Asymptomatic Carotid Stenosis: Natural History versus Therapy

José E. Cohen MD[1,2] and Eyal Itshayek MD[1]

[1]Department of Neurosurgery and [2]Endovascular Neurosurgery and Interventional Neuroradiology Unit, Hadassah University Hospital and Hebrew University-Hadassah Medical School, Jerusalem, Israel

KEY WORDS: carotid stenosis, carotid endarterectomy, carotid stents, stroke, atherosclerosis

IMAJ 2010; 12: 237–242

Internal carotid artery atherosclerotic stenosis is responsible for a significant proportion of transient ischemic attacks and for approximately 30% of ischemic strokes [1]. Patients suffering a TIA and stroke are at high risk of stroke 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 [2,3]. Mortality from myocardial infarction in stroke survivors can be as high as 39% within 5 years, underlining the importance of recognizing concomitant coronary disease in patients presenting with stroke or TIA.

Randomized, prospective multicenter studies have demonstrated the superiority of carotid endarterectomy over medical therapy in recently symptomatic patients with severe carotid stenosis [4,5]. However, therapeutic recommendations for asymptomatic patients are still uncertain and controversial [6,7].

At present, the natural history of an asymptomatic carotid artery stenosis in the individual patient is unknown

Population-based epidemiological studies using ultrasound show that the prevalence of asymptomatic ICA stenosis of ≥ 50% varies between 4% and 8% in adults [8]. Identifying patient subgroups with asymptomatic ICA stenosis and an increased risk of stroke has been the goal of many studies, which focused on epidemiologic, hemodynamic, clinical and pathologic variables including the evaluation of cerebral vasomotor reactivity and the detection of Doppler microembolic signals [9,10]. However, most of the studies were unable to identify baseline clinical characteristics that predict the risk of stroke in asymptomatic patients.

TIA = transient ischemic attack
ICA = internal carotid artery

ATHEROSCLEROSIS: A SYSTEMIC DISEASE

Atherosclerosis is a systemic disease not limited to certain parts of the circulation but affecting arteries throughout the body. Thus, patients with symptomatic atherosclerosis in one organ, i.e., the heart (ischemic heart disease), are not only at risk of myocardial infarction but also of atherosclerotic manifestations from the brain (stroke) or the peripheral circulation (claudication or critical limb ischemia).

Patients who previously suffered a stroke are at two to threefold higher risk of myocardial infarction compared to the general population. Similarly, patients with ischemic heart disease are at three or four times greater risk of stroke, and patients with peripheral arterial disease are at three or four times higher risk of developing ischemic heart disease compared to the general population [3].

Atherosclerosis deposition in the ICA begins as wall thickening; when the intima-media complex exceeds 1 mm the term plaque is used. Luminal narrowing is most often expressed as reduction in diameter, i.e., an 80% stenosis denotes a lesion reducing the diameter to 20% of the "normal" diameter (NASCET criteria). However, other factors might be taken into account when evaluating the natural history of carotid stenosis.

LOCAL FACTORS: DEGREE OF STENOSIS, PLAQUE MORPHOLOGY AND COMPOSITION OF THE LESION

The risk of any ipsilateral neurologic deficit increases with the severity of the asymptomatic ICA stenosis. The published annual risk of ipsilateral neurologic deficits for asymptomatic ICA stenosis < 50%, between 50 and 80% and > 80% is 0–3.8%, 2–5% and 1.7–18%, respectively [4-10]. The majority of these neurologic deficits seem to be transient neurologic attacks or amaurosis fugax, but risk of ipsilateral stroke or permanent neurologic deficit must not be underestimated and can affect up to half of these patients. Asymptomatic carotid artery stenosis < 50%, between 50 and 80% and > 80%, carries a risk of stroke of less than 1%, 0.8–2.4% and 1–5% per year, respectively.

