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## CREST-2: Identifying the Best Method of Stroke Prevention for Carotid Artery Stenosis:

National Institute of Neurological Disorders and Stroke Organizational Update

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One of the great achievements of modern medicine is the successful prevention of stroke and other cardiovascular diseases. While the incidence of stroke has substantially declined over the last 30 years, approximately 200,000 preventable stroke deaths still occur annually in the United States. According to a recent study based on the Greater Cincinnati/Northern Kentucky Stroke Study, annually ~41,000 strokes in the U.S. are attributed to extracranial ICA stenosis. Early revascularization for symptomatic carotid stenosis - i.e. in patients with recent ipsilateral stroke or TIA - is well established as very effective at preventing ipsilateral stroke. Carotid stenosis in the absence of symptoms is extremely common, but the best treatment is unclear. While two randomized trials showed a benefit of carotid endarterectomy over antiplatelet therapy with aspirin, the number needed to treat approaches 200. Does aggressive risk factor control change that balance? Population screening for carotid stenosis followed by revascularization is considered to cause net harm. Are complication rates from endarterectomy and stenting now low enough to justify expanding their indications in asymptomatic patients? The NINDS-funded CREST-2 trial is an ambitious attempt to further refine the treatment of asymptomatic carotid stenosis.

### Advances in Revascularization for Acute Ischemic Stroke

As one of the largest randomized stroke prevention trials, the first Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) was designed to compare the safety and efficacy of two stroke prevention procedures for carotid artery narrowing – carotid endarterectomy (CEA) and carotid artery stenting (CAS) - in symptomatic and asymptomatic individuals. Starting in December 2000, this NINDS-funded trial enrolled more than 2,500 patients at 117 sites in the U.S. and Canada. Because of slow enrollment the trial took 9 years to complete. In 2010, the results of CREST indicated that the two revascularization procedures were equivalent for the primary combined endpoint of stroke, myocardial infarction, or death between patients who underwent CAS and those who underwent CEA. The trial was of such high quality that a five year extension was funded by NINDS to study the durability of tested procedures. While CREST showed that these two treatments are safe and effective, it did not compare revascularization to intensive medical management. As compared to the centralized

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risk factor control rates in the Stenting vs. Aggressive Medical Therapy for Intracranial Stenosis (SAMMPRIS) trial, control of vascular risk factors in CREST and in the asymptomatic endarterectomy trials was not optimal.

## **CREST-2: Two Parallel Trials, Three Methods of Stroke Prevention**

An estimated 100,000 carotid procedures, either surgical or stenting, are performed in the U.S. every year, the majority in asymptomatic individuals. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) is designed to determine the best method of preventing stroke in asymptomatic individuals with severe carotid stenosis (<http://www.crest2trial.org/>). Started in December 2014, CREST-2 is being conducted across the U.S. and Canada as two parallel multi-center randomized, observer-blinded endpoint clinical trials. One trial will assess treatment differences between intensive medical management alone compared to CEA plus intensive medical management. The parallel trial will assess treatment differences between intensive medical management alone compared to CAS plus intensive medical management. Of note, CREST-2 was not designed to compare stenting to endarterectomy because referral patterns in the U.S. suggest that centralized randomization of patients to each of the three groups isn't feasible.

### **Method 1: Intensive Medical Management**

Stroke risk factors, including hypertension, cholesterolemia, diabetes, tobacco use, excess body weight, and sedentary lifestyle, are modifiable through intensive medical management. All participants in CREST-2 receive aggressive anti-hypertensive and anti-lipid treatment. Medications prescribed as part of study participation that are not covered by insurance are provided by CREST-2 at no cost to patients. To manage lifestyle and vascular risk factors, participants are also enrolled in the lifestyle management program INTERVENT for weight loss, smoking cessation, exercise and diabetes management ([www.INTERVENT.com/CREST-2](http://www.INTERVENT.com/CREST-2)) and work with a coach to assess and manage important risk factors for stroke prevention. Because carotid stenosis is a strong indicator of diffuse atherosclerosis leading to cardiovascular, peripheral and reno-vascular disease as well as stroke, leadership from the NIH, CMS, Agency for Healthcare Research and Quality and the FDA all felt strongly that aggressive, rather than standard medical care was the ethically defensible medical care algorithm for CREST-2.

### **Method 2: Intensive Medical Management plus Carotid Endarterectomy**

Carotid endarterectomy has been the standard of care for the treatment of carotid stenosis for 40 years and surgical technique has improved over this time with a low rate of <2% for peri-procedural stroke and death among asymptomatic patients in CREST.

