Asymptomatic CAS Trial Designs

John H. Rundback, MD, of the TACIT trial, and Sumaira Macdonald, MD, of ACST-2 discuss the necessary elements to evaluate the current state of care for treating asymptomatic carotid stenosis.

***John H. Rundback, MD**, of TACIT, is Director, Interventional Radiology, Holy Name Hospital, and Associate Professor of Radiology, Columbia University College of Physicians and Surgeons, Teaneck, New Jersey. Dr. Rundback may be reached at jr2041@columbia.edu.*

Endovascular Today: *What are the goals of your trial?*

Dr. Rundback: The Transatlantic Asymptomatic Carotid Intervention Trial (TACIT) is designed to be the definitive and pivotal trial evaluating the role of optimized medical therapy and both forms of revascularization (stenting and endarterectomy) for asymptomatic carotid stenosis that is hemodynamically significant (ie, at least 60% narrowing of the internal carotid artery).

Endovascular Today: *How is TACIT funded?*

Dr. Rundback: Funding for the trial is currently being explored. We applied for grants through the National Institute of Health (NIH), but in the current climate of funding for CREST, this was not awarded. However, there has been tremendous progress toward industry support of the trial, and we're hopeful that by the end of the year, we will have secured funding from some of the major stent manufacturers to proceed with the trial.

Endovascular Today: *What is the ideal source of funding for a major carotid artery stenting (CAS) trial?*

Dr. Rundback: In this particular instance, we believe collaboration with industry for funding is optimal. The funding level of the NIH is relatively low at this time,

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***Sumaira Macdonald, MBChB (Comm.), FRCP, FRCR, PhD,** of ACST-2, is a Consultant Vascular Radiologist and Honorary Clinical Senior Lecturer at Freeman Hospital, Newcastle upon Tyne, England. She has disclosed that she sits on the Steering and Technical Management Committees of the ACST-2 trial, of which the chief investigator is Alison Halliday, MS, FRCS, vascular surgeon, of St George's University, London. Dr. Macdonald may be reached at sumaira.macdonald@nuth.nhs.uk.*

Endovascular Today: *What are the goals of your trial?*

Dr. Macdonald: The main goal of the trial is to ascertain whether CAS is equivalent to carotid endarterectomy (CEA) in terms of procedural hazard and survival free of stroke to 5 years, in patients with asymptomatic carotid stenosis in whom the decision to intervene has been made, based on clinicians' interpretation of the results from the earlier ACAS and ACST trials.

Endovascular Today: *What is the ideal source of funding for a CAS trial? Why?*

Dr. Macdonald: Any trial that seeks to compare an established open surgical technique with a new and "technology-rich" procedure must, if possible, avoid funding by the manufacturers of that technology because (although the support of industry is, of course, always welcome) there is evidence to suggest that industry-sponsored trials are associated with pro-industry findings for both medical and surgical interventions.[1] The ideal source of funding for a trial such as ACST-2 is therefore an entirely independent and unbiased one.

ACST-2 has been granted £1.5 million from the British

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(Dr. Macdonald, continued from page 59)
National Health Service Health Technology Assessment Programme with additional funding offered by the BUPA Foundation.

Endovascular Today: *How should the participating centers and physicians be selected?*

