Endarterectomy and Stenting for Asymptomatic Carotid Stenosis

A Race at Breakneck Speed

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Abstract—Atherosclerotic carotid stenosis has been recognized for the past several decades as being responsible for a significant portion of ischemic stroke, particularly the major and disabling ones. This category of stroke distinguished itself as being one of the first ones to have an effective preventive treatment in carotid endarterectomy. It took over 4 decades before major randomized, controlled trials were completed in North America and Europe to provide enough definitive information about its effectiveness, risks, limitations, and categories of patients that most benefit from it. Just like any invasive surgery, endarterectomy is being challenged by minimally invasive stenting, which has already made major technologic leaps and rapid clinical inroads. Stenting has started by tackling patient populations like surgical high-risk patients who were largely avoided in the endarterectomy trials and demonstrated equivalence to it in such populations. The broader applicability of the technique, however, has not been yet adequately investigated. The results so far are greatly reassuring and encouraging to enroll patients in the ongoing randomized trials that will hopefully provide more definitive answers to this issue. (Stroke. 2007;38(part 2):707-714.)

Key Words: angioplasty and stenting ■ asymptomatic carotid stenosis ■ carotid endarterectomy ■ carotid stenosis ■ prevention

The first comprehensive description of the relationship between occlusive carotid artery disease and ischemic brain symptoms in 19551 by Fisher triggered a momentum in furthering clinical descriptive, experimental, diagnostic, and therapeutic efforts that continue to transform our understanding and management of carotid disease. It took over 40 years for carotid endarterectomy (CEA) to demonstrate its effectiveness and limitations through major randomized trials. Despite these advances and efforts, there remains a lot of uncertainties about many aspects of risks, prognosis, and treatment of carotid stenosis in certain populations and circumstances. Similar to any new technology, the introduction of carotid artery stenting (CAS) as a potential alternative to CEA brought new challenges, questions, and issues. I review the clinical evidence and its limitations including CEA trials and comparisons to published and presented clinical information about CAS.

Carotid Atherosclerosis

Carotid atherosclerotic disease is a continuum of stages spanning the spectrum from intima-media thickening, to asymptomatic carotid plaque, and to symptomatic carotid disease. Various factors and triggers determine the transformation and evolution from one stage to another. Increasing degrees of atherosclerosis develop in the carotid arteries with older age. The Framingham Heart Study2 suggests that by the age of 50, less than 1% of the population have carotid stenosis of 50% or greater, but by the age of 75, 9% to 7% of the population will develop a 50% or greater stenosis. Carotid intima-media thickness as measured by ultrasound is rapidly becoming a surrogate marker for systemic atherosclerosis and correlates well with the risk of stroke and other vascular events.3 In the Cardiovascular Health Study, the 6-year risk of myocardial infarction and stroke increased more than 3-fold for individuals in the highest quintile of carotid intima-media thickness.4

The triggers behind the transformation of a carotid atherosclerotic plaque from “asymptomatic” to “symptomatic” remain elusive despite significant advances. Thrombosis and thromboembolism from the atherosclerotic plaque are responsible for the majority of ischemic cerebral manifestations caused by carotid occlusive disease. The concept of a “vulnerable plaque” has become a well-established pathophysiological mechanism for acute coronary events.5 A similar pattern is emerging in carotid thromboembolism. A histopathologic study of 269 plaques from symptomatic and asymptomatic patients demonstrated thrombotically active carotid plaque associated with high inflammatory infiltrate in 74% of 96 patients with ipsilateral major stroke compared with 35.2% of 91 patients with transient ischemic attack (TIA) or 14.6% of 82 patients without symptoms.6 Additionally, ruptured carotid plaques of patients with stroke demonstrated a more severe inflammatory infiltrate than the
other two groups. Identifying the “vulnerable patient” with the “vulnerable plaque” remains difficult, because the individuals from all three groups had comparable risk factors. Comparable findings were shown in a study comparing carotid plaques obtained from endarterectomy in symptomatic and asymptomatic patients participating in the major North American carotid surgery trials.7

