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Landmark NIH Clinical Trial Comparing Two Stroke Prevention Procedures Shows Surgery and Stenting Equally Safe and Effective

Opportunities Exist to Target the Treatment to the Patient

A major study of people at risk for stroke showed that two medical procedures designed to prevent future strokes are safe and effective overall. Physicians will now have more options in tailoring treatments for their patients at risk for stroke. In the trial of 2,502 participants, carotid endarterectomy (CEA), a surgical procedure to clear blocked blood flow and considered the gold standard prevention treatment, was compared to carotid artery stenting (CAS), a newer and less invasive procedure that involves threading a stent and expanding a small protective device in the artery to widen the blocked area and capture any dislodged plaque. The results appeared in the early online edition of the *New England Journal of Medicine* on May 26, 2010.

One of the largest randomized stroke prevention trials ever, the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) took place at 117 centers in the United States and Canada over a 9-year period. CREST compared the safety and effectiveness of CEA and CAS in patients with or without a previous stroke. The trial was funded by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health, and led by investigators at Mayo Clinic, Jacksonville, Fla., and the University of Medicine and Dentistry of New Jersey in Newark.

Researchers specifically found that:

- After a median follow-up of 2.5 years, there was no difference in the estimated 4-year rates of the study's endpoints – early stroke, heart attack, or death and later stroke - between CAS vs. CEA – 7.2% in the CAS group and 6.8% in the CEA group.
- Differences were seen, however, depending on symptom status over the 4-year period of the study. In symptomatic patients, the rate of stroke and death was 8% in the CAS group and 6.4% in the CEA group, and in asymptomatic patients, the rates were 4.5% vs. 2.7% respectively.
- In the weeks following a procedure, there were differences in outcome between CAS and CEA (death .7 vs. .3%, stroke 4.1 vs. 2.3%, heart attack 1.1 vs. 2.3%).
- There was a low risk of recurrent stroke in both CAS and CEA groups (2.0 vs. 2.4%).

The study also found that the age of the patient made a difference. At approximately age 69 and younger, stenting results were slightly better, with a larger benefit for stenting, the younger the age of the patient. Conversely, for patients older than 70, surgical results were slightly superior to stenting, with larger benefits for surgery, the older the age of the patient.

The CREST trial results show “excellent safety and long-term results for patients with warning signs for stroke, as well as for patients without such warning signs,” said Thomas G. Brott, M.D., professor of neurology and director for research at Mayo Clinic in Jacksonville, and the study's national principal investigator.

“A vital next step is to understand the procedural risks of carotid stenting and endarterectomy in real world settings,” said Walter J. Koroshetz, M.D., deputy director of NINDS.

Stroke, the third leading cause of death in the United States, is caused by an interruption in blood flow to the brain by a clot or bleeding. The carotid arteries on each side of the neck are the major source of blood flow to the brain. The buildup of cholesterol in the wall of the carotid artery, called atherosclerotic plaque, is one cause of stroke. Because people with carotid atherosclerosis also usually have atherosclerosis in the coronary arteries that supply the heart, the CREST trial tracked the rate of heart attacks, in addition to stroke and death.

In CREST, approximately half the patients had recent symptoms due to carotid disease such as a minor stroke, or a transient ischemic attack (TIA), indicating a high risk for future stroke. The other half had no symptoms but were found to have narrowing of the carotid artery on one of a variety of tests assessing carotid narrowing and plaque. Such patients, termed asymptomatic, are at much lower risk of stroke than those with symptoms.

One of the strengths of the study, according to investigators, is that CREST was conducted in a variety of real world settings, including large and small public and private hospitals. Physicians had to demonstrate a high degree of proficiency and safety in order to participate in the trial. The study found no significant differences in the outcomes, no matter what type of medical specialist performed the stenting procedure, including cardiologists, neuroradiologists, interventional radiologists, vascular surgeons and neurosurgeons. “The idea was to design a study that reflects the U.S. experience,” said Dr. Brott.

“Although the purpose of the study was to compare the two procedures, we were pleased to find that both CEA and stenting have become extraordinarily safe,” said Gary Roubin, M.D. Ph.D., chairman, department of cardiovascular medicine, of the Lenox Hill Hospital in New York City, a lead investigator for CREST and study co-principal investigator for stenting.

The researchers point out that the rate of stroke and death in the surgical group was the lowest ever reported in a large stroke prevention trial. “The rate for stroke and death in carotid stenting was also the lowest yet reported in any randomized trial, and significant advances in technology, technique and patient selection for stenting have continued over the 8-year enrollment in CREST,” said Dr. Roubin.

As a result, the pivotal differences were the lower rate of stroke following surgery and the lower rate of heart attack following stenting, according to the investigators. A year after the procedure, the patients who had suffered a stroke reported that the effects of the stroke had a greater impact on their quality of life than was reported by those patients who had suffered a heart attack.

“CAS may offer a reasonable alternative to CEA, particularly in patients who prefer a less invasive procedure, and in younger patients. However, it should be kept in mind that for the endpoint of stroke, CEA has been shown to be the safer procedure. It is when heart attacks are added that the results of the two procedures become similar,” said Wesley S. Moore, M.D., professor and chief, emeritus, division of vascular surgery of the University of California at Los Angeles, and co-principal investigator for surgery in the CREST trial. Dr. Moore went on to say that it is also important to point out that the complications from either procedure in this study are the lowest reported to date and are a tribute to the quality of the surgeons and interventionists who participated in this trial.

The CREST investigators concluded that while CEA has a proven record and long-term durability, both CAS and CEA are safe and useful tools in the right setting for stroke prevention, and technology continues to improve each procedure.

“The CREST trial was a large, complex undertaking that will provide the medical community with important information on the comparative effectiveness of these two procedures. NINDS is committed to long-term follow-up of this group of patients, which will help us learn even more about how best to prevent stroke,” said Story Landis, Ph.D., NINDS director.

Partial funding for the study was supplied by Abbott, of Abbott Park, Ill., the maker of the stents.

*Brott, TG et al., Stenting Compared to Endarterectomy for Treatment of Carotid Artery Stenosis, *New England Journal of Medicine*, online first edition May 26, 2010.

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