Clinical considerations in the management of asymptomatic carotid artery stenosis

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Incidental findings pose considerable management dilemmas for the treating physician and psychological burden for the respective patient. With an aging population, more patients will be diagnosed with asymptomatic internal carotid artery stenosis. Patients will have to be counseled with regard to treatment options according to their individual risk profile and according to professionals’ knowledge of evidence-based data derived from large randomized control trials. Treatment consensus has long been lacking for patients with asymptomatic carotid artery stenosis prior to any randomized controlled trials. Additionally, an individual’s risk profile may be hard to assess according to knowledge gained from randomized controlled trials. Moreover, while earlier studies compared carotid endarterectomy and medical therapy, in the past years, a new therapeutic modality, carotid artery angioplasty and stenting, has emerged as a possible alternative. This has been evaluated in a recent randomized controlled trial, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which compared carotid endarterectomy with angioplasty and stenting in both symptomatic and asymptomatic patients. The following review summarizes current knowledge of the natural history, diagnosis, and treatment strategies to counsel patients with asymptomatic carotid artery stenosis.

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Key Words • stroke • revascularization • carotid occlusive disease • evidence-based medicine

Since the advent of modern neuroradiological imaging, incidental findings have become common, with clinically significant findings present in about 2%–8% of patients undergoing MR imaging of the brain. The management of these incidental findings poses considerable treatment dilemmas and psychological burden for the patient because there is no widespread agreement of treatment concepts. Treatment dilemmas have traditionally been particularly pronounced in patients with incidental or asymptomatic cerebrovascular pathological entities. This dilemma partly stems from the fact that, while most cerebrovascular pathological entities may cause catastrophic events, their proposed surgical treatment is not without important risks. The risk of treatment may further be accentuated in the mind of the patients because they are asymptomatic when the lesion is incidentally found and any intervention carries only a hypothetical benefit in the future.

Careful consideration of the natural history and possible benefit of various management options is particularly necessary in cases of asymptomatic carotid artery stenosis, for which treatment consensus has been lacking, prior to any randomized controlled trials. Given that roughly 2 million Americans may be harboring an asymptomatic carotid artery stenosis, the optimum treatment is of considerable public health interest. In the following review, we discuss the prevalence, natural history, progression rate, diagnostic modalities, and the results of randomized controlled trials highlighting our current understanding of the management of asymptomatic internal carotid artery stenosis.

Prevalence of Carotid Occlusive Disease

Carotid artery stenosis is one of the main causes of ischemic stroke, which remains a major public health issue with a high burden of disease in the US. To put the current epidemiology of stroke in perspective: stroke is the third leading cause of death in the US, with more than 143,579 people dying from strokes each year (http://www.strokecenter.org/patients/stats.htm). It is also the main cause of serious, long-term disability. Each year, about 795,000 people suffer a stroke. About 600,000 of these are first attacks and 185,000 are recurrent attacks. About 15%–20% of these strokes are estimated to be the result of carotid...
artery occlusive disease, with nearly 80% of these strokes occurring in asymptomatic patients without a history of stroke or transient ischemic attacks.7,26

The estimated prevalence of asymptomatic carotid artery stenosis varies significantly depending on the population studied. The overall prevalence of asymptomatic carotid artery stenosis ≥50% in the general population is estimated at 2%–9%.5 A higher prevalence of 5%–9% is anticipated in patients older than 65 years of age, which is of public health relevance because it means that 1.3–2.4 million Americans in this age group are being affected by carotid artery occlusive disease (http://www.stroke center.org/patients/stats.htm).11,25,48 The prevalence is even higher in patients who harbor additional atherosclerotic lesions. An estimated 11%–26% of patients with coronary artery disease and 25%–49% with peripheral artery disease have asymptomatic carotid artery stenosis.47 Table 1 summarizes the findings of some of the large studies assessing the prevalence of asymptomatic carotid artery stenosis in different populations.

