How Effective Is tPA 3 to 4.5 Hours After Acute Ischemic Stroke?

Efficacy and Safety of Tissue Plasminogen Activator 3- to 4.5-Hours After Acute Ischemic Stroke. A Metaanalysis.

Lansberg MG, Bluhmki E, Thijs VN:

Stroke 2009; 40 (July): epub ahead of print

This meta-analysis strengthens the case for IV tissue plasminogen activator administered up to 4.5 hours after the onset of acute cerebral ischemia.

Objective: To estimate the effect of tissue plasminogen activator (tPA), administered between 3 and 4.5 hours after the onset of acute cerebral ischemia, using data from all available randomized, controlled trials.

Design: A meta-analysis was performed involving all randomized, controlled trials comparing tPA and placebo, administered between 3 and 4.5 hours after the onset of acute cerebral ischemia using the intention-to-treat population. Only outcome measures common to all trials were used: (1) the "global" outcome measure (which combines the modified Rankin Scale [mRS], NIH Stroke Scale, and Barthel Index [BI]); (2) the mRS alone; and (3) mortality. The NIH Stroke Scale is a scored neurological exam; the BI quantifies function with respect to activities of daily living; and the mRS is a global assessment of overall functioning. Scores of 0 to 1 on the NIH Stroke Scale and mRS were considered good outcomes, as were scores of 95 to 100 on the BI. Another common outcome scale, the Glasgow Outcome Scale, was not uniformly used in all trials and, therefore, was not considered in the meta-analysis. If necessary, sponsors of the trials were asked for additional data. Pooled odds ratios were calculated with SAS software.

Results: All 4 trials, the European Cooperative Acute Stroke Study (ECASS)-1, ECASS-2, and ECASS-3, plus the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke trial, included at least some patients who received IV tPA or placebo in the 3- to 4.5-hour window. Only ECASS-3 was designed to test this window specifically; the other trials had 0- to 6-hour windows. ECASS-1 used a 1.1 mg/kg dose of IV tPA; the others used 0.9 mg/kg. Approximately 1600 patients were available for analysis. Median time to treatment was uniformly very close to 4 hours. Mean baseline NIH Stroke Scale scores at randomization varied between 15.2 (ECASS-1), 13.5 (ECASS-2), and 11.2 (ECASS-3). The baseline NIH Stroke Scale scores trended downward with each successive trial. The populations in each trial were otherwise similar with respect to age and percentage of diabetics. Overall, treatment with tPA in the 3- to 4.5-hour window produced significant odds ratios (approximately 1.3) favoring treatment over placebo. There was no negative impact on mortality. Because ECASS-1 used a higher dose of tPA, another meta-analysis was conducted excluding ECASS-1, with essentially identical results.

Conclusions: This meta-analysis strengthens the case for IV tPA administered up to 4.5 hours after the onset of acute cerebral ischemia.

Reviewer's Comments: The positive results of this meta-analysis were driven by ECASS-3, which supplied half of the data, and involved patients with less severe strokes. It is curious that ICH data were not analyzed at all, even though they are readily available. Perhaps this is because each trial had a different definition of what constituted a symptomatic ICH. (Reviewer-James W. Schmidley, MD).

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Keywords: Tissue Plasminogen Activator, Cerebral Ischemia

Print Tag: Refer to original journal article
The treating physician must watch for signs and symptoms of depression and possible suicidality in patients with epilepsy and other neurological disorders.

**Background:** In January 2008, the Food and Drug Administration (FDA) issued a formal alert that indicated an increased risk of suicidality in response to therapy with all antiepileptic drugs (AEDs). This obviously causes concern for patients and families when initiation of warranted therapy is considered. In some circumstances, there may be reluctance to begin therapy, or patients on established therapy may consider discontinuation of treatment in response to this alert.

**Objective:** To examine and discuss the FDA alert for increased suicidality associated with AED therapy.

**Results:** The issued alert was based on a meta-analysis that included 199 clinical trials with >40,000 participants that evaluated AED therapy for epilepsy, psychiatric disorders, and other disorders (including pain disorders). The 11 AEDs used in these trials included carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproic acid, and zonisamide. The meta-analysis revealed a 1.8-fold increased risk for suicidality. The 3 primary manifestations of suicidality include suicidal ideation, suicide attempt, and completed suicide. The authors of this report cited 3 main problems with the methodology used to support the FDA alert. First, adverse event data were assessed retrospectively based on patient reporting and not on prospective systematically collected data. It is notable that depression and suicidality are increased in patients with epilepsy, but pre-existing depression, other psychiatric disorders, and suicidality were not considered. The increased risk was simply based on comparison of adverse event reporting in subjects treated with the study AED versus those in the comparison arm of each trial. The second problem is that a blanket alert was issued with the AEDs grouped together as a class, and each AED was not evaluated independently. Given that AEDs are different compounds with different mechanisms of action, it does not make sense to consider them uniformly. When the studies are evaluated for independent AEDs, the majority do not appear to be associated with a statistically significant increased risk of suicidality. The third factor to consider is that there is a significant risk of adverse events (including death) associated with uncontrolled seizures, and these risks, in most circumstances, far outweigh the potential increased risk of suicidality.

**Reviewer's Comments:** The treating physician must watch for signs and symptoms of depression and possible suicidality in patients with epilepsy and other neurological disorders. Appropriate questions should be asked to screen for depression and the risk of suicidality. Proper identification and treatment of depression may result in improved quality of life for our patients. The authors suggest specific screening tools that can be used as indicated. We should also adequately inform patients about the risks of uncontrolled seizures and weigh all risks appropriately. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Suicidality, Antiepileptic Drugs

Print Tag: Refer to original journal article
What Is Nature of Frontal Lobe/Hippocampal Abnormalities in Schizophrenia?

Functional Integration Between the Posterior Hippocampus and Prefrontal Cortex Is Impaired in Both First Episode Schizophrenia and the At Risk Mental State.

Benetti S, Mechelli A, et al:

Brain 2009; May 6 (epub ahead of print):

The neural correlates of schizophrenia consist of "abnormal interactions within a distributed network of regions rather than localized deficits."

