ISC Reveals New Findings on Stroke Risks and Therapies

Quite a few research papers of potentially significant relevance to clinical practice were presented last month at the American Stroke Association's International Stroke Conference in New Orleans. Here are some of the highlights:

■ Intravenous tissue plasminogen activator used past the three-hour window in patients with mismatch on diffusion- and perfusion-weighted imaging didn't show lower infarct growth, according to a new phase II trial. However, there were some positive findings in secondary end-points such as relative growth and the proportion of patients with no infarct growth. Reperfusion was significantly increased.

Administering tPA "was non-significantly associated with lower infarct growth and significantly associated with increased reperfusion in patients who had mismatch," the study authors wrote. "Because reperfusion was associated with improved clinical outcomes, phase III trials beyond 3h after treatment are warranted" before any change in clinical practice is recommended. The geometric mean infarct growth was 1.24 in tPA patients and 1.78 for placebo. The median relative infarct growth was 1.18 with tPA and 1.79 with placebo. The study was published online in *Lancet Neurology* February 22nd.

■ Two studies reinforced the idea that stroke mortality is higher during night and weekend visits to hospitals. The first report, by Matthew J. Reeves, PhD of Michigan State University, discovered that all patients who came in after-hours and on weekends had a higher risk of in-hospital mortality, but was especially high for hemorrhagic stroke patients. The second study, by David S. Liebeskind, MD of UCLA, demonstrated that patients with any stroke had a higher mortality rate on a weekend versus a weekday.

Half of stroke patients in Dr. Reeves' study were treated during off-hours. Based on this, his team calculated the population-attributable risk of this differential between on- and off-hours was roughly five percent. In theory, getting rid of the difference between on-hours and off-hours could lower the mortality rate by five percent, Dr. Reeves said.

■ Lowering blood pressure in the 60 to 70 percent of people who became hypertensive directly after acute stroke decreases three-month mortality, while not compromising serious adverse effect risk or augmenting stroke severity, according to a new study. Results from the hypertension group of the Control of Hypertension and Hypotension Immediately Post Stroke (CHIPPS) demonstrated that active blood pressure-lowering treatment—lisinopril or labetalol—lowered mortality at three months compared to placebo group.

The study followed 179 randomized patients who endured a hemorrhagic or ischemic stroke in the previous 36 hours and also had hypertension (systolic blood pressure above 160mm Hg). Those in the placebo group were more than twice as likely to die three months following stroke compared to the treatment group.

■ Caffeinol, an agent with neuroprotective capabilities that combines caffeine and ethanol, can be safely given to patients after tPA and has some sign of improved outcome in ischemic stroke patients when compared to historical controls, a phase I study finds.

The good news was twofold: (1) no increase in hemorrhagic transformation was seen in the 10 patients who underwent tPA, and (2) a larger ratio of these patients were found to have little or no disability compared with historical cohort, as measured on the Modified Rankin Scale (equating to a 0 or 1). Dosing, safety and short-term outcome with caffeinol as an adjunct to tPA in acute stroke patients were tested. The authors called the small study "hypothesis-generating" and are prepared to move forward with a randomized trial to study tPA versus tPA plus caffeinol.

■ Stroke risk is quadrupled in elderly patients by unintentional recurring daytime dozing, and a large increase in risk of other vascular events is also associated with this finding, according to a study of 2,153 individuals that correlated scores on the the Epworth Sleepiness Scale with vascular disease events.

People with excessive daytime sleepiness were 4.5 times more likely to have a stroke compared to those who didn't nod off in the daytime. The study is the first (according to its lead author) to demonstrate that daytime sleepiness is an independent risk factor for stroke and all vascular events. A 60 percent increase in risk for all vascular events and a 2.6-fold increase in risk of stroke was seen in patients with daytime sleepiness who reported "some dozing."

■ It's long been known that stroke is more common in the US than Europe. What is understood is more limited, but a higher rate of risk factors and difficulty obtaining health care may be two major reasons. Data from 2004 on 13,667 US citizens and 30,120 people in 11 countries from Europe showed that men from the US were 61 percent more likely to have a stroke than their European counterparts. American women had nearly double the risk as European women to suffer a stroke.

Most of the gap in stroke risk is among relatively poor Americans who were much more likely to have a stroke than poor Europeans, whereas the gap in stroke prevalence is less marked between rich Americans and rich Europeans, the study author says. He also lists universal health care and countries with Mediterranean diets as possible reasons for the lower rates in European countries. **PN**

PCP Group Unveils Dementia Guidelines

The American College of Physicians and American Academy of Family Physicians has developed a set of guidelines on dementia treatment that says, "no convincing evidence demonstrates that one therapeutic treatment is more effective than another." The lead study author says the drugs' benefits are very modest.

Published online March 4th in *Annals of Internal Medicine*, the group reviewed 96 studies of the five FDA-approved drugs for dementia and looked for evidence the drugs improved cognition, global function, behavior, mood and quality of life. They then devised three recommendations for primary care physicians.

