

# The Asymptomatic Carotid Surgery Trial 2

Background and aims of the ACST-2 study.

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**T**he Asymptomatic Carotid Surgery Trial 2 (ACST-2) seeks to compare carotid artery stenting (CAS) and carotid endarterectomy (CEA). A 1:1 randomization construct is used for suitable patients with an asymptomatic carotid stenosis that is considered to warrant revascularization, in whom CAS or CEA are equally applicable, and when there is substantial uncertainty regarding which method of intervention is preferred. All patients recruited into the trial are on the contemporary best medical therapy. The recruitment target is 5,000 patients. The ACST-2 trialists consider that large, "simple" trials such as this are likely able to yield meaningful and generalizable results and lend themselves to valid subset analyses at completion. Furthermore, contemporary procedural all stroke/death rates for carotid intervention (taken from CREST) are < 3%, and any robust comparison of the two treatment arms will require a sizeable trial population. Basing eligibility on uncertainty should ensure the large-scale recruitment of an appropriately heterogeneous group. This increases the value of the study, perhaps making it possible to determine whether the net effects of CEA/CAS are influenced by certain patient characteristics recorded at enrollment.

## ENDPOINTS

The primary objectives include periprocedural hazard (myocardial infarction [MI], stroke, and death

within the first month after the allocated CEA or CAS is attempted by an experienced practitioner) and long-term (up to 5 or more years) prevention of all stroke, particularly disabling or fatal stroke, in subsequent years.

As for secondary objectives, depending on the number of patients that are eventually randomized, the data may enable subset analyses regarding identification of patients in whom one procedure is clearly preferable. As part of a health economic evaluation, procedural costs, stroke-related health care costs, and quality of life will be assessed.

## STATISTICAL ANALYSIS

The primary analysis will be by intention to treat. With 5,000 randomized patients, a decrease of approximately 60% in the periprocedural MI rate with stenting versus surgery (ie, 2% CEA vs 0.8% CAS) and an increase of approximately 60% in the 5-year stroke rate (ie, 3% CEA vs 5% CAS) could be detected at  $P < .001$  with 80% probability (ie, with 80% statistical power). The exact magnitude of any effect is not currently known, hence the need for the trial, but taking into account existing information from other trials of CAS versus CEA, data of this magnitude might be realistic, meaningful, and worthwhile. Even lesser effects could be of substantial interest but might require much larger numbers to be studied.

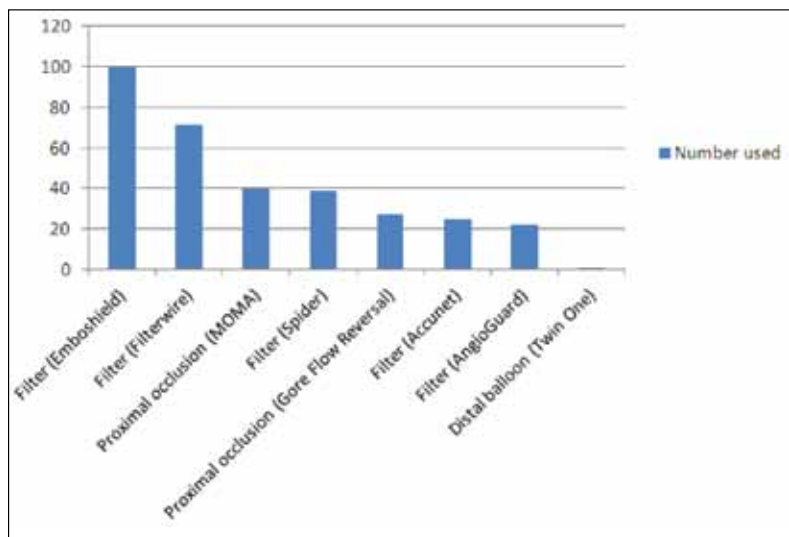


Figure 1. ACST-2 embolic protection device breakdown by name.

### AFTER CREST, ARE ONGOING TRIALS NEEDED FOR ASYMPTOMATIC POPULATIONS?

The CREST investigators reported that both symptomatic and asymptomatic patients had similar 4-year outcomes when CAS and CEA were compared. Just more than 1,100 asymptomatic patients were included, and the immediate procedural hazard (stroke/death/MI) rates for CEA (1.4%) and CAS (2.5%) were within the acceptable thresholds as specified by the American Heart Association. However, the confidence intervals suggest that the outcomes might still have differed significantly if larger numbers of patients had been included.