Carotid plaque morphology has recently been identified as a possible independent risk factor for stroke. Like atherosclerotic plaque in other vascular territories, plaque in the extracranial vessels may progress and develop ulcerations, intraplaque hemorrhage and thrombosis [11]. However, coronary plaque and carotid plaque behave in different ways. Sudden thrombosis, the mechanism considered the major cause of sudden death in ischemic heart disease, is relatively infrequent in extracranial vessels. In the coronary circulation, acute thrombotic occlusions resulting in myocardial infarction usually occur over small plaques that cause minimal hemodynamic effects [12]. In the carotid territory, there is a direct relationship between the degree of the carotid stenosis and the risk of clinical events. This relationship has been clearly defined in symptomatic patients and is less clear in asymptomatic patients.

Unstable atherosclerotic lesions are characterized by a lipid core separated from the lumen by a thin fibrous cap only. With rupture of the fibrous cap the highly thrombogenic lipid core is exposed to the circulating blood, resulting in thrombus formation [13]. Either the ICA may occlude or the thrombus may break loose and result in cerebral embolism. Studies evaluating the risk of morphologically different carotid plaques are based on different methods of quantification, either visually or computerized. In the former, the investigator visually and subjectively describes the plaque's appearance with regard to reflectance of the B-mode ultrasound signal: strong echoes (echo-lucent) appearing dark grey or perhaps even invisible. In the latter case, identifying the lesion is helped by the information obtained when performing the Doppler flow velocity evaluation. With the computerized methods, the plaque is outlined and a histogram reveals the grey-scale distribution within the plaque area. A grey-scale median may be derived and expresses the overall reflectance of the lesion. The risk of stroke was found to be related to the GSM value: the lower the GSM value the higher the risk [14,15]. Large ulcers have been related to a high risk of stroke [16].

It is of paramount importance to recognize concomitant coronary disease in patients presenting with stroke or TIA

DIAGNOSTIC IMAGING OF CAROTID ARTERY STENOSIS

The degree of carotid stenosis in the largest well-controlled randomized studies was determined with angiography. However, promising non-invasive techniques such as computed tomography angiography and magnetic resonance angiography are available, with sensitivity and specificity rates of between 62 and 100% subject to technique and diagnostic criteria.

Duplex ultrasound provides an excellent non-invasive, inexpensive means for assessing the degree of a stenosis and was used in the ASCT (Asymptomatic Carotid Surgery Trial). With duplex, both the peak systolic velocity and end-diastolic velocity are determined in the common and internal carotid arteries. In case of bilateral ICA disease the measurement of absolute velocities can overestimate the degree of the stenosis, and ratios of velocities are therefore recommended. The main difficulties with duplex ultrasound are the interlaboratory variations in stenosis evaluation and interpretation criteria. Therefore, recommending CEA based solely on duplex ultrasound remains a matter of debate. A proposed strategy is to combine imaging techniques. Duplex ultrasound is used as the primary screening tool for carotid artery stenosis, and if revascularization is considered MRA or CTA is performed. In case of discrepancies angiography is recommended.

HEMODYNAMIC PARAMETERS

- *Local parameters*: Atherosclerosis is thought to occur at the carotid bifurcation because of the effects of hemodynamic sheer stress, turbulence, boundary separation, and blood stagnation. The geometry of the carotid bifurcation, specifically the ratio of the internal carotid area to the common ICA area and the bifurcation angle, produces vortex flow and increased contact of platelets and atherogenic substances at the site of maximal plaque development [17].
- *Cerebral parameters*: Significant stenoses may result in a pressure drop ipsilateral to the stenosis. Several mechanisms are activated in a stepwise fashion to compensate this situation. Collateral pathways such as the primary collateral circulation through major anastomotic channels of the circle of Willis (anterior and posterior communicating arteries), the ophthalmic anastomosis, and the leptomeningeal collateral supply (secondary collateral supply) are sequentially opened. If the hemodynamic compensation is insufficient the brain tissue is capable of increasing the oxygen extraction from the circulating blood. An additional mechanism includes vasodilatation of the cerebral arterioles to ensure better tissue perfusion by decreasing vascular resistance. Cerebrovascular reserve capacity measurements are believed to be a valuable tool for selecting patients with significant carotid stenosis who are at higher risk for hemodynamic strokes [18,19].