Recommendation 1: "Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment. (Grade: weak recommendation, moderate-quality evidence.)"

Recommendation 2: "Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. (Grade: weak recommendation, low-quality evidence.)"

Recommendation 3: "There is an urgent need for further research on the clinical effectiveness of pharmacologic management of dementia."

For David Geldmacher, MD, Associate Professor of Neurology and Director of the Memory Disorders Program and Medical Director of the Fontaine Adult Neurology Clinic at the University of Virginia, the study didn't shed any new light on what's known to experts in dementia care. Commenting that the guidelines are consistent with the published literature, he says he does not believe the study will impact neurologists.

Explaining their first recommendation, the study authors say, "Evidence is insufficient to determine the optimal duration of therapy. A beneficial effect, if any, would generally be observed within three months on the basis of duration of trials. This effect could be an improvement or stabilization." In addition, they add that no evidence shows when it is appropriate to stop treatment if the patient becomes unresponsive or shows decline in various domains of dementia.

Because clinical trials rarely if ever include head-to-head comparisons of medications, evidence of comparative efficacy is not sufficient to advocate particular drugs for the treatment of dementia, the group says. "Therefore, tolerability, adverse effect profile, ease of use, and cost of medication are reasonable criteria to help select a treatment. For example, when the benefits and harms related to a drug are being evaluated, the severe side effects associated with tacrine make it an unreasonable choice."

Dr. Geldmacher thinks the study paints a picture that is complete, but perhaps unrealistic. "The medications it addresses have been evaluated and approved by the FDA for the treatment of AD. And in the meta-analyses that underlie the treatment

SHORTTAKES

■ **Bugged by Antibiotic Overuse.** Though it's not clear that the treatment has any benefit, nearly half of nursing home patients with advanced dementia are given antibiotics during the final two weeks of their lives, according to a study published in the February 25th *Archives of Internal Medicine* that followed 214 patients for 18 months or until death. Researchers found that 66 percent of people were given at least one course of antibiotic therapy during the study; 53 days per 1,000 was the average duration a patient spent on antibiotics. Of the 99 subjects who died during the study, 42 percent were on antibiotics during the last two weeks of life. The researchers questioned the efficacy of such regimens, particularly in light of MRSA concerns about antibiotic overuse.

■ **Get Smart.** Women have better cognitive function when they are fortunate enough to have above average levels of DHEAS. These women tested better on executive function, concentration and working memory, according to a study published in the *Journal of Clinical Endocrinology & Metabolism*, and is the first evidence that DHEAS is positively associated with cognitive function, per the study authors. The researchers followed 295 women aged 21 to 77 (mean age 55) recruited from a Australian dataset who had at least 12 years of education. They were tested on several cognitive scales, including verbal, visual, spatial and many others. On the reasons behind their findings, study authors propose: a possible direct action of DHEA and DHEAS; DHEAS may be a marker of androgen and estrogen production; or the two may simply be indicators of good health.

■ **Music Hath Charms.** Listening to a favorite album can be a calming escape from daily stress. It might also be an escape from part of the severity of a patient's early stroke recovery. A study of 54 patients, published in the February 20th issue of *Brain*, found that the group that listened to a few hours worth of music each day demonstrated more improvements in verbal memory and focused attention. The group, which consisted of patients who suffered a stroke of the right or left hemisphere middle cerebral artery, also experienced a better mood than those who listened to audio books or received no listening accessories. Three months following stroke, "verbal memory improved from the first week post-stroke by 60 percent in music listeners, by 18 percent in audio book listeners and by 29 percent in non-listeners," says first study author Teppo Sarkamo of the University of Helsinki in Finland.

■ **Cognitive Impairment is in Decline.** Among a seemingly continual news flow about increased risks and higher rates of disease comes one study that suggests the opposite. Published online in the February 20th issue of *Alzheimer's & Dementia*, a new study finds that rate of cognitive impairment declined from 12.2 percent in 1993 to 8.7 percent in 2002. The researchers couldn't explain the decline entirely, but speculated one reason may be that more formal education, higher economic status and a higher quality in care for

recommendations from the ACP, they've lumped all dementia together," he says. This has the effect of undermining efficacy because AD has a specific neurochemical basis, and cholinesterase inhibitors in particular were designed to address that basis. "If you start to throw in other forms of dementia, you're going to dilute the number of people who have the chemical need or whose chemical deficiency would reflect the need for cholinesterase inhibition."

Another issue is that the guidelines imply a treatment goal of clinical improvement rather than the delay of further decline, which is a more realistic endpoint, Dr. Geldmacher says. The authors likely understood that the typical response to these medications is delay of decline or in increase in stability, "but in the bullet points, that doesn't come through very well. I think it may unduly bias primary care physicians to underestimate the benefits of medicine."

