The natural history of patients with carotid stenosis

Henrik Sillesen, MD, DMSc

Chairman, Dept. of Vascular Surgery
Gentofte Hospital, University of Copenhagen
Denmark

Abstract
Atherosclerosis is a systemic disease affecting the circulatory system throughout the body. Thus, patients with atherosclerosis of the carotid arteries are not only at risk of stroke but also of other manifestations of the disease, i.e. vascular death, myocardial infarction etc. So far, intervention trials evaluating the effect of treatment of this patient group, i.e. by surgical removal of the carotid lesion, has focussed on degree of stenosis of the lesion. However, many other factors may be of importance: local factors of the lesion (morphology, degree of stenosis), hemodynamic factors (collateral compensation) and systemic factors (clinical symptoms, accompanying diseases, risk factor control). Recent findings suggest that plaque morphology (composition and structure) may be of greater importance than the degree of stenosis and it may be speculated if current indications for carotid endarterectomy are optimal.

Patients suffering transient ischemic attacks (TIA) and stroke are at high risk of recurrence or death. The 5 year stroke-rate following a TIA or stroke is 25-40% and approximately 50% of stroke patients will die within 5 years (1-3). Atherosclerosis of the carotid artery is a common condition affecting a large proportion of the elderly population. Atherosclerosis is a systemic disease, not limited to certain parts of the circulation, but rather affecting arteries throughout the body. Thus, patients with symptomatic atherosclerosis in one organ, i.e. the heart (IHD: ischemic heart disease), are not only at risk of myocardial infarction but also of atherosclerotic manifestations i.e. from the brain (stroke) or from the peripheral circulation (claudication or critical limb ischemia).

Patients who previously suffered a stroke are at 2-3 times higher risk of myocardial infarction compared to the background population. Similarly, patients with IHD are at 3-4 times greater risk of stroke (1-3). Patients with peripheral arterial disease (PAD) are at 3-4 times higher risk of developing IHD compared to the background population (3).

Atherosclerotic deposition in the carotid artery begins as wall thickening and when the intima-media complex (IMT) exceeds 1 mm the term plaque is used. Luminal narrowing is most often expressed as reduction in diameter, i.e. a 70% stenosis denotes a lesion reducing the diameter to 30% of the “normal” diameter. However, more precise definitions are needed. The most common method relates the minimal residual diameter to that of the normal distal vessel – also termed the NASCET criteria, derived from the differences between methods for measurement of degree of stenosis in the two large randomised trials of carotid endarterectomy: ECST and NASCET. However, other factors might be taken into account when evaluating the natural history of carotid stenosis:

- Local factors (plaque/stenosis)
- degree of narrowing
were not selected for surgery, i.e. because of a severe cardiac condition, which may alter their outcome and thereby result in higher risk in this patient category.

**Plaque morphology**

For more than 10 years carotid plaque morphology has been identified as a possible independent risk factor, however, only within the latest years has stronger evidence evolved. The idea behind looking at the vessel wall rather than evaluating the residual lumen reflects the current theory of why atherosclerosis may result in sudden thrombosis – the mechanism today considered the major cause of sudden death in IHD patients. Unstable atherosclerotic lesions are characterised by a lipid-core only separated from the lumen by a thin fibrous cap. With rupture of the fibrous cap the highly thrombogenic lipid-core is exposed to the circulating blood resulting in thrombus formation (7). Either the carotid artery may occlude or the thrombus may break loose and result in cerebral embolism. In both cases a stroke may result. As opposed to the unstable lesion is the plaque mainly composed of fibrous tissue or were the lipid-core is covered by a thick fibrous layer (cap) – the stable plaque.

Studies evaluating the risk of morphologically different carotid plaques are based on the different methods of quantification: either visually or computerised. In the former, the investigator visually (and subjectively) describes the plaques appearance with respect to reflectance of the B-mode ultrasound signal: strong echoes (echogenic) appearing more or less white on the ultrasound image or the opposite, poorly reflection of echoes (echolucent) appearing dark grey or maybe even invisible. In the latter case, the identification of the lesion is helped by the information obtained when performing the Doppler flow velocity evaluation. In the computerised methods, the plaque is outlined and a histogram reveals the grey-scale distribution within the plaque area. A grey-scale median (GSM) may be derived and expresses the overall reflectance of the lesion.

In a study from our own group 246 patients, not found eligible for endarterectomy, were followed for an average of 4 years. The risk of stroke was found to be related to the GSM value, the lower the higher risk, but not significantly related to degree of stenosis. Using Cox regression to evaluate the relative risk, the echolucent plaques were found to result in 2-3 times more ipsilateral strokes than echogenic, similarly stenotic lesions (8). Similar finding have been reported by other groups (9-11).

Other morphological features include irregularities of the plaque surface – by some authors termed ulcerations when exceeding 1 mm. A few retrospective paper’s have described the outcome of large ulcerated plaques and one group has reported a high stroke risk associated with large ulcer’s (12). However, these early studies were based on angiographical...
detection of the surface irregularities, a method which today is used less and less. Larger recent series based on other technologies are lacking. Thus, the prognostic value of surface characteristics remains unsolved today.

The role of hemodynamic parameters, i.e. is the risk the same in patients with equal severely stenotic lesions, but with differences in the ability of the Circle of Willis to serve as collateral source? In other words, is embolism into or thrombosis of a cerebral vessel with a low perfusion pressure not result in greater cerebral damage than if it had occurred in a vessel with normal hemodynamics. Laboratory data and data from patients with occluded carotid arteries support this theory (13) however, prospective data are lacking.

**Conclusion**

The risk of stroke in patients with carotid stenosis is related to the degree of stenosis and to the composition of the plaque (plaque morphology – echolucency). Other factors may be of importance, however, good data has so far failed unequivocally to prove this.

It may be speculated if previous randomised trials, today serving as the evidence for choice of treatment, are representative of the patients we are treating today. One major concern is that the level of risk factor control is much better than 15-20 years ago, when patients were randomised into these studies. Especially, statin treatment, which was not available at that time, is becoming widespread and smoking cessation among atherosclerotic patients is more common today. In addition, other medical preventive therapy may be improved as well, i.e. treatment of hypertension, diabetes etc.

**References**

4. European Carotid Surgery Trialists’ Collaborative Group: MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991; 337:1235-43
8. Gronholt MLG, Nordestgaard BG, Wiebe BM, Wilhelmy JE, Sillesen H: Low gray scale values of computerized ultrasound images of carotid atherosclerotic plaques are associated with increased levels of triglycerid-rich lipoproteins as well as increased plaque lipid content. Circulation 1998;97:34-40.