**Objective:** To examine prefrontal-hippocampal connectivity in patients with either first-episode schizophrenia or so-called "At Risk Mental State (ARMS)."

**Participants/Methods:** 16 patients had ARMS, criteria for which consisted of at least one of the following: "attenuated positive symptoms, a brief psychotic episode of less than a week duration resolving without antipsychotic medication, and either a first-degree relative with psychosis or a personal history of schizotypal personality disorder." Any of these factors had to be associated with a recent decline in social and occupational functioning. Ten patients had a first episode of schizophrenia; 3 were medication naïve and 7 had been treated with antipsychotic medication for a mean of 2 weeks. Fourteen healthy volunteers served as controls. Subjects performed a delayed matching-to-sample task known to engage the prefrontal cortex and hippocampus. During an encoding phase, subjects looked at an abstract pattern for 5 seconds; following a delay, during which they had to hold the sample in memory, they were shown 4 patterns and asked to identify the original sample. During the test, functional MRI with statistical parametric mapping compared regional brain responses, including right and left anterior and posterior hippocampi and inferior frontal gyri. A technique called dynamic causal modeling was used to estimate the effective connectivity between prefrontal and hippocampal regions (ie, the impact that one region exerted over another).

**Results:** In first-episode patients and subjects with ARMS, the normal pattern of effective connectivity from the right posterior hippocampus to the right inferior frontal gyrus was significantly decreased. Other interactions, including those in the left cerebrum and those involving the anterior part of the hippocampus and the inferior frontal gyrus on the right, were normal in all 3 groups.

**Conclusions:** Abnormal hippocampal-prefrontal interactions are present in patients who have just developed schizophrenic symptoms and in those at high risk of developing psychosis. These abnormalities cannot be attributed to chronicity of illness or to treatment. The findings are consistent with the view that the neural correlates of schizophrenia consist of "abnormal interactions within a distributed network of regions rather than localized deficits."

**Reviewer's Comments:** In the May 1, 2009, issue of Science, a report entitled "Neural mechanisms of a genome-wide supported psychosis variant" by Christine Esslinger describes similar findings. Subjects carrying a single nucleotide polymorphism that confers risk for both schizophrenia and bipolar disorder were found at functional MRI to have abnormal connectivity patterns between the hippocampus and dorsolateral prefrontal cortex and between amygdala and hippocampus, orbitofrontal cortex, and medial prefrontal cortex. (Reviewer- John C. Brust, MD).

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Keywords: Schizophrenia, At-Risk Mental State

Print Tag: Refer to original journal article
Even small gifts of very limited value can have a major impact on people’s cognitive assessment. The emerging body of social science data says that small gifts have a major impact on physician’s professional judgments.

(Card 2 of 3) Although professional conferences underwritten by a pharmaceutical company are not equivalent to the small gift of a pen with the company’s logo or a pizza lunch, the hazards of subtle influence and reciprocity arise from each. As physicians, we may be most acutely aware of these obligations in relation to an all-expenses-paid junket to some exotic location, but we may not be aware of subtle forms of influence that arise from small gifts. Even little things like a pen with the company’s logo or a pizza lunch actually affect people’s clinical judgments. Empirical data from social science studies demonstrate that even these interactions have an effect on practitioners’ decision making and professional judgment. Subtle Influence of Free Lunches: For example, 1 study looked at free lunches sponsored by drug companies. In many cases, these lunches affected physicians’ prescribing habits, even though they could not remember attending the lunch. All these interactions create different varieties of the same problem -- the often subtle and undetected obligations of reciprocity and influence. When you ask physicians whether they are impacted by these small interactions, most say they are not. Then, they will go on to say that they worry that their colleagues are indeed influenced. Self-Serving Bias: Cognitive and behavioral psychologists tell us that these responses are an example of self-serving bias. Self-serving bias is something that all human beings have -- we all identify and process information in a way that serves our own interests. This is why these interactions are particularly problematic. Subtle Influence of “Having”: There are some wonderful experiments in which the people on 1 side of a room receive free mugs, and those on the other side receive free pens. Next, the people are asked who would be willing to swap their mugs or their pens. Remember, neither group had either of these items for longer than 10 minutes. However, the process of possessing these items for 5 or 10 minutes causes people to endow them with special values that they would not have anticipated otherwise. Therefore, even tiny items of very limited value can have a major impact on people’s cognitive assessment. We should take into account this emerging body of social science data that says small gifts really have a major impact. (Reviewer-).

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Keywords: Bioethics, Conflicts of Interest

Print Tag: Refer to original journal article
Fragile X tremor ataxia syndrome is a neurodegenerative disorder affecting male carriers of the FMR1 gene premutation.

**Background:** Fragile X tremor ataxia syndrome (FXTAS) is a neurodegenerative disorder affecting older male carriers of the FMR1 gene. It is caused by an expansion of a CGG repeat within this gene, which nonetheless is smaller (only 50 to 200 repeats) than that seen in boys with mental retardation. Carriers of this "pre-mutation" experience the onset, in late middle age or beyond, of tremor, ataxia, parkinsonism, and dysautonomia. These subjects also may have dysphagia, incontinence, impotence, and cardiac rhythm disturbances.

**Objective:** To describe the neuropathological changes in the peripheral nervous system and autonomic ganglia of a man with FXTAS.

**Methods:** In addition to the standard neuropathological stains, sections were immunostained for ubiquitin (UBQ). Dorsal root ganglion, paraspinal sympathetic ganglia, adrenal medulla, sural and sciatic nerve, muscle, and pituitary were examined, as were multiple brain regions. A full systemic autopsy was also performed. Selected tissues were prepared by electron microscopy (EM).

