Asymptomatic Carotid Stenosis: Natural History and Therapeutic Implications

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Abstract
Carotid plaques with different degrees of carotid stenosis are a common condition in the aged population (10% or more after age 75). If the definition of "symptomatic" carotid stenosis (SCS) indicates association with homolateral neurologic hemispheric lesions and/or retinal deficits even in absence of ischemic changes at CT scan, the overwhelming majority of carotid stenoses can be defined asymptomatic (ACS).

Considering the low absolute risk of ipsilateral stroke, the additional risk of myocardial infarction, and the perioperative risk, surgery although beneficial in relative terms, should not be applied indiscriminately but rather in selected cases. There is therefore ample space for medical treatments as reduction of risk factors (especially hypertension), antiplatelet drugs, and statins, both in alternative with, as well as before and after surgery.

Introduction

The process of atherothrombotic deposition in carotid arteries, and especially in certain areas of the internal carotid artery (ICA), is the cause of ICA stenosis, a common condition with a high prevalence in the normal population (0.5% in patients over 65 y and 10% or more at age 75-85) [1]. Extracranial ICA stenosis is due to plaques mainly localized at the emergency of the ICA and in the carotid bulb. Most ICA stenoses are asymptomatic at the time of observation [2].

Extracranial ICA stenosis accounts for less than 20% of all strokes. As known, other causes of ischemic stroke are: stenosis or occlusion of intracranial arteries alone or in combination with extracranial (another 20%); cardiogenic embolism to the brain (20%), cerebral lacunae in hypertension and in diabetes (20%), and miscellaneous or undisclosed causes (20%) [1]. Atherothrombotic stenosing or occlusive lesions of the extracranial ICA are easily assessed by Echo-Duplex ultrasound investigation, a simple, non invasive, but operator dependent technology, and constitute a good model for prevention of a considerable although not prevalent number of strokes.

Intima-Media Thickness

Athero-thrombotic deposition at intimal sites of the carotid arteries, as well as of other arteries (femoral, coro-
naries) begins as a fibrotic thickening of the "intima-media complex", on the basis of hyperplastic fibro-sclerotic changes in the sub-intimal layers. Intima-media thickness (IMT) can be measured by Echo-Duplex ultrasonography in a standardized fashion usually at the common carotid artery but also elsewhere in the arterial tree.

By definition IMT does not exceed 1 mm and if increased, constitutes by itself a predictive factor for cardiovascular events (stronger for myocardial infarction than for stroke!), as an early expression of a diffuse atherothrombotic process [3].

**The Atherothrombotic Plaque in the Internal Carotid Artery**

A deposition of more than 1.5 mm constitutes an atherothrombotic plaque, mostly affecting the internal carotid emergency and bulb, and the extracranial portion of the ICA. The atherothrombotic plaque consists in a fibrous cap of variable thickness bordering a mass of tissue and blood derived materials and cells, and a "lipid pool". It includes an important cellular component containing leukocytes, macrophages and platelets, and a fibromuscular component including fibrin strands, collagen fibers, and proliferating smooth muscle cells. Carotid plaques are obviously similar in structure to plaques in the coronary and femoral arteries [4]; however, while both are submitted to high tensile strength from the blood flowing within the lumen, the excursions of the carotid wall are much larger than in the coronaries, that are supported by the heart-muscle contractions. Internal stress forces are therefore higher in the carotid wall and favour greater extension of the plaque, plaque fissuring and fragmentation, and hence microembolization to the cerebral vasculature and microvasculature.

Plaques induce narrowing of the lumen (stenosis): the extent of stenosis is easily measurable at the ICA with the Echo-Duplex instruments, capable of coupling imaging with flow velocity assessments. Internal carotid artery stenosis is considered "hemodynamically significant" when exceeding 70% of the lumen, thus leaving 30% or less of the section viable to blood flow. From a clinical point of view, a clear distinction must be introduced between symptomatic and asymptomatic internal carotid (ICA) stenosis.

**ICA Stenosis: Symptomatic**

An ICA stenosis is termed "symptomatic" [2] when associated with neurological symptoms of focal nature (stroke major and minor, TIA, amaurosis fugax ), and side-congruent (namely reflecting an ischemic lesion ipsilateral to the affected artery). As the risk of cerebral ischaemia due to ICA stenosis declines with time, the appropriate symptoms should also be relatively recent (previous 6 m or 2 y according to different criteria). The definition is essentially clinical and somewhat conventional: in fact neither the absence of cerebral ischemic lesions (at CT scan or MRI), nor the presence of other possible causes of cerebral ischemia will deny the definition of symptomatic ICA stenosis.

