Trends-in-Medicine

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by Lynne Peterson

Quick Pulse

Trends-in-Medicine
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AMERICAN STROKE ASSOCIATION'S INTERNATIONAL STROKE CONFERENCE (ISC)

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There were no blockbuster drug or device trials released at this year's stroke meeting. Much of the "news" was "soft" and did not have implications for specific drugs or devices. However, the meeting did provide an opportunity to take a look at some of the technology and medications being used or considered in this field.

THE BIG PICTURE

Stroke patients still are not seeking treatment early enough. Each year, nearly a million Americans experience a new or recurrent stroke, and more than 150,000 of them die. The ***good news*** is that the death rate from stroke has declined about 25% over the last 10 years, but stroke is still the third most common cause of death. About 6 million stroke survivors are alive today. Stroke is more common in the U.S. than Europe, and a European neurologist suggested this is because of a higher rate of ever smoking, diabetes, and obesity in the U.S.

The ***bad news*** is that people still are not getting to the hospital soon enough. Despite numerous different campaigns over the years aimed at getting out the message about the signs and symptoms of stroke and the need for prompt treatment, delayed arrival at the emergency department (ED) keeps most ischemic stroke patients from receiving thrombolytic therapy – Genentech's Activase (alteplase) – which can dramatically reduce disability and improve the chances of recovery but which must be administered within three hours of symptom onset.

In a large study presented at the meeting, fewer than half (45%) of stroke or transient ischemic attack (TIA) patients – or their caregivers – called 9-1-1, and that can make a big difference in the outcome of their stroke. Dr. Ralph Sacco, chairman of the American Stroke Association Advisory Committee and a neurologist from the University of Miami, said, "A number of studies now have shown that calling 9-1-1 makes a difference in terms of urgent care…If you walk in or drive in, you won't get the same urgent care as calling 9-1-1."

University of Cincinnati researchers studied which symptoms prompt the public to call 9-1-1. They took a retrospective look at 2,056 stroke/TIA patients in 1999 in the five-county Cincinnati area, documenting all stroke symptoms from the medical record. They found that 45% of the patients used emergency medical services (EMS). Older age, higher estimated stroke severity, and hemorrhagic stroke were all independently associated with increased odds of calling 9-1-1. Dr. Dawn Kleindorfer, a neurologist from the University of Cincinnati Hospital, said,

"We found people either come early or they come 12 hours later. There is a gap, and that is not changing, so it is really a dilemma. There are all these campaigns trying to teach people (about the signs and symptoms), but we don't know if any of them work."

Stroke Symptoms Prompting 9-1-1 Call

Symptom	Increased likelihood of 9-1-1 call
Weakness	50% more likely
Confusion/decreased level of consciousness	60% more likely
Other symptoms	40% more likely
Numbness/tingling	40% ***less*** likely
Speech/language	No association with EMS use
Headache	No association with EMS use

Another study, this one by Mathew Reeves PhD DVM, an epidemiologist at Michigan State University, analyzed the records of 1,922 stroke patients at six Michigan hospitals to find what caused people to seek medical care quickly for a stroke/TIA. He reported that 19% of patients arrived at the hospital in <2 hours from symptom onset, 22% from 2-6 hours, and 59% >6 hours (or time unknown).

Reasons for Stroke Patients Seeking Medical Care Quickly

Measurement	<2 hours	2-6 hours	>6 hours/unknown
Total patients	19%	22%	59%
Chief complaints associated with arrival	Unilateral symptoms, speech difficulties	Non-headache pain	Visual disturbance, confusion, difficulty walking/balance Non-headache pain

The conclusion was that the public awareness campaigns need to be repeated regularly. People need to be continually reminded about the signs of stroke. Dr. Sacco said, "The key to any campaign is repetition…and some of our campaigns have changed…We need a message that is consistent and continues to get reinforced."

Gender differences also complicate the picture. The signs and symptoms of stroke that are present when a patient arrives at the hospital are often different between men and women. Nivedita Jerath, a fourth year medical student at the Mayo Clinic, presented a retrospective analysis of ischemic stroke patients between 1985 and 1989, and she found that women presented with more diffuse symptoms: generalized weakness, fatigue, mental status change, and disorientation. Men more commonly complained of parethesia (a "prickly" skin feeling), ataxia (clumsiness, lack of coordination), visual disturbances, and double vision.