### THE EU LANDSCAPE: CAS FOR ASYMPTOMATIC CAROTID STENOSIS

The European Stroke Initiative recommendations state that “carotid angioplasty (balloon dilatation), with or without stenting, is not routinely recommended for patients with asymptomatic carotid stenosis. It may be considered in the context of randomized clinical trials.”<sup>1</sup> In April 2011, the UK National Institute for Clinical Excellence (NICE) recommended that stenting for asymptomatic carotid stenosis be carried out within the ACST-2 trial.<sup>2</sup>

### OPERATOR EXPERIENCE

Previous EU trials comparing CAS and CEA in symptomatic populations have been criticized for leniency regarding operator experience in the stenting limbs of those trials (particularly EVA-3S and ICSS). The ACST-2 trialists wished to ensure adequate experi-

ence in the stenting limb of this trial. Operator experience for both CAS and CEA is evaluated by the Technical Management Subcommittee; surgeons and interventionists should have performed at least 25 procedures with contemporary technique in the last 2 years and have their procedural outcomes validated by stroke physicians or neurologists before they can be deemed eligible for trial recruitment. In fact, the average number of previous CAS procedures for ACST-2 centers is 62, a number that compares well with the tightly proscribed SAPHIRE trial, in which two-thirds of the recruited population were asymptomatic.

### DEVICES

In this Oxford, UK-based international trial, we are fortunate that we have access to a number of CE Marked dedicated carotid stent and embolic protec-

tion systems, all of which are allowed within the trial. This affords the interventionist the luxury of equipment choice to most appropriately stent the lesion, thus approximating “real-world practice.” Standardization with a single stent and single protection device (eg, CREST) eliminates confounding variables that could affect outcomes but arguably does not reflect day-to-day decision making outside the remit of a randomized trial. Similarly, the trial is not proscriptive regarding anesthetic modality (local or general) or use of shunt or patching in the CEA limb of the trial. All that is necessary is that the operators in both limbs are familiar with their techniques and proceed as they would otherwise, outside of a trial construct. Although the use of embolic protection is not mandatory, almost all patients undergoing CAS within the trial have been “protected” (Figure 1).

### TRIAL RECRUITMENT TO DATE

Currently, 1,000 patients have been recruited, with a preliminary report of the first 700 patients with 30-day follow-up presented at the European Society of Vascular Surgery meeting in Bologna, Italy in September 2012. The major stroke and death rate (1%) in these patients (blinded to treatment) compares favorably with previous trials of surgery alone.

### COMPETITIVE LANDSCAPE

There are three other trials that have recruited or are actively recruiting in the sphere of asymptomatic carotid disease—ACT-1, SPACE-2, and ECST-2—and one proposed trial, CREST 2. ACT-1 (US) is reasonably comparable to ACST-2, given that it is a trial of CAS versus CEA in asymptomatic carotid stenosis, but dissimilar in the 2:1 randomization (CAS vs CEA) construct and the mandating of a single stent and protection device (Xact stent and EmboShield filter [Abbott Vascular, Santa Clara, CA]).

SPACE-2 (Germany, Austria, Switzerland) has a more complex construct involving a three-arm randomization: best medical therapy versus revascularization with the revascularization then being subrandomized between CAS and CEA. SPACE-2 has had some problems with recruitment, perhaps because it is not wholly intuitive to the patient population and in part due to German reimbursement issues.

ACST-2, SPACE-2, and ECST-2 have begun collaborating so that recruitment into all three trials may be facilitated, enabling them to reach their targets. To that end, one of the principal investigators of SPACE-2, Prof. Hans Henning Eckstein, has been co-opted onto the trial steering committee of ACST-2.

The ECST-2 trial has also been outlined by Principal Investigator Prof. Martin Brown in this edition of *Endovascular Today* (page 75). It has been funded for a pilot study and is seeking funding to proceed. It is currently actively recruiting. This is a trial of “optimized medical therapy” versus mostly CEA (and occasionally CAS, as the decision regarding type of intervention is made at the recruiting center). On the ECST-2 website,<sup>3</sup> the following statement is made:

“ECST-2 and ACST-2 both seek to recruit patients with asymptomatic carotid artery stenosis, but the trials are not competing for patients because the questions they ask are different and complementary. ACST-2 is recruiting patients in whom it has been decided that revascularization of asymptomatic stenosis is definitely required, but the clinicians are uncertain whether stenting or endarterectomy should be used. Patients in ACST-2 are therefore randomized between carotid endarterectomy and stenting. ECST-2 is recruiting patients with asymptomatic or symptomatic carotid stenosis in whom the clinicians are uncertain whether revascularization is required. Patients in ECST-2 are randomized to immediate revascularization or initial optimized medical management alone. All the patients in both trials will have appropriate medical management.”

The CREST 2 trial, with Thomas Brott, MD, serving as principal investigator, is currently seeking funding. ■

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