Dr. Macdonald: We have to be careful to compare like with like, and there are a number of issues to be considered. On the one hand, it might be argued that it may not be possible to generalize the results of CAS performed by a small number of experts working in specialized units. On the other hand, it is essential that interventionists performing CAS within the trial have a level of skill and experience that is comparable with those performing CEA. In this context, however, we must remember that the results of a procedure that has evolved over 40 years is being compared with one that (although, by now, is very well developed) is arguably still in evolution. Furthermore, previous trials of intervention in asymptomatic patients (against which ACST-2 will eventually be compared) have been highly selective. Almost 40% of surgeons who applied to join the ACAS trial were initially rejected on the basis of their outcomes.[2] Although the original ACST trial was far less proscriptive, there is therefore rationale for some form of participant selection. The ACT1 trial, sponsored by Abbott Vascular (Santa Clara, CA), in the US (with a 2:1 randomization between CAS and CEA) recruits interventionists by invitation only, based, presumably, on their throughput and outcomes. ACST-2 encourages expressions of interest from interventionists performing CAS, but their "Track Record Forms," which are subsequently anonymized and can be downloaded from the Web site (www.acst.org.uk), must be approved by the Technical Management Committee. Interventionists performing CEA must have performed at least 25 procedures over the preceding 2 years and their all-stroke death rate (listed distinctly for symptomatic and asymptomatic populations) must be acceptable. Essentially, the confidence interval (CI) upper limits for stroke/death should be <4% (for asymptomatic patients) and <8% (for symptomatic patients). Those performing CAS must have done the same number in the same period of time (implying contemporary CAS technique) with equivalent outcomes. The proportion of those cases that were proctored is borne in mind, but ACST-2 does not allow proctoring of inexperienced interventionists within the trial.

It should be noted that criteria for inclusion within the trial are applied to individuals and not to centers.

Endovascular Today: *What is the minimum number of patients that should be enrolled?*

Dr. Macdonald: It is unethical to conduct a trial that is too small. It will either fail to answer the question posed, or it may be published with inappropriate conclusions. CAVATAS,[3] although it ran to completion, reported a 10% risk of any stroke lasting longer than 7 days and death in both carotid angioplasty (as it was then) and CEA groups, suggesting that both interventions were equally hazardous. This may not be true; the 95% CI for 30-day stroke and death was ±4%, so it is quite possible that the 30-day stroke and death rate was 6% after one treatment and 14% after the other—a very different outcome from the interpreted results.

When comparing the outcome or complication rates of two treatments, it is not sufficient to compare the "headline" complication rates. These are no more than estimates of the true complication rates, which will lie somewhere between the CIs for each mean value. For each measured outcome, the CI depends on the standard error, which in turn depends on sample size. In general, the larger the sample size is, the smaller the standard error and the greater the precision of the measurement will be. This in turn will lead to narrower CIs and increases the likelihood that any observed difference (or absence of difference) is a real rather than a chance finding. In the case of ACST-2, power calculations have determined a required sample size of approximately 2,500 patients in each limb of the trial.

> "It is quite simply unethical to start a trial unless you can see it through to a meaningful result."

Endovascular Today: *What is the minimum duration of a properly powered CAS trial?*

Dr. Macdonald: Any prospective randomized trial should, of course, continue until the trial has answered the question(s) posed. A trial must therefore continue until a statistically significant result has been obtained (and the trial is stopped by the trial management and data-monitoring committees) or until the recruitment targets set at the outset have been met. To do otherwise is to run the risk that the trial will be meaningless and that the patients will have been placed at risk for no purpose.

EVA-3S was stopped prematurely because the difference between the 30-day outcomes after CAS and CEA was greater than expected and it was in the opinion of the trial management committee unethical to continue to randomize patients. SPACE, on the other hand,[4] was stopped when it became apparent that the original calculations had underestimated the number of patients required to show noninferiority. The organizers had to choose between increasing the number of patients in each arm of the trial or stopping the trial on the grounds that it was futile to continue because the trial could not deliver a meaningful result. In the absence of adequate funding, they chose the latter option.

These examples underline the importance of the power calculations and in particular of the need to secure adequate independent funding. It is quite simply unethical to start a trial unless you can see it through to a meaningful result.

It is important to note that follow-up must continue regardless of any difference in 30-day outcome. Thus, even if a result can be declared on the basis of 30-day outcomes (and recruitment into the trial is stopped), patients must be followed to determine whether or not there is any difference in long-term outcome. In ACST-2, all patients will be followed for a minimum of 5 years after treatment (or until death).