The current definitions of symptomatic and asymptomatic carotid stenosis have been clinically useful and allowed the stratification of patients in major groups according to future risk of stroke. Yet, they are less than ideal mainly as a result of our (1) poor understanding of what biologic mechanisms transform a plaque to become “symptomatic,” (2) inability to find reliable indicators that predict such transformation, (3) a variety of stroke mechanisms whose clinical definitions lack specificity, and (4) the variability in the collateral network and supply to the brain and its continuous reengineering. Therefore, such definitions cannot be blindly or rigidly used in every situation and with each individual patient. The period during which carotid plaque is considered symptomatic (entailing a significantly increased future risk of stroke strictly attributable to the carotid stenosis) has been continuously shrinking; starting from a lifetime, it initially decreased to 3 years,8 then to 12 months,9 and more recently down to 6 months.10 Therefore, it is difficult to speak about asymptomatic carotid disease without discussing symptomatic disease because the overlay of the two situations remains blurred.

What Have We Learned From Symptomatic Carotid Surgery Trials?

Two major randomized, controlled trials (RCTs) defined the risks and benefits of CEA in symptomatic patients: the North American Symptomatic Carotid Endarterectomy Study (NASCET)8 and the European Carotid Surgery Trial (ECST).11 The studies and their results depended on the stratification of patients according to severity of stenosis based on x-ray catheter angiography (XRCA) measurements. In both studies, the group of patients with the highest risk of stroke and with most benefit from CEA was the group with severe stenosis (70% to 99%), in whom ipsilateral fatal and disabling strokes were all significantly reduced by more than 60% over a 2-year period. Stroke risk decreased and the benefit became more diluted with more moderate degrees of stenosis (50% to 69%) and further eroded with milder degrees of stenosis (0% to 49%).

A reanalysis of pooled individual data from all three symptomatic CEA trials, that included the much smaller VA Symptomatic Carotid Surgery Trial, yielded 6092 patients.12 The new analysis concluded that CEA has the following effects:

1. It increased the 5-year risk of ipsilateral ischemic stroke in patients with <30% stenosis.
2. It lacked any effect in patients with 30% to 49% stenosis.
3. It produced marginal benefit in those with 50% to 69% stenosis at 3 years, but the benefit increased over 5 and 8 years.
4. It is highly beneficial in those with 70% stenosis or greater without near-occlusion.
5. It decreased disabling stroke only when the carotid stenosis was 80% or greater.
6. The overall perioperative risk of stroke or death is 7.1%.

Asymptomatic Atherosclerotic Carotid Occlusive Disease

In the absence of neurologic symptoms related to the carotid artery, the yearly risk of stroke, in patients entered into the RCT for CEA, varies between 1.3% and 3.3%. The traditional risk predictor for stroke in asymptomatic patients has been assumed to be dependent on the degree and severity of carotid stenosis, similar to symptomatic patients. Longitudinal studies in patient cohorts with carotid ultrasound suggested that higher degrees of stenosis are associated with the highest risk of stroke.13 A population-based study with ultrasound in the Cardiovascular Health Study also suggested a higher risk for stroke in elderly asymptomatic individuals with the highest degrees of stenosis.14 In RCT for symptomatic CEA, a strict relationship among increasing degrees of stenosis, higher risk of stroke and larger risk reduction from CEA is well established. The same relationship, however, has not panned out in RCT of CEA in patients with asymptomatic carotid artery stenosis.

Three major RCT recent studies evaluated CEA in patients with asymptomatic carotid stenosis. The main results of these studies are summarized in Table 1. The first major randomized study for asymptomatic carotid endarterectomy was the Veterans Affairs Cooperative Study Group trial (VACSG)15 that included 444 male veterans without other significant comorbidities and 50% or higher asymptomatic carotid stenosis measured by XRCA. Patients were randomized to either medical treatment with aspirin (650 mg twice daily) alone or combined with CEA. CEA demonstrated a 62% statistically significant relative risk reduction in the primary end point of TIA, stroke, and death over medical therapy alone. When stroke and death (excluding TIA) are considered alone, however, no significant difference is found. The perioperative risk of stroke or death was 4.7% in the surgical arm, including the angiographic risk.

