2. Persistence is set on low and frame rate on high the latter ensuring good temporal resolution.
3. The time gain compensation curve (TGC) is sloping through the tissues but is positioned vertically through the lumen of the vessel as there is little attenuation of the ultrasound beam as it passes through blood. This ensures that the brightness of the adventitia of the anterior and posterior walls is similar.
4. The overall gain is adjusted to give optimum image quality. This is achieved by adjustment of the gain control to minimize but not abolish noise.
5. A linear post-processing curve is used.
6. The ultrasound beam is at 90° to the arterial wall or as close to this as possible.
7. The minimum depth is used so that the plaque occupies a large part of the image.

The above settings are essential prerequisites for plaque texture analysis which is performed at the coordinating centre.

Plaques are classified into the following types according to a modification of the Geroulakos classification as listed below.[29]

Type 1.—Uniformly echolucent (black) (less than 15% of the plaque area is occupied by bright areas). If the fibrous cap is not visible, the plaque can be detected as a black filling defect only by using color flow or power Doppler.

Type 2.—Mainly echolucent (bright echoes occupy 15-50% of the plaque area).

Type 3.—Mainly echogenic (bright echoes occupy 50-85% of the plaque area).

Type 4.—Uniformly echogenic (bright echoes occupy more than 85% of the plaque area.

Type 5.—Calcified cap with acoustic shadow so that the rest of the plaque cannot be visualized.

Suspected plaque ulceration is confirmed with color flow or power Doppler and the ulcer size is measured (maximum width and depth). The maximum plaque thickness, minimum lumen and the vessel diameter (adventitia to adventitia) at the site of stenosis are also measured longitudinally and in transverse section. The intima-media thickness is measured in the common carotid artery between 1 and 2 cm proximal to the bifurcation on each side.

A resting 12 lead ECG and a CT-brain scan without contrast are performed and sent to the coordinating centre. They are reported centrally by 2 cardiologists and 1 neuroradiologist respectively. If brain infarcts are present they are classified as follows.

1. Watershed: hypodensities involving cortical and subcortical areas in the periphery of the middle cerebral artery.
2. Discrete subcortical: rounded well circumscribed hypodense lesions greater than 1 cm in size, adjacent to apparently non-involved cerebral cortex in the anterior and middle cerebral artery territory.
3. Large cortical: infarcts with cortical distribution occupying more than 50% of the entire anterior and middle cerebral artery territories.
4. Small cortical: cortical infarcts occupying less than 50% of the entire anterior and middle cerebral artery territories.
5. Diffuse white matter low density changes: areas of low density often not well circumscribed in the periventricular area.
6. Basal ganglia ischemic lesions: hypodensities in the striatum with diameter greater than 1 cm.
7. Lacunes: hypodensities in the striatum with diameter less than 1 cm.

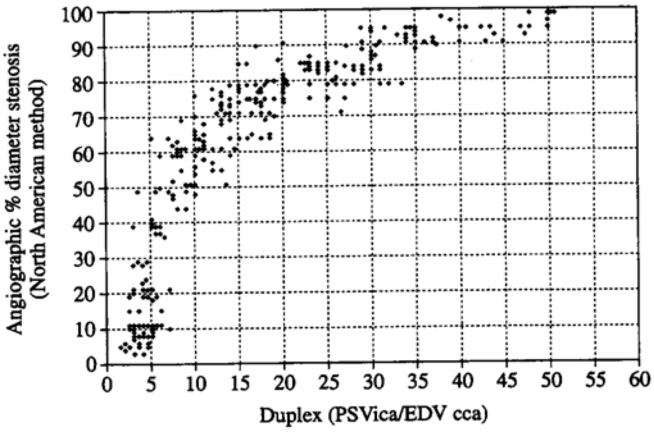

Figure 2.—The ratio of the peak systolic velocity (PSV) of the internal carotid (IC) artery to the end-diastolic velocity (EDV) of the common carotid (CC) artery (PSVIC/EDVCC) plotted against the percentage stenosis in relation to the distal internal carotid.

TABLE II.—*Percentage of adequately completed data from the first 50 centres recruited*

	Data at entry n=250 %	Data after feedback n=250 %	Fisher's exact test: p
Demographic data	96.5	99	NS
History	95	98	NS
Medication	90	96.5	0.007
Biochemical	89	91	NS
Duplex scanning	93.5	99	0.002
CT-brain scan	99	99.5	NS

Endpoints

Primary endpoints consist of ipsilateral ischemic stroke (including fatal) defined as a hemispheric neurological deficit lasting for more than 24 hours; any stroke, death from cardiovascular causes other than stroke and TIAs or amaurosis fugax.