Gender Differences in Stroke Signs/Symptoms

Sign/symptom	Women	Men
Symptoms		
Generalized weakness	21%	33%
Fatigue	21%	31%
Mental status change	24%	44%
Disorientation	21%	31%
Parethesia	24%	38%
Ataxia	61%	75%
Lack of coordination	61%	75%
Visual disturbances	6%	12%
Signs upon hospital arrival		
Language disorder	47%	37%
Fever	12%	5%
Sensory abnormalities	33%	44%
Nystagmus	5%	13%

The Softer News

Among the "softer" news items at the meeting were:

- **Cat cardioprotection.** A study by Dr. Farhan Siddiq of the University of Minnesota found that cat owners – but not dog owners – had a decreased risk of death from heart attack. They concluded, "Cats as pets may represent a novel strategy for reducing the risk of cardiovascular disease in high-risk individuals."

- **Stroke is more prevalent in the U.S. than Europe.** Mauricio Avendano PhD of the Netherlands reported that American adults have a higher prevalence of stroke than Europeans, which he suggested was due to higher rates of ever smoking, obesity, and diabetes in the U.S.

- **Stroke care varies by day and time.** Researchers from UCLA reported that weekend admissions for stroke in the U.S. between 1988 and 2004 were associated with a higher mortality rate than weekday admissions (10.1% vs. 7.9%, $p<0.001$). In another poster, researchers from Michigan State University, Mass General, and Duke reported that stroke patients who came to the hospital at night had higher in-hospital mortality than those who came in during the daytime.

- **No benefit to Pfizer's Aricept (donepezil) in a type of vascular dementia.** Dr. Martin Dichgans of Germany conducted a prospective clinical and MRI study of Aricept in 168 patients with CADASIL, an early-onset genetic form of subcortical ischemic vascular dementia less likely to be mixed with Alzheimer's disease. The trial missed the primary end-point, showing no effect on V-ADAS-cog.

- **Dietary fiber may reduce stroke severity.** Researchers from Massachusetts General Hospital said insoluble dietary fiber intake appears to be an independent predictor of stroke severity and disability.

- **Caffeinol may boost efficacy of IV tPA.** University of Texas Health Science Center, Houston, researchers continue to investigate, albeit slowly, the use of a 2-hour infusion of caffeinol – a combination of caffeine (8-9 mg/kg) and ethanol (0.3-0.4/kg) – after tPA (tissue plasminogen activator). The caffeinol research has been going on for 7-8 years, and so far only ~33 patients have been treated with this approach. In the latest 10 patients, reported on at ISC, a significantly higher percentage of caffeinol infusion patients had mRS 0-1 at hospital discharge vs. historical tPA ($p<0.05$). *Eventually*, researchers plan a Phase III trial, but that is unlikely to begin any time soon.

THROMBOLYSIS: TISSUE PLASMINOGEN ACTIVATOR (tPA)

GENENTECH'S Activase (alteplase)

Activase is the only FDA-approved drug to treat stroke, but it must be administered within three hours of symptom onset to be effective. By some estimates, fewer than 3% of all ischemic stroke patients get IV tPA, and fewer than 25% ischemic stroke patients who do get to the emergency room within three hours actually receive tPA. *Why don't more patients get intravenous(IV) tPA for ischemic stroke even when they do arrive at the hospital within the 3-hour window?* Experts offered a variety of reasons, including:

- **Legal liability** – a physician concern that they would get sued if a patient died after tPA administration. However, experts said this is changing, and in some cases there is now a legal liability if tPA is not administered. Dr. Todd Crocco of the West Virginia School of Medicine said, "In our setting, we don't have as much of an issue with that…We have reached a comfort zone …but it is fair to say there are emergency department physicians around the country who were in practice before tPA became approved, and you are talking about a new treatment intervention they have to learn, and there is a certain amount of time these physicians need to learn." Dr. Sacco said, "You can argue both sides. You can argue being risk averse, and you can argue withholding treatment."
- **Need for 24-hour CT interpretation.**
- **Neurologists not wanting to be on call 24 hours a day.**
- **Cost to the hospital.**

Can the 3-hour window be extended? The hope has been that another agent, a less time-sensitive agent – with a wider window, perhaps 0-6 hours after onset of symptoms – would be found, but so far the search has been fruitless and frustrating. In the meantime, even without data to support it, some stroke centers around the world give tPA outside the 3-hour window based on CT, MRI, ultrasound, or angiography, and they use different delivery routes (IV, intra-arterial, etc.). Some sites also use GP IIb/IIIa inhibitors in lieu of tPA after 3 hours.

The latest trial to fail to show efficacy of IV tPA after 3 hours was EPITHET, which was presented at ISC and published simultaneously in ***The Lancet***. This randomized, double-blind, placebo-controlled Phase II trial, conducted in Australia, New Zealand, and Europe, looked at 101 patients with MR perfusion-diffusion mismatch. It was an investigator-driven trial, funded by the Australian National Health and Medical Research Council (NHMRC), the National Stroke Foundation, and the Heart Foundation of Australia.