**Results:** The patient was a 69-year-old man with falls and syncope. Parkinsonism and limb and trunk ataxia were found on exam, but there was only minimal tremor. MRI showed typical changes in the middle cerebellar peduncles and generalized atrophy. Fragile X pre-mutation analysis revealed 84 CGG repeats. Formal autonomic nervous system studies, performed early in the course, were negative. At autopsy, the cause of death was pulmonary emboli and pneumonia. The brain showed cerebral atrophy with pale white matter. Microscopically, the typical changes of FXTAS were seen in neurons and astrocytes throughout the brain. These were “glassy” eosinophilic nuclear inclusions that were positive on UBQ immunostaining. Their EM appearance was as previously described. The inclusions were particularly prominent in the hippocampus and frontal cortex and, as is typical in FXTAS, absent from Purkinje neurons, oligodendrocytes, and anterior horn cells. The key finding was the identification of similar inclusions in neurons and astrocytes of the intermediolateral cell column of the spinal cord, neurons of the dorsal root ganglia, paraspinal sympathetic ganglia, ganglion cells of the adrenal medulla, the myenteric plexus of the stomach, and in an epicardial ganglion. There were no specific pathological changes in skeletal muscle or mixed peripheral nerve, nor were there changes in the urinary bladder, esophagus, or cardiac conduction system.

**Conclusions:** The neuropathology of FXTAS includes widespread changes in the autonomic nervous system. This likely explains the autonomic symptomatology seen in many patients.

**Reviewer’s Comments:** Peripheral neuropathy occurs in FXTAS, yet no specific changes were found in sensory and mixed peripheral nerve in this patient. Perhaps further such exhaustive studies of the autonomic nervous system in patients with FXTAS will disclose changes in myenteric plexus of other parts of the gastrointestinal tract and the urinary bladder. The paper also discusses the differentiation of FXTAS from neuronal intranuclear hyaline inclusion disease. (Reviewer-James W. Schmidley, MD).

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Keywords: Fragile X Tremor/Ataxia Syndrome, FMR1 Gene

Print Tag: Refer to original journal article
Statins Help Reduce Risk of Recurrent Stroke

Statin Therapy After First Stroke Reduces 10-Year Stroke Recurrence and Improves Survival.

Milionis HJ, Giannopoulos S, et al:

Neurology 2009; 72 (May 26): 1816-1822

Statins prescribed included fluvastatin, pravastatin, simvastatin, and atorvastatin. Of 794 patients hospitalized for a first-time ischemic stroke, 112 (14.1%) had a recurrent event. Recurrences were found in 97 of 499 (16.3%) stroke patients who did not receive a statin after discharge compared to 15 of 183 (7.6%) who received statin therapy. Thirty-seven patients in the statin-treated group and 97 in the non-statin group were lost to follow-up. At 12 months' post-discharge, the statin group exhibited an improved lipid profile compared to the non-statin group. Statin therapy remained a strong predictor of decreased recurrent stroke risk even after adjustment for efficacy of control of blood pressure and lipids. Of the 224 deaths that occurred, 11 were in the statin-prescribed group.

Conclusions: Subjects who had been prescribed a statin post-discharge from a first-ever stroke had a lower stroke recurrence rate and improved survival.

Reviewer's Comments: This study supports the use of statin medications for secondary stroke prevention. The mechanism of action of these medications for this effect remains unknown. Further studies should evaluate the efficacy of specific type and dosage of statin medications. (Reviewer-John Schwankhaus, MD).

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Keywords: Statins, Recurrent Stroke Risk

Print Tag: Refer to original journal article
Objective: To identify different gene mutations in patients with dopa-responsive dystonia (DRD), and to correlate genotype with clinical features.

Participants/Methods: 64 index patients with dystonia had sustained improvement of at least 50% after treatment with levodopa. Of the 64 patients, 57 had "pure DRD" with no other neurological manifestations except occasional mild parkinsonism. Seven patients had "DRD-plus syndromes," with additional symptoms that included mental retardation and oculogyric crisis. Forty-eight patients were female. Gene point mutations and deletions were identified using polymerase chain reaction and multiplex ligation-dependent probe amplification.

Results: 47 of the 64 patients had mutations affecting the gene encoding GTP cyclohydrolase 1, the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin (BH4), an essential co-factor for tyrosine hydroxylase and the synthesis of dopa and dopamine. Forty of the cyclohydrolase 1 mutations were point mutations, and 7 were large deletions. All 47 of these patients had pure dystonia except for one with a large deletion who had mental retardation. Dystonia began in the legs, usually in the first decade of life; in one patient, onset was before age 1 year, and in another, onset was at age 27 years. Three DRD patients had mutations in the tyrosine hydroxylase gene, and 2 in the gene encoding sepiapterin reductase, another gene involved in the synthesis of BH4. These 5 patients each had DRD-plus syndromes, including mental retardation, oculogyric crisis, dopa-responsive infantile parkinsonism, sleep disorders, and hyperphagia. Symptoms often began in early childhood. One DRD patient had mutation of the PARK2 gene; generalized dystonia plus postural and action tremor of the arms appeared at age 16, and response to levodopa was still maintained 7 years later. Eleven DRD patients who were negative for these 4 genes were tested for other genes involved in BH4 biosynthesis or BH4 regeneration. Three of these cases were familial. All cases were negative for each of the genes tested.

Conclusions: Mutation of the gene encoding GTP cyclohydrolase 1 produces pure dopa-responsive dystonia, whereas mutation of the genes encoding tyrosine hydroxylase or sepiapterin reductase and the PARK2 gene produces dopa-responsive dystonia-plus syndromes. The 11 patients with no mutation in any of the genes tested might have had undetected mutations in GTP cyclohydrolase 1 gene promoter or regulatory regions. The clinical features of hereditary dopa-responsive dystonia thus depend on the mutated gene.

Reviewer's Comments: The clinical features of hereditary dopa-responsive dystonia depend on the mutated gene, with cyclohydrolase 1 gene mutations producing "pure" dystonia and mutations of several other genes producing "dystonia plus" syndromes. (Reviewer-John C. Brust, MD).

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Keywords: Dopa-Responsive Dystonia, Gene Mutations

Print Tag: Refer to original journal article
Cardiac Evaluation After Ischemic Stroke--Each Patient Is Different

Cardiac Workup of Ischemic Stroke: Can We Improve Our Diagnostic Yield?

Morris JG, Duffis EJ, Fisher M:

Stroke 2009; 40 (August): epub ahead of print

For stroke patients with atherosclerosis or known sources of embolism presumed to be the cause of stroke, the diagnostic yield from TEE has been reported to be only 3% for identifying other cardiac sources of embolism altering treatment.

