CREST-2: Testing Approaches for Stroke Prevention

An international clinical trial led by Mayo Clinic will compare the effectiveness of medication and surgical interventions in preventing stroke (Figure 1). Funded by a $39.5 million grant from the National Institute of Neurological Disorders and Stroke, the CREST-2 study builds upon the earlier Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST).

CREST compared treatment with endarterectomy and stenting for patients with symptomatic or asymptomatic carotid artery stenosis. Results of the study, released in 2010, showed the two procedures to have similar overall safety and effectiveness, with stenting favored in patients under age 50 and endarterectomy in those over age 74.

CREST-2 consists of two parallel studies in asymptomatic patients. One compares medical treatment alone versus medical treatment and endarterectomy; the other compares medical treatment alone versus medical treatment and stenting.

“In the current era of medical management, the crucial question is whether it is still productive and appropriate to revascularize the carotid artery, either surgically or with stenting, in asymptomatic patients. Optimal medical management of asymptomatic carotid atherosclerosis might obviate the need for these procedures,” says James F. Meschia, M.D., a consultant in the Department of Neurology at Mayo Clinic in Jacksonville, Florida, and co-leader of CREST-2.

Approximately 140,000 carotid revascularizations are performed annually in the United States. Complications include heart attack and stroke, which CREST found to be slightly more common in patients who have surgery and stenting, respectively.

“The risk of complications from surgery and from stenting is very small,” says Giuseppe Lanzone, M.D., a consultant in the Department of Neurologic Surgery at Mayo Clinic in Rochester, Minnesota. “However, the information that we have when choosing treatment for patients with asymptomatic carotid stenosis is from studies in the early 1990s. It is very important to do an updated study with modern practices.”

Enrolling patients

CREST-2 is enrolling 2,480 patients at 120 centers in the United States and Canada, and possibly Europe and Australia. Mayo Clinic’s campuses in Arizona, Florida and Minnesota are all participating in the seven-year trial.
Patients must have at least 70 percent stenosis and be asymptomatic, defined as having no stroke or stroke-like symptoms ipsilateral to the stenosis within 180 days of randomization in the trial. Modeling clinical practice, referring physicians will recommend appropriate revascularization — surgery or stenting (Figure 2) — for each patient, based on clinical, radiologic and angiographic assessment, demographic information, and patient preference. Patients in each group will then be randomized to receive medical management alone or medical management plus revascularization.

“In many cases the patient may be a candidate for either surgery or stenting,” Dr. Meschia says. “But just as patients in standard practice can’t have both procedures, trial participants will select a procedure after informed consideration and discussion with the physician.”

Patients frequently express preferences for one procedure over the other, notes Thomas G. Brott, M.D., a consultant in the Department of Neurology at Mayo Clinic’s Florida campus, who with Dr. Meschia co-leads CREST-2. “Patients in CREST-2 have more input on this decision than study participants ever have experienced previously,” he says.

**Intensive medical management**

Unlike CREST, in which treatment of vascular risks was at the discretion of patients’ primary physicians, CREST-2 has a detailed protocol for medical management of all trial participants.

“The protocol insists on hitting hard objectives,” says Bart M. Damaerschalk, M.D., a consultant in the Department of Neurology at Mayo Clinic in Phoenix/Scottsdale, Arizona. “We’re targeting optimal lipid profiles, blood pressure, glycemic control, smoking cessation, ideal body mass index, nutritional and dietary recommendations, and physical activity and exercise.”

The trial will cover treatment with anti-platelets such as clopidogrel, several classes of blood pressure medications and statins. The primary outcome measurement will be a composite of all strokes and deaths within 30 days of randomization, and ipsilateral stroke for up to four years afterward. Patient follow-ups will continue until at least two years after the last patient is randomized.

“We expect this intensive medical care aspect of CREST-2 will be beneficial for all patients,” Dr. Brott says. “Because of improved medical treatments, asymptomatic carotid artery disease is not nearly as dangerous as it used to be. As a result, we expect very few patients in either study will actually have a stroke.”

Another innovative aspect of CREST-2 is cognitive testing, which all participants will undergo at baseline and at 48 months to determine if any changes are a surrogate for transient ischemic attack. “Cognitive information has the potential to be a cost-effective and patient-centered way of determining if there’s a benefit in preventing not only overt stroke but silent strokes that might manifest as cognitive impairment,” Dr. Meschia says.

**Pooling expertise**

Mayo Clinic has a distinguished history in the diagnosis and treatment of carotid artery disease. The range of expertise at Mayo Clinic is reflected in the institution’s leadership roles in CREST-2.