Exit points

Exit points are any of the above endpoints, death from any cause and carotid endarterectomy or carotid stenting. As the ACSRS is a natural history study the clinician in charge is free to treat the patient in any way considered to be the most appropriate by the local team. TIAs or amaurosis fugax are often exit points because patients are offered carotid endarterectomy.

Sample size

Assumptions.—Type I: error 2%; type II: error 10%; follow-up 5 years; attrition rate: 18% per year.

Aim.—To identify a subgroup whose annual risk of ipsilateral ischemic stroke is greater than 4%.

Sample size needed.—On the basis of the above assumptions, the prevalence of clinical risk factors, invasive findings and associated neurological events in published studies, it was estimated initially that 1 500 patients would be required of which 2/3 should have internal carotid artery stenosis greater than 70% (ECST). Recruitment started in January 1996. Power calculations repeated after the first 800 patients had been recruited with a mean follow up of 18 months indicated that meaningful results could be obtained with 1 200 patients.

Quality control

The ultrasound methodology in the ACSRS includes a set of procedures designed to control quality and monitor key components of measurements. They include instrumentation settings, method of recording data, standardization of the method of scanning and personnel training. Stan-

TABLE III.—*Percentage of correct duplex recording from the first 50 centres recruited.*

		At entry n=250 %	After training n=250 %	Fisher's exact test: p
B-mode	Gain setting	75.6	90	<0.001
	TGC	60	85	<0.001
Duplex	SV alignment	80.9	95	<0.001
	Doppler angle <60 degrees	78	92	<0.001
	Absence of aliasing	91	97.5	0.003

TABLE IV.—*Percentages of correct plaque recordings from the first 50 centres recruited*

	At entry n=250 %	After training n=250 %	Fisher's exact test: p
Area of noiseless blood present	69	92	<.001
Adventitia horizontal	67	85	<.001
Anterior and posterior walls visible	79	95	<.001
Real time B-mode images present	79	99	<.001
Real time color images present	92	100	<.001

dards are defined and the results are compared to the set standards.

A recorded video of a model ultrasound examination as a guideline was initially sent to all partner centers. All examinations performed on patients recruited for the study had to be recorded in the same way and sent to the coordinating centre in addition to the data forms, ECG and CT-brain scans. All centers received feedback information on the data forms and video recordings. This was followed by a visit to the co-ordinating centre for further training after the data from 5 patients had been received. Training consisted of an overview of the aims of the ACSRS study, review of the video-recordings made by the partner centre with recommendations for improvements on the scanning technique, a lecture on digital image processing with training on image normalization and measurements of the gray scale median of plaques. Software was provided to each partner centre. Although staff from partner centres was not expected to perform image processing routinely, it was felt that knowledge of how it was done would ensure that all the necessary "ingredients" (*e.g.* near noiseless lumen of the vessel and adequate visualization of the adventitia adjacent to the plaque) would be included in the images recorded on the video tape. In a small number of cases that the video recording of the 1st visit was technically inadequate the much improved video recording made at the 1st follow up visit was used for image analysis.

Results

Table II shows the percentage of data correctly filled on the data forms by the first 50 centers at entry into the study and after feed back to the coordinating center for training. Table III shows the percentage of correct B-mode settings on the duplex equipment and the scanning technique for obtaining velocity measurements before and after training. Table IV shows the percentage of correct feature recordings as required for image analysis before and after the visit at the coordinating centre.

Discussion and conclusions

Vascular surgeons often think of individuals with a cervical bruit and/or asymptomatic internal carotid artery stenosis as patients at increased risk for stroke and possible candidates for carotid endarterectomy. Yet there is more to be considered in such patients and much that should be done other than carotid endarterectomy to reduce mortality and morbidity. The incidence of death from myocardial infarction is 3 to 4 times greater than the incidence of stroke. Thus asymptomatic carotid stenosis is a marker for coronary artery disease and is now considered an indication for investigating the patient for myocardial ischemia. When investigated, many such patients without cardiac symptoms are found to have severe 3-vessel coronary artery disease and frequently silent myocardial ischemia.[31-33] For such patients this is a unique opportunity to have their coronary arteries investigated and treated if necessary. Such a moment may never again occur in their lifetime.

Another important message that has emerged more recently is that in patients with atherosclerotic arterial disease aggressive risk factor modification including therapy with antiplatelet and lipid lowering agents reduces the risk of myocardial infarction plus stroke by approximately 50%[34-39].

The ACAS study has provided the 1st scientific evidence that carotid endarterectomy performed by selected surgeons with a low complication rate on carefully selected good surgical risk patients with asymptomatic carotid stenosis can reduce the incidence of stroke. However, the ACAS study itself has some limitations: the patients were younger than 80 years and had stable cardiac disease and the benefit of surgery for women was very small.