The Asymptomatic Carotid Artery Surgery (ACAS) study16 randomized 1662 patients with ≥60% carotid asymptomatic stenosis as assessed by a centrally certified ultrasound evaluation. Only patients younger than 80 years and without major comorbidities were eligible for the study. All patients randomized to surgery underwent cerebral catheter angiography. CEA produced an absolute risk reduction of 5.9% and a statistically significant relative risk reduction of 53% for the primary end point of “cerebral infarction ipsilateral to the carotid and stroke or death” over a projected 5-year follow-up period. These results prompted the safety monitoring committee to stop the study. The perioperative risk of stroke or death in the surgical group was 2.3% with half being attributable to angiographic complications.

The largest study so far, the Asymptomatic Carotid Surgery Trial (ACST), recruited patients with asymptomatic (at least for more than 6 months) carotid stenosis ≥60% stenosis as determined by carotid ultrasound (unlike ACAS, not centrally certified) and without major comorbidity if there was “uncertainty about treatment.”10 A total of 3120 patients were randomized to undergo “immediate CEA” or “delayed CEA” if they developed related symptoms in the course of the study. An absolute reduction of 5.4% for the primary end point of stroke at 5 years follow up in addition to perioperative complications (stroke, myocardial infarction, or death)
translated into a significant relative risk reduction over 50%. Additionally, for the first time in asymptomatic CEA trials, fatal and disabling strokes were significantly reduced. There were no significant differences in the benefit among different subgroups, including sex, severity of stenosis, plaque echolucency, and the presence or absence of neurologic symptoms at baseline.

In summary, patients younger than 80 years old and without major comorbidities, with low surgical risk and with a moderate to severe asymptomatic carotid stenosis, have an increased risk of stroke or death over a period of 5 years of 12%. CEA in such a selected population produces a modest absolute risk reduction of 5% to 6% over medical therapy alone, which translates into approximately 50% relative risk reduction for stroke and death over a 5-years period if the perioperative risk is contained at less than 3%. These RCT also show that, contrary to symptomatic CEA studies, the risk of stroke and the benefit from CEA is not predicted by the degree of stenosis.

Special Unresolved Issues in Carotid Revascularization

The various randomized trials that evaluated CEA in different situations have undoubtedly resolved many controversies and issues. Special issues remain unsolved.

Applicability of Carotid Endarterectomy Randomized, Controlled Trial Results in the Community at Large in Octogenarians and High-Risk Carotid Endarterectomy

Almost all CEA trials evaluating symptomatic or asymptomatic patients excluded patients estimated to be at high risk for perioperative morbidity and mortality. Such exclusions encompassed octogenarians or patients with significant comorbidities (cardiovascular, pulmonary, renal, and so on), contralateral stenosis or occlusion, and a stenosis distant from the carotid bifurcation that recurred after CEA or was caused by radiation therapy. For this group of patients, the natural history of carotid stenosis has not been well explored nor is answered by any of the trials. The perioperative morbidity and mortality rates may potentially be much higher for CEA in such populations than in others, whereas the benefits remain undetermined. The need to study further such group of patients is necessary to determine more rigorously what constitutes periprocedural or operative risk factors for CEA or CAS and the natural history and risk of stroke under systematic medical therapy.