### **Method 3: Intensive Medical Management plus Carotid Artery Stenting**

Carotid artery stenting has become more common over the last 15–20 years. CMS reimburses stenting in symptomatic carotid stenosis and in asymptomatic individuals with difficult surgical anatomy. It does not reimburse for stenting in the majority of asymptomatic cases because randomized controlled trial data are lacking.

Endovascular physicians in CREST-2 are chosen based upon strict quality criteria. The CREST-2 Registry (C2R) commenced enrollment of CAS procedures in February 2015 (<https://clinicaltrials.gov/ct2/show/NCT02240862>). The primary objective of C2R is to promote rapid enrollment into CREST-2, and ensure that procedures are only performed by skilled operators at well-resourced sites. As of November 2016, 164 interventionists from 84 sites across the U.S. have done 1,245 prospective procedures. Of these, 34% were symptomatic, 21% were treated for post carotid revascularization restenosis, and 45% were asymptomatic. Only 6% were CREST-2 trial-eligible.

## Outcomes, Milestones and Goals

CREST-2 seeks to enroll 2,480 participants, 40% women and 12% minorities. Patients are eligible to participate if they are 35 years or older, have narrowing (70% or greater) of at least one of their carotid arteries, no medical history of ipsilateral stroke or TIA within 180 days of randomization in the distribution of the “target” artery, carotid stenosis that is treatable with CEA or CAS, and lack other serious medical conditions. More information about inclusion and exclusion criteria can be found at <https://clinicaltrials.gov/ct2/show/NCT02089217>.

The CREST-2 Clinical Coordinating Center at the Mayo Clinic in Jacksonville, Florida is directed by Thomas Brott, M.D., James Meschia, M.D., and Brajesh Lal, M.D. The Statistical and Data Coordinating Center is directed by George Howard, Dr.PH. at the University of Alabama at Birmingham. The Vascular Imaging Core Lab and CREST-2 Registry are led by Dr. Lal at the University of Maryland Medical Center. Sixteen co-investigators across the U.S. serve on the CREST-2 Executive Committee, that leads a rigorous credentialing process for surgeons and interventionalists. Specialties of the 104 site PIs include vascular surgery (33.7%), cardiology (28.8%), neurology (24%), neurosurgery (7.7%), interventional radiology (3.8%), and interventional neuroradiology (1.9%).

The primary outcome in CREST-2 is the proportion of patients who experience the composite endpoint of any stroke or death within 44 days of randomization or ipsilateral stroke up to 4-years thereafter. The secondary aims of CREST-2 are: whether intensive medical management differs from CEA and from CAS to maintain the level of cognitive function at 4 years of follow-up; if there are treatment differences in major stroke, minor stroke, disabling stroke, non-disabling stroke, and tissue-based stroke at 4-years follow-up; and if the CEA or CAS versus intensive medical management difference is affected by patient age, sex, severity of carotid stenosis, restenosis, risk factor level, and duration of asymptomatic period.

Two years into the study 448 of the 2,480 required patients have been enrolled across 37 states and five Canadian provinces. Of the 118 sites, 75% have enrolled at least one patient. Enrollment started out slowly but since October 1, 106 patients (or at least one patient per day) have been enrolled in the trial. With aggressive medical care, risk factor control for CREST-2 patients has shown steady improvement at each follow-up, as measured by SBP, LDL, Non-HDL, HgA1C1, smoking, physical activity and weight.

## Boosting Enrollment in CREST-2

Why should patients participate in CREST-2? In addition to receiving excellent care and health benefits of controlling risk factors, patients will help determine the safest and most effective method of stroke prevention in generations to come. In addition, both CEA and CAS are expensive at roughly \$15,000 per procedure, and CREST-2 will help clarify if such costs are justified compared to intensive medical management. Several recruitment mechanisms are being implemented to get the word out and encourage enrollment in CREST-2, including exhibits at national and regional conferences, online videos for potential enrollees (<http://www.crest2trial.org/for-patients.html>), a Facebook live session at Mayo Clinic for Stroke Awareness Month, \$95 reimbursement to patients for follow-up visits and \$100 per screening log of up to 10 patients per patient randomized for sites. In addition to a Facebook page, CREST-2 also launched a twitter account in February 2016 (@CREST2\_Study).

CREST-2 is critical in determining the best stroke prevention treatment for patients with carotid artery stenosis but no stroke symptoms. NINDS and CREST-2 leadership ask that physicians discuss the trial with patients with asymptomatic stenosis. Poor enrollment has plagued many of NINDS's prevention trials leading to long delays in obtaining and disseminating key information to physicians and patients. With your help, CREST-2 can meet its recruitment milestones and deliver the answers on how best to treat patients with asymptomatic carotid stenosis.