Emerging Therapies

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Carotid Angioplasty and Stent Placement after EVA-3S Trial

Adnan I. Qureshi, MD

A clinical trial is an endeavor where every attempt is made to optimize the quality and quantity of learning before venturing into the unknown. Recently, the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial investigators reported the results of a multicenter, randomized, noninferiority trial comparing stent placement with endarterectomy in patients with symptomatic carotid stenosis of ≥60%. Patients were eligible if they experienced a hemispheric or retinal transient ischemic attack or a nondisabling stroke (or retinal infarct) within 120 days before enrollment. Endarterectomy or stent placement was to be performed within 2 weeks after randomization. The primary end point was the occurrence of any stroke or death within 30 days after treatment. The trial started recruiting in November 2000. In January 2003, the safety committee recommended mandatory use of distal protection devices because of a higher risk of stroke in patients treated without distal protection. Although initially recruiting patients with stenosis of ≥70%, the trial started recruiting patients with stenosis of ≥60% in October 2003. In September 2005, the safety committee recommended stopping enrollment after 527 patients (intended target recruitment of 872 patients) had been randomized. On the basis of the observed 30-day risk of stroke or death after endarterectomy, >4000 patients were required to test the noninferiority of stent placement. Given the observed 30-day risks of stent placement, the committee considered it to be extremely unlikely that the trial would reach its objectives despite further enrollment.

The 30-day incidence of any stroke or death was 3.9% after endarterectomy and 9.6% after stent placement. The rate of disabling stroke or death was 1.5% after endarterectomy and 3.4% after stent placement. At 6 months, the incidence of any stroke or death was 6.1% after endarterectomy and 11.7% after stent placement. The higher rates of stroke or death undermined the lower rates of cranial nerve injury and shorter duration of hospital stay observed in patients treated with stent placement. Post hoc analyses demonstrated lower rates of 30-day stroke or death among patients who underwent stent placement with distal protection. However, most patients in the trial underwent the procedure with distal protection (227 of 247 patients), and the relative risk of stroke or death for stent placement did not change significantly after use of distal protection devices was mandated. No significant differences in outcome were observed related to the number of stent procedures performed in individual centers or to the experience of the interventional physicians, although these analyses were able to detect only large differences. There were 5 different carotid stent devices and 7 different distal protection devices used in the study that added an undefined bias.

The results appear somewhat contradictory to the existing data derived from other studies. A randomized trial compared carotid stent placement with the use of a distal protection device to endarterectomy in 334 high surgical risk patients with either a symptomatic carotid-artery stenosis of ≥50% or asymptomatic stenosis of ≥80%. The primary end point of death, stroke, or myocardial infarction within 30 days or ipsilateral stroke between 31 days and 1 year occurred in 12% of the patients assigned to undergo stent placement and in 20% of patients assigned to undergo endarterectomy. A subsequent meta-analysis analyzed 5 randomized trials totaling 1154 patients (577 randomized to endarterectomy and 577 to stent placement). The composite end point of 1-month stroke or death rate was not different (see the Figure) between patients treated with stent placement compared with those treated with endarterectomy (relative risk 1.3; 95% CI, 0.6 to 2.8; P=0.5). The 1-month stroke rate and disabling stroke rate were similar for stent placement and endarterectomy. The 1-month rates of myocardial infarction and cranial nerve injury were significantly lower for stent placement. No significant differences were observed in 1-year rates of ipsilateral stroke. A subsequent pooled analysis of 8 prospective trials including only high surgical risk patients, analyzed 3282 patients (3115 treated with stent placement and 167 treated with endarterectomy). The composite end

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point of 1-month stroke, myocardial infarction, or death was significantly lower among patients treated with stent placement (5.2%) compared with those treated with endarterectomy (9.6%; odds ratio, 0.5; 95% CI, 0.3 to 0.96; P<0.05). The 1-month stroke rate and death rate were similar for stent placement and endarterectomy. The 1-month rates of myocardial infarction were significantly lower for stent placement (1%) compared with endarterectomy (6%).

