Trials to Evaluate CEA Versus CAS in Carotid Artery Stenosis

Written by Emma Hitt Nichols, PhD

Several large trials evaluating the efficacy of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) are currently underway, with a large meta-analysis to include data from over 5000 patients planned for 2019. Alison Halliday, MD, University of Oxford, Oxford, United Kingdom, reflected on the results of the ACST-2 [Halliday A et al. *Eur J Vasc Endovasc Surg* 2013], SPACE-2 [Reiff T et al. *J Stroke* 2009], and CREST-2 trials.

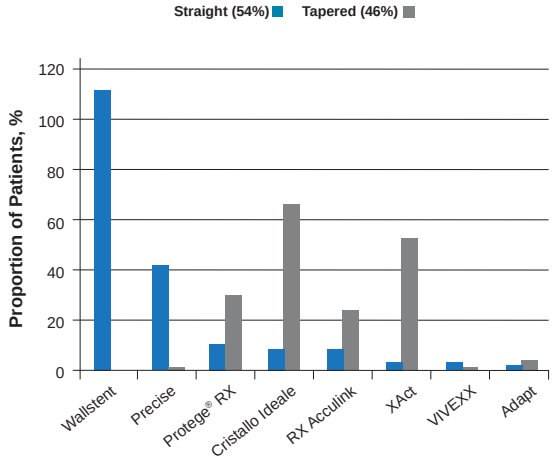
Carotid stenosis can be attributed to ~20% of ischemic strokes. Over the past 40 years, multiple clinical trials have evaluated the efficacy of CEA versus no intervention and CEA versus CAS. In the 1990s, the ACST-1 trial evaluated immediate versus deferred CEA, in which both physician and patients were substantially uncertain about the need for immediate CEA [Halliday A et al. *Lancet* 2004]. In the ACST-1 trial, the hazard of surgery was ~3%, but the absolute risk of stroke was decreased by 6% over 10 years in both men and women. In 2010, the CREST trial randomized 1183 asymptomatic patients with carotid artery stenosis to undergo CAS or CEA [Brott TG et al. *N Engl J Med* 2010]. The primary endpoint of the trial was the composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization. There was no difference in the primary endpoint of the trial between CAS and CEA (7.2% vs 6.8%; HR, 1.11; 95% CI, 0.81 to 1.51; p=0.51).

It would be ideal to design a randomized controlled trial that evaluates the efficacy of CEA, CAS, and best medical treatment (BMT) simultaneously; however, the number of patients required is too large. Therefore, several trials are currently ongoing that will evaluate the best intervention for carotid artery stenosis separately.

The SPACE-2 study will have two sub-trials: SPACE-2A will evaluate CEA plus BMT versus BMT alone and SPACE-2B will evaluate CAS plus BMT versus BMT alone [Reiff T et al. *J Stroke* 2009]. Approximately 1636 patients will be enrolled and randomized in each sub-trial.

In 2010, the multicenter ACST-2 trial began enrollment to directly evaluate CEA versus CAS in asymptomatic patients with tight stenosis requiring intervention [Halliday A et al. *Eur J Vasc Endovasc Surg* 2013]. Enrollment reached 1287 in 2013, and the first 1000 patients had a median age of 71, with 96% of patients having 70% to 99% stenosis and 20% of patients having 70% to 100% contralateral stenosis. In addition, 30% of patients had diabetes, 11% renal failure, 6% atrial fibrillation, and 37% ischemic heart disease. In ACST-2, 93% of patients were receiving antiplatelet therapy, 89% antihypertensive therapy, and 85% lipid-lowering therapy at study entry. In the first 800 patients, 54% received a straight stent and 46% received a tapered stent (Figure 1). Preliminary results demonstrate that the rate of disabling and fatal stroke or myocardial infarction at ≤30 days is 1%, which is reduced from 1.7% in the previous ACST trial. By 2019, it is expected that enrollment for ACST-2 will reach ~3000 patients, and a metaanalysis including CREST-2, SPACE-2, and ACST-2 is planned that will include >5000 patients.

Figure 1. Stents Used in the First 800 Patients of ACST-2



Data from large trials that evaluate CEA versus CAS head-to-head is greatly anticipated and has the potential to provide a foundation for evidence-based medicine in the treatment of carotid artery stenosis.