**Background:** Cardiac embolization causes 15% to 30% of strokes.

**Objective:** To determine the utility of prolonged cardiac monitoring and cardiac imaging in acute ischemic stroke.

**Design:** Literature review and meta-analysis.

**Methods:** Analysis of English publications on cardiac testing and stroke since 1950.

**Results:** ECG abnormalities occur in 60% to 90% of stroke patients; QT prolongation and nonspecific ST changes are most common. Atrial fibrillation (AF) may be detected on ECG in up to 25% of acute stroke patients. Left ventricular (LV) thrombus has been identified in 2.3% to 11.5% of patients with acute MI, with embolization risk over the next 12 months of 2.2% to 6%. Cardiac rhythm monitoring for 24 hours detects paroxysmal AF in 4% to 8.4% of cases. Holter monitoring may detect paroxysmal AF in 4.6% of stroke victims; event recorders worn for up to 30 days have detected AF in 6% to 7% of stroke patients. Transthoracic echocardiography (TTE) is widely available and less expensive than transesophageal echocardiography (TEE); both can accurately identify LV thrombus. TTE is less sensitive than TEE in the detection of other cardioembolic sources, including left atrial thrombus (sensitivity: TTE, 39% to 73%; TEE, 93% to 100%), patent foramen ovale (sensitivity: TTE, <50%; TEE, 89% to 100%), and vegetations (sensitivity: TTE, 58% to 62%; TEE, 82% to 100%). TEE is superior for identifying aortic arch atheroma that may be a source of emboli. Reported diagnostic yield for echocardiography to identify embolic sources in stroke victims is 2% to 37% for TTE and 8% to 32% for TEE. However, for stroke patients with large- and small-vessel atherosclerosis and those with known sources of embolism presumed to be the cause of stroke, the diagnostic yield from TEE has been reported to be only 3% for identifying other cardiac sources of embolism altering treatment.

**Conclusions:** The authors recommend a systematic approach to the utilization of prolonged cardiac rhythm monitoring and structural imaging, and they also provide an algorithm. They recommend that all acute stroke patients have a cardiovascular history and examination, ECG, chest x-ray, and 24-hour telemetry. Patients with no clinical evidence of heart disease by these tests and a likely noncardiac source of stroke do not need further rhythm monitoring or echocardiography. Patients with evidence of heart disease or suspected embolic stroke should have a TTE followed by TEE, if the TTE is nondiagnostic. If TEE is unrevealing and no arrhythmias are detected during hospitalization, extended outpatient rhythm monitoring should be considered. For young patients with cryptogenic strokes, it might be reasonable to proceed directly to TEE.

**Reviewer's Comments:** This article provides practical guidelines for the utilization of cardiac rhythm monitoring and imaging for stroke victims. It is obviously important to identify acute MI and cardiac sources of embolization in the setting of acute stroke. For many patients, prolonged rhythm monitoring >24 hours and echocardiography may be unnecessary. (Reviewer-W. Steven Metzer, MD).

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Keywords: Stroke, Echocardiography, Electrocardiography

Print Tag: Refer to original journal article
Multiple generic substitutions of antiepileptic drugs increase the risk of breakthrough seizures, increased hospitalization, injuries, and health-care costs.

**Background:** Most antiepileptic drugs (AEDs) in the United States are presently available in generic formulations, and generic substitution is increasing. The obvious benefit is a lower cost. Although in many circumstances the generic AED may be of adequate quality and not result in increased seizures in patients with epilepsy, there is a possibility that generic substitution may result in breakthrough seizures and other problems.

**Objective:** To evaluate the clinical and economic consequences of generic substitution of topiramate with single versus multiple generics.

**Methods:** An open-cohort study was performed in Canada on patients with epilepsy treated with topiramate with comparison of medical resource utilization and costs during periods of therapy with brand, single-generic, and multiple-generic use.

**Results:** A total of 948 patients were observed during 1105 person-years of brand-use, 233 person-years of single-generic use, and 92 person-years of multiple-generic use. Approximately one-fourth of those treated with generic topiramate received ≥2 generics. Compared to brand use, multiple-generic use resulted in an increase in hospitalization rates (almost double) and an increased duration of hospital stays. These were only minimally increased in the single-generic use group. The risk of head injury or fracture was increased almost 3-fold in the multiple-generic use group compared to brand use. Multiple-generic use resulted in a higher annual health care cost per patient compared to treatment with brand-name topiramate (Topamax).

**Reviewer's Comments:** FDA regulations require a generic medication to be bioequivalent to the brand name medication that it is replacing. The FDA defines a generic drug as "a copy that is the same as a brand-name drug in dosage, safety, and strength, how it is taken, quality, performance, and intended use." In actuality, the FDA's bioequivalence limits are from 80% to 125%. Most high-quality generics are likely closer to 95% to 105%, but there is a potential for a given generic to have a bioequivalence of up to 20% less than or 25% greater than what is prescribed for the patient. With many generic products available for a given drug, it is possible for a patient to be changed from one generic to another multiple times. This increases the likelihood that a generic with a greater discrepancy in bioequivalence will ultimately be used. There is a potential risk for increased seizures, hospitalizations, injuries, and health-care costs in patients treated with generic AEDs, especially when they are changed to multiple generics over time. Due to the fact that patients with epilepsy are treated chronically, with time, the use of multiple generics is likely and the associated risk will likely increase. 

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Keywords: Generic Substitution, Topiramate, Epilepsy

Print Tag: Refer to original journal article
**Graduated Compression Stockings Do Not Prevent DVT in Stroke Patients**

*Effectiveness of Thigh-Length Graduated Compression Stockings to Reduce the Risk of Deep Vein Thrombosis After Stroke (CLOTS Trial: A Multicentre, Randomised Controlled Trial.)*

CLOTS Trials Collaboration:


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Skin breaks, ulcers, blisters, and skin necrosis are significantly more common among stroke patients randomized to treatment with graduated compression stockings.