CLINICAL PARAMETERS: RISK OF STROKE IN PATIENTS WITH ASYMPTOMATIC ICA STENOSIS

Most short-term (2–3 years) natural history studies of asymptomatic ICA stenosis have reported an annual risk of ipsilateral

GSM = grey-scale median

CEA = carotid endarterectomy
MRA = magnetic resonance angiography
CTA = computed tomography angiography

stroke of approximately 1% to 3%, depending on the degree of stenosis [20-22]. Long-term studies are consistent with short-term follow-up studies indicating a stroke risk of less than 1% per year in patients with < 50% stenosis and about 1% per year in those with > 50% stenosis [23]. This finding shows that the low risk of stroke remains constant over time and that the risk increases slightly with increasing degree of stenosis.

When evaluating individual stroke risk based on the results of these studies, one has to remember that patients with ICA stenosis are at risk of ischemic strokes unrelated to the carotid disease, such as cardioembolic and lacunar strokes. Since a significant proportion of ischemic strokes in patients with severe and moderate carotid stenosis is not of large-artery origin (not of carotid origin), vigilant attention to risk factor management and ongoing scrutiny of cardiac function must be pursued in all patients.

CAROTID CEA FOR ASYMPTOMATIC PATIENTS

Carotid surgery for asymptomatic patients has been evaluated in many prospective studies. The CASANOVA trial (ICA Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin) enrolled 410 patients and had a follow-up of 3 years. This study determined that CEA was not more beneficial than medical treatment in patients with carotid stenosis of less than 90% [24]. The MACE study (Mayo Asymptomatic Carotid CEA) was terminated prematurely because of excessive myocardial infarction and transient ischemic attacks in the surgical group [25]. The Veterans Affair study enrolled 444 male patients with asymptomatic 50–99% carotid stenosis. The study concluded that CEA had no significant influence on ipsilateral stroke or on the combined incidence of stroke and death [9]. ACAS (the Asymptomatic Carotid Atherosclerosis Study) evaluated CEA versus medical treatment in 1662 asymptomatic patients. The study was terminated early because the projected 5 year relative risk reduction for CEA versus medical treatment was calculated at 53% [26]. This risk reduction appears impressive; however, several caveats in interpreting these results must be noted: the annual absolute difference was 1.2%, the risk of cardioembolic or lacunar infarctions was not altered, the outcome for any stroke was not different in both groups, patients and surgeons were highly selected, CEA was not beneficial for women, this group presented more surgical complications, and no substantial benefit from CEA was seen with increasing degrees of stenosis [27,28]. The ACST evaluated 3120 patients over a 10 year period. The overall 5 year risk of stroke was 6.4% in the patients who underwent CEA versus 11.8% in the medically treated group [22]. Although the favorable results of ACST confirm the results of ACAS, the benefit outweighs the risks only if operative complications are kept below 3%.

ACST = Asymptomatic Carotid Surgery Trial

According to recent meta-analyses of the major randomized clinical trials, CEA reduces the overall risk of stroke and death compared to medical treatment but with a low absolute risk reduction (2–3%, follow-up 3 years) [29,30]. Based on the available evidence, 53 patients would need to undergo CEA to prevent one stroke over a 3 year follow-up period [30].

It may be speculated that these randomized 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 higher than 10–20 years ago when patients were randomized into these studies. The best medical therapy of the 1980s is not the best medical therapy of today – particularly statin treatment and new antiplatelet agents, which were not available at that time.

