Current Perspective on Self-Expanding Stents for Acute Ischemic Stroke

Experience with this technique and a preview of the first
FDA-approved prospective trial, SARIS.

BY ELAD I. LEVY, MD, FACS, FAHA; SABAREESH K. NATARAJAN, MD, MS;
ADNAN H. SIDDIQUI, MD, PhD; KENNETH V. SNYDER, MD, PhD; ERIK F. HAUCK, MD, PhD;
J MOCCO, MD, MS; AND L. NELSON HOPKINS, MD, FACS

A portion of the Stent-Assisted Revascularization for Acute Ischemic Stroke (SARIS) trial data was presented at the International Stroke Conference in San Diego, California, on February 19, 2009, and the article will be published in Stroke.[1]

The SARIS trial was funded by Boston Scientific Corporation (Natick, MA); however, all data collection, analysis, and interpretation were performed by the authors, independent of Boston Scientific Corporation's input or interpretation.

Acute ischemic stroke intervention has been stimulated by the correlation of clinical outcome with radiographic revascularization.[2-7] Several trials demonstrate recanalization rate and time to recanalization[7-9] to be correlated with an improved outcome.[2-11] These realizations are directing government policy, reimbursement patterns, and overall physician interest toward increased commitment to developing rapid recanalization tools and creating an infrastructure to ensure patients receive such therapies. Recanalization rates achieved with intravenous (IV) recombinant tissue plasminogen activator (rt-PA) for proximal, large-vessel arterial occlusion are poor, ranging from only 10% for internal carotid artery (ICA) occlusion to 30% for middle cerebral artery (MCA) occlusion.[12] IV thrombolysis is less effective for thromboembolic obstruction of these large proximal vessels than more distal smaller vessels.[13] A National Institutes of Health Stroke Scale (NIHSS) score > 12 suggests an occlu-

sion of a proximal large vessel and, therefore, a high thrombus burden.[14] The main concerns with intra-arterial (IA) and IV pharmacological thrombolysis have been the rate of hemorrhage, the inability to effectively dissolve platelet-rich clots, lengthy times to recanalization, and the inability to prevent abrupt reocclusion at the initial site of the obstruction.[15] Reocclusion has been reported to occur after IV thrombolysis (in 34% of patients) and IA pharmacologic thrombolysis (in 17% of patients) and is associated with poor outcome.[16,17]