A number of risk factors have been established for the development and presence of asymptomatic carotid artery stenosis.7,13,31,47,58 Among these factors, age appears to be the most consistent. This may be due to a combination of factors, mostly inherent changes related to aging of the arterial wall but also prolonged exposure to risk factors with increasing age.7,33 Male sex is another significant risk factor, with men exhibiting a 2-fold higher prevalence than women in some studies and with a gradual increase in both males and females with increasing age.13,31,41 Large population-based studies in numerous countries have also established traditional modifiable cardiovascular risk factors, such as diabetes, hypertension, smoking, and dyslipidemia, as being consistently associated with carotid artery occlusive disease.38,41,70

Progression of Carotid Artery Occlusive Disease

The progression rate of asymptomatic carotid artery stenosis is important to the clinician because higher grades of stenosis are associated with a higher stroke risk, while the progression of carotid artery stenosis itself is a predictor of increased stroke risk.48,60 Numerous studies have analyzed the rate and severity of carotid artery occlusive progression, but the results show considerable differences.12,25,48 Table 2 summarizes the results of some of these studies.

In the first prospective study of its kind, Roederer and colleagues62 performed follow Doppler/duplex ultrasonography in 167 patients with carotid bruits. Of these patients, 31% exhibited stenotic progression unilaterally and 7% exhibited progression bilaterally. After 3 years, disease in one-third of the patients progressed to carotid artery stenosis of ≥50% and 3 of 5 studied arteries progressed to a more severe category of stenosis. In the largest prospective study, Muluk and coauthors48 followed 1004 asymptomatic patients with serial duplex ultrasonography for a mean 28-month follow-up period at the Pittsburgh Veterans Administration Medical Center. Progression was defined as a minimum increase in internal carotid artery stenosis of 50%, with a baseline of less than 50%, or as an increase to a higher category of stenosis if the baseline stenosis was ≥50%. The authors found a substantial and steady increase of stenosis at an annualized risk of progression of 9.3%. A multivariate analysis identified 4 variables affecting progression: baseline ipsilateral internal carotid artery stenosis ≥50% (relative risk 3.34), baseline ipsilateral external carotid artery stenosis ≥50% (relative risk 1.51), baseline contralateral internal carotid artery stenosis ≥50% (relative risk 1.41), and systolic pressure >160 mm Hg (relative risk 1.37). By the 7th year of follow-up, more than 50% of patients studied showed some degree of disease progression.48

Depending on the population studied, the rate of progression may even be higher. Liapsis and colleagues37 showed a 15% progression rate in a large cohort of asymptomatic patients with a large prevalence of significant risk factors, including coronary artery disease. Cina and colleagues7 studied a Canadian cohort of asymptomatic patients with peripheral vascular disease. They found

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Screening Population</th>
<th>No. of Pts</th>
<th>Age (yrs)</th>
<th>Male/Female Ratio</th>
<th>Diagnostic Tool</th>
<th>% Stenosis</th>
<th>Prevalence</th>
<th>Risk Factors Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hennerici et al., 1981</td>
<td>cardiovascular disease</td>
<td>2009</td>
<td>58</td>
<td>1647:362</td>
<td>Doppler</td>
<td>≥50</td>
<td>9.1%</td>
<td>peripheral vascular disease</td>
</tr>
<tr>
<td>Hennerici et al., 1987</td>
<td>vascular risk factors</td>
<td>3225</td>
<td>62</td>
<td>NS</td>
<td>Doppler</td>
<td>≥40</td>
<td>50–99: 7.5%; occlusion: 1.7%</td>
<td></td>
</tr>
<tr>
<td>Ellis et al., 1992</td>
<td>peripheral vascular disease</td>
<td>1196</td>
<td>68</td>
<td>826:370</td>
<td>duplex</td>
<td>50–99</td>
<td>13.8%</td>
<td>male, hypertension, smoking, CAD, wall thickness</td>
</tr>
<tr>
<td>O’Leary et al., 1992</td>
<td>age &gt;65 yrs</td>
<td>5116</td>
<td>NS</td>
<td>2210:2906</td>
<td>duplex</td>
<td>50–99</td>
<td>M 7.6%/F 5.1%; occlusion M 1.0%/F 0.6%</td>
<td></td>
</tr>
<tr>
<td>Fine-Edelstein et al., 1994</td>
<td>general</td>
<td>1116</td>
<td>66–93</td>
<td>441:675</td>
<td>duplex</td>
<td>≥50</td>
<td>M 9%/F 7%</td>
<td></td>
</tr>
<tr>
<td>Qureshi et al., 2001</td>
<td>general</td>
<td>1331</td>
<td>66</td>
<td>439:892</td>
<td>duplex</td>
<td>≥60</td>
<td>age &gt;65 yrs, smoking, CAD, hypercholesterolemia</td>
<td></td>
</tr>
</tbody>
</table>