The benefits and risks of CEA and CAS in octogenarians are largely unexplored, because they were excluded from the large trials, as a result of the potential higher perioperative

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No.</th>
<th>Population Studied</th>
<th>Follow Up</th>
<th>Outcomes</th>
<th>CEA, %</th>
<th>Medical, %</th>
<th>Absolute Risk Reduction, %</th>
<th>Relative Risk Reduction, %</th>
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<tr>
<td>VASC15</td>
<td>444</td>
<td>Asymptomatic ≥50% stenosis</td>
<td>48 months</td>
<td>Primary: ipsilateral TIA, stroke and death</td>
<td>8.0</td>
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<td>11.4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All TIA and stroke</td>
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<td>24.5</td>
<td>11.7</td>
<td>49</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>44.2</td>
<td>3.0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke and death 30 days</td>
<td>4.7</td>
<td>1.3</td>
<td>3.4</td>
<td>NS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke, MI, and death 30 days</td>
<td>6.6</td>
<td>NA</td>
<td>NA</td>
<td>NS</td>
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<tr>
<td>ACAS16</td>
<td>1662</td>
<td>Asymptomatic ≥60% stenosis by ultrasound validated with XRCA</td>
<td>2.7 years, estimated risk for 5 years</td>
<td>Primary: ipsilateral stroke 5 years, perioperative stroke/death</td>
<td>5.1</td>
<td>11</td>
<td>5.9</td>
<td>47</td>
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<td></td>
<td></td>
<td>Major ipsilateral stroke 5 years, perioperative stroke/death</td>
<td>3.4</td>
<td>6.0</td>
<td>2.6</td>
<td>NS</td>
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<td></td>
<td></td>
<td></td>
<td>Ipsilateral TIA/stroke 5 years, perioperative stroke/death</td>
<td>8.2</td>
<td>19.2</td>
<td>11</td>
<td>43</td>
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<td>NA</td>
<td>NS</td>
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<td></td>
<td></td>
<td>Any stroke 5 years/perioperative death</td>
<td>12.5</td>
<td>17.5</td>
<td>5.0</td>
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<td></td>
<td></td>
<td></td>
<td>Any stroke or death 5 years</td>
<td>25.6</td>
<td>31.9</td>
<td>6.3</td>
<td>NS</td>
</tr>
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<td>ACST10</td>
<td>3120</td>
<td>Asymptomatic (or symptoms &gt;6 months) ≥60% stenosis by ultrasound not validated</td>
<td>Mean=4.7 years, up to 5 years</td>
<td>Primary: any stroke 5 years/perioperative death</td>
<td>6.42</td>
<td>11.78</td>
<td>5.4</td>
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<td>Perioperative stroke/death 30 days</td>
<td>3.1</td>
<td>NA</td>
<td>NA</td>
<td>NS</td>
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<td>Stroke only 5 years</td>
<td>3.8</td>
<td>11.0</td>
<td>7.2</td>
<td>35</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal/disabling nonperioperative stroke 5 years</td>
<td>1.93</td>
<td>5.78</td>
<td>3.85</td>
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</table>

NA indicates not available; NS, not significant.
complications and a presumed shorter life expectancy. A subgroup analysis from NASCET suggests that patients aged 75 to 80 are at higher risk of stroke than younger individuals and derive a larger benefit from CEA. These findings were confirmed in the pooled analysis, but only few patients were older than 80 years old.8–17 Preliminary results from the CREST stenting trial in octogenarians suggested a significantly high perioperative CAS morbidity and mortality of 12.1% in octogenarians in the lead-in phase of the study compared with their younger counterparts and led to excluding them from the study.18 In the community, many patients with these high-risk criteria are commonly subjected to CEA with the false assumption that the risks and benefits of the published trials equally apply to them. Some community-based studies in different regions of the country show that the perioperative risks in the community are variable and could be astoundingly much higher than what has been demonstrated in the RCT.19–21 These uncertainties provided an opportunity for the stenting trials to focus on such patients and compare the two procedures.

Optimal Medical Therapy for Carotid Stenosis
The optimal medical therapy in carotid stenosis has been largely unstudied despite a growing armamentarium of medications that could impact outcomes such as statins, antihypertensive, and antiplatelet therapies. Whether an aggressive medical approach can be competitive with revascularization procedures, or the extent to which it can impact such procedures, is unknown at this time, particularly in high-risk patients.