The Table summarizes the characteristics of the recent studies2,3,6,7,8,9,10 that have evaluated the outcomes after carotid stent placement using a randomized clinical trial or postmarketing surveillance study. As can be observed in the Table, the 1-month stroke and death rate were prominently higher in the EVA-3S trial compared with the other trials (including postmarketing surveillance studies). The number of previously performed procedures required to qualify for participation in the trial as an interventionalist was lower than in other studies.11 The study allowed centers fulfilling all requirements except those with regard to the interventional physician to perform stent placement under the supervision of an experienced tutor until the local interventional physician performed a sufficient number of procedures according to the predefined criteria. This has prompted concerns that the qualifications required in the EVA-3S trial were not adequate to perform carotid stent placement. It remains unclear whether the higher rates of 30-day stroke or death are also affected by limiting patient selection to symptomatic carotid artery stenosis (90% or “near occlusion” in high surgical risk patients or those who refuse to undergo endarterectomy after proper informed consent. The Centers for Medicare and Medicaid Services15 concluded that the evidence is adequate to conclude that carotid stent placement with distal protection is reasonable and necessary for patients who are at high risk for endarterectomy and have symptomatic carotid artery stenosis (≥70%) in whom other specific circumstances exist such as radiation-induced stenosis or restenosis after endarterectomy, carotid stent placement is not inferior to carotid endarterectomy and may be considered (Class IIb, Level of Evidence B). Carotid stent placement was considered reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of carotid endarterectomy and carotid stent placement (Class IIa, Level of Evidence B). The Collaborative Panel of the American Society of Interventional and Therapeutic Neuroradiology, the American Society of Neuroradiology, and the Society of Interventional Radiology14 recommended stent placement for patients with symptomatic stenosis of ≥70% stenosis by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and symptomatic stenosis of ≥90% or “near occlusion” in high surgical risk patients or those who refuse to undergo endarterectomy after proper informed consent. The Centers for Medicare and Medicaid Services15 concluded that the evidence is adequate to conclude that carotid stent placement with distal protection is reasonable and necessary for patients who are at high risk for endarterectomy and have symptomatic carotid artery stenosis (≥70%). Coverage is limited to procedures performed using Food and Drug Administration approved carotid artery stents and distal protection devices. Patients at high risk for endarterectomy are defined as those having significant comorbidities or anatomic risk factors and would be poor candidates for endarterectomy in the opinion of a surgeon.

A major issue is how the results of the EVA-3S trial affect the existing regulatory approvals and recommendations from professional organizations. The Brain Attack Coalition12 acknowledges that stent placement may be an acceptable treatment option in patients at high risk for an endarterectomy (ie, restenosis after endarterectomy, radiation fibrosis, fibromuscular dysplasia, surgically inaccessible stenosis, contralateral carotid occlusion, and significant cardiac or pulmonary disease). Stent placement in extracranial carotid arteries for atherothrombotic disease is grade IIB recommendation and is considered an optional element of a comprehensive stroke center. Brain attack coalition recommends that for patients with average surgical risk, stent placement should be performed as part of a randomized clinical trial or under a local institutional review board approved protocol. The statement also recommended that stent placement be performed by individuals with training and expertise in cerebral angiography, cerebrovascular pathophysiology, hemodynamics, and neurovascular interventions. The American Heart Association/American Stroke Association council13 recommended that among patients with symptomatic severe stenosis (>70%) in whom other specific circumstances exist such as radiation-induced stenosis or restenosis after endarterectomy, carotid stent placement is not inferior to carotid endarterectomy and may be considered (Class IIb, Level of Evidence B). Carotid stent placement was considered reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of carotid endarterectomy and carotid stent placement (Class IIa, Level of Evidence B). The Collaborative Panel of the American Society of Interventional and Therapeutic Neuroradiology, the American Society of Neuroradiology, and the Society of Interventional Radiology14 recommended stent placement for patients with symptomatic stenosis of ≥70% stenosis by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and symptomatic stenosis of ≥90% or “near occlusion” in high surgical risk patients or those who refuse to undergo endarterectomy after proper informed consent. The Centers for Medicare and Medicaid Services15 concluded that the evidence is adequate to conclude that carotid stent placement with distal protection is reasonable and necessary for patients who are at high risk for endarterectomy and have symptomatic carotid artery stenosis (≥70%). Coverage is limited to procedures performed using Food and Drug Administration approved carotid artery stents and distal protection devices. Patients at high risk for endarterectomy are defined as those having significant comorbidities or anatomic risk factors and would be poor candidates for endarterectomy in the opinion of a surgeon.