* CAD = coronary artery disease; NS = not stated; Pts = patients.
† Age reflects the mean, except for the Fine-Edelstein et al. value, which represents the age range.
Management of asymptomatic carotid artery stenosis

While carotid artery auscultation is a consistent part of a routine physical examination, its accuracy in detecting carotid artery stenosis depends on the severity of the stenosis. In a large cohort of 1486 patients in whom 1555 carotid artery investigations were performed, Johanson and Wester\(^2\) demonstrated a sensitivity for carotid artery bruits of 55% for stenosis of 50%–69% and 77% sensitivity for stenosis of 70%–99%. Specificity was 52% for stenosis of 50%–69% and 71% sensitivity for stenosis of 70%–99%, as measured by carotid artery ultrasonography. Table 3 summarizes some of the medical statistical terms used here.

Ultrasoundography has been the most commonly used diagnostic modality to screen for carotid artery stenosis because of the modality’s noninvasive nature, lack of radiation exposure, and widespread availability. Its limitations in carotid artery stenosis include its association with the operator’s skill, experience, and large interpersonal variability. Two meta-analyses examined the accuracy of ultrasonography to detect carotid artery stenosis. A meta-analysis by Nederkoorn and colleagues\(^{24}\) included studies published from 1993 through 2001 and estimated the accuracy of carotid duplex ultrasonography using digital subtraction angiography as the reference standard. The authors found that carotid duplex ultrasonography had an estimated sensitivity of 86% and a specificity of 87% for detecting carotid artery stenosis of 70%–99%.\(^{24}\) In a meta-analysis by Jahromi and colleagues,\(^{29}\) the authors reported comparable results for sensitivity and specificity. Using their analysis, a sensitivity of 94% was estimated, as was a specificity of 92% for carotid artery stenosis of 60% or greater.\(^{29,72}\) The reliability of carotid artery duplex ultrasonography, however, has significant limitations with important differences in the measurement properties applied by different ultrasound laboratories, which may result in clinically relevant differences.\(^{29}\)

More commonly, with the advent of modern neuroimaging modalities, MR angiography and CT angiography have become common noninvasive screening tools. While similar in many aspects, MR angiography and CT

### TABLE 2: Studies analyzing the percentage of carotid artery stenosis progression over time*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>% of CAS Progression</th>
<th>Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Javid et al., 1970</td>
<td>22</td>
<td>1–9 yrs</td>
</tr>
<tr>
<td>Roedder et al., 1984</td>
<td>31</td>
<td>36 mos</td>
</tr>
<tr>
<td>Lewis et al., 1997</td>
<td>21.3</td>
<td>5.6 yrs</td>
</tr>
<tr>
<td>Olin et al., 1998</td>
<td>15.5</td>
<td>60 mos</td>
</tr>
<tr>
<td>Muluk et al., 1999</td>
<td>22.6</td>
<td>10 yrs</td>
</tr>
<tr>
<td>Liapis et al., 2000</td>
<td>18.6</td>
<td>10 yrs</td>
</tr>
<tr>
<td>Sabeti et al., 2007</td>
<td>5</td>
<td>6–9 mos</td>
</tr>
<tr>
<td>Hirt, 2011</td>
<td>5.2</td>
<td>≥5 yrs</td>
</tr>
</tbody>
</table>

* CAS = carotid artery stenosis.

progression from one class of stenosis to a more severe class in 15% of patients and progression from a lower degree of 50% to 99% stenosis in 6.5% of patients during a follow-up period of 6–9 months.

In summary, the risk of progression of an asymptomatic carotid artery stenosis increases with time and varies from 4% to 29% annually, mainly depending on the population studied. Numerous studies have addressed the question of predictors of stenotic progression to identify asymptomatic patients in need of regular follow-up and possible early intervention.\(^{7,23,37,48}\) Carotid artery disease progression appears to be associated with diabetes, smoking, hypertension, and, in patients with more severe stenosis, heterogeneous plaque and contralateral disease.\(^{6,11,37,48,60}\) Moreover, the severity of the stenosis is a risk factor for progression, with moderate stenosis being 5-fold more likely to progress than mild or no stenosis.\(^{40,48}\)

### Diagnostic Studies

Traditionally, asymptomatic carotid artery stenosis was identified on hearing a carotid bruit during physical examination or on carotid artery ultrasound screening.