NUMBER NEEDED TO TREAT

The number of patients that must be treated by CEA to prevent one additional ipsilateral stroke in the 2 year period after the procedure, compared to medical therapy, is known as number needed to treat. As an example, the NASCET established that the NNT to prevent one stroke was 19 for symptomatic patients with moderate stenosis and 6 for those with severe stenosis [27]. This is reasonable considering the high risk of stroke in patients presenting with symptomatic carotid stenosis. In contrast, due to the low medical risk faced by the asymptomatic patients, the NNT to prevent one additional stroke in 2 years was 83, too high to be accepted without asking questions [27]. The annual risk of stroke in the medical arm of some large trials in asymptomatic subjects was so low that a reliable reproducible operative risk below this event rate has been hard for most of the participant centers to achieve.

Recommending carotid revascularization based only on duplex ultrasound remains a matter of debate

ASYMPTOMATIC CAROTID ARTERY STENOSIS IN THE SURGICAL PATIENT

Most data suggest that asymptomatic carotid bruits and stenoses do not increase the stroke risk for patients who undergo general, non-cardiac surgeries [31]. Patients with carotid stenosis who undergo coronary artery bypass graft have a higher risk of stroke than those without carotid stenosis [32]. Carotid bruits and/or stenoses in asymptomatic and symptomatic patients who undergo CABG surgery are associated with a 5–7% risk of stroke. Although carotid stenosis is

ACAS = Asymptomatic Carotid Atherosclerosis Study
NNT = number needed to treat
CABG = coronary artery bypass graft

positively correlated with stroke after CABG surgery, this may be because carotid stenosis is a marker for advanced systemic atherosclerosis, specifically aortic arch atherosclerosis, rather than being causative for ischemic strokes. Less than half of the increased risk is likely to be due to the carotid lesion.

CHANGING TRENDS IN CAROTID INTERVENTIONS

Although the evidence fails to support the routine indication of carotid interventions in asymptomatic patients, carotid interventions in this population have increased steadily during the last few years. Halm et al. [33] revised the appropriateness of CEA during the period 1997 to 1998 in six hospitals in New York State. They observed a dramatic shift in the patient population undergoing CEA. In 1981, only 34% of procedures were performed for asymptomatic carotid stenoses. During the 1980s and mid-1990s, between 41% and 47% of operations were performed on asymptomatic patients. During 1997–1998, nearly three-quarters of CEAs were performed on asymptomatic patients.

In the last decade, carotid angioplasty with stenting emerged as a valuable alternative to CEA and is the therapy of choice for selected patients. Carotid stenting gained acceptance and popularity mainly due to the perceived advantages of a less invasive treatment for carotid occlusive disease. The SAPPHIRE trial (Stent and Angioplasty with Protection in Patients at High Risk for CEA) [34], for example, is a class I study that attempted to compare carotid stenting with carotid CEA in patients with asymptomatic carotid stenosis. In this trial, 71% of the patients were asymptomatic. The SAPPHIRE study was a randomized non-inferiority trial involving 29 institutions throughout the United States and included 334 high risk patients considered ideal candidates for either stenting or surgery. Patients had to have either symptomatic stenosis of 50% or asymptomatic stenosis of 80% on ultrasound. Of the 334 patients 238 (71%) were asymptomatic. Patients were then randomized to stenting or surgery, with both groups receiving low dose aspirin starting 72 hours prior to the procedure and continuing indefinitely. Primary endpoint comparison at one year post-intervention revealed a risk of 12.2% in the stenting group compared to 20.1% in the surgery group. This difference was significant ($P = 0.05$) to prove non-inferiority of stenting versus carotid CEA at one year post-treatment. The overall incidence of stroke within one year of treatment was 6.2% in the stenting group and 7.9% in the surgery group, a difference that was not significant ($P = 0.60$). The trend towards stenting leading to reduced stroke incidence compared with surgery lent support to the non-inferiority of stenting versus carotid CEA at one year follow-up. The National Institutes of Health have expanded the CREST study (Carotid Revascularization CEA Versus Stenting Trial) to include asymptomatic patients.

