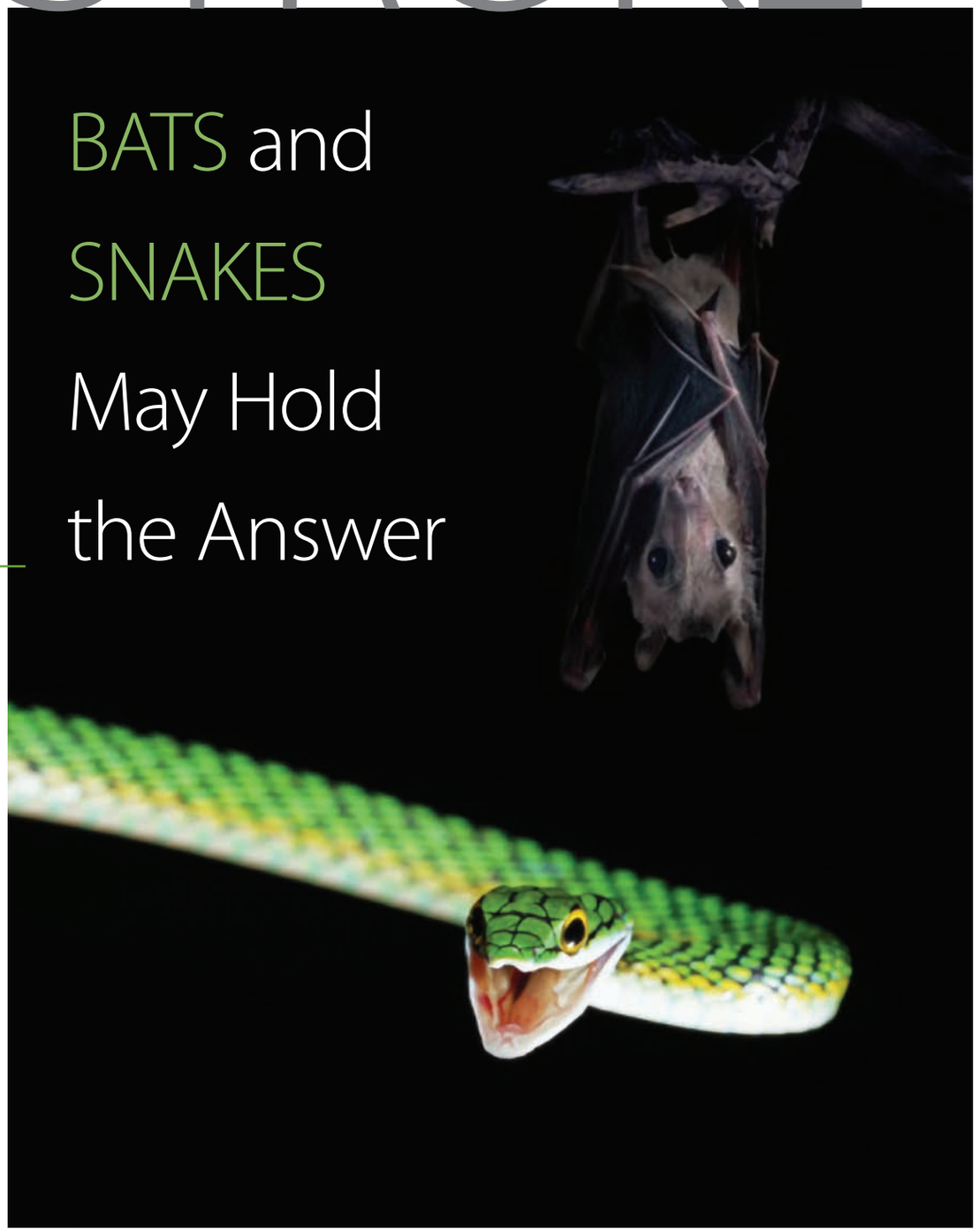
BY CYNTHIA BORDA

STROKE

BATS and SNAKES May Hold the Answer



A DECADE AGO, THE INTRODUCTION OF TPA WAS A MAJOR STEP FORWARD IN STROKE TREATMENT, and the hope was that other approaches and additional therapies would soon be available. UNFORTUNATELY, THE NEXT GENERATION OF PRODUCTS HAS YET TO MATERIALIZE.

Every 45 seconds, someone in the United States has a stroke. Treatments for this debilitating and deadly disease, however, are lacking.