The researchers, led by Dr. Stephen Davis of the University of Melbourne in Australia, had hoped to show that tPA is effective in patients with penumbra (hypoperfused, but not

Results of Phase II EPITHET Trial

Measurement	tPA n=37	Placebo n=43	p-value
Mean NIHSS	13.7	12.8	Nss, 0.39
Mean time to treatment	293 minutes	291 minutes	0.87
Results			
Primary endpoint #1: Mean growth ratio at 90 days	1.23	1.78	Nss, 0.239 (a non-significant 30% reduction)
Secondary endpoint #1: Median infarct relative growth	1.18	1.79	Nss, 0.054
Secondary endpoint #2: Median absolute infarct growth	4.1 mL	28.7 mL	Nss, 0.126
Secondary endpoint #3: Mean difference in cube root volume	0.50	0.75	Nss, 0.415
Reperfusion assessed			
	n=34	**n=43**	**p-value**
Reperfusion ≥90%	56%	26%	0.010
Median reperfusion	91%	65%	0.045
Recanalization assessed at Day 3-5			
	n=19	**n=28**	**p-value**
Recanalization	74%	57%	Nss, 0.356
Clinical outcomes			
	n=42	**n=43**	**p-value**
Good neurological outcome (NIHSS improvement ≥8 or 0,1)	50%	37%	Nss, 0.278
Good functional outcome (mRS 0-2)	45%	40%	Nss, 0.663
	Reperfusion ≥90% n=30	**No reperfusion ≥90% n=47**	**p-value**
Recanalization	3.2%	N/A	Nss, 0.054
Median reperfusion	91%	65%	0.045
Efficacy based on reperfusion			
	Reperfusion ≥90% n=30	**No reperfusion ≥90% n=47**	**p-value**
Geometric mean infarct growth	0.79	2.25	0.001
Mean relative infarct growth	0.86	2.07	<0.0001
mRS 0-2	63%	32%	0.01
NIHSS improvement ≥8 or 0,1	73%	27%	<0.01
Efficacy based on Recanalization			
	Recanalization n=30	**No recanalization n=47**	**p-value**
Mean infarct growth	1.45	3.49	0.05
mRS 0-2	50%	18%	0.03
NIHSS improvement ≥8 or 0,1	53%	12%	<0.01

irreversibly damaged, tissue surrounding the ischemic core) in the 3-6 hour time window, but the trial missed its primary endpoint, failing to show a statistically significant reduction in infarct growth. Experts warned that any positive news in the secondary endpoints is hypothesis-generating at best, but researchers were still encouraged that the trial showed a "strong trend" toward infarct growth attenuation and significantly increased reperfusion with tPA in the 3-6 hour period and insisted that a better-designed Phase III trial is warranted.

The researchers wrote: "The findings lend support to the use of reperfusion as a robust surrogate for clinical outcomes… More evidence is needed about thrombolysis in non-mismatch patients. EPITHET provides further evidence that the time window for thrombolysis treatment might be extended beyond 3 hours in some patients. These results emphasize the need for Phase III trials with primary clinical endpoints in this time window (e.g., IST-3 and ECASS-3)." The results of the European ECASS-3 study will be available in Fall 2008, and the international IST-3 trial will be finished in 2034 (*sic*).

In an accompanying editorial in ***The Lancet***, Dr. Peter Schellinger of Germany criticized the trial for using CT instead of MRI to select patients and for assessing reperfusion at Day 3-5, which he called "suboptimum for this surrogate endpoint because many patients already have spontaneous recanalization by this time." Dr. Schellinger also cautioned that the positive secondary outcomes with tPA didn't translate to better outcomes for those patients. However, Dr. Schellinger still holds out hope that tPA will be effective beyond 3 hours in this subgroup of patients. For future trials, he urged researchers to develop standardized definitions of mismatch and perfusion and to conduct a randomized, international, placebo-controlled trial based exclusively on MRI mismatch.

GENENTECH's TNK-tPA (tenecteplase, TNK) vs. GENENTECH's Activase (alteplase, tPA)

Dr. Carlos Molina of Spain reported on the TNK-TPA study of 122 stroke patients which found that TNK, which already has FDA approval to treat acute myocardial infarctions (AMIs), unblocked the middle cerebral artery (MCA) faster and more completely than tPA without increasing the risk of brain hemorrhage. The tPA was given 10% immediately and the balance in a one-hour infusion vs. a one-time infusion for TNK.