Major criticism of randomized clinical trials comparing carotid stenting and CEA focused on the incomplete learning curve of interventionists and the inadequate and outdated technology used, which might have contributed to the high stroke and death rates in the carotid stent arm of some studies [35]. The effect of the learning curve related to technical expertise and patient selection strongly influences the results of carotid stenting. Due to the devastating potential complications when compared with other endovascular minimally invasive procedures, carotid stenting requires a more stringent analysis of operator training and outcome, because improvement in the learning curve is accompanied by a comparative reduction in complication rates. Today, there is general agreement that requirements for training in carotid stenting are higher than in other fields [36]. Carotid artery angioplasty and stenting is continually developing into a safer and more efficacious method of stroke prevention. Embolic protection, improved stent designs, and ever-increasing surgeon experience are propelling carotid stenting towards equipoise with and possible superiority to CEA [37,38].

REAPPRAISAL OF MEDICAL THERAPY

In a recently published systematic review, Abbott [39] showed that the risk of ipsilateral and any-territory stroke in patients with asymptomatic carotid stenoses with medical intervention alone has fallen since the mid-1980s. Taken together with evidence of no similar reduction in the operative risk of CAE in recent years, it is possible that the absolute benefit from CAE for asymptomatic stenosis will now be even smaller than in previous randomized trials [39,40]. However, there are few studies on the risk of stroke distal to asymptomatic stenoses managed by what would now be regarded as best medical treatment. In other words, if the risk of stroke after intensive contemporary medical intervention alone is now lower than in large, randomized controlled trials, it is highly unlikely than any overall benefit from surgery would remain. Some useful data should be available in the future from the SPACE II trial, which will randomize patients with asymptomatic carotid artery stenosis to CAE versus stenting versus medical intervention alone.

Antihypertensive, antiplatelet, and statin drugs remain the cornerstone of therapy

FINAL REMARKS AND IMPLICATIONS FOR MANAGEMENT

The annual risk of stroke in asymptomatic ICA stenosis is low. Carotid revascularization reduces this risk and should be considered for medically stable patients presenting with

significant carotid stenosis who are expected to live more than 5 years and only in centers with a demonstrated low periprocedural complication rate [28]. Carotid revascularization procedures may also be justified in patients presenting rapidly progressing carotid stenosis, patients selected for surgery, patients with asymptomatic ICA stenosis of > 60% and contralateral carotid occlusion, and in selected patients presenting significant post-CEA restenosis. There may be other subgroups of asymptomatic subjects who clearly benefit from CEA, but the characteristics of such subgroups cannot be determined from existing evidence.

Patients with asymptomatic carotid stenosis present an increased risk of myocardial infarction and vascular death. Thus, an intensive plan for vascular risk factor control should be started in every patient with carotid stenosis. Further experience and study are needed, and the results of two trials – the Carotid Stenting versus Surgery of Severe ICA Disease and Stroke Prevention in Asymptomatic patients (ACT I) study (comparing stenting and surgery in asymptomatic carotid stenosis) and the ongoing CREST trial (comparing stenting and surgery in symptomatic and asymptomatic carotid stenosis) – are eagerly awaited. CREST is the largest randomized clinical trial in progress comparing CEA and stenting for the prevention of stroke. Enrolment in CREST has ended and follow-up should be completed this year. Until then, clinicians should continue to weigh individual patient risks and benefits when referring patients for surgical or endovascular treatment of carotid atherosclerotic disease. Regardless of whether revascularization is undertaken, maximal medical therapy with the use of antiplatelet agents, blood pressure control, and statin therapy remains the mainstay of treatment.

Correspondence:
Dr. J.E. Cohen
Dept. of Neurosurgery, Hadassah University Medical Center, P.O. Box 12000, Jerusalem 91120, Israel
Phone: (972-2) 677-7092
Fax: (972-2) 641-6281
email: jcohenns@yahoo.com

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CREST = Carotid Revascularization CEA Versus Stenting Trial

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