Endovascular mechanical therapies yield higher recanalization rates and allow a broader treatment window (up to 8 hours) and therefore lead to better clinical outcomes. The Merci mechanical clot retriever (Concentric Medical, Inc., Mountain View, CA) and the Penumbra device (Penumbra, Inc., Alameda, CA) are mechanical thrombectomy devices that have been approved by the US Food and Drug Administration (FDA) for patients with stroke symptoms in whom IV rt-PA therapy has failed or is a contraindication.[10,18] Although recanalization with the newer-generation Merci mechanical clot retriever in conjunction with pharmacological therapy is successful in 70% of patients,[10] this rate is only marginally superior to the 66% recanalization rate in the PROACT (Prolyse in Acute Cerebral Thromboembolism) II trial.[19] The recanalization rate with the device alone was only 50%; multiple passes (average five to six) were required before establishment of flow in the
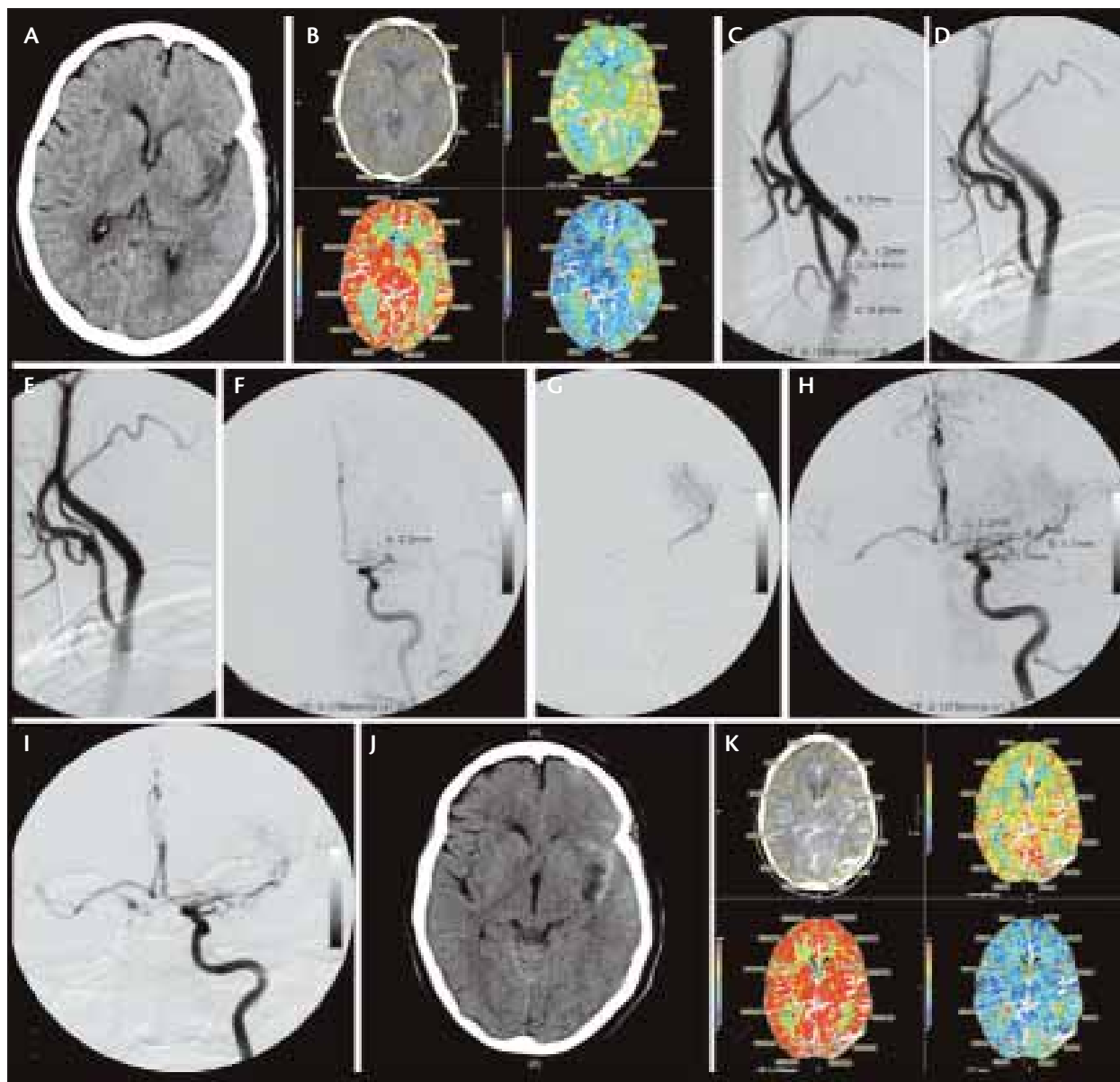
Figure 1. Noncontrast cranial computed tomography (CT) scan showing hypodensity in the left basal ganglia region (A). CT perfusion imaging showing minimal core in the left MCA territory with a surrounding penumbra (B). Left common carotid artery injection showing 75% narrowing of the proximal portion of the left cervical ICA (C). Placement of a 6- to 8- X 40-mm Xact stent (Abbott Vascular, Santa Clara, CA) in the narrow segment with a distal protection device (EPI Embolic Protection Inc., Boston Scientific Corporation) (D). Poststent placement angiogram showing good flow through the left cervical ICA (E). Selective injection of the left ICA showing left proximal M1 occlusion (F). Selective microrun of the left MCA branches after crossing the lesion with a microcatheter (G). Angiogram showing narrowing of the left M1 (H). Angiogram after placement of a 4.5- X 22-mm self-expanding Enterprise stent (Codman Neurovascular, Raynham, MA) across the M1 narrowing (arrows showing proximal and distal stent tines) and thrombolysis in myocardial infarction (TIMI) 3 flow in the distal MCA branches (I). Postrevascularization noncontrast cranial CT scan showing minimal contrast staining/subarachnoid hemorrhage in the left Sylvian fissure (the patient improved and was not symptomatic for the subarachnoid hemorrhage) (J). Postrevascularization CT perfusion image showing minimal core and disappearance of the penumbra (K). Reprinted with permission from Natarajan SK et al. Hemorrhagic and Ischemic Stroke: Surgical, Interventional, Imaging, and Medical Approaches (In press).[20]
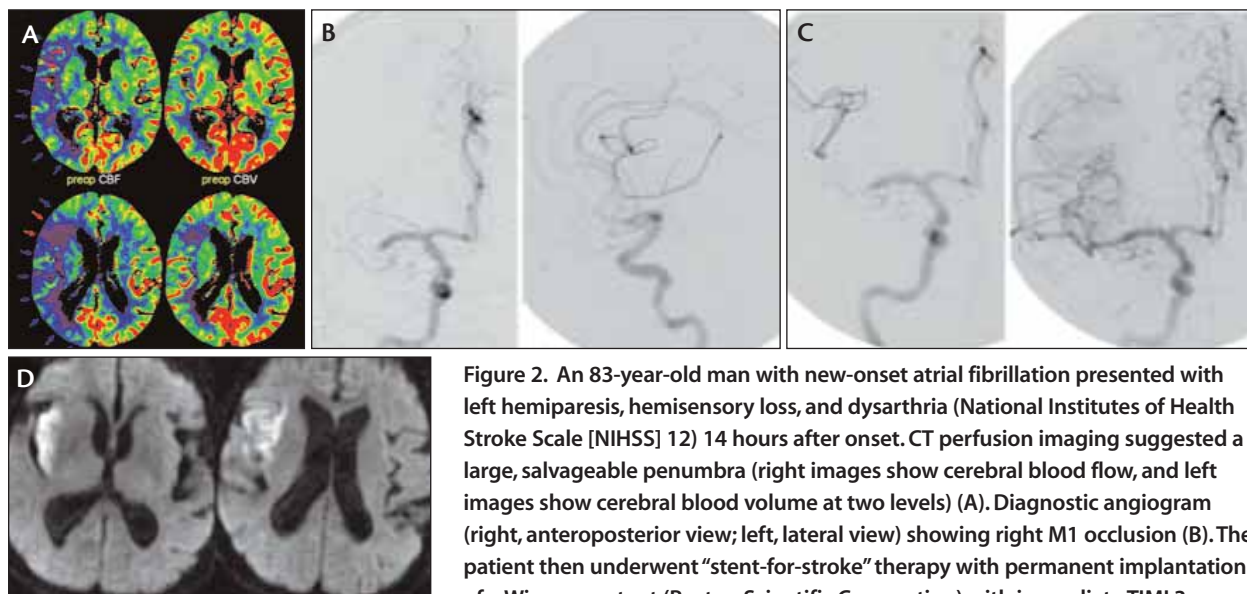
Figure 2. An 83-year-old man with new-onset atrial fibrillation presented with left hemiparesis, hemisensory loss, and dysarthria (National Institutes of Health Stroke Scale [NIHSS] 12) 14 hours after onset. CT perfusion imaging suggested a large, salvageable penumbra (right images show cerebral blood flow, and left images show cerebral blood volume at two levels) (A). Diagnostic angiogram (right, anteroposterior view; left, lateral view) showing right M1 occlusion (B). The patient then underwent "stent-for-stroke" therapy with permanent implantation of a Wingspan stent (Boston Scientific Corporation) with immediate TIMI 3 recanalization. Angiogram after crossing the lesion with a microwire (right); flow restoration immediately after stent deployment (left) (C). The patient quickly recovered from these deficits. Of note is a small, right frontal area that remained ischemic (D, at the same two levels as shown for pretreatment perfusion imaging). During preoperative imaging, diminished cerebral blood volume was noted in this region. Reprinted with permission from Natarajan S et al. Vascular Disease Management (In press).[21]