Endovascular Today: *Which primary endpoints should be included?*

Dr. Macdonald: Carotid intervention by any means (CEA or CAS) has prophylactic intent, and so the endpoint of most relevance to the efficacy of the interventions is the survival free of stroke, and ACST-2 intends to follow the patient population out to 5 years. Any benefit for the intervention will be offset by procedural hazard, so 30-day stroke, death, and myocardial infarction rates are an important part of the primary outcome of the trial.

Endovascular Today: *Which secondary endpoints should be included?*

Dr. Macdonald: It may be possible if numbers recruited are sufficiently large to compare, for example, gender, the influence of degree of stenosis on outcomes, the influence of the presence of contralateral disease, etc, but these endpoints are not preset. Also, ACST-2 has some of the same secondary endpoints as TACIT, namely a detailed cost-effectiveness analysis comparing CAS against CEA (as the base case). This will be performed by health economists at the University of Oxford who are collaborating with the ACST-2 trialists.

Endovascular Today: *How should inclusion and exclusion criteria be determined? Which patients should be eligible?*

Dr. Macdonald: The trial should not be so proscriptive that it fails to represent "real-world" practice. Any patient with a carotid artery stenosis that has not been the source of neurological symptoms for the preceding 6 months in whom the responsible physician considers an intervention to be warranted is eligible to enter. There should have been no previous procedure performed on the index carotid artery. Medical therapy (antiplatelets, statins, etc) should already have started, and the patient should have recovered from any previous coronary intervention. Previous overview anatomical imaging (catheter arch aortography, CTA, or MRA) should have been performed and should have demonstrated that both CAS and CEA are practicable. The patient's doctor should be substantially uncertain whether CAS or CEA is better and see no definite indication/contraindication for either.

> "It is important to emphasize that ACST-2 is intended to compare CEA and CAS in patients on current best medical therapy in whom the physician believes intervention is appropriate and justified."

Endovascular Today: *Should octogenarians and nonagenarians be included?*

Dr. Macdonald: Subset analyses from the CREST trial lead-in data[5] and from SPACE have suggested that octogenerians are at a higher procedural risk from CAS than younger patients. It should be appreciated that SPACE and the CREST lead-in trials were not set up to detect differences in outcome between older and younger populations; however, if CREST and ICSS show the same outcomes, I think we can be more convinced that the findings are valid.

It is not clear why octogenarians might incur a higher procedural penalty. Octogenarians have a higher incidence of adverse anatomical features, such as tortuously at the arch origin and increased burden of atheroma at the aortic arch;[6] these features and reduced cerebral reserve capacity may partially explain the results. Pragmatically, one could continue to offer octogenarians intervention by CAS if they have straightforward

anatomy and reasonable reserve (eg, a normal contralateral carotid artery and circle of Willis).

Octogenarians and older patients are not excluded from the ACST-2 trial; entry will be at the physicians' discretion, but the protocol does specify that decision making should be within the remit of a multidisciplinary team (to include interventional radiologists, cardiologists, vascular surgeons, and stroke physician/neurologists). Ethically, one can justify this practice because our evidence base regarding CAS in older populations is currently based on subset (*post hoc*) analyses.

Endovascular Today: *Is a medical therapy arm necessary? Why or why not?*

Dr. Macdonald: The organizers of ACST-2 do not believe that a medical arm is necessary. ACST, which compared CEA with best medical therapy in asymptomatic patients, clearly demonstrated a significant reduction in all-stroke and death at 5 years in patients who underwent immediate CEA.

There have been some concerns that a proportion of patients within the ACST trial were not on best medical therapy as we now understand it. Remember that recruitment for this trial started around a decade ago. However, the number of patients on current best medical therapy at last follow-up (2006) has increased dramatically with 88.5% on an antiplatelet, 80% on lipid-lowering medication, and 87.2% on an antihypertensive agent. The 10-year outcomes from ACST will be published next year, demonstrating excellent long-term compliance with current best medical therapy.