### TABLE 3: Definition of commonly used statistical terms*

<table>
<thead>
<tr>
<th>Statistical Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>the probability that the test says a person has the disease when in fact he/she does have the disease</td>
</tr>
<tr>
<td>specificity</td>
<td>the probability that the test says a person does not have the disease when in fact he/she is disease free</td>
</tr>
<tr>
<td>95% CI</td>
<td>indicates the range of values w/in which the value would fail 95% of the time if the researcher were to calculate the value from an infinite no. of samples of the same size, drawn from the same population</td>
</tr>
<tr>
<td>absolute risk</td>
<td>the probability that an individual will experience the specified outcome during a specified period; it lies in the range 0–1, or is expressed as a percentage</td>
</tr>
<tr>
<td>relative risk</td>
<td>the no. of times more likely (relative risk &gt;1) or less likely (relative risk &lt;1) an event is to happen in one group compared w/ another; the ratio of the risk in the treated group to the risk in the control group</td>
</tr>
<tr>
<td>absolute risk reduction</td>
<td>the absolute difference in risk btwn the treated &amp; control groups in a trial; this value does not give any idea of the proportional reduction btwn the 2 groups: for this, relative risk reduction is needed</td>
</tr>
<tr>
<td>relative risk reduction</td>
<td>the proportional reduction in risk btwn treated &amp; control participants in a trial; it is the percentage reduction in events in treated patients vs controls</td>
</tr>
<tr>
<td>hazard ratio</td>
<td>compares 2 treatments: if the hazard ratio is 2.0, then the rate of deaths in one treatment group is twice the rate in the other group</td>
</tr>
</tbody>
</table>

* CI = confidence interval.
angiography exhibit differences not only because CT angiography is radiation based and uses contrast cleared by the kidneys, but because these diagnostic options show different sensitivity and specificity profiles, which are summarized in Table 4.

Nederkoorn and colleagues\(^4\) examined 203 consecutive patients in whom there was suspicion of carotid artery stenosis, using MR angiography and conventional angiography. The sensitivity and specificity of the MR angiography with projection that showed the maximal stenosis on angiography were 92.6% (95% CI, 85.3%–97.0%) and 82.7% (95% CI, 78.1%–87.3%), respectively. The mean difference between maximal stenosis on MR angiography and angiography was 7.5% (95% CI, 5.2%–9.9%).\(^5\) A meta-analysis by the same research group showed a pooled sensitivity of 95% (95% CI, 92%–97%) and a pooled specificity of 90% (95% CI, 86%–93%) for stenosis of 70%–99%. For occlusions, MR angiography yielded a sensitivity of 98% (95% CI, 94%–100%) and a specificity of 100% (95% CI, 99%–100%).\(^6\)

More recently, CT angiography has been introduced as a diagnostic tool to evaluate carotid artery stenosis. While it exposes the patient to radiation and iodine-based contrast medium, many clinicians prefer this modality because it is based on tomography scanning and thought to depict the pathoanatomical features more directly than MR angiography. Disadvantages include the possible overlap with bone and venous structures, as well as its inaccuracy in the presence of calcified plaque.\(^7\) A recent systematic review analyzing CT angiography and standard angiography found a pooled sensitivity and specificity for detection of a 70%–99% stenosis were 85% (95% CI, 79%–89%) and 93% (95% CI, 89%–96%), respectively.\(^8\) For detection of an occlusion, the sensitivity and specificity were 97% (95% CI, 93%–99%) and 99% (95% CI, 98%–100%), respectively.\(^8\) This compares favorably with the sensitivity and specificity found in MR angiography.