occluded vessel. Concomitant use of IA fibrinolytic agents increased the rate of hemorrhagic transformation. With the Penumbra device, despite an 81.6% recanalization rate, only 25% of patients recovered to a modified Rankin Scale (mRS) score of ≤ 2, with mortality at 3 months in 32.8% and symptomatic intracranial hemorrhage (ICH) in 11.2%; moreover, it took an average of 40 minutes to achieve flow restoration after delivery of the device to the target vessel.[22]

RATIONALE FOR STENT-ASSISTED RECANALIZATION

The acute coronary occlusion literature has shown evolution from pharmacological thrombolysis to angioplasty, and finally, stenting as primary therapy for acute occlusion of coronary arteries. Although a similar progression could be traced for intervention in acute ischemic stroke, there are major differences in the pathology of an acute intracranial artery occlusion when compared to an acute coronary artery occlusion, as well as differences between intracranial and coronary vasculature. In the coronary vasculature, the arterial wall contains equal thicknesses of intima, media, and adventitia, and it is supported by the cardiac muscles. By contrast, in cerebral arteries, the media occupies three-fifths of the thickness, with intima and adventitia occupying one-fifth each; these vessels are surrounded by cerebrospinal fluid, and the lack of a supporting structure places them at a higher risk of dissection or rupture. Most acute coronary artery occlusions are the result of destabilization of an in situ plaque, causing plaque rupture and thrombosis, where-

as most acute cerebral artery occlusions are due to an embolus in a normal vessel. The major benefit of stent-assisted revascularization over other mechanical revascularization strategies is the resulting high rates of immediate, sustained flow restoration in occluded vessels.[23-25] Stents are obviously of value for acute occlusion in an intracranial vessel narrowed by atherosclerotic plaque.

SELF-EXPANDING STENTS

Self-expanding stents (SES) designed for cerebral vessels are now available. These devices can be delivered to target areas of intracranial stenosis with a success rate exceeding 95% and have an increased safety profile because they are deployed at significantly lower pressures than balloon-mounted coronary stents.[26] Higher rates of recanalization and lower rates of vasospasm and side-branch occlusion were noticed with SES compared with balloon-mounted stents in a canine model of vessels acutely occluded with thromboemboli.[27] Because acute intracranial vascular occlusions are related to an embolus in the absence of any in situ vascular pathology, balloon angioplasty with high-pressure balloons and balloon-expandable stents is typically not necessary to recanalize the vessel and may only increase the chance of serious complications, such as vessel rupture or dissection. Finally, SES cause less endothelial damage and, therefore, may result in lower rates of early reocclusion or late stent restenosis. SES with higher radial force (eg, Wingspan) will likely play a key role in the management of

patients with acute stroke related to intracranial atherosclerotic disease.[26]

Five intracranial SES are now available: Neuroform (Boston Scientific Corporation), Enterprise (Figure 1), Leo (Balt Extrusion, Montmorency, France), Solitaire/Solo (ev3 Inc., Plymouth, MN), and Wingspan (Figures 2 and 3). The first four listed devices are currently marketed for stent-assisted coil embolization of wide-necked aneurysms; the Wingspan stent is approved for the treatment of symptomatic intracranial atherosclerotic disease. Both the Neuroform and the Wingspan stents have an open-cell design, whereas the Enterprise, Leo, and Solitaire/Solo stents have a closed-cell design. The closed-cell design allows resheathing of the stent after partial deployment (70% deployment for the Enterprise; 90% for the Leo) or even full deployment (Solitaire/Solo).