There is one product on the market — Genentech's Activase — that is effective in treating ischemic stroke, the most common type of stroke, and it is the only approved product shown to improve the prognosis of stroke patients. But after more than 10 years on the market, only about 10% of patients are eligible to receive Activase since it must be administered within three hours of the onset of the stroke. A 2005 survey by the University of Michigan Stroke Program found that 40% of emergency-room physicians say they are unlikely to administer Activase to stroke patients, mostly because of a fear of causing brain bleeding.

Because stroke is the third-leading cause of death in the United States and a leading cause of long-term disability, there is a tremendous need for effective therapies, and the most promising pipeline candidates are coming from some unlikely sources: vampire bats and pit vipers. Industry experts say stroke is one of today's most significant unmet

DR. JULIE KERNER
DECISION RESOURCES

WHAT WE ARE DEALING WITH HERE ARE BRICKS AND FEATHERS. We are either slamming patients with "bricks" and creating safety risks, or we are hitting them with "feathers" that don't touch them. What we need is something in between.

DR. DAVID LEVY
NEUROBIOLOGICAL TECHNOLOGIES

BIG PHARMA SEEMS TO HAVE BACKED OFF FROM DEVELOPING STROKE TREATMENTS, BUT THE SMALLER PHARMA COMPANIES ARE STILL INVOLVED. Treating stroke is complicated and necessary, and many of us are dedicated to finding appropriate treatments.

DR. RAGHURAM SELVARAJU
RODMAN & RENSHAW

WE STILL DON'T KNOW THAT MUCH ABOUT NEURONAL DEATH, so we need to go after the problems that we know and try to make a difference to a stroke patient.

medical needs, representing a market valued at about $54 billion in the United States.

A report published by Decision Resources in June 2005 listed several factors that analysts believe are constraining the market for acute ischemic stroke therapy. The biggest challenge is time. The need to treat patients quickly remains an issue, since the brain succumbs to permanent injury very quickly. Delay in presentation time and the time needed to rule out hemorrhagic stroke can impact treatment.

"Issues include stringent guidelines for the administration of thrombolytics, the acute nature of stroke, which limits the market, and the FDA requirement that stroke treatments prove effective as monotherapies," says Julie Kerner, Ph.D., a research analyst with Decision Resources.

Each year, about 700,000 people experience a new or recurrent stroke, according to the American Heart Association. Of all strokes, 87% are ischemic; intracerebral and subarachnoid hemorrhage strokes make up the remainder. The estimated direct and indirect cost of stroke in the United States is expected to be $62.7 billion in 2007.

Acute ischemic strokes are caused by a blood clot stopping or diminishing blood flow to an area of the brain. Thus, acute ischemic stroke, or "brain attack," has comparable physiological cause as an acute myocardial infarction, or heart attack.

For nearly a decade, following the 1996 approval of Genentech's Activase (alteplase), no new stroke drugs have made it to market, they usually fail at the final hurdle in expensive Phase III trials.

Activase is a tissue plasminogen activator (tPA) that is produced by recombinant DNA technology. It is a thrombolytic agent approved for use in certain patients having a heart attack or stroke. Activase works by stimulating the body's own clot-dissolving mechanism by activating plasminogen, a naturally occurring substance secreted by endothelial cells in response to injury to the artery walls that contributes to clot formation.

Each year, 700,000 people experience a new or recurrent stroke.

There are many issues with tPA, including a treatment window of three hours from first symptoms and side effects of neurotoxicity and hemorrhage. Therefore, only 2% to 4% of diagnosed stroke patients receive tPA, according to Decision Resources.

DEVELOPMENT CHALLENGES

Companies have tested products for administration longer than three hours after stroke onset, but they haven't had much success. Developing stroke treatments has proved difficult, experts say, because it is not clearly understood what happens in the brain after a stroke.

"We really do not know why there have been no successes with stroke treatments," says David E. Levy, M.D., VP of clinical development for Neurobiological Technologies Inc. "What we do know is that there are many variables. Companies may have rushed into human trials when animal trials that do not directly translate to human stroke have shown positive outcomes. There may have been too long a window of time for treatment, incorrect dosing, or the products may or may not have crossed the blood-brain barrier."

Additionally, he says, stroke is a clinical diagnosis that has to be evaluated quickly.

"There often is no possibility or time for imaging studies," he says. "Patients will often try to wait and see how they feel before going to the hospital. Stroke studies are not easy to conduct; some of them require complicated imaging and instrumentation, which is coupled with a lack of time."

A report, Medicines in Development for Heart Disease and Stroke, published in February 2005 by the Pharmaceutical Research and Manufacturers of America, reported that there are 17 products in development for all causes of stroke. But since that time many of the products have failed in various stages of development.