The gold standard, against which all diagnostic modalities are compared, remains conventional angiography. The degree of carotid artery stenosis was determined by angiography in the ACAS, ECST (European Carotid Surgery Trial), and NASCET (North American Symptomatic

<table>
<thead>
<tr>
<th>Extent of Stenosis/Diagnostic occlusion expressed in percentage, as represented in the literature*</th>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Stenosis ≥70</td>
</tr>
<tr>
<td>Duplex</td>
</tr>
<tr>
<td>CTA</td>
</tr>
<tr>
<td>Occlusion</td>
</tr>
<tr>
<td>Duplex</td>
</tr>
<tr>
<td>CTA</td>
</tr>
</tbody>
</table>

* Data were derived from studies by Koelemay et al., Nederkoorn and Brown, 2009, and Nederkoorn et al., 2003. Abbreviations: CTA = CT angiography; MRA = MR angiography.

Table 4: Representation of sensitivity and specificity in the diagnosis of carotid artery stenosis expressed in percentage, as represented in the literature*

Carotid Endarterectomy Trial), but most centers currently do not use angiography as a regular diagnostic tool. The main disadvantages of angiography are its invasiveness, associated costs, and infrastructural needs, as well as the reported 1.3% neurological complication rate.\(^9\) As a result, cerebral angiography is used by most clinicians only in selected patients in whom noninvasive diagnostics were not conclusive, or when MR angiography cannot be performed due to claustrophobia or the presence of metal implants.

**Natural History**

Several short- and long-term cohort studies have analyzed the natural history of asymptomatic carotid artery stenosis to define risk factors, or predictors, for stenosis progression by multiple linear regression analysis and also to evaluate stroke risk and predictors of stroke risk. Depending on the population studied, most short-term follow-up studies report an annual risk of unheralded ipsilateral stroke of approximately 1%–3%; within this group, higher degrees of stenosis are associated with higher risks of stroke. Conversely, some studies report higher stroke rates in patients with clinically manifest atherosclerotic disease: In the Dutch Smart Study, a large prospective cohort study, 2684 consecutive patients with clinical manifestations of arterial vascular disease or Type 2 diabetes mellitus were followed after undergoing baseline carotid artery ultrasonography.\(^9\) Asymptomatic carotid artery stenosis of 50% or greater was present in 221 patients (8%). During a mean follow-up period of 3.6 years, a first vascular event occurred in 253 patients (9%). The cumulative incidence for the composite of subsequent vascular events after 5 years was 12.3% (95% CI, 10.7%–13.9%), for cerebral infarction 2.2% (95% CI, 1.4%–2.8%), and for myocardial infarction 8.0% (95% CI, 6.6%–9.4%). Adjusted for age and sex, asymptomatic carotid artery stenosis of 50% or greater was associated with a higher risk of subsequent vascular events (hazard ratio 1.5, 95% CI, 1.1%–2.1%). Longer follow-up studies show 10- and 15-year risks of ipsilateral stroke to be 5.7% (95% CI, 0%–12%) and 8.7% (95% CI, 1%–17%), respectively, in patients with 0%–49% stenosis, and 9.3% (95% CI, 1%–18%) and 16.6% (95% CI, 1%–32%), respectively, in patients with a stenosis of 50%–99%.\(^9\)

Despite the clear association shown in these studies between asymptomatic carotid artery stenosis and stroke risk, our ability to predict stroke risk in any individual patient is limited.\(^9\) While large cohort studies demonstrate a higher stroke risk with a higher degree of stenosis, and patients with classic cardiovascular risk factors are at a higher risk of experiencing cerebrovascular events, individualized data remain difficult to obtain because of the multifactorial etiology of ischemic events. Uncertainty in interpreting the current data in an individualized fashion stems, in part, from the following factors. Inzitari and colleagues\(^10\) showed that, while the stroke risk increases with a higher degree of stenosis, it actually decreases again in asymptomatic patients whose stenosis is between 94% and 99%. Moreover, in the same study, approximately 80% of the first strokes were not heralded by a prior transient ischemic attack. A large number of
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actual cerebral ischemic events may have been unrelated to the carotid artery stenosis and were of a cardioembolic nature or related to lacunar infarcts, further complicating any true risk assessment. A complex interaction of both patient factors and lesion factors turn an asymptomatic stenosis into a symptomatic one, but these factors are poorly understood.45

Treatment Evidence

Finally, the question needs to be addressed of whether patients with asymptomatic carotid artery stenosis benefit from any particular treatment option. Historically, studies on this issue compared maximal medical management and carotid endarterectomy. Later studies compared these treatment modalities with carotid artery angioplasty and stenting.32