EVIDENCE SUPPORTING
SES-ASSISTED RECANALIZATION

Early support for mechanical displacement modalities for stroke treatment (of which stenting is one), as a contrast to clot removal modalities (such as Merci or Penumbra), can be found in the literature on angioplasty for stroke.[28-31] These studies are among the first to discuss the possibility that clot removal is not critical in and of itself, but rather that recanalization should be the focus of intervention. Springboarding from these early experiences, the concept of stent placement for acute stroke became a serious consideration. Two cases were reported in 2006 of successful SES use in stroke due to MCA occlusion as a bailout after failed revascularization with other modalities.[32,33] Levy et al[24] described the use of SES (Neuroform or Wingspan) to treat 18 patients (19 lesions) presenting with acute ischemic stroke. Stent placement was the initial mechanical maneuver in six cases; other cases involved a combination of pharmacologic and/or mechanical maneuvers, and glycoprotein IIb/IIIa inhibitors were administered in 10 patients. TIMI grade 2 or 3 revascularization[34] was achieved in 15 of 19 lesions (79%). Seven patients had ICH (either intraparenchymal or subarachnoid) on postprocedural CT imaging, two of which were fatal. One patient developed early stent rethrombosis. The in-hospital mortality rate was 38.9% (seven of 18 patients). Four patients had mRS scores of ≤ 3 at the 3-month follow-up evaluation. Zaidat et al[25] evaluated the use of Neuroform (four patients) or Wingspan (five patients) stents in nine patients with acute stroke. Successful stent deployment across the clot occurred in eight out of nine (89%) patients. In one patient, a Wingspan stent could not be tracked beyond the MCA/ICA junction and was deployed in the proximal clot. TIMI 2 or 3 recanalization
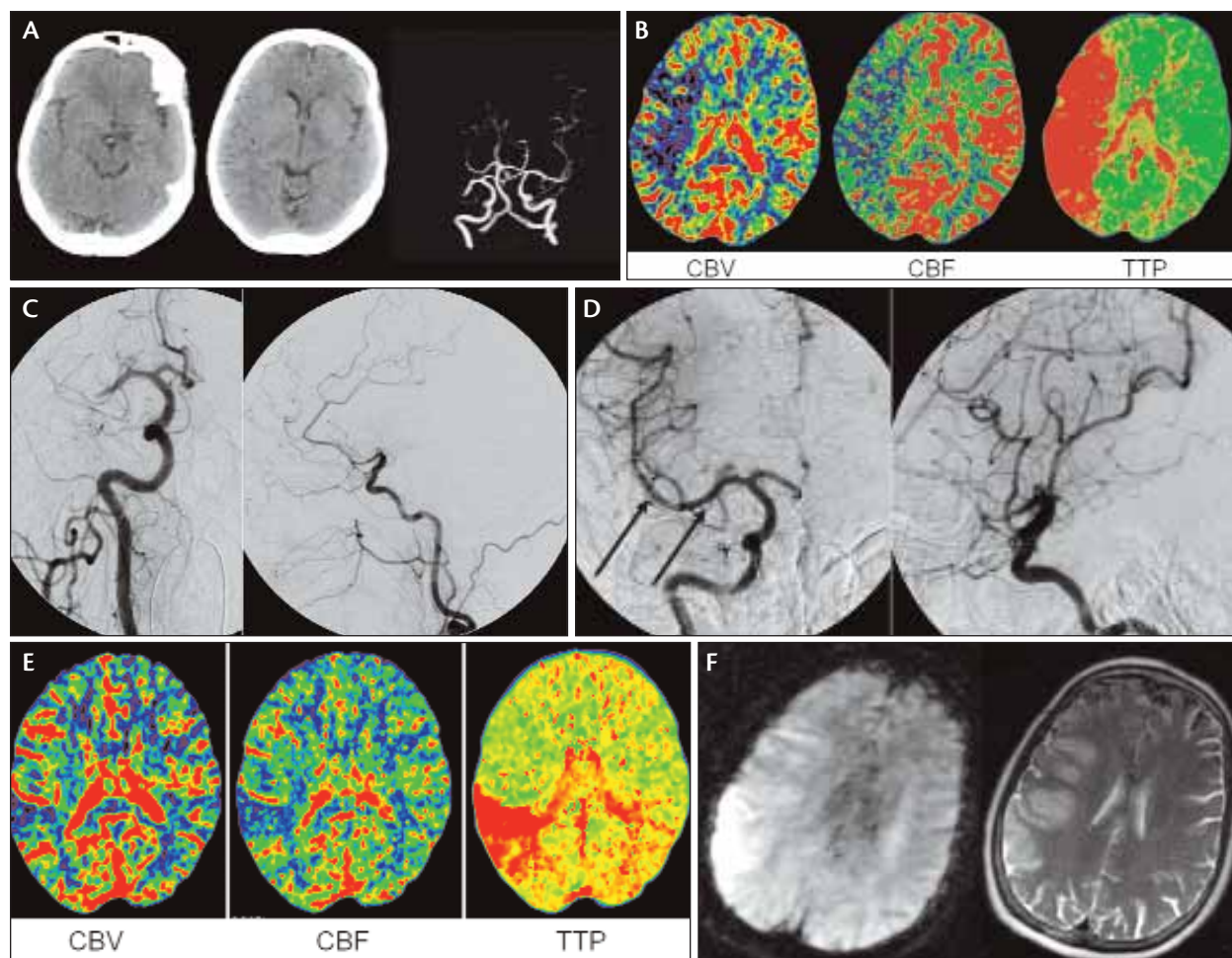
Figure 3. A 61-year-old woman with acute onset of left-sided weakness and left hemineglect that started 7 hours before presentation for treatment. She was a smoker but had no other significant comorbidities. On examination, she had left-sided hemiplegia, hemisensory loss, dysarthria, and aphasia; she also had an NIHSS score of 25 at presentation. A noncontrast cranial CT scan (left and middle images) shows no bleeding or signs of early ischemic changes; the right image is a 3D reconstruction of a CT angiogram that shows acute right distal MCA-M1 occlusion (A). CT perfusion images (left to right: cerebral blood volume [CBV], cerebral blood flow [CBF], and time to peak [TTP]) showing a large CBV lesion in the MCA territory with relative sparing of the basal ganglia region (B). Diagnostic angiogram (left, anteroposterior; right, lateral) with right ICA injection showing an acute distal MCA-M1 occlusion with sparing of the lenticulostriate perforators (C). The patient underwent immediate Wingspan-assisted recanalization that resulted in immediate TIMI 3 flow restoration (immediate poststent angiogram: left, anteroposterior; right, lateral of immediate poststent angiogram; arrows show the proximal and distal ends of the stent) (D). Posttreatment CT perfusion images (left to right: CBV, CBF, and TTP) (E) showing complete salvage of the CBV lesion with a minimal infarct core in the posterior parietal region that corresponds to the lesion seen on magnetic resonance diffusion-weighted images on the first day after treatment (F). The patient's deficits were almost completely reversed on the second day after treatment, and she had an NIHSS score of 6.