For example, AstraZeneca said in October 2006 that it would halt development of a promising neuroprotectant, Cerovive or NXY-059, after it failed in clinical studies.

The company's previous study, published in February 2006 in the *New England Journal of Medicine*, found a statistically significant

reduction with NXY-059 versus placebo on the primary outcome of stroke-related disability. The study, an international Phase III SAINT I trial (Stroke Acute Ischemic NXY-059 Treatment), was a double-blind, placebo-controlled study in which patients were randomized to receive NXY-059 or placebo within six hours of acute ischemic stroke.

But in October 2006, the company announced that results from a second trial, the SAINT II (Stroke Acute Ischemic NXY-059 Treatment), showed that the investigational drug did not meet its primary outcome of a statistically significant reduction in stroke-related disability. Subgroup analyses, including time to treatment, did not demonstrate a treatment benefit. In addition, NXY-059 did not cause a statistically significant improvement in neurological status versus placebo on the National Institutes of Health Stroke Scale.

Only 10% of stroke patients are eligible to recieve Activase.

AstraZeneca is analyzing the pooled data from the SAINT I and SAINT II trials and will present a review of the data at the International Stroke Congress meeting in February 2007.

"Disturbingly, this product was the 50th neuroprotectant to fail for stroke, and this has soured the industry to this class of drugs," says Raghuram Selvaraju, Ph.D., MBA, a biotechnology analyst with Rodman & Renshaw LLC. "NXY-059's failure was the death knell for neuroprotectants. It may not be warranted but it will be a while before more dollars are put into this area of research."

Another stroke product discontinued in late-phase development was Centocor Inc.'s/Eli Lilly & Co.'s ReoPro (abciximab). The product already is marketed as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications in patients undergoing percutaneous coronary intervention.

ReoPro was in Phase III trials for treatment of ischemic stroke when enrollment was halted and the trial stopped in October 2005 because of safety concerns.

Preliminary results from other trials had suggested that ReoPro might be useful in the treatment of stroke beyond the three-hour time window. The trials were discontinued after a review of efficacy and safety data on most of the 808 enrolled patients. The study was to have enrolled about 1,800 patients. About 150 clinical-trial sites were participating in the study.

In addition, a separate trial of ReoPro was also stopped in May 2005 because of an increased risk of intracranial hemorrhage. This trial had looked at using ReoPro to treat a small segment of patients awakening after having suffered a stroke.

PIPELINE HOPEFULS

Despite the setbacks in the development of new stroke products, research continues. The need to treat patients quickly remains an issue, says Scott E. Kasner, M.D., associate professor of neurology and director of the Comprehensive Stroke Center, University of Pennsylvania Medical Center. He also is a spokesman for the American Stroke Association (ASA), which is a division of the American Heart Association (AHA).

"Nevertheless, ongoing trials are still hoping to push the time window so that more patients can be treated, while the AHA/ASA is trying to educate the public about the signs and symptoms of stroke, as well as the importance of getting to a stroke center immediately," Dr. Kasner says.

One of the more promising products in the stroke pipeline is the thrombolytic agent desmoteplase. The product is being developed by Forest Laboratories Inc., which is conducting a Phase IIb/III study. Desmoteplase is a plasminogen activator being studied for the treatment of acute ischemic stroke. Earlier Phase II studies demonstrated the potential of desmoteplase to treat acute ischemic stroke in patients up to nine hours after the onset of stroke symptoms. Lengthening that window may expand the number of patients who could benefit from treatment.

Desmoteplase, the first in a new class of plasminogen activators, is a genetically engineered version of a clot-dissolving protein found in the saliva of the vampire bat, Desmodus rotundus. It possesses high fibrin selectivity, allowing it to dissolve a clot locally without affecting the blood coagulation system, which is thought to potentially reduce the risk of intracranial bleeding (a common risk when administering blood-clot dissolvers) as compared with less fibrin-specific plasminogen activators.

Desmoteplase was licensed from Paion GmbH, a biopharmaceutical company based in Aachen, Germany. Forest and Paion have partnered for the development and marketing of the product in the United States and Canada. H. Lundbeck A/S and Paion have a partnership agreement for the development and marketing of desmoteplase for stroke in Europe, Japan, and the rest of the world.

"We are optimistic about this product," says Neil H. Shusterman, M.D., senior VP of clinical development at Forest Research Institute. "There are certain unique factors associated with desmoteplase that set it apart from tPA. First, on the molecular level, it has fibrin specificity. Also, the half-life is much longer than tPA, Where tPA must be delivered by infusion over 60 minutes, desmoteplase can be given by bolus in less than a minute."