The earliest studies analyzing the role of surgery in asymptomatic carotid artery disease was provided by the CASANOVA trial (Carotid Artery Stenosis with Asymptomatic Narrowing Operation Versus Aspirin) and the MACE trial (Mayo Asymptomatic Carotid Endarterectomy).44,45 These studies have been regarded as suboptimal.14 The MACE trial was prematurely stopped after enrollment of only 71 patients due to a high rate of myocardial infarction (22%) in the surgical group. This may have been a direct result of the trial policy of withholding aspirin from the surgical group. For the CASANOVA study, a total of 410 patients with 50%–90% stenosis were enrolled. A total of 17% of the surgical patients never underwent a carotid endarterectomy, and in 20% of the medical patients, a unilateral or bilateral carotid endarterectomy was performed. This high rate of crossovers made the final interpretation of this study problematic.

The Veterans Affairs Trial included 444 asymptomatic men with angiographically demonstrated stenosis of 50%–99%; the patients were randomly assigned to 1 of 2 groups: the best medical management or the best medical management with carotid endarterectomy. The primary end points after 48 months were incidence of transient ischemic attack, transient monocular blindness, and stroke. The combined incidence of ipsilateral neurological events was 8.0% in the surgical group and 20.6% in the medical group (p < 0.001), given a relative risk of 0.38 (95% CI, 0.22–0.67) for the surgical group compared with the medical group.42 The incidence of ipsilateral stroke alone was 4.7% in the surgical group and 9.4% in the medical group. An analysis of stroke and death combined within the first 30 postoperative days showed no significant differences between groups in terms of all strokes and deaths (surgical group 41.2%, medical group 44.2%; relative risk 0.92; 95% CI, 0.69–1.22).44 Overall mortality, including postoperative deaths, was primarily due to coronary artery disease.

The ACAS is considered the first modern well-designed and conducted study to examine the role of carotid endarterectomy in asymptomatic patients for stroke prevention.12 Its results were reported in 1995. A total of 1662 patients with asymptomatic carotid artery stenosis of 60% were randomized to either medical management alone or medical management with carotid endarterectomy. The study was halted by the Data Safety and Monitoring Board 2.7 years after it began because of a projected 5.9% absolute risk reduction at 5 years favoring carotid endarterectomy. The 5-year projected rate of ipsilateral stroke was 11.0% for the medically treated patients and 5.1% for the surgically treated patients. This translated into a 47% relative risk reduction of stroke or perioperative death in the surgical group. The perioperative stroke rate was 2.3%, which is lower than that in more contemporary studies and is most probably due to accepting only surgeons with an excellent safety record. The ACAS calculated that 17 carotid endarterectomies need to be performed to prevent 1 stroke, but a 1000 endarterectomies need to be performed to prevent 59 strokes by 5 years.30 At the time of its publication, ACAS was the largest and methodologically best study of this kind. However, the study also produced some controversial findings.30,57 Its results provided no evidence that the incidence of disabling stroke was reduced. Reduction seemed to be only in nondisabling stroke, although this may have been a chance finding.30 While men benefited significantly from surgery at 5 years (absolute risk reduction 8%, relative risk reduction 66%), women derived no advantage (absolute risk reduction 1.4% at 5 years, relative risk reduction 17%).30 Another controversial issue was there appeared to be no association between stenosis severity and long-term stroke risk.

Many of these uncertainties could be settled once the results of the ACST were published.20 The ACST enrolled 3120 patients with greater than 60% stenosis documented on ultrasonography and assigned groups to immediate carotid endarterectomy (88% by the 1st year) or indefinite deferral of carotid endarterectomy with a 5-year follow-up at 1 of 126 centers in 30 countries. Eligibility included carotid artery diameter reduction of at least 60% on ultrasonography and no symptoms within the last 6 months. Enrollment began in 1993 and continued until 2003. A total of 3120 patients were randomized (1560 in each group). The study included 2044 men and 1076 women. Combining the perioperative events (stroke and death within 30 days) and the non-perioperative strokes, the net 5-year risks were 6.4% (immediate carotid endarterectomy) compared with 11.8% (deferred carotid endarterectomy) for all strokes (p < 0.0001) and 3.5% compared with 6.1% for fatal or disabling strokes (p = 0.004). Subgroup analyses demonstrated significant benefits for patients younger than 65 years and those between 65 and 74 years, but uncertain benefits for those older than 75 years. Both men and women benefited from carotid endarterectomy. The 5-year benefit of carotid endarterectomy appeared to be as great for those with about 70%, 80%, and 90% carotid artery stenosis on ultrasonography. The results showed no significant difference in patients who were never symptomatic (7.1% absolute 5-year gain) compared with those with symptoms greater than in the previous 6 months (4.6% absolute 5-year gain). And finally, surgery was performed very safely with a low operative risk of 2.8%.