occurred in 67% and 89% of the patients, respectively. There was one case of ICH (11%) and one case of acute in-stent thrombosis (successfully treated with abciximab and balloon angioplasty). The mortality rate was 33% (three of nine patients). All survivors achieved an mRS score of ≤ 2. Follow-up angiography was performed in four of the nine patients

at a mean of 8 months (range, 2–14 months) and showed no stent restenosis. Brekenfeld et al[23] reported use of the Wingspan stent as rescue therapy (in combination with different thrombolytic agents, percutaneous balloon angioplasty, and mechanical thromboembolectomy) in 12 patients with acute ischemic stroke (anterior circulation, six; posteri-
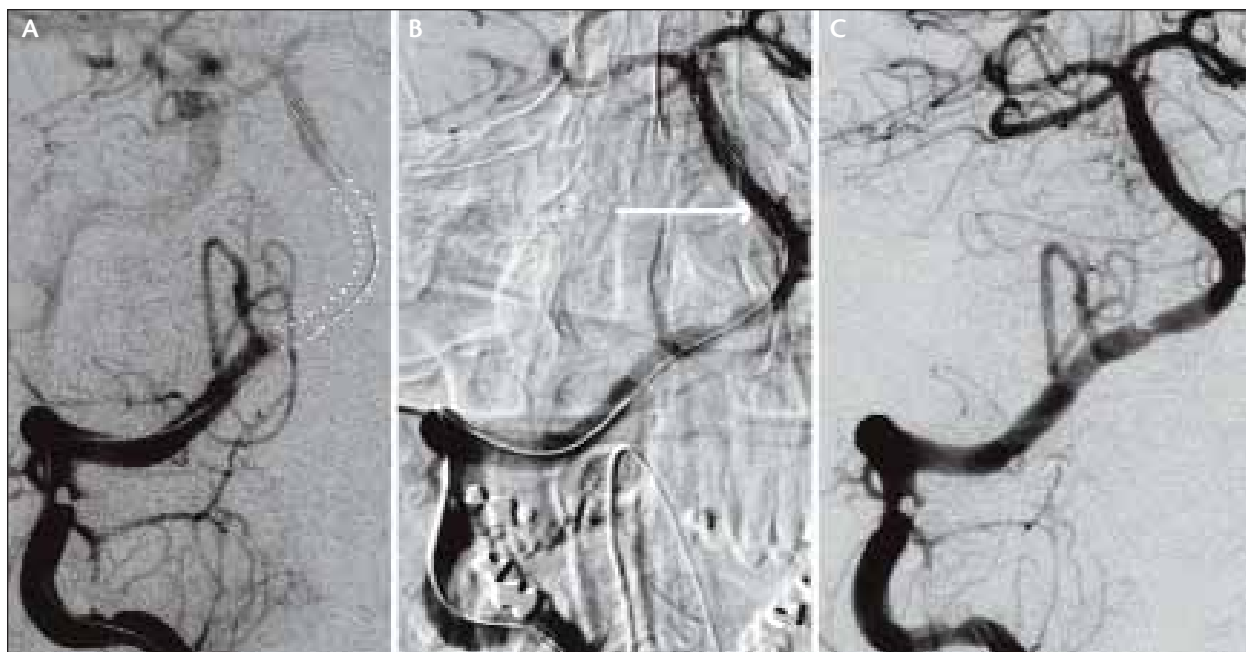
Figure 4. Temporary endovascular bypass. Right vertebrobasilar arteriogram, dual-injection technique (A). Right vertebral artery occlusion distal to the posterior inferior cerebellar artery origin (A). A large vertebrobasilar thrombus is outlined by the dotted lines. Right VA angiogram, close-up view (B). The stent (4.5- ≥ 37-mm Enterprise) is partially unsheathed. Close inspection of the image reveals three small dots marking the distal end of the stent (arrow). The proximal end is still within its sheath, allowing recapture. Recanalization is already successful, but has not yet reached its full extent. Right vertebral artery angiogram 10 minutes after B was obtained (C). The stent is still partially deployed. Recanalization continues to improve (relative to A). After this run, the stent was recaptured and withdrawn. Reprinted with permission from Hauck EF et al. AJNR Am J Neuroradiol (Published online March 13, 2009).[35]