Additionally, treatment with desmoteplase is done in conjunction with neurological imaging.

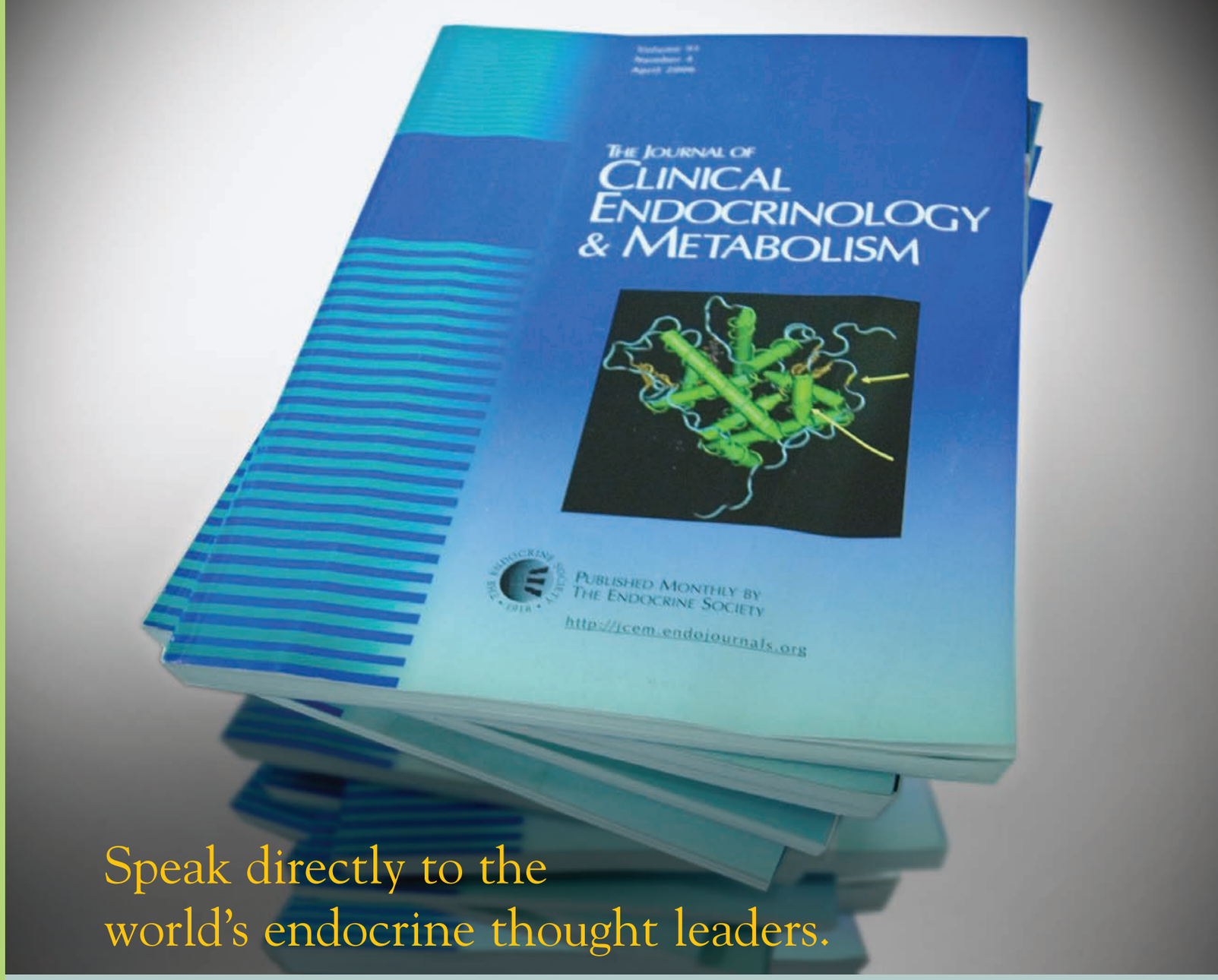
"This is done to locate the tissues at risk (penumbra) since the physiology over time is an element of stroke outcome," Dr. Shusterman says.

