

Pacific Stroke and Neurovascular Center Newsletter: Updates from the 2016 International Stroke Conference (ISC)

Stroke's biggest meeting was held in Los Angeles from Feb 16-19. Last year's meeting was dominated by numerous positive trials of Thrombectomy for acute ischemic stroke. We had another very successful meeting this year and here are some of our selected highlights of this very exciting meeting.

4 results that could change current practice:

1. CREST and ACT 1 - Carotid stenting and endarterectomy were equivalent treatments for symptomatic (CREST) and asymptomatic (ACT 1) carotid artery stenosis
2. IRIS - Treating insulin-resistance in non-diabetics with pioglitazone prevented a second stroke
3. MR WITNESS - MRI can be used to establish a "brain clock" for wake-up strokes, enabling us to treat some wake up strokes with IV-tPA.
4. CLEAR III - In patients with intraventricular brain hemorrhage, infusion of t-PA into the brain ventricles cleared the intraventricular blood and improved mortality.

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Notable Negatives:

1. ICTUS-2 - This trial of hypothermia in acute stroke was stopped early because there was no endovascular arm. The next ICTUS study will test hypothermia in patients who also receive endovascular thrombectomy.
2. Virtual Reality rehabilitation for motor impairment after stroke had no benefit compared to intensive recreational therapy
3. ARUBA - Interventional treatment of unruptured arteriovenous malformations failed to show benefit in preventing hemorrhage and caused increased procedural morbidity and mortality compared to conservative management. 5 year follow up data were presented.

Exciting Prospects:

1. GAMES - In patients with large hemispheric strokes, IV glyburide which acts by blocking the SUR-1 sodium channel which is implicated in cerebral edema improved midline shift and outcomes
2. Natilizumab - This monoclonal antibody binds to leukocytes and prevents their migration into the brain. It's a very effective treatment of multiple sclerosis and leukocyte migration also seems to underlie an inflammatory response during ischemic stroke. Natilizumab given in acute ischemic stroke improved clinical outcomes. Interestingly, it did so without affecting MRI signs of stroke.

CREST and ACT-1 – In the CREST trial (Brott et al NEJM, 2010), we learned that stenting and endarterectomy were equivalent therapies for carotid artery stenosis. The composite outcome of stroke, heart attack, or death was equivalent and low for both treatments but there were more heart attacks with surgery and more strokes with stenting. At ISC, the 10 year outcomes were presented and showed continued durability and equivalence for these two treatments with very low rates of stroke and restenosis. While surgery was previously favored for asymptomatic carotid artery stenosis, last week's report of ACT-1 showed non-inferiority of stenting in asymptomatic carotid artery stenosis in patients with standard surgical risk. The next question is how medical therapy stacks up against these 2 treatments for asymptomatic carotid artery stenosis. This is the subject of CREST-2 which is now ongoing.

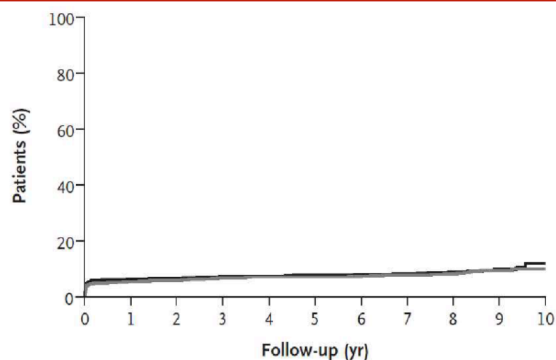
IRIS – There is established benefit to controlling blood sugar in diabetic patients to prevent index and recurrent stroke. However, the IRIS trial showed that pioglitazone prevented recurrent stroke and heart attack by 24% in patients with recent stroke or TIA who had insulin resistance but not diabetes. Pioglitazone also reduced the percentage of patients that went on to develop diabetes. These significant reductions came at the cost of causing weight gain, increased edema and shortness of breath, as well as increased fractures. However, it seems that carefully selected patients without history of CHF or osteopenia/osteoporosis could benefit significantly from the treatment.

MR WITNESS – In ischemic stroke, time is brain. IV-tPA has previously been shown to be a very effective treatment of acute ischemic stroke when given within 4.5 hours of stroke onset. But what if you don't know when the stroke started? MR Witness showed that the delivery of IV-TPA can be done safely in patients with MRI signatures of early stroke. This signature of early stroke on MRI is DWI signs of stroke but no signs of stroke on FLAIR images as shown below. The study reached it's primary endpoint of safety. Additionally, the IV-tPA treated patients had clinical outcomes that were comparable to t-PA treated patients in prior trials proving tPA's benefit.

CLEAR-III – The CLEAR-II trial infused t-PA into the ventricles of the brain through an EVD as a means of clearing intraventricular hemorrhage. The trial's outcome was measured radiographically and showed clearance of the intraventricular blood on CT scans. The trial was scaled up for CLEAR III which now shows a clinical benefit i.e. decreased mortality with intraventricular TPA. This benefit was isolated to patients with intraventricular hemorrhage greater than 20cc and when done within 48 hours of the inciting hemorrhage.