or circulation, six; median presentation NIHSS score, 14). TIMI 2 or 3 recanalization was achieved in 92% of patients; no complications or hemorrhage occurred.

A multicenter retrospective review of prospectively collected data[36] of 20 acute ischemic stroke patients (mean presentation NIHSS score, 17) treated with Enterprise stent placement as a bailout procedure after current embolectomy options had been exhausted showed TIMI 2 or 3 recanalization in all patients (100%) and improvement in NIHSS of ≥ 4 points at discharge in 75% of patients. Adjunctive therapy included Merci retrieval (12 patients), angioplasty (seven patients), glycoprotein IIb/IIIa inhibition (12 patients), IA nitroglycerin administration (one patient), Wingspan stent deployment (three patients), and Xpert stent (Abbott Vascular) deployment (one patient). The investigators of this review found that the Enterprise stent could be more easily navigated and deployed to the occlusion site than the Wingspan stent, attested by its use in three cases of failed Wingspan stenting.

In our experience with endovascular acute ischemic stroke revascularization in 193 patients treated between 2006 and 2008 (S. K. Natarajan, written communication July 2009), there were 52 (26.9%) patients who underwent stent-assisted recanalization as a bailout after failed attempts with FDA-approved modalities. TIMI 2 or 3 recanalization was achieved in 71.2% of patients with a symptomatic ICH rate of 11.5%. The outcomes at 3 months were mRS ≤ 2 in 42.3% of patients and death in 21.2% of patients. One patient (1.9%) who had an acute ischemic stroke with a chronic MCA-M1 occlusion with moyamoya collaterals had immediate occlusion of a Neuroform stent, which was salvaged by balloon angioplasty. No further restenosis occurred in any of the patients in our series (including this patient) at 3 months.

SARIS: STENT-ASSISTED REVASCULARIZATION FOR ACUTE ISCHEMIC STROKE

Several case series[23-25,32,37] have reported excellent outcomes with SES in patients with acute intracranial occlusions in whom other recanalization methods have failed. Despite using stent deployment as a "salvage" technique in patients with recalcitrant occlusions, these data suggest that stent-assisted revascularization results in high recanalization rates with a reasonable safety profile. However, problems inherent
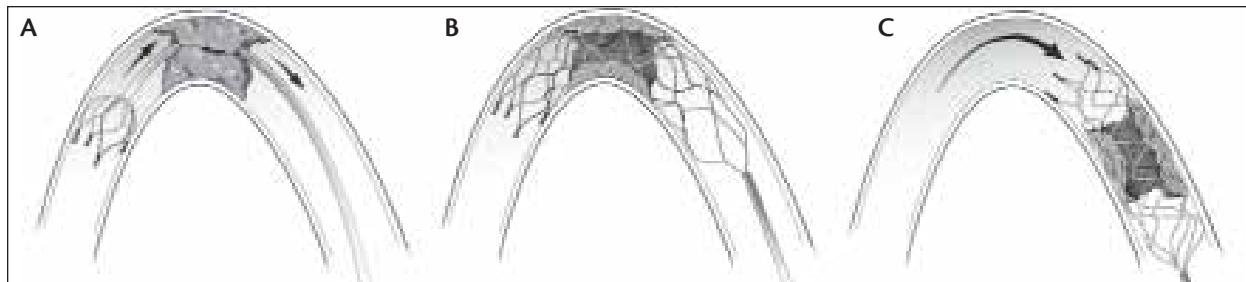
Figure 5. Illustration showing an occlusive clot in the vessel that has been crossed by the Rebar microcatheter (ev3 Inc.) (A). The microwire has been exchanged with the Solitaire FR Revascularization Device (ev3 Inc.) that is being deployed in the direction shown by the arrows. The Solitaire device is completely deployed and pushes the clot to the side, restoring blood flow immediately in the occluded vessel (B). The Solitaire with the clot and the Rebar are pulled with the clot into the guide catheter with constant syringe aspiration from the guide catheter (C). Reprinted with permission from Natarajan SK et al. Cardiovascular Interventions in Clinical Practice (In press).[37]

to the quality of data in retrospective case series and concerns about early rethrombosis and longer-term durability exist without a doubt. Therefore, we sought and received FDA approval for a 20-patient prospective pilot study, SARIS, to evaluate the safety and efficacy of primary stent deployment for revascularization in acute stroke patients.[1]

Eligibility criteria included presentation ≤ 8 hours after stroke onset, aged 18 years or older, NIHSS score ≥ 8, angiographic demonstration of focal intracerebral artery occlusion ≤ 14 mm, and either contraindication to IV rt-PA or failure to improve 1 hour after IV rt-PA administration. Exclusion criteria included known hemorrhagic diathesis or coagulopathy, platelet count < 100,000, ICH, blood glucose level of < 51 mg/100 mL, or CT perfusion imaging demonstrating more than one-third at-risk territory with nonsalvageable brain (low CBV).