**Background:** As many as 42% of acute stroke victims develop deep vein thrombosis (DVT). Many national stroke guidelines recommend the use of graduated compression stockings (GCS) for DVT prevention with acute stroke patients. With the exception of one small study, this recommendation is based on successful utilization of GCS for DVT prophylaxis among surgical patients.

**Objective:** To investigate the efficacy of GCS for DVT prevention in acute stroke patients.

**Design:** Multicenter randomized controlled trial.

**Participants:** 2518 subjects who had suffered an acute stroke.

**Methods:** Subjects were randomized to routine care plus thigh-length GCS (n=1256) or to routine care plus no use of GCS (n=1262). Doppler ultrasound of both legs was performed at about 7 to 10 days post-admission, and again at 25 to 30 days after enrollment. The primary outcome was occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins.

**Results:** This was a negative study. DVT was detected in 126 (10%) patients assigned to thigh-length GCS, and DVT was detected in 133 (10.5%) patients randomized to no treatment with GCS. This difference was not statistically significant. This study had 90% power to detect a 4% absolute risk reduction in the primary outcome. Skin breaks, ulcers, blisters, and skin necrosis were significantly more common among patients randomized to GCS than to those randomized to no treatment with GCS.

**Conclusions:** The results of this study do not support the use of thigh-length GCS for DVT prophylaxis among acute stroke patients. The authors propose that this recommendation be dropped from guidelines for the treatment of acute stroke.

**Reviewer's Comments:** This useful study emphasizes that what may be an effective DVT prophylaxis for patients undergoing elective surgery may not be effective for acute stroke patients. The authors point out that patients undergoing elective surgery begin the use of GCS prior to immobilization. This is not true for acute stroke victims. My personal preference is to use a low-molecular-weight heparinoid for DVT prophylaxis in stroke patients, unless it is contraindicated. An ongoing study is investigating the effectiveness of intermittent pneumatic compression for DVT prophylaxis in stroke victims. (Reviewer-W. Steven Metzer, MD).

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Keywords: Stroke, DVT, Compression Stockings

Print Tag: Refer to original journal article
Strokes with stenosis in the vertebrobasilar circulation carry a high risk of recurrent TIA or stroke.

**Background:** The early recurrent risk of posterior circulation stroke is unknown.

**Objective:** To determine the early recurrent stroke risk and whether vertebrobasilar (VB) stenosis is predictive of higher risk.

**Methods:** Consecutive patients with posterior circulation transient ischemic attack (TIA) or stroke were prospectively recruited. The presence of hypertension, diabetes, hypercholesterolemia, and smoking history were recorded. All 216 patients had head CT and 180 had structural brain MRI; 194 patients had vertebrobasilar circulation imaging with either contrast-enhanced MRA (CE-MRA) or CT angiography (CTA). The vessels were imaged from the aortic arch to vertex. All images were reviewed to determine the presence of 50% to 99% stenosis. Patients were then prospectively followed for 3 months to identify recurrent TIA or stroke. The primary end point was any clinical stroke in the VB territory. Secondary end points were TIA or stroke in the VB distribution and stroke in any arterial territory. The relationship between stenosis and recurrent events was determined with reference to both the first and presenting TIA or stroke. Cases of vertebral dissection were excluded.

**Results:** 216 patients were recruited (191 stroke, 25 TIA); 19 had a cerebrovascular event (14 TIAs and 5 strokes) in the 30 days before the presenting event. Overall, 194 had imaging of the VB circulation with CE-MRA or CTA. Prospective follow-up to 90 days or death was available for 203 patients. Death within 90 days occurred in 23; 5 were lost to follow-up. A total of 182 patients had imaging at presentation and follow-up. Taking the first event (including TIA/stroke in the previous month) as the index event, 33 had a recurrent VB event (29 strokes, 4 TIAs). Another 3 had a recurrent stroke in the carotid distribution. The risk of stroke alone at 90 days, taking the first event as the index event, was 30.5% for those with VB stenosis and 8.9% in those without stenosis. Taking the presenting episode as the index case, the risk was 13.8% versus 4.1%. Statistical analysis showed the presence of VB stenosis to be an independent risk factor for recurrent stroke.

**Conclusions:** The presence of VB stenosis identifies a group of patients with posterior circulation stroke who have a high recurrent stroke risk.

**Reviewer’s Comments:** With the high recurrence rate of stroke with vertebrobasilar stenosis after posterior circulation ischemia, noninvasive vascular imaging as well as preventive treatments must be employed quickly. It will be helpful to compare CE-MRA with CTA as well as intra-arterial angiography in the future. Randomized trials of stenting and angioplasty for treatment of these lesions are also needed. (Reviewer-John Schwankhaus, MD).

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Keywords: Vertebrobasilar Stenosis, Stroke Risk

Print Tag: Refer to original journal article
**Genetic Mutations Responsible for Bilateral Frontoparietal Polymicrogyria**

**Bilateral Frontoparietal Polymicrogyria, Lennox-Gastaut Syndrome, and GPR56 Gene Mutations.**

Parrini E, Ferrari AR, et al:

Epilepsia 2009; 50 (June): 1344-1353

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**GPR56 mutations are rare, but can be tested for when MRI reveals bilateral cortical malformation with polymicrogyria in the frontoparietal regions.**

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**Background:** Neuronal migration abnormalities are commonly associated with medically refractory epilepsy in children. The identification of these abnormalities with MRI has always raised questions concerning the underlying mechanism that results in these malformations. In the last few years, a group of specific gene mutations on chromosome 16q12.2-21 has been identified and associated with a specific pattern of regional polymicrogyria. Bilateral frontoparietal polymicrogyria (BFPP) has now been found to be associated with 11 different mutations in the GPR56 gene that have been identified to date in 29 patients from 18 families. The GPR56 gene encodes for an evolutionarily dynamic G-protein-coupled receptor. The primary clinical features of this disorder include severe mental retardation, developmental delay, gait and language impairment, and epilepsy.

**Objective:** To report 3 consanguineous families with 4 affected individuals with BFPP, GPR56 mutations, and Lennox-Gastaut syndrome.