Another drug generating interest is Viprinex (ancrod) from Neurobiological Technologies. Viprinix is a drug that breaks down fibrinogen, and it is in Phase III trials. The studies are being conducted in the United States, Europe, South Africa, New Zealand, and Australia. Derived from the venom of the Malayan pit viper, Viprinex is a thrombin-like enzyme that is highly specific to fibrinogen. Previous studies have shown that in patients receiving Viprinex within six hours of stroke onset, blood viscosity is progressively reduced by 20% to 30% from pretreatment levels,

At a Glance: STROKE

- **The estimated direct and indirect cost of stroke** in the United States is expected to be $62.7 billion in 2007.
- **Each year, about 700,000 people** experience a new or recurrent stroke.
- **On average, every 45 seconds,** someone in the United States has a stroke.
- **African-Americans** have twice the risk of first-time stroke.
- **Of all strokes, 87% are ischemic;** intracerebral and subarachnoid hemorrhage strokes make up the remainder.
- **Stroke accounted for** about one in every 16 deaths in the United States in 2004.
- **When considered separately from other cardiovascular diseases,** stroke ranks No. 3 among all causes of death, behind diseases of the heart and cancer.

Source: American Heart Association, Dallas.
For more information, visit americanheart.org.



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"Viprinex removes fibrinogen from the blood, resulting in two direct modes of action," Dr. Levy says. "It is an anticoagulant and reduces the viscosity of blood. Indirectly, it stimulates fibrinolysis."

Rodman & Renshaw analysts predict that this product will have a market penetration of about 40% if it receives regulatory approval, since it could be used within a six-hour time window. Its exclusionary factors include hypertension and hemorrhaging. The fact that this product is derived from snakes makes generic intrusion an unlikely competitor.

Drugs in the stroke pipeline have a longer treatment window.

And while Lilly and Centocor have stopped their development of ReoPro for ischemic stroke, the National Institute of Neurological Disorders and Stroke is continuing to enroll patients in its trial of ReoPro in combination with Retavase. This Phase II study will determine the dose of Retavase (reteplase) that can safely be combined with ReoPro in treating acute ischemic stroke. The study is an open-label, dose escalation, safety, and proof of principle study of the combination of intravenous abciximab and reteplase.

Although AstraZeneca's neuroprotectant failed, other companies continue with their development efforts in this area. For example, an Israeli company, D-Pharm Ltd., has completed a Phase IIb clinical trial of DP–b99, a neuroprotective drug that addresses the array of damaging processes occurring in the brains of stroke patient.

A significantly higher recovery rate after stroke was found in the DP-b99 treatment group compared with the placebo group. The study also confirmed the excellent safety and tolerability profile of DP-b99. There was no difference in response to DP-b99 treatment between those patients treated within six hours or within six to nine hours following stroke onset, confirming the wide therapeutic treatment window for DP-b99.

DP-b99 is a rationally designed drug using D-Pharm's proprietary technology, membrane active chelators (MAC). Evidence suggests that redistribution of metal ions and disturbances in metal ion homeostasis are key components in the cascade of events underlying cell damage in stroke. In the first hours post-stroke, ion disturbances cause excitatory cell damage and in the days and weeks following they contribute to edema, inflammation, and cell death.

"Though D-Pharm's Phase II trial in acute ischemic stroke with its neuroprotectant drug reported encouraging results, the significance of these results has yet to be determined given that the study involved only 150 patients," Dr. Selvaraju says.

Any new drugs that reach the market, however, could face competition from interventional devices, as these also are increasing in popularity as treatments within hours post stroke.

In July 2006, Concentric Medical received European approval for its Merci L5 Retrieval System, indicated for clot removal in ischemic stroke patients. The Merci Retriever is a corkscrew-type device that is delivered into the brain using standard catheterization techniques. Upon reaching the targeted area, the Merci Retriever is designed to restore blood flow in ischemic stroke patients by engaging, capturing, and removing the blood clot.

A trial conducted by Concentric Medical demonstrated a 69.4% blood flow restoration rate in 111 ischemic stroke patients after the study procedure. Clinical outcomes for moderate to severe stroke patients treated also were improved as demonstrated by 34.3% of patients treated.

Another device company, CoAxia Inc., is conducting a multicenter pivotal trial of NeuroFlo cerebral perfusion augmentation therapy for treating ischemic stroke. Patients are treated with NeuroFlo up to 10 hours after stroke onset and are evaluated neurologically at 90 days. The product is a dual-balloon catheter that works by increasing blood flow to the brain via restricting flow in the descending aorta. This cerebral perfusion augmentation uses the brain's collateral circulation to treat the stroke periphery (penumbra) and may limit the size and damage of the stroke.

CoAxia also is conducting an initial safety study that would look at NeuroFlo for treating ischemic stroke patients up to 24 hours after the onset of their symptoms.

"There are issues with interventional devices," Dr. Kerner says. "It will be interesting to see how these fit into medical practice going forward." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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