Randomized clinical trials: How will results influence clinical practice in the management of symptomatic and asymptomatic extracranial carotid occlusive disease?

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Evaluation of the efficacy of carotid endarterectomy and stenting requires careful consideration of clinical trial methodology as applied to the primary clinical end points of the specific trial. Although publication of observational data including registries is helpful in selecting options for further study, these reports are not considered replacements for the randomized clinical trial. This article reviews methodology and results of registries and randomized clinical trials. Pending publication of larger clinical trials on the management of symptomatic and asymptomatic carotid stenosis within the next 1 to 3 years, carotid endarterectomy remains the preferred technique for cerebral revascularization. The only exceptions to this recommendation come from higher risk categories of patients; however, their identification is frequently difficult and controversial. (J Vasc Surg 2007;45:158A-163A.)

Carotid endarterectomy (CEA) stands as an approved method for revascularization of symptomatic and asymptomatic patients with extracranial carotid occlusive disease. Enthusiasm has grown for carotid artery stenting (CAS) as a less invasive procedure, but the lack of efficacy data compared with CEA in better-risk patients has limited acceptance of the technique. Although CAS has been recommended in specialized subsets of patients, such as restenosis after CEA, radiation-induced carotid stenosis, anatomically high lesions above the second cervical vertebra, and in higher-risk patients, its use in better-risk patients has generally been reserved for patients enrolled in clinical trials. The purpose of this review is to update the results and status of relevant clinical trials and to estimate when the presentation and publication of additional more definitive trial data may be anticipated.

CLINICAL TRIAL METHODOLOGY

In evidence-based analyses, the roles for randomized clinical trials (RCTs) and observational studies have been debated extensively. RCTs are used for efficacy analyses when anticipated differences in treatment modalities are not great and each patient’s treatment is chosen by randomization to preclude the risk of selection bias and other differences that may not be related to the treatment itself. Investigators define a population for study through the trial’s inclusion and exclusion criteria and select experienced clinicians to perform the treatments.

RCTs have limitations in terms of generalizability. An example of this issue would be the recommended management for octogenarians with extracranial carotid occlusive disease. The North American Symptomatic Carotid endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS) investigators excluded patients in that age group, and definitive recommendations are not available. If the selected clinicians are highly skilled, the study results from an RCT may also be criticized as not being applicable to all centers.

Observational studies are useful to evaluate effectiveness and can supplement the results of RCTs. These studies evaluate effectiveness in the application of the treatments in routine practice. Observational studies are not considered replacements for RCTs in terms of providing level I evidence and class A clinical recommendations for the management of symptomatic and asymptomatic extracranial carotid occlusive disease. As described by Califf, data from RCTs are used to devise guidelines, measure performance, and conduct further outcome analyses. Consequently, these data have significant influence on the practice patterns of all clinicians compared with the more limited applications for observational study data.

Of additional importance is the analytic method used by the authors of a clinical trial. In many trials, the results are presented as a superiority analysis that allows the investigators to conclude whether one treatment is better or worse than the other treatment. The noninferiority or equivalency trial is unable to make the same conclusions
but will answer the question of which of the treatments may or may not be inferior to or equivalent to the established treatment.

In a superiority trial, the investigators’ proposal generally leads to rejection of the null hypothesis and a demonstration of differences between the two interventions. In the noninferiority trial, the investigators are comparing an innovative new treatment with a gold standard within a noninferiority interval or delta, which has been evaluated and recommended by the investigators for the primary outcome. The noninferiority trial is frequently used to assess a new therapy against a gold standard in which the new therapy may be considered safer or less invasive.

As emphasized by Gotzsche,¹⁹ the confusing part of a noninferiority trial is the proper selection of the delta or difference in planning the trial, which then impacts the calculations of sample sizes. In one of his examples, which is comparable to issues related to CEA, if the estimated event rate was 3.1% but a delta of 2% were chosen, it would be arguably too large and may lead to a report in which the new treatment is “at least as effective” as the gold standard, which may be unwarranted unless the entire confidence interval lies outside the noninferiority interval corresponding to a \( P \leq .05 \) in a test of superiority. Unfortunately, the delta can also be modified if the early analysis demonstrated that the treatment was inferior; with this change in delta, an altered conclusion can be made that the new treatment was not inferior and that the sample size was sufficient.