With ACST largely supporting and extending the results of ACAS, there now exists Level I evidence demonstrating a net benefit of surgery for asymptomatic patients with stenosis ≥ 60% in reducing disabling or fatal strokes.55

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Even with the advent of endovascular techniques, carotid artery angioplasty and stenting has been considered an alternative to carotid endarterectomy in both studies of symptomatic and asymptomatic patients. Thus, with the established benefit in stroke reduction for asymptomatic patients, questions were raised with regard to optimal treatment. While the first large modern study in which carotid endarterectomy was compared with carotid angioplasty and stenting, the ICSS study (International Carotid Stenting Study), included only symptomatic patients; the later CREST enrolled both symptomatic and asymptomatic patients. The CREST study enrolled 2502 patients at 117 centers in the US and Canada. The trial included 1321 symptomatic and 1181 asymptomatic patients who were randomized to undergo either stenting with the same stent and distal protection devices (Acculink and Accunet devices) or carotid endarterectomy. Inclusion criteria were as follows: patients with symptomatic stenosis had 50% or greater stenosis documented by angiography, 70% or greater by ultrasonography, or 70% or greater by CT or MR angiography. In asymptomatic patients lesions were identified by angiography (≥ 60%), ultrasonography (≥ 70%), or CT/MR angiography (≥ 80%). The primary end point for the study was any periprocedural stroke, myocardial infarction, death, or postprocedural ipsilateral stroke up to 4 years after intervention. A rigorous training and credentialing process for interventionalists was required prior to participation. In short, there was no significant difference in the rates of the primary end points between carotid angioplasty with stenting and carotid endarterectomy (7.2% vs 6.8%, respectively; hazard ratio with stenting 1.11; p = 0.51) at a mean follow-up of 2.5 years. No modification of a treatment effect was detected with respect to symptomatic status or sex, but an interaction with age was established (p = 0.02). Surprisingly, outcomes were slightly better with carotid artery stenting in patients aged younger than 70 years, with greater benefit the younger the patient; outcomes were also better with endarterectomy in patients older than 70 years of age, with an increase in age demonstrating an increase in benefit. Overall, the periprocedural (30-day incidence) end point did not differ for carotid artery stenting and endarterectomy, but there were statistically significant differences in the components for stent- and endarterectomy-treated patients (stroke 4.1% vs 2.3%, respectively [p = 0.012], and myocardial infarction 1.1% vs 2.3%, respectively [p = 0.032]). The CREST showed endarterectomy to be superior to carotid angioplasty and stenting with respect to the outcomes of ischemic stroke, perioperative stroke, or death in both asymptomatic and symptomatic patients. However, addressing the primary end point of any stroke, myocardial infarction, or death up to 4 years after intervention, both procedures proved equal.

The inclusion of asymptomatic myocardial infarction as a primary end point in CREST has been criticized by a number of commentators. The clinical relevance of including silent cardiac events is questionable because results from the SF-36 (36-Item Short Form Health Survey) in CREST showed no adverse effects on the quality of life as a result of cardiac events, whereas the occurrence of a stroke significantly affected the patient’s quality of life in a negative manner. Without inclusion of asymptomatic cardiac ischemia in CREST as a primary end point, endarterectomy would be a safer procedure because of a greater incidence of perioperative strokes and death in the angioplasty and stenting group. This difference is still significant at 4 years. A post hoc analysis of outcome and safety according to patients’ symptomatic status included an analysis of 1181 asymptomatic patients. For these asymptomatic patients, the stroke and mortality rates were 2.5% and 0.6% for carotid artery stenosis and 1.4% and 0.5% for carotid endarterectomy (hazard ratio, 1.88; 95% CI, 0.79–4.42; p = 0.15).