It is, of course, the late and cumulative benefit of best medical therapy that is of most relevance, and the difference between best medical therapy and CEA for all-stroke death at 5 years within ACST was so sizeable that the proportion of patients recruited early in the trial who were not on best medical therapy probably would not influence these results.

Finally, it is important to emphasize that ACST-2 is intended to compare CEA and CAS in patients on current best medical therapy in whom the physician believes intervention is appropriate and justified.

Endovascular Today: *What are the major clinical roadblocks to acceptance of treating asymptomatic patients?*

Dr. Macdonald: There are two major roadblocks. One is cost and cost-effectiveness. The numbers needed to treat to prevent one stroke in an asymptomatic population is an order of magnitude greater than for a symptomatic population, and this will have cost implications. Neither CEA nor CAS are inexpensive procedures, but to my knowledge, robust cost-effectiveness analyses have not yet been performed for CAS versus CEA in asymptomatic patients, perhaps because there currently is limited level-one evidence to support CAS in this setting.

The second major roadblock is that the intervention offered must have a much lower procedural risk in order to benefit the patient as compared with the margin of error "allowed" when treating a symptomatic patient (the American Heart Association suggests ≤3% procedural stroke and death for asymptomatic patients).

Endovascular Today: *What questions remain to be answered by the next generation of trials?*

Dr. Macdonald: The current generation of trials is intended to determine whether CAS is "noninferior" or "equivalent" to CEA. If they do, we will then need to determine which patients are better treated by CEA or by CAS, and which patients can reasonably be offered the choice of intervention.

Within any clinical subgroup (symptomatic, asymptomatic, etc), it is likely that there will be a group of patients who fare better with CAS, a group that fares better with CEA, and a third (probably larger) group in whom the two interventions are broadly equivalent. ■

1. Bhandari M, Busse JW, Jackowski D, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. CMAJ. 2004;170:477-480
2. Moore WS, Young B, Baker WH, et al. Surgical results: a justification of the surgeon selection process for the ACAS trial: the ACAS investigators. J Vasc Surg. 1996;23:323-328.
3. CAVATAS investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty study (CAVATAS): a randomized trial. Lancet. 2001;357:1729-1737.
4. The SPACE Collaborative Group. 30-day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet. 2006;368:1239-1247.
5. Hobson RW II, Howard VJ, Roubin GS, et al. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. J Vasc Surg. 2004;40:1106-1111.
6. Lam RC, Lin SC, DeRubertis B, et al. The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting. J Vasc Surg. 2007;45:875-880.

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(Dr. Rundback, continued from page 59)
with much of their funding going into CREST, which is a salutatory and valuable trial but does not answer all of the questions needed to resolve the ongoing debate regarding revascularization in asymptomatic patients. Moreover, with trials of this sort, there are a number of goals that the parties involved are seeking to attain. First of all, device approval could potentially be linked to the results of a trial such as this; once we have a trial showing clinical benefit of particular devices, they might simultaneously be fast-tracked for labeling for this use. Another element is that with NIH trials, the data remain blinded until the completion of the trial, so we do not see meaningful results reported for anywhere from 5 to 7 years after study initiation. With an industry-funded trial, we can look at interim analyses and report meaningful outcomes at planned periods as long as they are statistically valid, such that we can hopefully have an impact on the scientific and clinical community earlier.

Endovascular Today: *How should the participating centers and physicians be selected?*

Dr. Rundback: We have learned from recently conducted trials, particularly EVA-3S and SPACE, that the appropriate choice of experienced investigators who are particularly skilled with the devices being used in the trial is critical for success. In TACIT, the site selection committee, co-chaired by Drs. Kenneth Rosenfield and Marc Sapoval, is working hard to ensure that we have multidisciplinary involvement, with experts in radiology, surgery, and cardiology, as well as vascular medicine, participating. Our selection is based on experience, clinical trial exposure and success, good enrollment records, and previously demonstrated success using the devices being utilized in the trial. There will also be extraordinarily strict monitoring of individual site outcomes throughout the trial, so that we can remediate any problems early on, before they affect overall endpoints.