Robert D. Brown Jr., M.D., a consultant in the Department of Neurology at Mayo Clinic’s campus in Minnesota, chairs the trial’s Endpoint Adjudication Committee. John Huston III, M.D., a consultant in the Department of Radiology at
Despite increased awareness of concussion, athletes with the condition may go unrecognized and return to play prematurely, risking subsequent and more serious injury. Telemedicine links athletes on the field to neurologists at remote locations, offering expert concussion evaluation in real time. Mayo Clinic in Phoenix/Scottsdale, Arizona, a pioneer in teleneurology, is testing the feasibility of teleconcussion assessments at collegiate football games.

“The final results are still pending. But preliminarily, it looks as though our telemedicine evaluations are consistently in agreement with the assessments of team doctors on the sidelines,” says Bert B. Vargas, M.D., a consultant in the Department of Neurology at Mayo Clinic’s campus in Arizona.

In addition to the collegiate study, Mayo Clinic is conducting remote concussion assessments of high school and youth football players. “About 60 percent of high schools do not have access to the care they need to identify concussion on the sideline,” Dr. Vargas says. “Teleconcussion is one way to bridge this gap.”

**Expertise for vulnerable brains**

Mayo Clinic’s extensive telemedicine network began by linking rural hospitals in Arizona with stroke specialists at the Phoenix/Scottsdale campus. Like stroke, concussion is an acute condition requiring rapid assessment with a standardized protocol. Mayo Clinic’s protocol for remote concussion evaluation incorporates the King-Devick Test along with elements of the Sports Concussion Assessment Tool, including the Standardized Assessment of Concussion and the Balance Error Scoring System. Assessments are performed at baseline and also at the time of suspected injury.

“We can easily do these tests rapidly through the telemedicine equipment,” says Amaal J. Starling, M.D., a consultant in the Department of Neurology at Mayo Clinic’s campus in Arizona. She notes that the King-Devick Test, which measures the speed and accuracy of rapid eye movements and attention, “is very sensitive for detecting concussion since the networks that control eye movements are distributed widely throughout the brain.”

Although concussion in professional sports has garnered much attention, the dangers are even greater for young athletes. “The developing brain appears to be more vulnerable to the shear and strain forces placed on the brain during a concussion,” says David W. Dodick, M.D., a consultant in the Department of Neurology at Mayo Clinic’s campus in Arizona. “We have seen many young people who have had a decline in academic performance that persists...
High school or younger athletes also tend to recover more slowly than older athletes. “The reasons for that are not entirely clear,” Dr. Dodick says. “But the normal recovery time for concussion that’s found in the literature — seven to 10 days — is, I believe, an underestimate for youth athletes. They are more susceptible to repeat concussion and may be more likely to have symptoms and neurological impairments that persist.”

**Full-field perspective**

Mayo Clinic’s collegiate football study was done in partnership with Northern Arizona University (NAU). A Mayo Clinic mobile telemedicine robot was stationed on the sidelines during NAU home games in Flagstaff (Figure 1) and taken to away games. Neurologists at Mayo Clinic’s campus in Phoenix/Scottsdale controlled the robot remotely (Figure 2). NAU medical staff performed their normal duties, assessing injured athletes and making decisions about return to play.

However, when a player was pulled aside with suspected concussion, the Mayo neurologists conducted a parallel evaluation remotely and reached their own conclusion about whether a concussion had occurred. Subsequent analysis showed strong agreement between decisions made remotely and on the sidelines. In addition to controlling the robot, the Mayo neurologists watched live broadcasts of the games, gaining an important perspective not available to medical personnel positioned on the sidelines.

“Physicians standing in a fixed location on the sideline have a relatively limited view of what’s happening on the field,” Dr. Vargas says. “There have been a number of situations in collegiate and professional football where an athlete looks altered. Even the broadcasters can identify that something is wrong. But the medical staff may not have seen the problem. Although the field physicians are experts at recognizing and evaluating athletes with concussion, sometimes they are unable to see everything from the sidelines.”

The Mayo neurologists hypothesized that watching a game from multiple camera angles, with the ability to rewind and slow down the broadcast, would help identify players who need assessment. Although the utility of that perspective requires further study, “the NAU medical staff was very pleased that we could alert them if someone needed to be pulled and evaluated,” Dr. Vargas says.

**Testing high school and youth athletes**

In fall 2014, Mayo Clinic is providing teleconcussion coverage for high schools in Phoenix and surrounding cities. “We can be at home on call and available for these schools in case of an injury,” Dr. Starling says. In schools where a telemedicine robot isn’t feasible, a tablet computer can be used.