Results of TNK-TPA Study

Measurement	TNK n=42	tPA 0.9 mg/kg n=80	p-value
Time from bolus to beginning of recanalization	27 minutes	35 minutes	Nss, 0.11
% recanalization at 2 hours	69%	53%	0.028
Complete recanalization at 2 hours	42.4%	33.4%	0.014
Symptomatic ICH	2.3%	3.7%	---
Asymptomatic ICH on CT	28%	21%	Nss, 0.089
>4 point improvement in NIHSS score at 24 hours	63%	51%	0.041
"Dramatic clinical recovery" at 24 hours	24.5%	11%	---
mRS <2 at 3 months	66%	52%	0.039

Transcranial doppler boosts tPA efficacy

One of the most interesting findings at the meeting may have been a study by Dr. Georgios Tsivgoulis and colleagues at the University of Alabama at Birmingham. They conducted a retrospective meta-analysis of six randomized Phase I and II trials of ultrasound-enhanced thrombolysis, looking at the impact of doppler on tPA. They found that ordinary transcranial doppler (TCD) ± microspheres – but not transcranail color-coded duplex doppler (TCCD) ± microspheres and not low frequency ultrasound (LFUS) – had a signal of ***therapeutic*** effect, not just a diagnostic effect. A Phase III trial comparing tPA ± TCD is now in the planning stage.

tPA and Transcranial Doppler

Measurement	tPA n=105	tPA + TCD n=78	tPA +TCCD n=27	tPA + LFUS n=14
ICH	2.9%	3.8%	11.1% (p=Nss)	35.7% (p=0.002)
Recanalization	17.2%	37.2% (p=0.003)	26.9% (p=Nss)	Study stopped

ImaRx Therapeutics, which makes microbubbles for use with doppler, also had a poster on the effect of ultrasound in stroke. A researcher speculated, "The ultrasound has to be in the 1-2 MHz range, which has been shown to be safe in the diagnostic field…It appears to enhance the transport of tPA to receptor sites...but perhaps we need more power than the doppler level."

NOTE: Ultrasound is used to liquefy cataracts, but the power for that is substantially higher. In a stroke patient, the thought is that doppler ultrasound "jiggles" the clot and makes it more "porous" so the tPA gets in better and can dissolve it better, not that it liquefies the clot.

BLOOD PRESSURE AND INTRACRANIAL HEMORRHAGE (ICH)

Should blood pressure be treated to prevent hematoma expansion or cardiac decompensation? Experts are divided, but Dr. Adnan Qureshi of the University of Minnesota argued that acute hypertensive response probably should be treated, "We think blood pressure lowering in acute ICH appears to be safe…but we don't know if it reduces hematoma expansion or improves outcomes. We need an efficacy clinical trial…We think keeping systolic blood pressure <180 mm Hg may be the way to go; that is guideline-supported and safety validated …but more aggressive targets (may be beneficial)."

The ATACH trial at 10 U.S. sites looked at three step-down blood pressure goals: 170-200, 140-170, and 110-140. Enrollment was completed in all three cohorts, and the safety stopping rule was not activated in any tier. The study found aggressive systolic blood pressure reduction to ≥110 and <140 for 24 hours was well tolerated, with a low rate of safety events and low in-hospital and 3-month mortality.

However, Dr. Qureshi pointed out that this trial still doesn't answer the question of whether the blood pressure reduction reduces hematoma expansion. Thus, the NIH-funded ATACH-II trial with 200-250 sites is being planned to look at that in conjunction with aggressive blood pressure lowering.

What is the best way to address blood pressure in this situation? "The only data we have so far is with IV nicardapine (PDL Biopharma's Cardene), but that doesn't necessarily mean another agent wouldn't be the same or better." One drug on the horizon that might be useful: The Medicine Company's clevidipine.

Australian researchers also reported that early intensive blood pressure lowering is well tolerated and appears to attenuate the growth of hematoma in ICH. In the investigator-initiated, open-label, blinded-outcome, randomized INTERACT trial, they studied 404 patients from 44 hospitals in Australia, China, and Korea with CT-confirmed ICH and elevated systolic blood pressure (SBP ≥150 and ≤220 mm Hg) within 6 hours of ICH. Patients were randomized to either intensive blood pressure lowering (target SBP <140 mm Hg) or to American Heart Association (AHA) guideline-based blood pressure lowering (target SBP 180 mm Hg). There was no evidence that the intensive approach increased the risk of serious adverse events or a poor outcome at 90 days.

Results of INTERACT Trial

Measurement	Intensive SBP lowering	AHA guideline SBP	p-value
SBP at 1 hour	13.3 mm Hg lower	---	<0.0001
Mean hematoma growth	33.6 ml (22.6% lower)	13.7 ml	Nss, 0.06
"Substantial" hematoma growth (>33% or 12.5 ml)	36% lower	---	0.05

HYPOTHERMIA

Therapeutic hypothermia – cooling to 32-34° C (89.6-93.2° F) – for both stroke and heart attacks has been controversial. American Heart Association (AHA) treatment guidelines recommend the use of therapeutic cooling as part of the critical care procedures for patients with out-of-hospital cardiac arrest following ventricular fibrillation, but there is no CMS or insurance reimbursement for cooling; hospitals have to absorb the cost. An expert said, "I don't think any of the companies will ever try for specific reimbursement. The odds of that are just not very good. It is not the right mountain to climb."