**ICA Stenosis: Asymptomatic**

Asymptomatic ICA stenosis is a frequent condition [5]. An ICA stenosis is defined asymptomatic when it lacks the above criteria for symptomatic stenoses, that is in absence of recent, focal and side-congruent neurological episodes. Global symptoms of cerebral non-focal anoxia as amnesia, dizziness, drowsiness, headache do not make an ICA stenosis symptomatic[2]. For inclusion in clinical trials, the definition of asymptomatic should be kept strictly clinical with no consideration for the presence of silent ischemic lesions, as disclosed by CT scan or MRI. However, it is obvious that the individual patients with such silent lesions will be considered by the clinician with a special care, in particular from the point of view of the risk-benefit ratio [2].

Thus, the definition of asymptomatic ICA is somewhat conventional and definitely not clearcut. The results of the clinical trials based on the merely clinical definition of asymptomatic ICA stenosis deserve careful individual application in the single patient.

**Risk of Symptomatic ICA Stenosis**

Conventionally, ICA stenosis is considered easily conducive to cerebral ischaemia when it exceeds 70% narrowing of the lumen section. However, as the overwhelming majority of patients with severe carotid stenosis remain asymptomatic for years and even indefinitely, it is self-evident that degree of stenosis is not the only factor conducive to cerebral ischaemia. The concept of "vulnerable" or "unstable" plaque that has become so popular in the coronary domain, can be applied also to those carotid plaques that have a predisposition to breaking and fissuring [6] and hence for embolization to the brain or sudden occlusion of the lumen, with consequent congruent neurological symptoms. Plaque ulceration, surface irregularity and, with lesser evidence intraplaque hemorrhage have been identified as factors conducive to a higher probability of a plaque to become symptomatic [2] It is however true that these features are often closely associated with higher degrees of stenosis.

Patients with ICA symptomatic stenosis have an annual average risk of stroke about 15%, namely a high risk [7]. Carotid Endo-Arterectomy (CEA) proved to be superior to antiplatelet plus standard medical treatment in the secondary
prevention of stroke and TIA in patients with ICA stenosis of more than 70%, symptomatic [8, 9].

**Risk of Asymptomatic ICA Stenosis**

Evaluation of the risk of this condition is mainly based on the ACAS study [10] in patients with moderate to severe ICA asymptomatic stenosis, in which CEA was compared with conventional medical therapy that included aspirin. In the "medical" group the risk of ipsilateral stroke was no more than 2% per year. This is less than the figure attributed for instance to atrial fibrillation (5-6%). The figure of the ACAS study (2%) is anyway higher than that obtained in observational studies as the Cardiovascular Health Study [5] where the risk of ipsilateral stroke for ICA stenosis was only 1% in a population with prevalently mild to moderate carotid narrowing.

It is however essential to know that patients with asymptomatic ICA stenosis also have a 2% per year additional risk of myocardial infarction or cardiac death [10]. Thus, the patient with asymptomatic ICA stenosis rather shows a considerable "overall cardiovascular" risk than a merely specific risk of ipsilateral stroke [11]. In the NASCET trial [8] of CEA for symptomatic ICA stenosis, a substudy of the asymptomatic contralateral ICA [12] showed that 45% of the new strokes occurring in appropriate territories were of lacunar or cardioembolic type, thus again stressing the general cardiovascular risk burden of these patients.

**ICA Asymptomatic Stenosis and Surgery**

In symptomatic ICA stenosis two large randomized multicenter studies [7, 8] established the superiority and cost-effectiveness of CEA versus antiplatelet and standard medical therapy in prevention of ipsilateral stroke.

Also in asymptomatic ICA stenosis, the ACAS study demonstrated that surgical therapy was able to reduce by 50% the ipsilateral stroke rate observed in the medical group, that is from 2% to 1% per year [10]. However in a systematic review of various trials by the Cochrane group, [13] considering also perioperative stroke or death besides subsequent ipsilateral stroke, event rates were 6.8% in the medical vs 4.9% in the CEA group, with a relative risk of 0.73 in favour of surgery. This risk reduction was borderline significant (p=0.06), and corresponded to an absolute risk reduction with CEA of only 1.9% over 3 years.

These results seem not very encouraging towards generalized application of surgical therapy of asymptomatic ICA stenosis, especially if we consider that CEA likely does not affect the global cardiovascular risk burden, while medical therapy is proven to do so.

Moreover, the cost-benefit ratio of CEA in this indication is doubtful as, according to the ACAS study, approximately 20 operations need to be performed to prevent one stroke for a 5 year follow-up, or 100 operations for a 1 year follow-up. Thus, it is recommended to perform CEA only in patients with > 70% stenosis with additional clinical or plaque related (see below) risk factors, provided the perioperative stroke/death risk rate is less than 3% [7]. From the above data and considerations, it appears evident that a better definition of the additional risk factors associated to stenosis and its degree are needed (see Note in Proof).