Carotid Stenosis Screening, Measurement, and Clinical Implications
Measurement of carotid stenosis with XRCA was the method of choice for eligibility, stratification, and randomization of patients in the symptomatic CEA trials. These measurements, particularly the NASCET method, have successfully demonstrated a good correlation between increasing degrees of carotid stenosis and risk of stroke prediction as well as a strong correlation with risk reduction from surgery.5 The same was not true in RCT for asymptomatic CEA in which the correlation between angiographic stenosis severity in ACAS and ultrasound stenosis severity in ACAS and ACST did not predict a higher risk of stroke.10,16 In the VACSG, the risk of first ipsilateral stroke or TIA in the medical arm was not significantly higher in patients with more severe carotid stenosis (76% to 99%) compared with those with a moderate stenosis (50% to 75%) as measured by XRCA.15 Although the number of patients in the VACSG and ACAS in which angiographic measurements were obtained was relatively small, the trend would have been expected to be in the same direction as the degree of stenosis and risk of stroke, which did not happen. An argument can be made for the inaccuracy of ultrasound measurements in ACST to explain the lack of correlation, although it is common practice by many clinicians to rely on ultrasound as the only measurement of stenosis needed to make decision about CEA. These findings bring at least the possibility that asymptomatic patients may have different biologic mechanism, activity, and tempo that could distinguish them from symptomatic patients regarding the stroke risk.

Carotid Plaque Constitution and Ulceration
Because an ulcerated plaque suggests a possible trigger for thrombosis, the debate has centered over whether, independently from the degree of stenosis, it represents a risk for stroke and warrants CEA. The NASCET study showed that ulcerated plaque risk (defined angiographically) is only slightly additional to the risk from stenosis severity.22 An exception occurs at the higher degrees of stenosis in which it significantly adds to the risk from stenosis. Because ulcerated plaque is defined differently by carotid ultrasound, the clinical implications may be different. The ACST study10 evaluated plaque echolucency, which failed to independently impart a higher stroke risk. More reliable ways to evaluate ulcerated plaque in the future may come from intravascular ultrasound, axial plaque MRI, or the addition of a nuclear tracer to measure inflammation within the plaque.

Carotid Endarterectomy in Women
Do women benefit from CEA? Data from the symptomatic CEA trials show that women benefit from endarterectomy as well as men do, but to a lesser degree for unclear reasons. A recent analysis from two CEA trials focused on women and showed a higher perioperative morbidity and mortality in women (7.6%) compared with men (5.9%).23 For asymptomatic carotid stenosis in women, the ACAS study showed no benefit for CEA with higher perioperative complications, whereas ACST showed an equal benefit.10 A meta-analysis of both studies showed a trend for benefit but without statistical significance.24 So far, the CAS studies, as opposed to CEA, show no difference in perioperative morbidity and mortality between women and men.

Carotid Artery Stenting
As a carotid revascularization procedure, CEA is demonstrated effective at reducing the risk of stroke in symptomatic and asymptomatic patients without major perioperative risk. The periprocedural morbidity of most concern to CEA relate to stroke, myocardial infarctions (MI), or death, particularly in patients considered at high surgical risk. Although less disabling, local complications at the site of surgery such as scarring, bleeding, and infection can be discouraging for patients. Additionally, recurrent laryngeal nerve palsy with hoarseness and dysphagia occurs in 8% to 10% of patients after CEA. Carotid revascularization with nonsurgical interventions began 2 decades ago with balloon angioplasty and rapidly evolved almost exclusively toward primary CAS. Stenting efforts began initially with the use of stents designed for other body locations (ie, trachea, biliary tract, and so on) and only recently replaced with stents specifically designed for the carotid artery. Distal endovascular protective devices were introduced only in the past decade to address the risk of embolism from stent deployment.

Most CAS studies focused on patient populations in which CEA had not been adequately tested, ie, patients considered to be at high risk for CEA as discussed previously. Significant information about safety and feasibility of stenting was derived from large case series with periprocedural stroke and mortality and patency not too dissimilar from CEA trials.25 An international survey by Wholley et al,26,27 from major centers perform-
ing CAS, reported 12,392 procedures performed in 11,243 patients and suggested an acceptable periprocedural stroke and mortality of 4.75% that falls somewhere between NASCET and ACAS rates. The validity of these results is hampered by the uncontrolled nature of the data and potential verification and reporting bias of complications. Nonetheless, they provide useful information and a vague idea about frequency of use, feasibility, and complications.