One of the issues in cooling stroke patients that is different from cooling cardiac arrest patients is that the stroke patients are generally awake. An expert explained, "When they are awake and they are cooled, they shiver, which is a very negative issue."

Japanese researchers reported that induction of very mild hypothermia with ice packs plus an oral NSAID can be useful in the treatment of acute embolic stroke within 3-12 hours. They cooled patients to a mean temperature of 36.4° C (97.5° F) with a combination of 60 mg of Sankyo's Loxonin (loxoprofen sodium), which is not available in the U.S., plus ice packs applied to the axillary and femoral arteries.

Results of Japanese Study of Very Mild Hypothermia Therapy

Measurement	Cooling to 36.4° C n=20	Historical control with no hypothermia (37.1° C) n=60	p-value
Maximum midline shift on CT	3.7 mm	8.2 mm	<0.01
Massive hemorrhagic infarcts	15%	33%	Nss, 0.159
Improvement in NIHSS at 30 days	8.8	5.1	<0.05
mRS at 90 days	---	---	Nss
Barthel Index ≥75 at 90 days	35%	13%	<0.05

Several companies are trying to develop this market, including:

- **ALSIUS's CoolGard and Thermogard.** Alsius is the market leader in the U.S., and that's where Alsius started.

- **CARDIUM THERAPEUTICS/INNERCOOL THERAPIES' Celsius Control System.** This endovascular catheter-based system has FDA 510(k) clearance for use in inducing, maintaining, and reversing mild hypothermia in neurosurgical patients, both in surgery and in recovery or intensive care. The system also has FDA approval for use in cardiac patients in order to achieve or maintain normal body temperatures during surgery and in recovery/intensive care as well as for adjunctive treatment of fever control in patients with cerebral infarction and intracerebral hemorrhage.

- **MEDIVANCE'S Arctic Sun.** This is a non-invasive cooling approach. An expert said, "The cooling space is not so much data-driven as sales-driven…There's never been a trial really…It is easy to get non-specific approval (from the FDA), but it is very difficult to finance a study for a specific indication…Cardiac arrest has been the best application. One reason that has been successful is there are a whole series of cases of patients dead on arrival at the hospital who (with cooling) walk out of the hospital and go back to work a week later." Medivance is the market leader in Europe, which he said is because that's where the company started.

- **RADIANT MEDICAL's Reprieve Endovascular Temperature Therapy System.**

➢ **VELOMEDIX.** This portable, non-invasive device is intended for emergency room use. It is not yet FDA-approved. An official said the advantage is that it "works 75% faster than Alsius." Pricing is expected to be "competitive" to Alsius.

THROMBECTOMY

Most mechanical clot removal device procedures are performed by neurointerventional radiologists, not neurologists, so this was not a key meeting for determining the outlook for the thrombectomy devices. However, the results were presented at the International Stroke Conference from the pivotal trial of Penumbra's Penumbra System, on which the FDA based its decision to approve Penumbra on December 28, 2007. Penumbra now competes with Concentric Medical's Merci Retriever.

PENUMBRA's Penumbra

Penumbra is a microcatheter-based thrombus aspiration and removal/retrieval device for intracranial clots. The results of the pivotal 125-patient, single-arm Phase II Penumbra study used for FDA approval was first made public at ASA. It was conducted at 24 international sites. Patients who presented <3 hours from symptom onset had to be ineligible for, or refractory to, tPA. Oddly, the trial did not have a principal investigator. Dr. Cameron MacDougall of Barrow Neurological Institute in Phoenix AZ, one of the investigators, presented the results.

90-Day Results of Phase II Penumbra Trial

Measurement	Penumbra
Primary endpoint #1: Target vessel revascularization to TIMI-2 or TIMI-3	82%
Primary endpoint #2: Procedural serious adverse events	3.2% *
Favorable outcome (4-point improvement on NIHSS at discharge or a 30-day mRS ≤2)	41.6%
ICH at 24 hours	28% (11.2% symptomatic)
All-cause mortality at 30 days	26.4%
All-cause mortality at 90 days	32.8%
90-day mRS ≤2	25%
Symptomatic ICH	11.2%
Asymptomatic ICH	16.8%

*** None related to device malfunction or breakage.**

CONCENTRIC MEDICAL's Merci Retriever

This system uses a catheter to deliver a corkscrew-like coil that snares clots and "retrieves" them from an intracranial artery. There are three parts to Merci – a retriever, a microcatheter, and a balloon guide catheter.