The results of the EVA-3S are not going to affect the existing guidelines and regulatory approvals. However, the results place more premium on rigorous and standardized training criteria required for interventionalist performing carotid stent placement, a need already recognized in guidelines provided by several professional organizations. The
Characteristics and 1-Month Stroke and Death Rates Observed in Recent Clinical Studies Involving Carotid Stent Placement With Distal Protection

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Design Description</th>
<th>Patients Included</th>
<th>Devices Used</th>
<th>Credentialing Requirements</th>
<th>1-month Any Stroke or Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenting and Angioplasty with Protection in</td>
<td>Randomized clinical trial at 29 centers (n=167)</td>
<td>High surgical risk patients with symptomatic stenosis ≥50% or asymptomatic stenosis ≥60%</td>
<td>Smart or Precise nitinol stent and Angioguard or Angioguard XP emboli capture guidewire distal protection device</td>
<td>Required to submit experience and results. The median total No. of carotid stent procedures performed per operator was 64 (range, 20 to 700) and the mean stroke, death, or myocardial infarction complication rate was 4%</td>
<td>4.8% (includes myocardial infarction)</td>
</tr>
<tr>
<td>Patients at High Risk for Carotid Endarterectomy (SAPPHIRE) trial</td>
<td>Lead in-phase for randomized clinical trial at 51 centers (n=789)</td>
<td>Patients with symptomatic stenosis ≥50% or asymptomatic stenosis ≥70%</td>
<td>Acculink carotid stent system. In September 2001, Accunet distal protection device added</td>
<td>Required to submit data on 10–30 cases previously performed and depending on this data had to perform up to 20 lead-in cases</td>
<td>4.6% (No variation according to physician specialties)</td>
</tr>
<tr>
<td>Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs Endarterectomy (SPACE) trial</td>
<td>Randomized clinical trial at 35 centers (n=605)</td>
<td>Patients with symptomatic stenosis ≥50% according to the NASCET criteria</td>
<td>Wallstent, Precise, or Acculink stent; and PercuSurge GuardWire, FilterWire EX, AngioGuard, NeuroShield, or Carotid Trap distal protection device</td>
<td>Perform at least 25 successful consecutive percutaneous carotid angioplasty or stent procedures</td>
<td>7.8%</td>
</tr>
<tr>
<td>Endarterectomie Versus Angioplastie chez les patients ayant une Sténose carotide Symptomatique Serrée (EVA-3S)</td>
<td>Randomized clinical trial in 20 academic and 10 nonacademic centers (n=247)</td>
<td>Patients with symptomatic stenosis ≥60%</td>
<td>Wallstent, Precise, Zilver, or Acculink stent; and PercuSurge GuardWire, FilterWire EZ, AngioGuard RX, Spider RX, Emboshield, NeuroShield, or Accunet distal protection device</td>
<td>Perform at least 12 carotid-stenting procedures or at least 35 stenting procedures in the supraaortic trunks, of which at least 5 were in the carotid artery</td>
<td>9.6% (no significant differences in outcome related to the experience of the interventional physicians, although analyses only able to detect large differences)</td>
</tr>
<tr>
<td>Carotid Artery Stenting With Emboli Protection Surveillance-Post-Marketing Study (CASES-PMS)</td>
<td>Postmarketing surveillance study at 70 centers (n=1279)</td>
<td>High surgical risk patients with symptomatic stenosis ≥50% or asymptomatic stenosis ≥60%</td>
<td>Precise nitinol stent and Angioguard distal protection device</td>
<td>Training included didactic review, case observations and simulation training, and hands-on experience at the Regional Education Centers</td>
<td>4.8% (includes myocardial infarction)</td>
</tr>
<tr>
<td>The Carotid Acculink/Accunet Post Approval Trial to Uncover Rare Events (CAPTURE)</td>
<td>Postmarketing surveillance study at 144 centers (n=3500)</td>
<td>Predominantly asymptomatic patients (90%)</td>
<td>Acculink stent with Accunet distal protection device</td>
<td>Guidant’s physician training program tailored to the experience level of each physician; majority of physicians (71%) performing the procedures had a medium level of experience (performed 10 carotid stent procedures as the primary operator); only one third or less of patients enrolled at hospitals with a high level of experience</td>
<td>6.3% (includes myocardial infarction); no difference according to operator experience levels or physician specialties</td>
</tr>
</tbody>
</table>

Devices used and manufacturers: Acculink stent and Accunet (Guidant); Wallstent and FilterWire EX (Boston Scientific); Smart and Precise stents and Angioguard (Cordis); Zilver vascular stent (Cook Inc); PercuSurge GuardWire (Medtronic); NeuroShield (MedNova); Spider Rx (ev3, Inc); Emboshield (Abbott Vascular); and Carotid Trap (Microvena).

NASCET indicates North American Symptomatic Carotid Endarterectomy Trial.

results also mandate that further data be acquired through ongoing trials such as the Carotid Revascularization Endarterectomy versus Stenting Trial before carotid stent placement is recommended as a first line treatment for patients with symptomatic carotid stenosis who are candidates for carotid endarterectomy with an acceptable periprocedural risk.

Disclosures

None.

References


Key Words: angioplasty ■ stent placement ■ carotid stenosis ■ carotid artery ■ carotid endarterectomy
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