In addition to acute evaluation, the teleconcussion network is used for follow-up evaluation in rural clinics. “We can make recommendations about returning to school, about appropriate accommodations for learning and about return to play,” Dr. Starling says. “It’s a huge advantage for rural areas without a comprehensive concussion center nearby to have this service.”

Mayo Clinic is also partnering with Arizona Pop Warner, a youth sports organization, to conduct baseline neurologic testing and future research on more than 2,500 youth football players and cheer athletes. The inspiration for Mayo’s initiative came from a White House summit on concussion, where President Barack Obama urged physicians to advance research on protecting young athletes.

“We believe Mayo Clinic can set an example for the rest of the nation,” Dr. Dodick says. “We need to do everything we can, starting at the Pop Warner level, to protect these players.”

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**Success With Treating Some Superficial Siderosis Cases**

Superficial siderosis of the central nervous system is a rare condition caused by hemosiderin deposits in the subpial layers of the brain and spinal cord. The hemosiderin deposition results from recurrent bleeding into the subarachnoid space. Patients often present in adulthood with hearing loss and slowly progressive gait ataxia. A remote history of injury or intradural surgery is
common, but many cases are idiopathic, with no source of bleeding evident.

It has been noted by Mayo Clinic neurologists, neurosurgeons and neuroradiologists that an intraspinal fluid-filled collection accompanies some cases of superficial siderosis. Intraspinal fluid-filled collections have also been seen in patients with craniospinal hypovolemia and dural defects.

“We have had some patients with superficial siderosis and intraspinal fluid collection in whom repairing the defect has resulted in resolution of the fluid collection, resolution of red blood cells in the cerebrospinal fluid and clinical stability,” says Neeraj Kumar, M.D., a consultant in the Department of Neurology at Mayo Clinic in Rochester, Minnesota.

**Diagnostic challenges**

Before MRI, superficial siderosis was generally diagnosed only postmortem. The condition progresses slowly over the course of decades and remains rare. Clinical presentation can include orthostatic headache and cognitive difficulties.

“Superficial siderosis can also present as a myelopathy. Not infrequently, I have seen patients who are misdiagnosed as having a degenerative cerebellar condition,” Dr. Kumar says.

MRI of the head is key to diagnosis. “There are MRI sequences, such as gradient-echo sequencing, that allow the iron pigment to be detected in the brain. But these sequences are not routine,” says David G. Piepgras, M.D., a consultant in the Department of Neurologic Surgery at Mayo Clinic’s campus in Minnesota.

Further, neuroradiologists may view hundreds of images on a CT myelogram from a patient to see the single image showing contrast leakage from a dural defect (Figure). “The MRI findings are striking but somewhat subtle,” Dr. Kumar says. “The abnormality is very confluent, and it sort of coats the surface of the brain.”

**Improvement or arrest?**

A dural defect can usually be repaired with surgery. The procedure is especially complex if the defect is located in front of the spinal cord. “However, for surgeons experienced in the condition and repair, it’s not a great technical challenge,” Dr. Piepgras says.

Anecdotal evidence from patients treated at Mayo Clinic suggests clinical stability after surgery. However, in the absence of longitudinal studies of this slowly progressing condition, it isn’t clear whether repairing the dural defect improves symptoms or merely arrests neurological deficit. “There has already been significant iron deposition in the central nervous system of these patients, which could have future toxic effects even if the mechanism is arrested,” Dr. Piepgras says.

**For more information**


**Immunotherapies for Glioblastomas**

Mayo Clinic in Rochester, Minnesota, is enrolling patients in clinical trials of immunotherapies for glioblastomas. Separate trials are testing novel treatments for patients with newly diagnosed tumors and patients with recurring disease.

Glioblastomas are the most common primary brain tumors affecting adults, and few patients survive five years after diagnosis. Therapeutic vaccines, which combine tumor antigens with dendritic cells created from patient monocytes, are an effort to boost the patient’s immune system to eliminate the tumor. The clinical trials reflect advances in obtaining tumor antigens and in culturing dendritic cells.

“We are making huge strides at a basic-science level that can be translated to patients,” says Ian F. Parney, M.D., Ph.D., a consultant in the Department of Neurologic Surgery at Mayo Clinic.
in Rochester, Minnesota, who is leading the clinical trials. “We understand much more about these tumors and about how we can stimulate the immune system to eradicate them.”