**Randomized Studies of Carotid Artery Stenting**

Compared with CEA, there is a paucity of RCT in CAS and a much larger number of nonrandomized registries.

**Early Randomized Studies**

A limited number of RCT evaluated carotid angioplasty and/or stenting compared with CEA, the majority of which are no longer relevant to the current treatment methods. These studies are summarized in Table 2. The first randomized study of CAS was stopped by the safety monitoring committee after only 17 patients were randomized attributable to a cluster of periprocedural strokes in the stenting arm.28 Another study comparing stenting with the Wallstent with CEA was also stopped prematurely after the randomization of over 200 patients because of higher incidence of stroke and death in the stenting arm and remains unpublished.29 A small single-institution study randomized over 100 patients with symptomatic carotid stenosis to CAS or CEA and found equivalent and very low rates of complications in either arm.30 The largest study so far (CAVATAS)32 consisted mainly of carotid balloon angioplasty (74%) with a small number of implanted stents and randomized over 500 patients to CEA or endovascular therapy. It showed a periprocedural rate of stroke and death of approximately 10%, which was similar for both arms, but much higher than NASCET’s rate.

**The SAPPHIRE Study**

The largest and so far only published randomized study in carotid stenting with EDP is the SAPPHIRE study33 (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) enrolled 710 patients with carotid stenosis of ≥80% asymptomatic and ≥50% symptomatic with at least one additional risk factor considered to raise the risk of CEA (Table 2). Of those patients, 334 patients were considered eligible for randomization to either CEA or stenting, and the rest of the patients were entered either into a surgical or interventional registry when they did not qualify for randomization. Only the results of the randomized part of the study are published.33

The SAPPHIRE study design tested the hypothesis of at least noninferiority of stenting compared with CEA, which was achieved along with a nonsignificant trend for superiority. The primary end point was the combination of 30-day perioperative morbidity and 1-year risk of ipsilateral stroke, which was achieved in 20.1% of CEA and in 12% of the stenting group. Based on these results, the US Food and Drug Administration granted conditional approval for the stenting system used in the study for high-risk CEA patients.

Criticisms of the study were summarized in an accompanying editorial that also addressed them34 and included the main concerns about the high-risk eligibility definitions, the