Endovascular Today: *What is the minimum number of patients that should be enrolled?*

Dr. Rundback: TACIT is a three-armed trial, comparing carotid endarterectomy (CEA), CAS, and best medical therapy alone. The trial is structured to demonstrate noninferiority between CAS and CEA, and superiority for revascularization compared with BMT. In this trial design, we need 3,700 patients, who will be randomized between the trial arms, with 1,140 patients in each of the revascularization arms, and 1,250 patients in the best medical arm. This also accounts for an approximately 5% anticipated rate of attrition or lost follow-up.

Endovascular Today: *What is the minimum duration of a properly powered CAS trial?*

Dr. Rundback: I think that there is a general consensus, and it has become the standard in carotid intervention clinical trials that we need to evaluate outcomes out to 5 years. TACIT is unique in that our primary endpoint is a composite of standard accepted hard outcomes, including all strokes at 5 years and 30-day periprocedural mortality, and we have added to that a measure of neurocognitive decline using the Trail-Making Test on all patients to evaluate neuropsychological function. Patients who hit the neurocognitive decline endpoint will continue to be observed in the trial for emergence of stroke events.

> "TACIT is the only trial of this scale that will look at [plaque echogenicity], which may be one of the best elements for determining the most suitable candidates for carotid stenting."

Endovascular Today: *What are the secondary endpoints?*

Dr. Rundback: The secondary endpoints are numerous, but there are several that are unique and somewhat exciting, and we feel they really distinguish TACIT. We will have a detailed neurocognitive battery at approximately 400 patients. This will include seven tests evaluating multiple domains of cognitive and neurologic function. Secondly, through Giorgio Biasi, MD, we will have a detailed evaluation of plaque characterization. The ICAROS trial and other observational studies have suggested that hypoechoic plaque using the grayscale median method is associated with *de novo* adverse events. In TACIT, we are going to look at grayscale median method plaque echogenicity as a predictor not only of *de novo* events in the medically treated arm, but also as a predictor of procedure-related events in the revascularization arms. TACIT is the only trial of this scale that will look at this feature, which may be one of the best elements for determining the most suitable candidates for CAS. We will also have an extensive duplex evaluation, so we will be looking both at natural history in the med-

ically treated arm, as well as restenosis in a very critical way in the revascularization arms. There will be many other secondary endpoints and exploratory tertiary endpoints in which we try to index outcomes based on a large array of initial demographic, angiographic, duplex, and neuropsychometric data. Finally, we have a detailed cost-economic analysis and quality-of-life analysis plan, which we have not been done before in a comparative trial of carotid interventions.

Endovascular Today: *How should inclusion and exclusion criteria be determined? Which patients should be eligible?*

Dr. Rundback: Eligible patients for TACIT must be asymptomatic, which by TACIT standards is defined as no previous event attributable to the index extracranial carotid lesion within 6 months before enrollment, and they must have a suitable atherosclerotic carotid lesion. In asymptomatic trials, we need to make sure that the patients have hemodynamically relevant stenoses. We don't want to make the error of *post hoc* analyses showing that treated lesions were actually below the level we currently consider to be clinically significant.

Furthermore, as in any revascularization trial, we need to make sure that prior to enrollment, patients do not have anatomic exclusion for stenting, or for surgery. In TACIT, patients being randomized must have a baseline >60% stenosis by duplex ultrasound, utilizing a duplex peak systolic criteria of 125 cm/s or greater in the internal carotid artery. All duplex studies will be reviewed by the core lab. Then, because the patient may be randomized to stenting, we must ensure they are stenting candidates, which will be done using a second confirmatory imaging test (MRA, CTA, or angiography). These tests will confirm stenosis severity and will look at arch anatomy to assess suitability for stenting. In a similar fashion, the identification of high bifurcation or arch lesions that are exclusions to CAE would render patients ineligible for TACIT.