**Trial for newly diagnosed tumors**

Previous versions of therapeutic vaccines have typically required samples of a patient’s tumor to provide antigens. The supply of antigens from an individual patient’s tumor sample is limited, yet fresh antigens are needed to make vaccine for long-term therapy.

The Mayo Clinic trial for newly diagnosed glioblastomas takes a different approach. Dr. Parney and Allan B. Dietz, Ph.D., co-director of the Mayo Clinic Human Cellular Therapy Laboratory, have created a library of clinical-grade brain-tumor cell lines from patients, eliminating reliance upon tumor samples from individual patients. As with previous versions of glioblastoma vaccines, dendritic cells will be cultured from individual patients’ white blood cells.

“Proteins from the tumors will be expressed in the context of the patient’s own molecules. From that point of view, treatment is individualized,” Dr. Parney says. “But we aren’t required to get fresh tumor for any given patient, and we can make much more vaccine to give to each patient.”

Manufacture of the trial vaccine, which is done at a good manufacturing practices-approved facility at Mayo Clinic, incorporates improved techniques for culturing dendritic cells. Successful vaccine treatment requires mature dendritic cells; immature dendritic cells work to suppress the immune system. But standard methods for culturing dendritic cells — which were developed using healthy donors’ white blood cells — generate a higher number of immature dendritic cells when applied to white blood cells from glioblastoma patients.

“With the Human Cellular Therapy Lab, we’ve developed a technique that allows us to generate large numbers of mature dendritic cells from the monocytes of brain tumor patients,” Dr. Parney says. “We think this is a much more potent way of making dendritic cells.”

Analysis of the laboratory’s glioblastoma cell lines pinpointed antigens commonly present in brain tumors, and allowed for the development of tests for specific antigen responses. “That is something which we’ve never been able to do previously in trials,” Dr. Parney notes. “From as little as 5 milliliters of whole blood, we can test 120 different markers on the surface of white blood cells. We get a very detailed picture of the immune system in the peripheral blood of any individual patient.”

Preliminary data from an earlier study suggest it may be possible before treatment to differentiate patients who might respond to immunotherapy. “Replicating that finding will help us tailor treatment going forward,” Dr. Parney says. “At some point, if we can identify groups of patients who aren’t going to respond to vaccine, we might be able to alter their immune systems to achieve response.”

**Recurring glioblastomas**

The development over the next few months of a similar trial for patients with recurrent glioblastomas “looks very promising,” Dr. Parney says. In the meantime, Mayo Clinic is participating in a multicenter study, through the Alliance for Clinical Trials in Oncology, of heat shock protein peptide complex treatment for recurrent glioblastomas.

Heat shock proteins chaperone other proteins into the immune system. The clinical trial uses vaccine made from heat shock protein peptide complexes extracted from individual patients’ tumor samples. Patients must undergo surgery to remove all visible tumor to provide antigens for their vaccines.

Trial participants are randomized into one of three groups: one receiving bevacizumab (Avastin) alone, one receiving the medication plus vaccine, and one receiving the vaccine alone. Patients in the third group may be prescribed medication if their tumors progress.

Mayo Clinic is also investigating nonvaccine methods — notably, immune checkpoint inhibitors — to modulate the immune systems of glioblastoma patients. Ipilimumab (Yervoy), used to treat melanoma, blocks the immune-suppressing CTLA-4 receptor, and may be used in clinical trials for glioblastoma. Other work focuses on the PD-L1 checkpoint.

“Ultimately, we may arrive at a point where we combine immune-modulation treatment and the vaccine,” Dr. Parney says. “Although we have made great progress, we have a ways to go to really optimize immunotherapy for brain tumors. Right now, we’re kind of at the Model T version. We want to get a Ferrari.”
Research Highlights in Neurology and Neurosurgery

Potential Biomarker for ALS and FTD

Every year, 6,000 people in the United States are diagnosed with amyotrophic lateral sclerosis (ALS), which typically is fatal within three to five years of onset. The related neurological disorder frontotemporal dementia (FTD) is the second most common form of early-onset neurodegenerative dementia. Researchers at Mayo Clinic in Jacksonville, Florida, in collaboration with colleagues from The Scripps Research Institute in Florida, have discovered a potential biomarker for the most common genetic risk factor for ALS and FTD. Previously, Mayo Clinic investigators found that a mutation — r(GGGGCC) — in a portion of the C9ORF72 gene is the most common genetic cause of ALS and FTD. RNA of the r(GGGGCC) expression forms nuclear foci or undergoes repeat-associated non-ATG (RAN) translation, producing proteins termed c9RAN. In this study, the researchers designed bioactive molecules targeting r(GGGGCC) expression and found that they significantly inhibited RAN translation and foci formation in cultured cells expressing r(GGGGCC). The researchers also found that c9RAN proteins are detected in the cerebrospinal fluid of patients with c9ALS. The results highlight r(GGGGCC)-binding small molecules as a possible therapeutic agent for c9ALS and c9FTD and suggest that c9RAN proteins could potentially serve as a pharmacodynamic biomarker to assess efficacy of therapies that target expression of r(GGGGCC). (Su Z, et al. Discovery of a biomarker and lead small molecules to target r(GGGGCC)-associated defects in c9FTD/ALS. Neuron, 2014;83:1043.)