Among the 20 patients enrolled, the mean age was 63 ± 18 years, and 14 were women. Mean presenting NIHSS score was 14 ± 3.8 (median, 13). Presenting TIMI score was 0 (85%) or 1 (15%). Mean time from stroke onset to intervention was 5 hours and 13 minutes. Total time from procedure onset to vessel recanalization was 45 minutes. Occluded vessels included the right MCA (11 patients), left MCA (five patients), basilar artery (three patients), and right carotid-T (one patient). Intracranial SES were placed in 19 of 20 enrolled patients. One patient experienced recanalization of the occluded vessel with positioning of the Wingspan stent delivery system before stent deployment. In two patients, the tortuous vessel did not allow tracking of the Wingspan stent. The more navigable Enterprise stent was used in both these cases. Twelve patients had other adjunctive therapies: IA eptifibatide (10 patients), IA rt-PA (two patients), angioplasty (eight patients), and IV rt-PA (two patients). In 40% of cases, no adjuvant therapies were utilized and, except for one case in which 4 mg of IA reteplase was used to treat a distal occlusion after recanalization, the remaining adjuvant-treated patients received some combination of eptifibatide or postdeployment angioplasty (among which one further patient also received IA rt-PA administration). These treatments were supportive in nature to improve and/or maximize the partial recanalization that had already occurred.

Recanalization to TIMI 3 (60% of patients) or 2 (40%) ($P < .0001$) was achieved; 65% of patients improved > 4 points in NIHSS score after treatment. One (5%) symptomatic and two (10%) asymptomatic ICHs occurred. At 1-month follow-up, an mRS score of ≤ 3 was achieved in 12 of 20 (60%) patients, and an mRS of ≤ 1 was achieved in nine of 20 (45%) patients. Mortality at 1 month was 25% (five patients). None of the patients enrolled in this study died due to any cause related to stent placement; all deaths were due to the severity of the initial stroke and associated comorbidities.

On the basis of these encouraging results from SARIS, we are currently conceptualizing two prospective studies: (1) ERAIS (Enterprise-Assisted Recanalization for Acute Ischemic Stroke), a pilot prospective study like SARIS, to assess the safety of the Enterprise stent for stent-assisted recanalization and (2) SMARTS (Stenting vs Maximal Medical Treatment for Acute Revascularization Therapy After Ischemic Stroke), a prospective, pilot phase II, randomized, controlled trial to test the safety and efficacy of the Wingspan bare-metal stent compared to best medical therapy in patients presenting within 8 hours of symptom onset who have contraindications to IV rt-PA or have failed to improve despite IV rt-PA therapy.

LIMITATIONS OF CURRENT STENT-ASSISTED REVASCULARIZATION TECHNOLOGY

The SES available at present are mainly useful for occlusions in large vessels like the ICA, proximal MCA-M1, basilar artery, intracranial vertebral artery, anterior cerebral artery-

A1, and posterior cerebral artery-P1. They cannot be used in smaller vessels and for clots that are located at bifurcations or that are longer in length than the stent. The need for aggressive antiplatelet therapy for 3 to 6 months after SES placement[24,25,38-40] is a major disadvantage. Patients treated for the prevention of recurrent stroke with aspirin face a hemorrhagic complication rate of 2.22 per 100 patient-years.[41] With dual-antiplatelet therapy, the risk is increased.[42-45] Zaidat et al[25] reported an 11% hemorrhage rate associated with stent placement for acute stroke. Moreover, Levy et al[24] reported lethal hemorrhages as a complication in 11% of patients treated with stent placement for acute stroke.

The current experience with stent-assisted recanalization is very limited, and the longer-term results have not been reported. Using SES for revascularization involves leaving a permanent implant in the vessel, and this may not be justifiable because most occlusions in acute ischemic stroke are caused by an embolic occlusion of a normal cranial artery. Embolectomy would be the appropriate option in such cases, in preference to a permanent implant. Thus, long-term surveillance of patients treated with stent-assisted revascularization for acute ischemic stroke is critical, especially in view of the midterm results of Wingspan stent implantation for atherosclerotic intracranial stenosis showing a 25% to 29% in-stent stenosis rate.[40,46-48] Although most patients with in-stent stenosis are asymptomatic, some may require target lesion revascularization.[47,49] Zaidat et al[25] reported one case (11%) of immediate in-stent restenosis after acute stroke treatment. The Enterprise stent has a lesser radial expansive force than the Wingspan stent and may incur lower rates of in-stent stenosis.[50]

Another limitation of stent-assisted revascularization is that, despite the higher recanalization rates, the rates of symptomatic ICH are high, and the outcomes are only marginally better than those reported with other modalities. One should also understand that all outcome data regarding stent-assisted revascularization is derived from small case series that attempt to establish the safety and effectiveness of stent-assisted revascularization and did not primarily try to prove better outcomes. Better patient selection supported by physiology-based imaging may decrease hemorrhage rates and improve outcomes in the future.