It is important to recall that a noninferiority trial can only demonstrate that the new intervention is not worse than the comparable gold standard by more than a prespecified amount or delta. A noninferiority trial’s publication should include definitions and justification of the noninferiority equivalency margin or delta, calculations of the sample size taking this margin into account, presentation of both intention to treat and protocol analysis, and provide confidence intervals for the results. In their absence, the conclusions of a noninferiority trial are suspect.²⁰

### CLINICAL PROTOCOLS AND RESULTS

This report is intended to review clinical trials that compare the results of CAS and CEA. Many nonrandomized registry results were published in a recent review by Naylor.²¹ Stroke, death, and myocardial infarction rates at 30 days postprocedure were 3.8% to 8.5%, and 30-day stroke and death rates alone were 3.6% to 6.9%. These registries were not controlled, however, and assignment of patients may have been related to clinical biases of the treating physicians. Although they do reflect information about the effectiveness of treatment in the referenced institutions, these data will not replace information from RCTs and will not result in level I evidence or class A clinical recommendations.

A comparison of RCTs (>200 patients) in symptomatic and asymptomatic patients will be presented. Data from four randomized trials among symptomatic patients and one with predominantly asymptomatic patients are summarized in Table I. Data on larger (>1500 patients) RCTs, some of which will be completed within the next 1 to 3 years, are summarized in Table II.

The Wallstent trial²² was conducted in the early 1990s using a Wallstent (Boston Scientific, Natick Mass) without cerebral protection and demonstrated significant differences for symptomatic patients with 60% to 99% stenoses. Stroke and death rates at the 30-day postprocedure interval were reported as 12.1% for CAS and 4.5% for CEA, which favored CEA. However, absence of cerebral protection may have contributed to the unacceptably high stroke and death rate with CAS.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial²³ randomized >500 symptomatic patients with stenoses of 50% to 99%. Stents were used in only 22% of the patients, however, and cerebral protection was not available. The stroke and death rate at 30 days postprocedure was 9.9% for CEA and 10% for CAS, and death or disabling strokes were observed in 5.9% of CEA patients and 6.4% of CAS patients. Cranial nerve palsies were recognized in 8.7% of CEA patients, and none was observed with CAS. The evaluation of this study was clouded, however, because the death and any stroke rate was higher than anticipated and higher than the American Heart Association’s recommendations for carotid endarterectomy.²⁴

More recent publications by the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy²⁵ (SPACE) and Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S)²⁶ investigators have suggested a preference for CEA in symptomatic patients. These differences were quite controversial in their analyses, however. The SPACE trial²⁷ randomized 1200 patients with stenoses of 50% to 99%. Stents were used universally, and cerebral protection devices were used in 26% of the patients in SPACE. The SPACE investigators reported 30-day stroke and death rates of 6.8% for CEA and 6.8% for CAS, which were not significantly different. As an inferiority trial, however, randomization of patients was...
stopped at the time of publication because CAS was not
owned to be noninferior to CEA and possibly would
not have been proven according to the trial’s authors, even with
the recruitment of twice the sample size of 1200 patients.
The trial was, unfortunately, also abandoned because of
limited funding, but the investigators emphasized a result
that favored CEA over CAS.

The EVA-3S investigators26 randomized 527 symp-
tomatic patients with stenoses of 70% to 79%, and 73% were
treated with cerebral protection devices. These trialists
reported a 30-day death and any-stroke rate of 3.8% for
CEA and 9.5% for CAS, which was a significant (P < .05)
result favoring CEA. Two major flaws have been noted in
the trial, however. First, the 27% of patients who were not
treated with cerebral protection demonstrated a trend to-
ward poorer outcomes than in patients with cerebral pro-
tection, although the differences were not significant.

Second, the credentialing of interventionalists was also
a matter of some concern: some interventionalists gained
approval for participation in the trial by being proctored on
as few as two cases. The investigators then were permitted
to choose any one of five stents or seven cerebral protection
devices. Also, the number of patients randomized during
58 months at 30 centers26 resulted in an average of five
patients randomized per year per center. These procedures
were performed infrequently by interventionalists who may
not have been experienced or well credentialed.