The Utility of VEEG in Children

Distinguishing between seizures and nonepileptic events is a key challenge in pediatric neurology. The diagnostic gold standard is prolonged inpatient video electroencephalogram (VEEG) monitoring. However, VEEG requires hospitalization and often long-distance travel for an indeterminate period of time. In a retrospective study, researchers at Mayo Clinic in Rochester, Minnesota, found that prolonged inpatient VEEG captured an event of interest in two-thirds of children studied, with most events obtained within 4.5 hours of recording onset. The records of 213 children undergoing VEEG at Mayo Clinic from 2009 to 2012, to distinguish between seizures and nonepileptic events, were studied. Median recording time was 25 hours. An event of interest was recorded in 66 percent of patients; 20 percent of those events were associated with changes in EEG pattern during seizure. Factors predicting a greater yield of events included the patient’s event frequency, latency since the most recent event, and the presence of intellectual disability. The results suggest that the utility of VEEG monitoring for events that don’t occur at least weekly is limited, and VEEG is beneficial for patients with more-frequent events. (Wyatt KD, et al. Predictors of recording an event during prolonged inpatient video electroencephalogram monitoring in children. Pediatric Neurology, 2014;50:458.)

The Role of TDP-43 in Alzheimer’s Disease

Beta-amyloid and tau proteins have long been correlated with the cognitive impairment and brain atrophy seen in Alzheimer’s disease (AD). However, a significant portion of AD patients remains cognitively normal up to the time of death, despite the presence of beta-amyloid and tau. TDP-43 protein has recently been found in the brains of patients with pathologically diagnosed AD. Researchers at Mayo Clinic in Rochester, Minnesota, have found that TDP-43 is independently associated with cognitive impairment and brain atrophy in AD, and hence an important contributor to the AD phenotype. The researchers screened the brains of 342 subjects pathologically diagnosed with AD for the presence, burden and distribution of TDP-43. Patients had been classified as cognitively impaired or normal prior to death. Atlas-based parcellation and voxel-based morphometry were used to assess regional atrophy on magnetic resonance imaging. Regression models controlling for age at death, apolipoprotein e4 and other AD-related pathologies were utilized to explore associations between TDP-43 and cognition or brain atrophy. TDP-43 was found in 195 subjects (57 percent). After accounting for age, apolipoprotein e4 and other pathologies, TDP-43 had a strong effect on cognition, memory loss and medial temporal atrophy in AD. These effects were not mediated by hippocampal sclerosis. TDP-positive subjects were 10 times more likely to be cognitively impaired at death compared with TDP-negative subjects. Greater cognitive impairment and medial temporal atrophy were associated with greater TDP-43 burden and more extensive TDP-43 distribution. The study suggests that TDP-43 is an important factor in the manifestation of the clinical-imaging features of AD, and therefore should be considered a potential therapeutic target for treatment of the disease. (Josephs KA, et al. TDP-43 is a key player in the clinical features associated with Alzheimer’s disease. Acta Neuropathologica. 2014;127:811.)

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March 11-13, 2015
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Tackling Problematic Sinonasal Disease: Debates and Consensus
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May
2nd Annual Laryngology Conference: Focus on Dysphagia and Laryngeal Hyper-Responsiveness
May 15-16, 2015
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July
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July 16-18, 2015
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San Francisco

September
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Sept. 24-27, 2015
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November
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Nov. 8-12, 2015
The Ritz-Carlton, Kapalua, Maui, Hawaii

December
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Information and registration
Mayo Clinic in Rochester, Minnesota
Phone: 800-323-2688 (toll-free) or 507-284-2509
Email: cme@mayo.edu

Mayo Clinic in Jacksonville, Florida
Phone: 800-634-1417 (toll-free)
Email: cme-jax@mayo.edu

Mayo Clinic in Phoenix, Arizona
Phone: 480-301-4580
Email: mca.cme@mayo.edu

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