### Table 2. Randomized Trials of CAS vs CEA in Symptomatic and Asymptomatic Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population Studied</th>
<th>Emboli Protection Device</th>
<th>Manufacturer(s)</th>
<th>Primary Outcome</th>
<th>CAS, %</th>
<th>CEA, %</th>
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<tbody>
<tr>
<td>Leicester, UK28</td>
<td>17</td>
<td>Symptomatic ≥70% stenosis</td>
<td>Wallstent</td>
<td>Schneider/Boston Scientific</td>
<td>Stroke and death 30 days</td>
<td>70</td>
<td>0</td>
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<td>Wallstent Schneider/Boston Scientific29</td>
<td>219</td>
<td>Symptomatic 60% to 90% stenosis</td>
<td>Wallstent</td>
<td>Schneider/Boston Scientific</td>
<td>Ipsilateral stroke, operative death</td>
<td>12.1</td>
<td>4.5</td>
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<tr>
<td>CAVATAS32</td>
<td>504</td>
<td>Symptomatic + asymptomatic (4%)</td>
<td>Various</td>
<td>Various</td>
<td>Stroke and death 30 days</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Lexington, Kentucky-Symptomatic30</td>
<td>103</td>
<td>Symptomatic ≥70% stenosis</td>
<td>Wallstent</td>
<td>Boston Scientific</td>
<td>Stroke and death, 2 years</td>
<td>0</td>
<td>0.5</td>
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<td>Lexington, Kentucky-Asymptomatic31</td>
<td>84</td>
<td>Asymptomatic ≥80% stenosis</td>
<td>Wallstent</td>
<td>Boston Scientific</td>
<td>Stroke and death, 48 months</td>
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<td>0</td>
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<tr>
<td>SAPPHIRE33</td>
<td>334</td>
<td>High-risk symptomatic + asymptomatic (70%)</td>
<td>Precise Angioguard</td>
<td>Cordis</td>
<td>MAE 30 days + ipsilateral stroke or death 1 year</td>
<td>12.2</td>
<td>20.1</td>
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<td></td>
<td>Stroke and death 30 days</td>
<td>4.2</td>
<td>4.8</td>
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<tr>
<td>EVA-3S35</td>
<td>520</td>
<td>Symptomatic ≥60% stenosis</td>
<td>Various</td>
<td>Various, not required</td>
<td>Stroke or death 30 days</td>
<td>9.6</td>
<td>3.9</td>
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<td>SPACE36</td>
<td>1200</td>
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<td>NA</td>
<td>Various, not required</td>
<td>Ipsilateral stroke or death 30 days</td>
<td>6.84</td>
<td>6.34</td>
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NA indicates not available; MAE, major adverse events (stroke, myocardial infarction, death).
inclusion of MI as an end point, the elevated rate 30-day outcomes in the CEA arm compared with RCTs of carotid surgery, and the lack of a medical control arm in the study. In the populations studied with a significantly higher coronary risk, not including MI in the outcome would have certainly provoked criticism in the opposite direction stemming from avoiding the inclusion of an important end point. The much higher rate of primary outcome in the surgical arm compared with CEA trials can be potentially explained by the inclusion of MI in the primary end point and by the different population studied. The study was stopped earlier than planned attribut-

Recent Major Carotid Artery Stenting Randomized Studies

Two large European randomized studies comparing CAS with CEA in symptomatic patients with severe carotid stenosis, SPACE and EVA-3S, were completed and recently reported at scientific meetings. Both studies used different methodologies for determining carotid stenosis and in the use of EDP in the CAS arm. They have still not been published and the preliminary results are summarized in Table 2. EVA-3S (Endarterectomy versus Angioplasty in patients with Severe Symptomatic carotid Stenosis) randomized 520 symptomatic patients with carotid stenosis of ≥60% as measured by a combination of carotid ultrasound and MRI. It showed a lower risk for early outcomes in the CEA arm compared with CAS. The longer-term outcomes are pending. SPACE (Stent-Protected Percutaneous Angioplasty of the Carotid versus Endarterectomy) randomized 1200 symptomatic patients with over 70% stenosis, as measured by ultrasound, to CAS or CEA and was stopped before achieving the target number of patients attributable to slow enrollment and lack of funds. The two arms achieved similar early morbidity without any significant differences between the two arms. There are several ongoing studies that will help provide further information.

Nonrandomized Studies of Carotid Artery Stenting

The vast majority of nonrandomized studies consist of pro-

Nonrandomized Prospective Carotid Stenting Registry Studies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Stent</th>
<th>Emboli Protection Device</th>
<th>Manufacturer(s)</th>
<th>Population Studied</th>
<th>Symptoms</th>
<th>Design</th>
<th>Total Patients Studied</th>
<th>30 Days, MAE (%)</th>
<th>1 year, S/D (%)</th>
<th>1 year, S/D (%)</th>
<th>1 year, MAE (%)</th>
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<td>ARCHER-1</td>
<td>AccuLink</td>
<td>AccuNet</td>
<td>Guidant</td>
<td>HR CEA</td>
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<td>PNR Registry</td>
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PNR Registry indicates prospective nonrandomized registry; Ip S/D, ipsilateral stroke and death; MAE, major adverse events (stroke, myocardial infarction, death); HR CEA, high-risk carotid endarterectomy; A, asymptomatic; S, symptomatic.
Comparative, Prospective, Nonrandomized Studies
A new methodology of clinical study design appears to be gaining momentum in CAS, in which no randomization exists, but investigators are allowed to enter patients into either CAS or CEA arms. The advantages of such design include leaving the freedom to the patient and investigator in the selection of the therapy while allowing for direct comparisons between treatments in concomitant patients as opposed to registries, which allow comparisons only to historical ratios. This could overcome the current tendency to channel patients exclusively to registries. The drawbacks include investigator and patient bias in procedure selection, but in the end, the groups may potentially equal out by chance as demonstrated in the CARESS study (37) (Table 3).