**Methods:** As part of a research effort to establish correlations between cerebral cortex developmental abnormalities and associated clinical features with phenotype and genotype identification when possible, 3 probands with BFPP and Lennox-Gastaut syndrome were identified. The fourth was identified through family studies. Mutation analysis of the GPR56 gene was performed on the 4 probands and available family members. Neuroimaging included MRI on 3 and CT on 1. EEG and video-EEG results were also reviewed.

**Results:** Seizure onset had occurred at 1, 2, 5, and 8 years of age. Slow spike-and-wave was present on EEG. All 4 patients had severe mental retardation, brisk deep-tendon reflexes, broad-based or unsteady gait, and poor language skills. One had nystagmus with upgaze, and one had pendular nystagmus. The child with seizure onset at 2 years of age had infantile spasms initially. All 4 had multiple seizure types that included various combinations of tonic, atonic, tonic-clonic, and atypical absence seizures. Two experienced recurrent episodes of nonconvulsive status epilepticus.

**Conclusions:** 3 different GPR56 mutations were identified. Two of the patients were siblings and possessed the same abnormality.

**Reviewer's Comments:** Much progress has been and is being made in the identification of genetic mutations and other abnormalities that appear responsible for multiple forms of childhood epilepsy and neuronal migration abnormalities. I suspect that we have only uncovered the tip of the iceberg, and many more are going to be identified as we progress into the future. GPR56 mutations are rare, but can be tested for when MRI reveals bilateral cortical malformation with polymicrogyria in the frontoparietal regions. (Reviewer-Gregory B. Sharp, MD).

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Keywords: GPR56 Mutations, Polymicrogyria

Print Tag: Refer to original journal article
Cyclophosphamide therapy is effective and can be considered in children with severe MS that is refractory to first-line therapies.

**Background:** The onset of multiple sclerosis (MS) occurs prior to 18 years of age in 2% to 10% of cases. Onset during childhood is commonly associated with more aggressive disease with frequent relapses. Intravenous cyclophosphamide therapy is generally reserved for patients who do not respond satisfactorily to first-line therapies that include corticosteroids, intravenous immunoglobulin (IVIg), and plasmapheresis for acute relapses, and prophylactic therapy with beta-interferon and glatiramer acetate.

**Objective:** To review and report on the results of treatment of MS with cyclophosphamide in children with either severe relapses or poor response to conventional therapies.

**Design/Methods:** A multicenter review identified 17 children with a diagnosis of MS who were treated with cyclophosphamide. Information was collected concerning demographic data, clinical features, treatment, and MRI findings.

**Interventions:** Treatment with cyclophosphamide was performed with 1 of 3 regimens: induction therapy alone, induction therapy followed by pulse maintenance therapy, or pulse maintenance therapy alone.

**Results:** The age at the time therapy with cyclophosphamide was initiated ranged from 9 to 18 years with a mean disease duration of just over 3 years. There were 7 boys and 10 girls; 9 were Caucasian and 8 non-Caucasian. All 17 patients were initially diagnosed with relapsing remitting MS, and 2 had developed secondary progressive MS at the time cyclophosphamide therapy was initiated. First-line therapy had been given in 14 patients and included interferon beta 1a in 12, interferon beta 1b in 2, and glatiramer acetate in 4. Prior second-line therapy had been used in 9 patients and included monthly IVIg in 6, mitoxantrone in 2, ACTH in 1, and azathioprine in 1. The mean number of steroid courses during the prior year was 2.5 and ranged from 0 to 4.0. All but one patient had either experienced significant worsening of Expanded Disability Status Scale (EDSS) scores or multiple relapses prior to starting cyclophosphamide therapy. Monthly maintenance therapy was used in 14 children with or without induction therapy. Additional ongoing concomitant therapy was used in 10 patients. During the year following initiation of cyclophosphamide therapy, 13 of 14 patients experienced a decrease in relapse rate and 1 had the same number of relapses compared to the prior year. There were no relapses during the first cyclophosphamide treatment year in 4 patients. EDSS scores were available before and after 1 year of therapy for 12 patients and improved in about three fourths with a decrease in the mean score from 3.5 to 1.5. Cyclophosphamide was well tolerated by most patients. Reported adverse events included vomiting, transient alopecia, osteoporosis, and amenorrhea. One patient developed carcinoma of the bladder that was successfully treated.

**Reviewer's Comments:** Cyclophosphamide therapy is effective and relatively well tolerated, and can be considered in children with severe MS that is refractory to first-line therapies. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Cyclophosphamide, Children

Print Tag: Refer to original journal article
Cervical Disc Replacement vs Anterior Discectomy and Fusion

Results of the Prospective, Randomized, Controlled Multicenter Food and Drug Administration Investigational Device Exemption Study of the ProDisc-C Total Disc Replacement Versus Anterior Discectomy and Fusion for the Treatment of 1-Level Symptomatic Cervical Disc Disease.

Murrey D, Janssen M, et al:


Cervical disc replacement is equivalent to anterior discectomy and fusion over the short-term.

**Background:** Anterior cervical discectomy and fusion (ACDF) is considered the gold standard surgical treatment for patients with cervical radiculopathy. Fusion could be achieved using for allograft or autograft bone, but bone graft has been largely replaced by fusion with anterior cervical plates.

**Objective:** To determine the safety and efficacy of an artificial disc (the ProDisc-C) replacement versus ACDF at a single level for the treatment of symptomatic cervical disc disease from C3 to C7.

**Design:** Prospective randomized controlled multicenter clinical trial in the United States with a 2-year follow-up.

**Participants:** 209 adult patients (18 to 60 years old) were randomized (ProDisc-C, 103; ACDF with allograft and plate, 106). All patients had a single level (between C3 and C7) symptomatic cervical disc disease resulting in radicular pain that was unresponsive to conservative treatment for at least 6 weeks and/or neurological deficit due to nerve root/spinal cord compression. About half of the patients had C5-C6 disease.

**Methods:** The ProDisc-C comprises 2 cobalt chromium molybdenum alloy end plates with central keels and an ultrahigh-molecular weight polyethylene convex inlay. The outcome measures included visual analog scale (VAS) pain and intensity (neck and arm), VAS satisfaction, neck disability index (NDI), neurological exam, adverse events, and Short Form-36 questionnaires.