System Changes to Ensure Patient Safety and Access to Innovative Devices

Written by Mary Mosley

The Center for Devices and Radiological Health (CDRH) of the United States Food and Drug Administration (US FDA) has undertaken work to refine its direction towards smart regulation, to protect public health by ensuring safe devices, and to promote public health by facilitating device innovation, according to Christy Foreman, Director of the Office of Device Evaluation at CDRH. She reviewed the updated mission, vision, and strategic plan for the CDRH, and its impact on regulatory science, clinical trials, feasibility trials, and pre- and postmarketing data.

In particular, the CDRH strives to ensure that patients in the US have access to high-quality, safe, and effective medical devices that will be available in a timely fashion. In accordance with this mission and vision, six strategic priorities have been developed to achieve the CDRH goal:

- Patients in the US have early access to high-quality, safe, and effective medical devices of public health importance
- The US is the world's leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety
- US postmarket surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance
- Devices are legally marketed in the US and remain safe, effective, and of high-quality
- Consumers, patients, their caregivers, and providers have access to understandable science-based information about medical devices and use this information to make healthcare decisions
- Strengthen the CDRH workforce and workplace

To achieve its priority regarding regulatory science, the CDRH has identified the need to improve the computer modeling used in order to augment bench, animal, and clinical testing for device development, because a single model alone cannot demonstrate safety and effectiveness.

The CDRH has planned changes to enhance the process for first-in-human and early feasibility trials to promote the more timely initiation of clinical studies in the US. This is to improve patient access to new devices by encouraging innovation to address clinical needs and improve patient care, particularly when alternative treatments are unavailable, ineffective, or they are associated with significant risk. The goal of these changes is to reduce the time from bench testing to initial clinical studies, and accelerate the implementation of changes to the product or study design after a study is initiated, while maintaining protection of human subjects. Foreman noted that the approval of an early feasibility study, including some first-in-human studies, may be based on less nonclinical data than for other types of studies, such as traditional feasibility or pivotal studies. To this end, a benefit-risk assessment to consider the appropriate level of evidence needed to initiate a clinical study will be conducted, and consideration given to patient perspectives on benefits and risk tolerance as well as risk mitigation strategies.

The CDRH has planned changes to strengthen and streamline the clinical trial enterprise, so that medical device clinical trials can be conducted in a safe, efficient, least burdensome, and cost-effective manner, stated Ms. Foreman. A framework is being developed for appropriate, timely, and efficient decisions for investigational device exemptions (IDE) that is tailored to the type of study and to the benefit-risk decision-making. The CDRH is developing guidance regarding the benefit-risk determinations for the IDE decision process, which will be based on the type of study, such as early or traditional feasibility study or pivotal study. It will also establish metrics to assess the progress of the CDRH in this process of improving the clinical trial enterprise.

The CDRH is evaluating the right balance for the data that are needed pre- and postmarket. One consideration in this regard is whether a decision can be made about the safety and effectiveness of a device with potentially less data or follow-up if there is a prospective plan to collect postmarket data. Another consideration is whether premarket data requirements can be adjusted for mature technology with significant real-world experience.

Device registries are an effective mechanism for postapproval studies. Benefits of registries include the ability to obtain data on short- and long-term outcomes of devices and procedures, and the ability to provide information about clinical safety and effectiveness after devices are on the market. For example, a labeling change for a transcatheter heart valve was made based on data from the TVT registry. Also, postapproval studies can lead to expanded indications, which was the case for drug-eluting stents and for endograft treatment of complicated type B aortic dissection. The MitraClip Post-Approval Study will use registries for data collection.

A system of unique device identifiers (UDI), a numeric or alphanumeric code assigned to a specific medical device, has been established by the FDA for all medical devices in the US. Ms. Foreman stated the UDI system would provide more reliable data on how medical devices are used, provide the capacity for nearly real-time data collection, and represents a step towards modernizing postmarketing surveillance by the CDRH. Furthermore, the UDIs may prove to be very powerful when used in conjunction with electronic health records and may contribute to medical device innovation based on insights from real-world use of the medical devices.

The CDRH will provide guidance documents regarding the Leapfrog program. These mapping documents will outline a simplified regulatory pathway for new, emerging technologies to enter the market. The CDRH welcomes comment from the device industry about areas for which the Leapfrog program will be useful.