Nonrandomized Prospective Registries
Several nonrandomized studies, or registries, were completed evaluating the newer stents designed for the carotid artery. Most of these studies were supported by industry and planned to obtain governmental approval for the devices tested. Many of these studies were presented at meetings but remain unfortunately unpublished today, making the data difficult to evaluate fully. These registries are summarized in Table 4. Although no control arms of either medical or surgical therapy were part of the studies, the perioperative morbidity and primary end points were comparable to historical contemporary rates for CEA when the high-risk patient population studied is considered. Based on these studies, the Federal Drug Agency has granted an approval to three stent systems in patients at high risk for CEA. Numerous other nonrandomized studies are ongoing.

Summary
Carotid atherosclerotic disease is common and responsible for a large number of ischemic. Even in asymptomatic patients, half of the strokes they develop are fatal or disabling without surgery. Fortunately, in a small proportion of patients, carotid occlusive disease is sometimes preceded by ischemic warning symptoms that place them at a much higher immediate risk for minor or disabling stroke. Forty years after the first CEA, we have sufficient evidence to select the appropriate patient and effectively reduce the future risk of stroke with CEA in symptomatic patients. In asymptomatic patients overall, CEA significantly decreases the risk of future stroke by half if the perioperative risk is modest. Better stratification of those at highest risk for stroke could improve its effectiveness and allow better selection of patients who would benefit most from revascularization. Although CEA still represents the best studied revascularization procedure for the carotid artery, it remains an invasive surgery and can be associated with various complications.

Stenting is an attractive and less invasive alternative to CEA. The knowledge about it and the technical and material improvements achieved over the past decade have been astounding. To date, it is proven to be equivalent to CEA only in patients with high surgical risk. Whether any revascularization procedure is more beneficial than medical therapy in such a population is a whole different question that has not been addressed by the CEA studies. Of course, the long-term outcomes over several years will be essential for determining the safety and durability of CAS. Despite the limited long-term follow up, it appears that there is little difference between the two procedures at 1 year or more. The periprocedural outcomes in the first month are becoming the focus for most of the ongoing studies in comparison to CEA. The overall need for revascularization in high-risk patients will need to be further studied with comparisons to medical therapy alone before subjecting a large number of patients to potentially unnecessary and harmful procedures.

Before it becomes an alternative to CEA in most patients, there is much need for further rigorous evaluations through randomized trials in different groups of patients. The CREST study (Carotid Revascularization Endarterectomy versus Stent Trial) is enrolling symptomatic patients with 50% or greater carotid stenosis and asymptomatic patients with 60% to 70% stenosis using the Acculink stent system. The International Carotid Stenting Study (ICSS or CAVATAS-2) is evaluating symptomatic patients with severe stenosis. The profile gathered through the different studies of CAS is encouraging and very reassuring to include patients in the ongoing trials whose results will undoubtedly bring more clarity to the place that CAS will occupy as a carotid revascularization procedure.

Disclosures
The author received honoraria as consultant with travel-related expenses from Cordis Endovascular, A Division of Johnson & Johnson, for serving on the Executive Committee of the SAPPHIRE study. He also received honoraria as consultant and speaker with travel related expenses from Boehringer Ingelheim Pharmaceuticals. He is also a local principal investigator on a multicenter study funded by Boehringer Ingelheim Pharmaceuticals.

References
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Endarterectomy and Stenting for Asymptomatic Carotid Stenosis: A Race at Breakneck Speed
Pierre Fayad

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