Dr. Raul Nogueira of Massachusetts General Hospital presented a pooled, retrospective analysis of the MERCI and MULTI-MERCI trials of Concentric's Merci Retriever. He reported that (1) patients with abnormal hemostasis who undergo thrombectomy do not appear to be at significantly higher risk for ICH or other serious complications, and (2) successful revascularization appears to be associated with an overall improvement in clinical outcomes and lower mortality.

Pooled, Retrospective Analysis of MERCI and MULTI-MERCI Trials

Measurement	Abnormal hemostasis * n=35	Normal hemostasis n=270	p-value
Baseline (well-matched except for these)			
Onset to groin	3.7 hours	4.4 hours	0.027
Failed IV tPA	0	18%	0.002
Efficacy			
Post-retriever revascularization	51.4%	51.9%	Nss
Final revascularization	60.0%	65.2%	N/A
mRS ≤2 at 90 days	9.4%	35.3%	0.002
Clinically significant serious adverse events	1.4%	5.6%	Nss, 0.25
Mortality at 90 days	40.0%	37.9%	Nss, 0.85

*** INR >1.7 of PTT >45, or platelet count <100,000/uL**

Penumbra vs. Merci

How does the Penumbra data compare to the results with Concentric's Merci? A Penumbra official said, "Concentric did a lot to get the field going, but we came behind with a device with some advantages…Ours uses a proximal working position, so it doesn't have to cross the lesion. There is better visualization, and we have three different size catheters, allowing access to a wider range of vessels…At the end of the day what will make people choose Penumbra over Merci is ease of use and less risk." He also claimed that device-related serious adverse events were lower with Penumbra (3.2%) than in the MERCI-1 trial (5%).

Concentric CEO Gary Curtis pointed out that there is much more – and longer – data on Merci. Concentric had planned to do an IPO earlier this year but cancelled it. An official said this was because of "marketplace softening." He said the company's quarter-to-quarter growth was 38%, adding, "We want to be >50% to do an IPO."

Asked what has held doctors back from using Merci more often, a Penumbra official said, "Sales have been less successful than anticipated. I think people felt it needed to be more (procedurally) successful (an 80%-90% success rate), and that has been difficult for them. But they have iterated, and the success rate has improved…Neurointerventionalists are very concerned with safety, and they still need to be convinced of the safety of these devices, and the outcomes."

What is the experience in Europe? Concentric has had a C.E. Mark since 2002, but only started selling in Europe in late 2005. Penumbra started selling in Europe in June 2007, though the company had a C.E. Mark for some time before it started selling. Officials of both companies declined to speculate on market share in Europe. A Concentric official said, "Penumbra has not been aggressive in Europe as it waited for U.S. approval."

Penumbra is priced slightly higher than Merci, at ~$5,500 per case vs. ~$5,000 per case for Merci. However, the DRG for a stoke patient who goes to the interventional suite is ~$27,000 vs. ~$5,700 for a stroke patient who is not sent to the interventional suite.

Penumbra has its own direct sales force, but officials wouldn't say how big that is. A Concentric official said they have 14 sales reps now and expect to have 24 by the end of 1Q08 – plus six stroke market development managers and 6 other managers. Initially, Penumbra reportedly plans to target the ~250 neurointerventional specialists in the U.S., but Concentric Medical is in virtually all these sites already. A Concentric official said, "We sell now to hospital CEOs. It is not a cath lab sell any more."

Will Penumbra expand the market or simply cannibalize Merci sales? Officials of both Penumbra and Concentric predicted that having a second player in the market would expand the market. A Penumbra official said, "We are more about market expansion than head-to-head competition." A Concentric official said, "My belief is that a second company will grow the market with us…Growth will come mostly from increased use by existing customers."

Several neurointerventionalists interviewed at the meeting said they were waiting for this data before trying Penumbra. They said that if the data were positive, they would try Penumbra. Then, if it performs as promoted, they predicted that it would both expand the thrombectomy market (slightly, not dramatically) and cannibalize Merci use. Comments included:

- "This is a single-arm trial without a control and without a principal investigator. I'm not sure the results will even be accepted for publication by one of the medical journals…We will not try Penumbra based on this trial."
- "The DRG for tPA alone is $8,000, but if you use Merci, the DRG is $23,000…Interventionalists have experience with Merci, and Penumbra didn't have many sites. There was not a big enough difference in the data (between Penumbra and Merci) to sway me. Is there an advantage to Penumbra? In some cases, Penumbra could be easier to use, but with doctors who do a lot of procedures, that isn't an issue…The increased attention (with a second company) has already increased the number of devices, but it is still a small market."
- "I have more experience with Merci, but I've tried Penumbra. Merci only can go to mid-size arteries, not smaller arteries and branches. Penumbra can go much smaller…Penumbra will expand use of retrievers, but I'll probably use both devices…I did 33 patients in the last 2.5 years, but there were 10-12 patients I couldn't do, and that is where Penumbra will make a difference. But the Merci data are very strong, so Penumbra won't replace it completely."
- "I'll use both; I want to put every tool in the tool shed. Penumbra is sexy, a nice system. If it does everything the company says it does and there is a lack of complications, then it will be a better mousetrap. But there will still be clots which won't respond to Penumbra's style of retrieval, so there will still be a role for Merci, especially with foreign body retrieval (e.g., errant coils)."

COILS FOR ANEURYSMS

As with mechanical clot retrieval devices, coils are generally used by neurointerventional radiologists, not neurologists, so information on coil preferences was limited at this meeting. The key meeting for coils is probably the Society of Neurointerventional Surgery (SNIS), which is scheduled for July 28-August 1, 2008, in Lake Tahoe. However, sources estimated that coils are increasing slightly in use vs. clips. A Virginia doctor said, "Patients (and their families) actually ask about coils."

Whether or not there is a change in the average number of coils used per procedure could not really be determined from these sources. The choice of coil often has no affect on the choice of microcatheters or guidewires; doctors insisted that they often mix and match.

BOSTON SCIENTIFIC

A study by University of Cincinnati researchers compared Boston Scientific's GDC and Matrix coils to MicroVention's HydroCoil in 100 consecutive patients with ruptured aneurysms (5-15 mm). They found: "Data other than coil surface coating attenuates aneurysm recurrence."

Comparison of Bioactive Coils

Measurement	GDC n=31 *	HydroCoil n=26	Matrix n=43 *
Re-treatment	6.4%	11.5%	20.9%

*** 1 patient got a Boston Scientific Neuroform stent.**

EV3's Axium

Doctors said the difference with this coil is the way it detaches, but there was little excitement about it. Doctors described this as very soft but pointed out that there is not a lot of follow-up data on it. One said, "It does have an advantage in delivery. It is quicker to deliver, so it is good for in-patients."

MICRUS

➢ **Cerecyte.** At a Micrus breakfast, Dr. Beverly Aagaard Kienitz of the University of Wisconsin reviewed the status of the prospective, non-randomized, multicenter Cerecyte registry. The registry is blinded until 100 of the 250 planned patients have reached full 12-19 month follow-up. She said that in the first 174 patients, most doctors were coiling with 100% Cerecyte, and the majority were doing this without a balloon. No deployment issues occurred, and 92% of patients had no complications of any kind. There have been 3 intra-procedural hemorrhages, which she called "a very reasonable number," as well as 3 thromboembolisms (2 with no sequelae, and 1 stroke with sequelae). She concluded, "From our own personal experience, we have had very good results with Cerecyte." A Micrus official said the registry is expected to complete enrollment in spring 2008.

Dr. Italo Linfante of the University of Massachusetts Medical School provided a retrospective review of his hospital's database. Of 194 stroke patients, 51 patients got Cerecyte either alone or in combination with other coils. He said, "I'm very excited about Cerecyte…Personally, I like Cerecyte because it provides very stable framing. It is anatomically compliant to conform to the aneurysm shape…It really adapts to the anatomy."

➢ **Cashmere.** Sources said that this coil is preferred by doctors who are less experienced. As one explained, "If they have no experience, they want to use as many coils as possible."

Comments

Other comments on coils included:

- "We use ~90% Cerecyte. We use it everywhere we can. On average, we use 8-9 per patient, but that hasn't changed from last year…Micrus lets us get denser packing, but I don't particularly like the very long Cerecyte coil."
- "The steerable (Micrus) catheter is very early. It will have advantages in certain aneurysms, but it will have limited utility. Every aneurysm doesn't need filling with the current technology level."
- "In the early days Target was connected to users. At Boston Scientific, it (coils) just became another product line. Micrus is now like Target was in the early days… The steerable (Micrus) catheter has a helpful, deflatable tip, but it isn't as helpful as we had hoped."

INTRACRANIAL STENTS

Again, this was not the meeting to determine stent trends. However, sources did emphasize that for intracranial purposes self-expanding stents are preferable to balloon-expandable stents.

BOSTON SCIENTIFIC's Neuroform

A neurointerventionalist said, "I use stents, but infrequently. When I do, it is generally Neuroform. Most balloon expandable (intracranial) stents have been knock-offs of coronary stents, not 'designed for the brain,' so they are difficult to maneuver."