"I think that a primary care physician who is quickly thumbing through this as a part of a busy day could think, 'Well, if people don't improve, I shouldn't treat.' And the improvement that they'd be looking for is different than the nature and quality of the improvement that's been demonstrated in the placebo-controlled trials," he says. **PN**

SECOND OPINIONS

Be Mindful of FDA Rules on Sponsored Lectures, MD/JD Warns

I have enjoyed the recent articles by Dr. Devere and would like to comment about a remark in his response to Dr. Gilbert (February 2008, p. 5). I am also an occasional speaker for pharmaceutical companies. However, last year I participated—as an attorney—in a legal compliance lecture at one company's speaker training meeting.

Dr. Devere mentions that "you can pick and choose PowerPoint slides the company gives you, but **you can also make your own slides with your own points**" [emphasis added]. Several years ago, I often did the same. Now, on the other hand, I would be very surprised if any manufacturer would knowingly allow a physician speaker to insert his or her own slides. The FDA has been enforcing its rules more strictly. Physician speakers are regarded as agents of the manufacturers and must follow FDA guidelines. Company-created slides must be approved by the FDA. If you are speaking on behalf of a manufacturer, even in an informal one-on-one office setting, using your own slides could run afoul of the FDA.

Recently, one manufacturer paid a very hefty fine because one of its speakers testifying on his own initiative to a legislative committee, distributed materials discussing off label use of its drug. More importantly, the risk nowadays extends beyond the manufacturers to speakers. At least one physician is facing federal criminal charges for his alleged off label presentations on behalf of a manufacturer. In that case, apparently, one physician was a cooperating witness who secretly taped (or allowed taping) the presentation.

Another physician speaker found himself named as a codefendant in a multimillion dollar suit seeking reimbursement for plaintiff insurance companies that had spent money on the off label indications allegedly promoted by the manufacturer. (For you legal buffs, the physician was named in the suit in order to defeat the diversity requirement that would have allowed the defendant manufacturer to remove the suit from the plaintiffs' home state court to a federal District Court across the country where similar lawsuits were being gathered.)

These restrictions are only relevant if you are speaking at a company-sponsored event. If you are speaking at an independent program that is not controlled by the manufacturer, then you can certainly use your own slides. Be aware, however, that the manufacturer might not want you to use its slides in those programs.

— Sincerely yours,
Jeffrey Wishik, MD, JD

cognitive impairment is more likely to be experienced by recent generations than their predecessors. Roughly 40 percent of the 3.5 percent decrease was due to increased education and personal wealth, the report proposes.

■ **FDA Issues Toxin Warning.** The FDA announced that botulinum toxin types A and B have been linked to respiratory failure and death, thought to be found in overdosing cases. The adverse effects were found in both FDA-approved and nonapproved uses. According to the agency, the worst adverse effects were seen in children treated for limb spasticity associated with cerebral palsy, an off-label use in children and adults. The reactions seem related to the spread of botulinum toxin to areas beyond the site of injection, and mimic symptoms of botulism (*e.g.*, difficulty swallowing, weakness, respiratory problems). There is no advisement to health care professionals to discontinue prescribing these products and there is no proof that the reactions are related to any defect in the products, the FDA says.

■ **New AED Gets Closer to Market.** Neuronal potassium channel opener retigabine performed well in the RESTORE 1 trial, the first of two Phase III studies as an adjunctive treatment for adult epilepsy patients with refractory partial-onset seizures, according to manufacturer Valeant Pharmaceuticals. The trial evaluated a 1200mg daily dose of retigabine versus placebo in patients currently taking one to three additional AEDs. Retigabine "demonstrated statistically significant results on the primary efficacy endpoints important for regulatory review by both the FDA and the European Medicines Evaluation Agency," the company says. The RESTORE 2 results should be released in the next few months, and the company anticipates marketing approval before the end of 2008.

■ **Donepezil Misses the Mark in CADASIL Trial.** CADASIL patients taking donepezil experienced no change from baseline in the vascular AD assessment scale cognitive subscale, the primary endpoint of an 18-week study of 168 patients published online February 22nd in *Lancet Neurology*. "Improvements were noted on several measures of executive function, but the clinical relevance of these findings is not clear," the authors write. "Our findings may have implications for future trial design in subcortical vascular cognitive impairment."

■ **Non-Dopaminergic Agent for RLS in the Works.** Top-line results from the final Phase III trial of XP13512, a non-dopaminergic agent, show positive results in the treatment of moderate-to-severe symptoms of primary RLS, according to its makers, XenoPort and GlaxoSmithKline. The trial was a 12-week, double-blind, placebo-controlled study that followed 325 patients with moderate to severe RLS. The co-primary endpoints were change from baseline on the IRLS rating scale score and percentage of patients showing "significant improvement" on the CGI-I scale at the conclusion of treatment. The company hopes to file a new drug application for primary RLS in the third quarter of 2008.