Endovascular Today: *Should octogenarians and nonagenarians be included?*

Dr. Rundback: At this time, the TACIT Executive Committee is still debating the inclusion of octogenarians and nonagenarians. Part of this decision will depend on the result of discussions at a planned FDA forum on asymptomatic carotid trials to be convened this autumn.

Endovascular Today: *Why is a medical therapy arm necessary?*

Dr. Rundback: Despite the ACAS, CASANOVA, and ACST trial results, the neurology and primary care medical communities have not embraced revascularization for patients with asymptomatic carotid stenosis, particularly for female patients. The predominant reason for this is that those previous trials failed to achieve targeted medical endpoints with rigorously controlled risk-factor reduction and optimized contemporary medical therapy. The rigorous mandated use of statins and antiplatelets, in addition to aggressive reduction of other vascular risk factors, is likely to reduce the rate of stroke events in patients with carotid stenosis. This has already been seen in the CAPRIE (clopidogrel), 4S (simvistatin), ATP group (antiplatelet therapy) and HOPE (ramipril) trials. Because previous revascularization trials such as ACST and ACAS found only modest absolute rates of reduction in strokes with intervention (8% and 5%, respectively), the incorporation of these new and effective drugs may well have reduced stroke rates in the medical arms to below statistically different levels. In ACST, only 17% of the medical cohort was on antilipemic medications from 1993 to 1996, 58% from 2000 to 2003, and 70% at study completion. This is not adequate compliance, so ACST did not really test best medical therapy. Even before that, the SAPPHIRE trial did not lead to the approval of CAS in asymptomatic patients because the predominant thought by the review panel was that there was no comparison to optimal medical therapy alone.

> "Patients who are in their 80s and 90s are not uncommon anymore, and I think this will be a critical issue in future trials."

Endovascular Today: *What are the other major clinical roadblocks to acceptance of treating asymptomatic patients?*

Dr. Rundback: Many clinicians believe that the number of patients needed to treat to prevent one stroke following carotid revascularization is too high. Depending on how this is evaluated, the number needed to treat ranges from 17 to more than 50 patients, in order to prevent a single stroke from CEA. Neurologists and internists believe that good control of lipids, as well as antiplatelet therapy, may sufficiently reduce stroke risk to the point where revascularization is not beneficial, that is, the risk-benefit ratio is too high. That is the barrier we need to overcome and the reason we need a medical therapy arm. In the absence of a strong evidence base supporting CAS or CEA over contemporary medical care, it will be hard to convince clinicians to refer their patients for revascularization.

Endovascular Today: *Could TACIT solve device approval issues for multiple vendors?*

Dr. Rundback: We have had ongoing conversations with the FDA, and at this point, they have expressed early support for seeing a trial design like TACIT. Our conversations have led us to believe that TACIT could be used to support the labeling of two or perhaps three devices. Between the number of patients who are randomized to stenting, in addition to those who are placed in the medical therapy arm but have a later event that will require stenting, we could have more than 1,200 carotid stents implanted in patients in TACIT. Based on other comparable trial sizes that have led to device approval, that should be sufficient for the approval of two or three devices.

Endovascular Today: *What questions remain to be answered by the next generation of trials?*

Dr. Rundback: The issue we discussed earlier regarding how to treat the extremely elderly population will be important. Patients who are in their 80s and 90s are not uncommon anymore, and I think this will be a critical issue in future trials. Another important question will be how to treat patients who have carotid disease risk but also significant comorbidities that put them at risk for other events. In this clinical scenario, is the risk of revascularization warranted when there is a relatively high overall morbidity and mortality related to significant comorbidities? That issue may remain unresolved for some time. Finally, stenting devices and drugs will continue to evolve, and in the next decade or so, there will likely be a need for new evaluations of these therapies.

All this being said, the TACIT trial provides a unique and unparalled opportunity for collaboration between the scientific community, industry, the FDA, and CMS to finally provide defining data that can resolve most of the current controversy regarding the care of patients with cervical carotid disease. ■