**Individualized Decision-Making Strategies**

The assessment of an individual patient’s risk based on our knowledge from large randomized controlled trials remains challenging. An individual’s risk profile depends on many factors and may not be easily interpolated from clinical trials because of differences in the individual’s clinical factors or anatomical characteristics. While both carotid endarterectomy and carotid artery stenting have been proven to be safe and effective treatment options in the context of asymptomatic carotid artery stenosis, a number of different patients’ characteristics need to be considered when choosing the optimal treatment modality for any single patient. Table 5 summarizes the clinical and anatomical features favoring either endarterectomy or stenting.

**Discussion and Outlook Into the Future**

With increasing prevalence due to an aging population, asymptomatic carotid artery stenosis is a significant

| TABLE 5: Clinical and anatomical factors influencing decision making for either carotid endarterectomy or carotid stenting* |
|---|---|---|
| Factor | Favoring Endarterectomy | Favoring Stenting |
| age >69 yrs | X | |
| female sex | X | |
| severe plaque calcification | X | |
| severe common or internal carotid artery tortuosity | X | |
| cardiac disease (CHF, CAD) | | X |
| kidney disease | X | |
| complex aortic arch | | X |
| carotid bifurcation above C-2 | X | |
| tandem stenosis | X | |
| contralateral laryngeal palsy | X | |
| contralateral carotid occlusion | X | |
| prior radiotherapy | X | |
| prior neck op | X | |
| prior endarterectomy | X | |

* CHF = congestive heart failure.
cause of stroke morbidity and mortality; prevention and treatment remain major public health concerns. Although large randomized controlled trials on carotid endarterectomy for symptomatic patients have provided impressive results in terms of stroke risk reduction, uncertainties about the optimum treatment of asymptomatic patients persist. These uncertainties are mainly related to a lack of data on prevalence, progression rates, and the natural history of patients suffering from asymptomatic carotid artery stenosis. In the meantime, 2 large randomized controlled trials, ACAS and ACST, with a combined population of 4782, established a net benefit of carotid endarterectomy for asymptomatic patients with a stenosis exceeding 60%. Moreover, surgery was shown to be safe, with a perioperative neurological complication rate of less than 3%. In a recent 10-year update on the findings of the ACST, Halliday and colleagues reported a sustained benefit with carotid endarterectomy in stroke risk reduction. Half of this reduction has been in disabling or fatal strokes.

Clearly, the treatment benefit for any patient diagnosed with an asymptomatic carotid artery stenosis needs to be weighed against the natural history of the disease and treatment risks. Determination of any patient’s individual risk for future cerebrovascular events is an equivocal task. Ideally, stroke risks and best treatment options may be predicted and individualized according to a number of different factors evaluating a patient’s individual risk profile. Such factors may include an analysis of plaque characteristics and plaque instability, fludeoxyglucose-based PET scanning of brain metabolism, and transcranial Doppler monitoring of high-intensity transient signals. Indeed, some researchers have hypothesized that in the future, 3 subgroups of patients will benefit from surgical interventions: patients with plaque instability; patients with insufficient collateral circulation demonstrated on transcranial Doppler ultrasonography and/or MR angiography; and patients with severe metabolic compromise, characterized by increased oxygen-extraction fraction on PET. Other patients may best be treated by medical management. While improvements in medical management may change the future risk profile, the outcome impact remains to be seen. In fact, in the 10-year follow-up study of ACST, 80% of patients received aggressive modern medical management, including lipid-lowering medications. Carotid endarterectomy, however, reduced the stroke risk by about one-third of patients. By 10 years, the overall risk of stroke (including perioperative events) was 13.4% for those undergoing early operation compared with 17.9% with delayed or no carotid endarterectomy. Currently, carotid endarterectomy remains the gold standard for asymptomatic patients with an incidental asymptomatic carotid artery stenosis of 60% or greater.

Disclosure

Dr. Hanel is a consultant for Neurovax. Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Taussky. Analysis and interpretation of data: Taussky. Drafting the article: Taussky, Hanel. Critically revising the article: all authors. Reviewed submitted version of manuscript: Taussky.

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