Three of four RCTs with larger sample sizes of >1500
patients (Table II) among symptomatic and asymptomatic
patients are scheduled for completion and publication of
data within the next 1 to 3 years. These include the Carotid
Revascularization Endarterectomy vs. Stenting Trial
(CREST) in asymptomatic and symptomatic patients
(funded by National Institute of Neurological Disorders
and Stroke [NINDS], National Institutes of Health
[NIH]); the Asymptomatic Carotid Stenosis Trial II
(ACST I) in asymptomatic patients (funded by the Na-
tional Health Service, United Kingdom), the Asymptom-
atic Carotid Trial (ACT-1), funded by Abbott Vascular,
and the International Carotid Surgery Study (ICSS) in
symptomatic patients (funded by the Medical Research
Council, United Kingdom).

CREST. Stimulated by our clinical experience11,12,27-30
and other reference reports, the CREST investigators re-
ceived approval for funding from the NINDS, NIH, for a
trial to compare the efficacy of CEA and CAS in symptom-
atic patients with high-grade (≥70%) stenosis.18 The
threshold lesion for symptomatic patients27 was lowered to
≥50% stenosis, and asymptomatic patients with ≥70% ste-
noses by ultrasound were included in CREST after April
2005. However, recognizing that CAS was a relatively new
procedure at many sites, each participating center was
required to complete a credentialing phase to reassure
clinicians that the safety of these procedures had been
reviewed and established before approval for the random-
ized phase of the trial.

The lead-in or credentialing phase required the perfor-
man of up to 20 interventional procedures using the
CREST study devices at each of more than 100 participat-
ing centers. Once this was completed to the satisfaction of

Table I. Summary for published results from four randomized trials in symptomatic patient and one trial in
predominately asymptomatic patients (CEA vs CAS)

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Year published</th>
<th>No randomized</th>
<th>Stent used</th>
<th>SCD used (%)</th>
<th>30-day outcomes</th>
<th>Wound/access complications</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>CAS</td>
<td>Wallstent</td>
<td>None available</td>
<td>0.9/0.7</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22% stented</td>
<td>None available</td>
<td>6.3/6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.5/2.1</td>
<td>6.5/7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.9/6.4</td>
<td>3.8/4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.7/1.2</td>
</tr>
</tbody>
</table>

CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy; EVA-3S, Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy


*This trial was in predominately asymptomatic patients.
†Cordis, Miami Lakes, Florida.
the study’s Interventional Management Committee, randomization of patients between the two treatments was then approved. The primary outcome events for this clinical trial include (1) any stroke, myocardial infarction, or death during the 30-day perioperative or periprocedural period, or (2) ipsilateral stroke 30 days.

End points are reviewed by an Adjudication Committee, blinded to the assigned treatment. Stroke will be determined by a positive transient ischemic attack/stroke questionnaire and NIH stroke scale as performed preoperatively and postoperatively and at 30 days by a study neurologist. The diagnosis of postoperative or procedural myocardial infarction is determined by the electrocardiography and enzyme abnormalities.

Secondary goals include to (1) describe differential efficacy of the two treatments in men and women, (2) contrast perioperative and procedural (30-day) morbidity and postprocedural mortality rates for the CEA and CAS procedures, (3) estimate and contrast the restenosis rates for the two procedures, (4) identify subgroups of participants at differential risk for the two procedures, and (5) evaluate differences in health-related quality-of-life issues and cost-effectiveness.

A differential gender-based efficacy assessment of CEA and CAS is a secondary goal for CREST. In patients with high-grade asymptomatic stenosis that were reported by ACAS, CEA offered a 66% relative risk reduction in events during a 5-year period for men but only a 17% reduction for women. In NASCET, although no differential gender effects were reported among symptomatic patients with 70%-99% stenosis, men demonstrated greater benefit after CEA than women for 50% to 69% stenoses.