CREST Long Term Results for stenting vs. surgery for carotid artery stenosis reported by Dr. Thomas Brott from the Mayo Clinic. At 10 years, there was no difference between stenting and surgery for the composite outcome of stroke, MI, and Death.

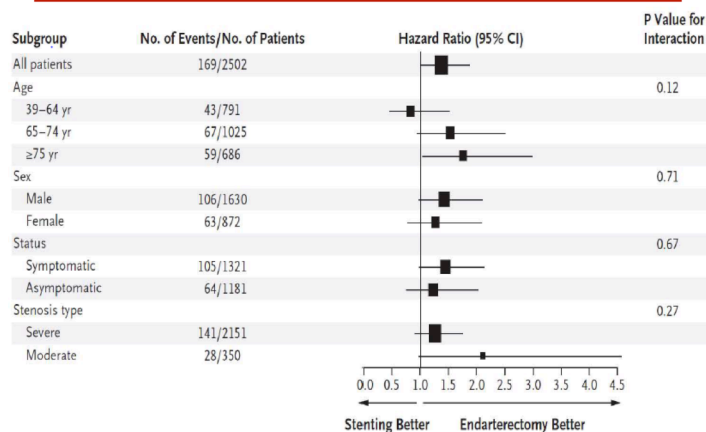
Primary Composite End Point



No. at Risk

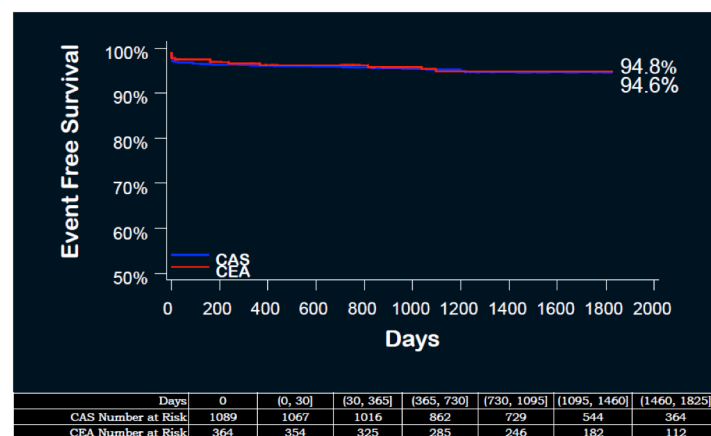
Endarterectomy	1240	1104	1036	949	833	736	695	620	438	243	66
Stenting	1262	1103	1041	972	884	774	738	676	477	264	68

Stroke or Death



ACT 1- Surgery vs. Stenting with embolic protection for asymptomatic carotid artery stenosis

Freedom from Death, Stroke and MI within 30 Days and Ipsilateral Stroke 31 Days to 5 Years



ACT 1

For asymptomatic, non-octogenarian, standard surgical and anatomical risk patients with significant carotid stenosis:

Carotid Artery Stenting is non-inferior to Carotid Endarterectomy for 30 day composite outcome of death, stroke, and myocardial infarction and 1 year ipsilateral stroke.

Stenting and Surgery had similar 5 year rates of stroke and survival

CLEAR-III Summary Slide

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) Results

Purpose: In patients with small intracerebral hemorrhage (ICH) and large intraventricular hemorrhage (IVH), evaluation of functional/benefit improvement of clot removal using extraventricular drainage (EVD) and recombinant tissue plasminogen activator (rt-PA).

Trial Design: N=500. 73 centers. Phase 3, randomized, multi-center, double-blinded, placebo-controlled efficacy trial. EVD+ (rt-PA) up to 12 doses every 8 hours vs. EVD+ placebo every 8 hours (normal saline) until the 3rd & 4th ventricles opened. Function was measured by modified Rankin Scale (mRS); blinded assessment: 30, 180 and 365 days.

Primary Endpoint: at 180 days, % mRS 0-3; **Secondary:** Mortality, residual blood @ 180 days

Trial Results 1 year	EVD+ (rt-PA) vs. EVD+ placebo	P value
Functional Outcome % mRS	3% increase - Primary Endpoint	NS
Mortality	10 % decrease	< 0.007
mRS	More clot removal (>20 ml): 10% more % mRS 0-3	<0.001

Conclusions: Less mortality was seen with EVD+ (rt-PA). More trials using stricter clot removal are needed to evaluate functional outcomes and mortality benefits.

Presented by: Daniel F Hanley, AHA ISC 2016, Los Angeles, Calif.
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MR Witness

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Shown at the right is the MRI signature of early stroke used in the MR WITNESS Trial. DWI is positive for stroke but FLAIR is not. Patients with this signature but uncertain last known normal time were safely treated with IV-tPA