**Definition of Associated Risk Factors: The ACSRS Study**

The ACSRS (Asymptomatic Carotid Stenosis and Risk of Stroke Study) is a multicenter trial supported by the European Commission, coordinated by A. Nicolaides [14]. Aim of the study was to sort out within the generality of patients with asymptomatic ICA stenosis, those with a higher (ca. 4%) and those with a lower (ca. 1%) risk of ipsilateral ischemic stroke. This would allow to optimize the cost-benefit ratio in relation to CEA. Admission criteria were: patients with asymptomatic ICA stenosis > 50% excluding those with contralateral symptoms within last 6 months. Standardized requirements were issued to the Centers. Follow-up was planned to be 5 years; primary endpoints were ipsilateral ischemic strokes, TIA and amaurosis, plus cardiovascular deaths.

As a participating center, we quote here some partial results referring to a population of about 1000 patients [15]. Cardiovascular deaths were 7.6% of which 80% cardiac and only 20% due to stroke. Neurological ipsilateral events were 9.1% and 3.9% were contralateral. Independent predictors of stroke were: degree of stenosis, plaque type, hypertension duration, creatinine, and CT-infarcts. Regarding plaque type, the Echo-Duplex based classification by Geroulakos as modified by Nicolaides [14] was adopted:

- Type 1: Uniformly echolucent (hypoechoic)
- Type 2: Mainly echolucent
- Type 3: Mainly echogenic (hypechoic)
- Type 4: Uniformly echogenic
- Type 5: Calcified with acoustic shadow

It was confirmed, as in previous studies [16], that the mainly hypechoic or echolucent plaques carry a higher risk of stroke, especially when associated to inhomogeneity and surface irregularity. The aim of the study appears to be within reach: it seems indeed that ICA stenosis asymptomatic patients can be divided into a high risk group (cca. 4% per year) and a low risk group for stroke (< 1% per year), the latter including around two thirds of all patients. Application of these results will lead to more appropriate indication(s) of
surgical or interventional treatment of this condition with better risk and cost-benefit outcomes.

**Medical Therapy for Patients with Asymptomatic Carotid Stenosis**

As seen above, the patient with asymptomatic ICA is at even higher risk of acute myocardial infarction and vascular death than for stroke itself. Medical therapy whether alternative to CEA or both previous and consecutive, is essential and necessarily lifelong lasting.

Regarding antiplatelet therapy, in the present indication, we mostly deal with asymptomatic patients and hence with primary prevention in presence of risk factor(s). A recent metanalysis of primary prevention studies with aspirin [17] showed efficacy in relation to non fatal event, and especially for AMI, but neither for stroke nor for fatal events. This therefore seems what we can expect from Aspirin also in the present indication. No specific indications are available for other antiplatelet agents.

**Monitoring and control of hypertension** is essential; in hypertensives with a high atherothrombotic burden some ACE inhibitors have proved to be effective for prevention of stroke and other events.

**Treatment of obesity, hyperlipidemia, diabetes** is also crucial. The use of statins in association with aspirin is recommended in the attempt of inducing "plaque passivation" but lacks objective demonstration.

**Smoking cessation** is also essential as it has been shown to reduce stroke and AMI risk. Also regular physical activity, even moderate, decreases risk of stroke and other events.

**Dietary measures** are important: reduction of salt intake, of animal fat and cholesterol, of alcohol consumption are crucial. **Increased consumption of fish**, vegetables, fruit, antioxidants is beneficial, and intake of folic acid and vitamins B6, B12 is important to control homocysteine metabolism.

In conclusion, in asymptomatic carotid stenosis surgical (CEA) or interventional measures for stroke prevention should be limited to patients at higher risk of stroke, that can presently be better identified. For all patients with this condition medical treatment including aspirin, control of hypertension and other risk conditions, the use of ACE inhibitors and of statins, appropriate dietary measures, are essential weapons to counteract the global cardiovascular risk that characterizes these patients.

Better knowledge of the genetic factors predisposing to ischemic stroke (as for instance the two recently identified genes that control 5-Lipoxygenase and 4D-Phosphodiesterase activities) will help in identifying those patients that deserve more intense medical, surgical or interventional care, to remove or counteract the acquired and lifestyle related factors predisposing to cardiovascular events.

**Note in Proof**

Just at the time of delivery of this manuscript the results of the Asymptomatic Carotid Artery Trial (ACST, Lancet 2004;353:1491-1502) showed that CEA within 1 year versus deferred CEA halved the 5-year stroke risk (6% vs. 12%) but did not significantly reduce total and cardiovascular mortality.

**References**


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