**Results:** VAS neck and arm pain were lower at 24-month follow-up compared with preoperative values ($P < 0.0001$), and NDI was much improved ($P < 0.0001$) with no statistical difference between both groups. Comparing the ProDisc-C group to the ACDF group, neurologic improvement (or stabilization) occurred equally in both groups at 24 months (90% and 88%, respectively), and adverse effects were not statistically different (3% and 6%, respectively). Reoperation in the 2-year period was more common with ACDF than the ProDisc-C (8.5% vs 1.8%; $P = 0.33$).

**Conclusions:** The ProDisc-C is a safe and effective surgical procedure in patients with a symptomatic single level cervical disc disease. The outcome at 24 months is essentially similar to anterior cervical discectomy and fusion.

**Reviewer's Comments:** Despite its success, ACDF is associated with an increased incidence of disc herniation at adjacent levels, resulting in additional surgical intervention in about one fourth of these patients >10 years. This complication has triggered the need for an alternative surgical treatment for herniated cervical discs. This artificial cervical disc is promising since the 2-year outcome is similar to ACDF. However, it remains to be seen whether this positive outcome will withhold over the long-term. (Reviewer-Bashar Katirji, MD).

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Keywords: Cervical Disc Disease, Surgical Treatment

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Background: The evaluation and counting of unmyelinated epidermal nerve fibers (ENF), using immunoreactivity to gene product 9.5 protein, has been increasingly used in the confirmation of a suspected small fiber sensory neuropathy. An alternate method is a skin blister biopsy, in which negative pressure to the skin separates the epidermis from the dermis and provides a bird's eye view of the ENFs.

Objective: To compare skin suction blister method to the punch skin biopsy.

Participants/Methods: 25 healthy volunteers were recruited. Their age ranged from 35 to 62 years old (15 women and 10 men). None had diabetes mellitus, alcoholism, or other potential causes of peripheral neuropathy. All had normal neurological examination including detailed sensory examination. All had normal sensory and motor conduction studies in the leg and hand. Two 3-mm suction blister specimens and a 3-mm punch biopsy were obtained from the right foot and calf.

Results: Skin blistering was quicker in the calf than the foot (ranges, 47 to 85 minutes and 63 to 158 minutes, respectively). ENF quantification showed no difference in ENF density between the skin blister and skin biopsy methods ($P=0.29$). Additionally, the results from both methods correlated for the foot ($r=0.64$) and the calf ($r=0.57$). There was also no difference in ENF density between 2 adjacent blisters from the same location ($P=0.15$).

Conclusions: Suction skin blister method is comparable to skin punch biopsy in determining ENF density in the foot and calf.

Reviewer’s Comments: In recent years, the diagnostic tools to confirm the presence of small fiber neuropathy have increased. Skin blister is added to skin punch biopsy, quantitative axon reflex studies (QSART), quantitative sensory testing, and the sympathetic skin response. Skin blister has the advantage of being painless and not requiring staining. Its disadvantages include the long blistering time (47 to 158 minutes), which may be difficult in a busy clinic setting, and the inability to analyze dermal nerves. Finally, this technique needs to be compared to skin punch biopsy in patients with neuropathy. (Reviewer-Bashar Katirji, MD).

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Keywords: Small Fiber Neuropathy, Skin Blister vs Punch Biopsy

Print Tag: Refer to original journal article
Adding memantine to a cholinesterase inhibitor significantly delays the need for nursing home placement in patients with AD.

**Background:** A previous study by the authors concluded that treatment with a centrally acting cholinesterase inhibitor (ChEI) delays the need for nursing home care in patients with Alzheimer’s disease (AD).

**Objective:** To determine whether adding memantine might delay the need further.

**Design:** Observational cohort study.

**Participants:** All 943 patients with probable AD who were followed for at least 1 year at a referral center for dementia were evaluated. Their mean score on the Mini-Mental State Examination (MMSE) was 18 ± 5, and the mean duration of follow-up was 5 ± 3 years.

**Interventions:** Patients were treated with no cognition enhancer (n=416, 40%), a ChEI alone (n=387, 45%), or both ChEI and memantine (n=140, 15%), at the discretion of their physician.

**Methods:** The data were analyzed with a multivariate Cox proportional hazard model, which controlled for covariates that are important in determining nursing home placement, including age, severity of dementia, psychosis, disruptive behavior, and antipsychotic drug use.

**Results:** The baseline characteristics of the 3 treatment groups differed in many respects, including education level, MMSE score, scale of activities of daily living score, and use of vitamin E, estrogens, and antidepressant, antipsychotic, and lipid-lowering drugs. Patients taking a ChEI alone were less likely to be placed in a nursing home during follow-up than the untreated patients (relative hazard [RH], 0.37; 95% CI, 0.27 to 0.49). The risk of nursing home placement was further reduced by a factor of 3.4, when the combination therapy group was compared to the ChEI-alone group (RH, 0.29; 95% CI, 0.11 to 0.72). There was no difference in survival among the 3 groups.

**Conclusions:** Adding memantine to a ChEI significantly delays the need for placement in a nursing home in patients with AD.

**Reviewer’s Comments:** Because there were many baseline differences among the 3 treatment groups and because assignment to treatment group was not randomized, I wonder whether something other than their treatment, in spite of efforts to control for confounders, might account for the difference in the course of disease noted in this study. Maybe the patients who entered a nursing home later had less aggressive cases of AD. It is conceivable to me that the families and physicians of such patients, who seemed to have had "a good response" to a ChEI, might give memantine more readily to them than to patients whose symptoms had rapidly progressed despite treatment with a ChEI. Also, to keep a balanced view of this topic, we should recall that the randomized, controlled, AD2000 study concluded that the ChEI donepezil does not delay nursing home placement in patients with AD (Lancet 2004; 363: 2105-2115). (Reviewer-Marc D. Winkelman, MD).

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Keywords: Alzheimer's Disease, Memantine, Cholinesterase Inhibitor

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Among patients with asymptomatic hyperCKemia not caused by dystrophinopathy, a considerable proportion (14%) will be found to have LGMD.