### TABLE II. Methodology and contact details for the current randomized trials

<table>
<thead>
<tr>
<th>Methodology</th>
<th>ACT I</th>
<th>ACST II</th>
<th>CREST</th>
<th>TACIT</th>
</tr>
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<tbody>
<tr>
<td>Type of trial</td>
<td>Noninferiority</td>
<td>Equivalence</td>
<td>Superiority</td>
<td>Superiority</td>
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<td>Multicenter</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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<td>Recruiting country</td>
<td>North America</td>
<td>Worldwide</td>
<td>North America</td>
<td>North America, Europe</td>
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<td>Treatment options</td>
<td>CAS vs CEA</td>
<td>CAS vs CEA</td>
<td>CAS vs CEA</td>
<td>CAS vs BMT</td>
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<tr>
<td>Funding source</td>
<td>Abbott Vascular</td>
<td>NHS R + D HTA</td>
<td>NINDS</td>
<td>To be determined</td>
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<tr>
<td>Number intended to be in trial</td>
<td>1858</td>
<td>5000+</td>
<td>2500</td>
<td>2500</td>
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<tr>
<td>Randomization ratios</td>
<td>CAS:CEA 3:1</td>
<td>CAS 1:CEA 1</td>
<td>CAS 1:CEA 1</td>
<td>CAS 1:BMT 1</td>
</tr>
<tr>
<td>Participant record review</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Proctoring/mentoring for CAS</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Stenosis range</td>
<td>“Severe”</td>
<td>“Severe”</td>
<td>60%-99% angio</td>
<td>70%-99% US</td>
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<tr>
<td>Stenosis measurement method</td>
<td>NASCET</td>
<td>NASCET/ECST</td>
<td>NASCET</td>
<td>NASCET</td>
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<tr>
<td>Stent used in study CPD</td>
<td>Xact Rapid Exchange</td>
<td>CE approved</td>
<td>Acculink</td>
<td>FDA/CE approved</td>
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<tr>
<td>Obligatory/optional</td>
<td>Obligatory</td>
<td>Optional</td>
<td>Obligatory</td>
<td>Obligatory</td>
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<tr>
<td>Type</td>
<td>Emboshield</td>
<td>CE approved</td>
<td>RX Accunet</td>
<td>FDA/CE approved</td>
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<tr>
<td>Dual antiplatelet therapy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>End points at 30 days</td>
<td>Death/stroke/MI &gt;30-d to 1-y ipsilateral stroke</td>
<td>Death/stroke/MI 5-y stroke (any/disabling)</td>
<td>“Late” ipsilateral stroke</td>
<td>5-y stroke rate</td>
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<tr>
<td>Contact details</td>
<td><a href="mailto:dana.fletcher@abbott.com">dana.fletcher@abbott.com</a></td>
<td><a href="mailto:acst@sgul.ac.uk">acst@sgul.ac.uk</a></td>
<td><a href="http://www.umdnj.edu/crestweb">www.umdnj.edu/crestweb</a></td>
<td><a href="http://www.sirfoundation.org/misc/tacit.shtml">www.sirfoundation.org/misc/tacit.shtml</a></td>
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</table>

ACT I, Asymptomatic Carotid Trial; ACST II, Asymptomatic Carotid Stenosis Trial II; CREST, Carotid Revascularization Endarterectomy vs Stenting Trial; TACIT, Trans Atlantic Carotid Interventional Trial; MI, myocardial infarction.


From Naylor RA. Where next after SPACE and EVA-3S: The good, the bad, and the ugly. Eur J Vasc Endovasc Surg 2007;33:44-47, with permission.

aNoninferiority, equivalence, superiority.
bCarotid angioplasty (CAS), carotid endarterectomy (CEA), best medical therapy (BMT).
cNumber of patients that power calculation deems necessary for trial completion.
dRatio of CAS to CEA/BMT in trial.
eTrack record review undertaken in order to select trial participants.
fDoes the trial allow for less experienced CAS practitioners to randomize patients but be proctored by more experienced practitioners before being allowed to perform CAS independently within the trial?

gRange of stenoses being randomized.
hStenosis measurement method; ie, North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST)

iFood and Drug Administration (FDA) approved, Conformité Européenne (CE) mark indicates that the product meets the requirements of all relevant European Directives.

jNational Health Service Research Health Technology Assessment program.
kNational Institute of Neurological Disorders and Stroke.
lNote the slightly different stenosis thresholds depending upon whether imaging is done by angiography or duplex ultrasonography.
a higher complication rate for CEA in women, possibly caused by their reported smaller arterial sizes and a greater surgical morbidity.

Unfortunately, neither ACAS nor NASCET suspected the possibility of a differential gender effect. However, given the results of these two randomized clinical trials, a requirement for a priori plans to evaluate the possibility of a differential gender effect has become an important component of CREST. Centers are being selected with a goal of recruiting 40% women in the randomized sample of patients, which if achieved, will provide an 80% power to answer this question.