JOHNSON & JOHNSON's Enterprise

This self-expanding nitinol stent is designed for wide-neck aneurysms. The advantages are its smaller delivery catheter, closed cell design, and good markers for precise placement. A J&J sales rep explained that it can be recaptured if it is partially deployed. A physician said, "We've begun to use Enterprise over (Boston Scientific's) Neuroform because we can get it where we want. The delivery system is more flexible."

TESTING

ACCUMETRICS' VerifyNow

The concept of measuring platelet aggregation – to measure the effects of aspirin, Sanofi-Aventis's Plavix (clopidogrel), or a GP IIb/IIIa inhibitor such as Johnson & Johnson's ReoPro (abciximab) – with a point-of-care test, even if that test is done in a hospital's central lab, sounds appealing, but neurologists simply are not interested. An Accumetrics official said that currently the device is mostly being used for pre-surgical applications, "Currently, we have 400 sites in the U.S. using VerifyNow…About two-thirds of neurointerventionalists use VerifyNow today…We hope to penetrate the cath labs next. We are waiting for big studies. Next month the 10,000-patient GRAVITAS drug-eluting stent trial will begin, and that is using VerifyNow. We hope there will be results by the end of 2009, perhaps at TCT."

Neurologists questioned at the meeting about VerifyNow showed little enthusiasm for the test:

- *Florida:* "We might start using it if and when we start a neurointervention program. We are looking to hire a neurointerventionalist."
- *North Carolina:* "There is not a single trial showing treatment decisions based on these measurements change patient outcomes."
- *Minnesota:* "There are a bunch of platelet aggregation tests. How to use them in clinical practice still needs to be clarified. It is an emerging application that is not quite there yet."
- *Texas:* "VerifyNow is in our ER lab…It is good for helping to determine the dose of ReoPro in acute stroke patients, but it is a niche use…We don't use it for secondary prevention. You don't know if the patient is compliant with the aspirin and Plavix they are supposed to be taking, or when the test was done vs. the last dose of Plavix."

- *Alabama:* "No, no, no, we don't use it, and we don't plan to start. We don't know the reproducibility of the results, and there are no clinical correlates."

CVRx's Rheos Baroreflex Hypertension Therapy (BHT) for blood pressure reduction

This is a device therapy for treatment-resistant hypertension. While it is reminiscent of Cyberonics' VNS (vagus nerve stimulation), it works differently: a pacemaker-type generator is implanted in the chest, with a lead running up both sides of the neck and wrapped around the carotid bulb. The leads are positioned over the left and right carotid baroreceptors. The device energy-activates the baroreceptors, generating afferent nerve impulses that travel to the cardiovascular control center in the brain, which perceives the signaling as an increase in blood pressure that needs to be corrected and then modulates the autonomic nervous system and neurohormonal activity, reducing blood pressure an average of ~20 mm Hg, though company officials have pointed out that some patients see drops of 30-40 mm Hg. An external programmer can adjust the energy delivered, which presumably can boost the efficacy.

The 300-patient pivotal RHEOS trial is underway. To be enrolled, patients must be stable for at least 2 months on ≥3 medications, including a diuretic, and still have systolic blood pressure ≥160 mm Hg and diastolic pressure ≥85 mm Hg. The trial has two primary endpoints, both of which must be met:

1. 10 mm Hg reduction in systolic blood pressure (SBP) at 6 months.
2. Sustained systolic blood pressure reduction at 12 months. The key reason for this time point is to gain some assurance that the brain doesn't stop responding to the activation of the carotid baroreflex signal, causing the effect to wane with time.

Two-year follow-up data from the initial feasibility trial are expected at the American College of Cardiology meeting in March 2008. DEBUT, the pivotal European trial also is underway, with a similar design to the RHEOS trial, but no announcement has been made as to when that data will be presented.

While this therapy is being developed to treat refractory patients as an add-on to maximum medical therapy, the company obviously and openly hopes and expects that Rheos BHT will be used off-label in lieu of medications, a much larger market. This approach raises significant regulatory questions as non-CVRx sources all agreed that the FDA is likely to take a dim view of this. A CVRx source said, "After commercialization, one of the things we will look at is taking patients off medications…We expect that patients would get this (device) to reduce or eliminate medications."

Asked if this means patients would be taken off medications before their blood pressure was normalized – say in a patient whose blood pressure was reduced from 190 to 150 mm Hg, the CVRx source said, "We leave that to the physicians, but potentially this device could be used to get patients off medications without getting them to normal…And some patients have normal SBP higher than 120. The goal really is to minimize the risk of diastolic heart failure, chronic kidney disease, stroke, or TIA. A patient dropping from 190 to 150 mm Hg might want to get off a medication because of the side effects of that drug (for example, a beta blocker)…But we don't want patients to go off their medications while in our trial."

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