The natural history of patients with carotid stenosis

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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. Sofar, 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
treatment. However, most of the literature evaluating patients with
carotid stenosis mainly report on degree of stenosis in relation
to outcome, although more recent studies also included mor-
phology of the carotid lesion. Natural history studies stratify-
ing for other atherosclerotic manifestations and risk factors are
scarce (lacking).

**Degree of stenosis**

The best available data concerning risk of carotid stenosis
stratifying for degree of stenosis are that from the randomised
trials: ECST, NASCET and ACAS; the latter dealing with
asymptomatic patients and the first two evaluating patients
with previous symptoms of cerebral ischemia. In these studies,
only patients eligible for surgery were included. Therefore,
these data may not necessarily reflect the average patient seen
in clinics since the trials excluded a number of patients and it
is well recognised that patients included in trials like these, and
who accept participation, generally are in better “shape” than
those who are rejected or who decline. However, randomised,
controlled trials are the best means for testing if one treatment
is superior to another (surgery versus best medical treatment).

Symptomatic patients: Patients with carotid stenosis of
70% or more carry a 3 year risk of ipsilateral stroke or death
of approximately 30-35% (4,5). With moderate degree of
stenosis (50-69%), the risk is 15-20% over 3 years. An inter-
esting finding in the medically treated patients, observed both
in the NASCET and ECST trials, was that the risk of stroke
from the side stenotic carotid artery apparently declined 2-3
years after randomisation (and after the initial qualifying cere-
bral event) and then remained at the same relatively low level
as that of the contralateral side (1-2%/year). This implies that
other factors than the stenosis is of importance for the risk of
stroke.

Asymptomatic patients: The ACAS trial included patients
with 60% stenosis or greater and found the annual stroke risk
in the untreated arm to be 2.2%, the risk remaining more or
less the same throughout the trial (6).

Other studies have reported on risk of carotid stenosis and
reported similar or higher risk, however, there may be selec-
tion bias in a number of these studies because these patients
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 athero-
sclerosis 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 tis-

tue 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 quantifi-
cation: either visually or computerised. In the former, the
investigator visually (and subjectively) describes the plaques
appearance with respect to reflectance of the B-mode ultras-
ound 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 per-
forming the Doppler flow velocity evaluation. In the comput-
erised 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 256 patients, not found eli-
gible 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 rela-
tive risk, the echolucent plaques were found to result in 2-3
times more ipsilateral strokes than echogenic, similarly stenot-
ic 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**

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