Patients will be evaluated at baseline, at 24 hours after the procedure, at 30 days, at 6 months, and thereafter at 6-month intervals. Baseline procedures will include a brief medical history and physical examination, a risk-factor evaluation, and the results of a neurologic status questionnaire will be evaluated by a neurologist. The sample size for the study is approximately 2500 symptomatic patients, which will be sufficient to detect a relative risk reduction at a minimum of 25% to 30% between treatment groups. Lesser differences would be considered sufficiently small to declare the treatments equivalent.

An analysis of the lead-in CREST registry on 1246 patients was recently published and represents the largest cohort of CAS patients with protocol-driven neurologic examinations. The 30-day stroke and death rate was 3.9% (5.6% for symptomatic patients and 3.4% for asymptomatic patients). These rates are similar to those reported for CEA in symptomatic patients. Despite inclusion of the higher-risk octogenarians in the asymptomatic group, the stroke and death rates approach the reported data from ACAS5 and are only moderately above the 3% limit recommended by the American Heart Association consensus report. These data confirm clinical equipoise for the randomization of patients between CAS and CEA. CREST has randomized 1584 patients (approximately 50% symptomatic) as of February 1, 2007, and anticipates completion of patient enrollment (n = 2500) by mid-2008.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) investigators randomized 327 patients among 30 centers. Two thirds of the sample were asymptomatic patients with stenoses of >80% (Table I), and the rest were symptomatic and had stenoses >50%. These investigators were unable to show any reduction in stroke and death rate with CAS compared with CEA in symptomatic or asymptomatic patients. However, with the addition of myocardial infarction, some associated with enzyme changes only, investigators concluded that CAS was not inferior to CEA (P = .047) for the study’s entire cohort of patients. One needs to keep in mind the prerequisites recommended for a noninferiority or equivalency trial, which these investigators did not fulfill in their publication. As a consequence, the results are not as decisive as clinicians require and are restricted to high-risk patients only.

The extension of the prior CAVATAS trial to the ICSS anticipates the randomization of 1500 to 1800 symptomatic patients. The trial’s design is similar to CREST but does not specify the type of stent or cerebral protection to be used. However, combined analyses of data will be arranged as the ICSS and CREST complete enrollments. This will also apply to the soon to be initiated ACT II trial which anticipates randomization of 5000 patients in centers originally selected for the ACST study.

ACT-1 (sponsored by Abbott Vascular) investigators will randomize asymptomatic patients in a ratio of one CEA to three CAS procedures (personal communication by K. Rosenfield and J. Matsumura, Co-Principal Investigators, 2006). The study initiated patient enrollment in 2006 and has randomized >300 patients. No further plans or data have been published by these investigators.

The results of these trials should clarify indications in symptomatic and asymptomatic patients of good risk compared with the registries and prior randomized trials that generally have used higher-risk patients. The goal of defining indication for CEA and CAS may also be achieved. It is possible that specified lesions such a restenosis may be better treated by CAS and heterogeneous ulcerated lesions may be better treated with CEA. This may result in a complementary relationship for CAS and CEA in the management of extracranial carotid occlusive disease.

Finally, the Trans Atlantic Carotid Interventional Trial (TACIT) investigators are in the planning phase of a superiority trial that anticipates recruitment of 2500 patients (personal communication, B. Katzen, MD, Principal Investigator, 2007). Originally designed to randomize symptomatic and asymptomatic subjects to one of three arms, CEA vs CAS vs best medical therapy, this plan was recently modified to randomize patients between CAS and best medical therapy. Sponsors are being recruited and initiation of the trial is anticipated this year.

CONCLUSIONS

For the immediate future, patients with symptomatic and asymptomatic disease should be treated preferentially with CEA rather than CAS. Clinicians also must be encouraged to participate in RCTs that involve better-risk patients. Until such time as more definitive data from larger efficacy trials are available (Table II) to guide a change in practice, the only exceptions to such a recommendation must be based on each interventionalist’s experience for specialized subsets of patients, such as restenosis after CEA, anatomically high lesion, radiation-induced stenosis, or the symptomatic high-risk patient group.

REFERENCES


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