**Background:** Because the numerous types of limb-girdle muscular dystrophy (LGMD) are clinically and genetically heterogeneous, it can be difficult to know which ones to test for in a given patient.  
**Objective:** To establish clinical-genetic correlations and relative frequencies among the LGMDs.  
**Design:** Retrospective study.  
**Participants:** Patients referred to an academic neuromuscular program over 25 years were evaluated. Inclusion criteria included biopsy showing muscular dystrophy and a clinical syndrome of progressive proximal-limb weakness or progressive distal-limb weakness (Miyoshi myopathy). Patients with asymptomatic hyperCKemia, without apparent cause, were also included, but it is not clear if their biopsies had to show muscular dystrophy. Patients with low quality muscle biopsy and dystrophinopathy were excluded.  
**Methods:** Muscle biopsies were tested for the proteins calpain-3 (LGMD2A), dysferlin (LGMD2B), sarcoglycan (LGMD2C-F), caveolin-3 (LGMD1C), and emerin (Emery-Dreifuss muscular dystrophy [EMD]). DNA from muscle or blood was tested for mutations of the genes DYSF (for dysferlin), CAPN3 (for calpain-3), FKRP (for fukutin-related protein, LGMD2I), LMNA (for lamin A/C, LGMD1B), CAV3 (for caveolin-3), EMD (for EMD), and of the genes for sarcoglycans. All patients did not have all tests.  
**Results:** 550 patients, with proximal myopathy (n=308), distal myopathy (n=38), and asymptomatic hyperCKemia (n=204), were studied. A protein defect was found in the biopsy of 41% of patients (calpain-3, 21%; sarcoglycan, 14%; dysferlin, 8%; caveolin-3, 2%; emerin, 1%), and a genetic mutation in 42% of patients. In those with defective dysferlin, caveolin-3, and emerin proteins, the expected genetic defect was always found. The correlation was less perfect, though still strong, for sarcoglycan (77%) and calpain-3 (84%) protein defects. A genetic diagnosis was arrived at in most patients with proximal myopathy (59%) and distal myopathy (66%), but in few with asymptomatic hyperCKemia (14%). All patients with distal myopathy had LGMD2B. LGMD2C-F (36%) and LGMD2A (30%) accounted for most cases of childhood-onset (age 2 to 12 years) proximal myopathy; only LGMD1C did not cause the phenotype. LGMD2A (27%), LGMD2B (8%), LGMD2I (4%), and LGMD1C (3%) caused most cases of adult-onset (age >12 years) proximal myopathy with a molecular diagnosis; among the sarcoglycanopathies, only LGMD2D caused the phenotype. Asymptomatic hyperCKemia was found to be a phenotype of LGMD2A (7%), LGMD2B (2%), LGMD2D (3%), LGMD2I (0.5%), and LGMD1C (2%). Only 2 patients, with proximal myopathy, had EMD.  
**Conclusions:** LGMD2A is the most common form of LGMD. Among patients with asymptomatic hyperCKemia not caused by dystrophinopathy, a considerable portion (14%) will be found to have LGMD.  
**Reviewer's Comments:** Among the LGMDs, distal myopathy is always due to LGMD2B, but LGMD2B can also cause proximal myopathy and hyperCKemia. A dysferlin protein defect in a muscle biopsy is always due to LGMD2B; gene mutation analysis is not needed to confirm the diagnosis. Proximal myopathy is the most genetically heterogeneous phenotype. (Reviewer-Marc D. Winkelman, MD).  

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Keywords: Limb Girdle MD, Molecular Diagnosis  

Print Tag: Refer to original journal article
After presentation, sICAD seldom causes cerebral or retinal ischemia, regardless of treatment with aspirin or warfarin.

**Objective:** To determine whether aspirin or warfarin is the better treatment of spontaneous dissection of the extracranial internal carotid artery (sICAD).

**Design:** Prospective cohort study with retrospective analysis of data.

**Participants:** Consecutive patients with sICAD treated from 1987 to 2005 at 2 academic stroke centers.

**Interventions:** The type of antithrombotic treatment was chosen by the treating neurologist; no selection criteria were applied. **Outcome Measures:** 3 months after treatment had begun, patients were evaluated for the occurrence of a new ischemic stroke, transient ischemic attack (TIA), or retinal ischemia, symptomatic intracranial hemorrhage, and major extracranial bleeding.

**Results:** There were 298 patients, of which 168 (56%) were men and 130 were women aged 46 ± 10 years. In total, 156 (56%) patients presented with ischemic stroke, 37 (12%) with TIA, and 8 (3%) with retinal ischemia; 80 (27%) patients presented with local symptoms and signs only, such as pain in the head or neck, pulsatile tinnitus, Horner syndrome, and cranial-nerve palsy ipsilateral to the sICAD; and 8 (3%) patients had asymptomatic sICAD that accompanied symptomatic dissection of a vertebral artery. A larger portion (41%) of the 88 patients who presented with only local symptoms or no symptoms were treated with aspirin alone than those who had presented with ischemic symptoms (29%). During the 3-month follow-up, only 1 patient (0.3%) had an ischemic stroke and only 13 (4.4%) had a cerebral or retinal TIA. All events occurred in the territory of the sICAD. Two patients (0.6%) had a symptomatic intracranial hemorrhage and 3 (1%) had major extracranial bleeding. None of the events correlated significantly with treatment with aspirin or warfarin.

**Conclusions:** After presentation, sICAD seldom causes cerebral or retinal ischemia, regardless of treatment with aspirin or warfarin.

**Reviewer's Comments:** As the authors admit, their study was not powered to detect differences between the treatment groups, because of the low frequency of ischemic events, but they cite 2 recent meta-analyses that reached the same conclusion they did. The ideal way to settle the issue would be a large randomized controlled trial, but the rarity of sICAD makes that unlikely to happen. Nevertheless, most of us will choose aspirin rather than warfarin for sICAD, because the data we have point that way. (Reviewer-Marc D. Winkelmann, MD).

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Keywords: Carotid Dissection, Antithrombotic Treatment

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