The Asymptomatic Carotid Surgery Trial [40, 41] is the European study in which patients with any degree of asymptomatic internal carotid stenosis, based on the individual surgeon's surgical "grey" area, have been randomized into carotid endarterectomy plus best medical therapy *versus* best medical therapy alone. According to the protocol grading of internal carotid stenosis was done on the basis of duplex scanning and note was taken of plaque echolucency (whether less than 75% of the plaque was black) and of the presence or absence, of ipsilateral cerebral infarcts on CT scanning. This study does not utilise all the features of plaque characterization now known to be associated with an increase in stroke risk. The information and necessary technology were not available when the study was organised. Also, there has not been quality control centrally using video recordings of the duplex examination that could be analysed to check that the velocities detected and recorded are interpreted the same way by different centres. For example the criteria used for grading internal carotid stenosis vary from laboratory to laboratory. Also, the methods of reporting vary so much so that the same velocities expressed as 80% stenosis in relation to the carotid bulb diameter (ECST) by some centres could also be expressed as the equivalent of 65% stenosis in relation to the distal internal carotid diameter (NASCET) in other centres. The ACST is well powered and it is expected to confirm the results of the ACAS study. However, it remains to be seen whether it will be able to provide stratification of risk in terms of severity of stenosis, plaque classification or type of CT infarction.

Although the ACSRS study was set up in 1995 and started in 1996, its aims, the identification of high and low risk groups for stroke are even more appropriate today. In addition, in this study adequate information is collected in terms of cardiac history and function to attempt to identify individuals at risk of early death from myocardial infarction. Such patients may not benefit from carotid endarterectomy if they do not live long enough after the operation.

A number of rules were stipulated in order to avoid the introduction of bias. The individuals selected for the study should be identified from new attendees to various clinics rather than from the records of the vascular laboratory. Selection of patients with asymptomatic carotid stenosis from existing records might miss those with unstable carotid plaques who may have already had their stroke. After considerable deliberation and discussion with international experts it was decided to include patients with stenosis in the range of 50-99% stenosis in relation to the bulb (ECST). This would ensure that information would be available for low and moderate grade stenosis below the 60% NASCET method used in the ACAS study which is equivalent to 77% ECST method; also the wide range of stenosis would increase the chances of stratification in relation to stenosis as performed by previous natural history studies.[6-13] A downside of this wide range was the risk of the reduction of events because of a low incidence in patients with low grade stenosis.

Over the past 2 decades ultrasound imaging has emerged as a scientific tool for reliable and reproducible, detection and quantification of carotid bifurcation atherosclerosis. It has now become the 1st line of investigation of both symptomatic and asymptomatic patients. Because of its non-invasive nature, serial examinations can be performed to recognize, document and quantify hemodynamic and grayscale changes of the arterial wall including plaques in longitudinal studies.

Ultrasound technology is advancing rapidly and persons from different backgrounds are entering the profession. Training of individuals and accreditation of laboratories have become important issues. In a single centre, ultrasound measurements can be compared with angiography and thus local quality control can be developed. Also, a proportion of scans (say 10%) can be repeated and verified by senior experienced ultrasonographers. However, in a multicentre natural history study, the question arises as to how one can ensure and measure quality. The sources of errors which produce variability in the measurements from one department to another depend on the quality and settings of the equipment and operator skill. Variability needs to be minimized.

In contrast to multicentre randomised controlled studies in which bias is avoided by the randomization itself, quality control is essential in a multicentre natural history study in which many of the selection and follow-up criteria are dependent on ultrasound. As indicated above, vascular ultrasound is operator dependent and credentialing of vascular laboratory staff varies from country to country. Technologists have historically come from diverse backgrounds (nursing, radiology, medicine) and training courses leading to accreditation have only recently been introduced to Europe. A regularly audited performance with periodical recertification is not practised in all vascular centres. In the ACSRS study high quality color duplex scanning equipment has been used by all centres and the variability of instrument settings, including criteria for grading internal carotid artery stenosis have been minimised; also expressing the stenosis in terms of the carotid bulb diameter (ECST) method and corrections to that effect have been possible.

The detailed criteria disseminated at the beginning of the study (Table I), the training provided to the staff of the partner centers, the recording of the whole duplex examination on videotape and sending the latter together with the ECG recording and CT-brain scan for reporting centrally combined with feed back information and regular newsletters ensured an adequate quality as reported. The results indicate that the goal of prospectively controlling quality in the ACSRS study has been achieved to a great extent. Monitoring quality with regular feed-back through correspondence and conferences continues. The coordinators feel confident that this level of quality control will add credibility to the results of the ACSRS study and will eventually promote the development of international standards of plaque imaging and characterization. If such methods are shown to identify individuals at increased risk of stroke they may reliably enter the clinical arena.

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