STENT-PLATFORM–BASED REVASCULARIZATION STRATEGIES
Temporary Endovascular Bypass
The introduction of closed-cell stents, which can be used as a temporary endovascular bypass to achieve immediate high rates of flow restoration and then resheathed or removed after recanalization is achieved, has obviated the need for dual-antiplatelet therapy and the long-term risk

involved in leaving a permanent implant. Kelly et al[51] and Hauck et al[35] (Figure 4) reported the use of the Enterprise stent as a temporary endovascular bypass in acute stroke. In both cases, the stent was partially deployed for some time and retrieved with successful recanalization of the occluded vessel.

Stent-Platform–Based Thrombectomy Device
The Solitaire FR Revascularization Device (Figure 5) is a recoverable, self-expanding thrombectomy device that was developed based on the Solitaire/Solo stent. The advantage of this device is that it is a fully recoverable SES-platform–based device that can be used as both a temporary endovascular bypass and a thrombectomy device. Moreover, it can be electrolytically detached like a coil in case permanent stent placement is necessary, such as in the setting of an atherothrombotic lesion. We evaluated the safety and efficacy of this device in a canine stroke model with soft and firm clots (S. K. Natarajan, written communication, June 2009). The device could be easily deployed and recovered and restored TIMI 2 or 3 flow immediately in all cases. Minimal residual clot in two of four instances required a second pass for complete clot retrieval. Minimal vasospasm was observed in two of four cases.

THE FUTURE
Although limitations of current stent technology may not allow the rationalization of stent-assisted revascularization as a primary therapy in all ischemic stroke patients, it is obviously a good bailout modality that achieves immediate sustained flow restoration in a high percentage of patients in certain vessel locations. It is envisioned that improvements in stent technology in the future will allow stent-assisted revascularization in more distal locations. Improvements in systemic drugs, drug-eluting stents, and stents coated with stem cells may accelerate stent endothelialization, thus obviating the need for or decreasing the duration of antiplatelet therapy after stent implantation. Drug-eluting stents and biodegradable stents specially designed for the intracranial circulation may decrease neointimal hyperplasia and in-stent stenosis in the future. Stent-platform–based thrombectomy devices that can be deployed if necessary and afford flexibility (depending on the type of occlusive lesion) may become the primary therapy for acute ischemic stroke. ∎

Elad I. Levy, MD, FACS, FAHA, is Associate Professor of Neurosurgery and Radiology, Director of the Endovascular

Fellowship, and Codirector of the Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences at the University at Buffalo, State University of New York in Buffalo, New York; and an attending physician in the Department of Neurosurgery at Millard Fillmore Gates Hospital, Kaleida Health in Buffalo, New York. He has disclosed that he receives research grant support, other research support (devices), and honoraria from Boston Scientific Corporation and research support from Micrus Endovascular and ev3. He further disclosed that he has ownership interests in Intratech Medical Ltd. and Mynx/Access Closure; serves as a consultant on the Board of Scientific Advisors to Codman Neurovascular/Cordis Corporation; serves as a consultant per project and/or per hour for Micrus Endovascular, ev3, and TheraSyn Sensors, Inc.; and receives fees for carotid stent training from Abbott Vascular and ev3. Dr. Levy may be reached at (716) 887-5200; elevy@ubns.com.

Sabareesh K. Natarajan, MD, MS, is a clinical endovascular research fellow and Clinical Assistant Professor (HS) of Neurosurgery and of the Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences at the University at Buffalo, State University of New York in Buffalo, New York; and with the Department of Neurosurgery at Millard Fillmore Gates Hospital, Kaleida Health in Buffalo, New York. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Adnan H. Siddiqui, MD, PhD, is Assistant Professor of Neurosurgery and Radiology, Director of Research, and Codirector of the Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences at the University at Buffalo, State University of New York in Buffalo, New York; and an attending physician in the Department of Neurosurgery at Millard Fillmore Gates Hospital, Kaleida Health in Buffalo, New York. He has disclosed that he has received a research grant from the University at Buffalo; he is a consultant to Codman Neurovascular/Cordis Corporation, Concentric Medical, ev3, and Micrus Endovascular; serves on speakers' bureaus for Codman Neurovascular/Cordis Corporation and Genentech; and has received honoraria from Genentech Inc., Neocure Group LLC, an American Association of Neurological Surgeons' course, an Emergency Medicine Conference, and from Codman Neurovascular/Cordis Corporation for training other neurointerventionists.

Kenneth V. Snyder, MD, PhD, is Clinical Assistant Professor of Neurosurgery in the School of Medicine and Biomedical Sciences at the University at Buffalo, State University of New York in Buffalo, New York; and with the Department of Neurosurgery at Millard Fillmore Gates Hospital, Kaleida Health in Buffalo, New York. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Erik F. Hauck, MD, PhD, is a neuroendovascular fellow, Department of Neurosurgery and Toshiba Stroke Research

Center, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York in Buffalo, New York; and Department of Neurosurgery, Millard Fillmore Gates Hospital, Kaleida Health in Buffalo, New York. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

J Mocco, MD, MS, is Assistant Professor of Neurosurgery, University of Florida in Gainesville, Florida. He has disclosed that has received a research grant from the Brain Aneurysm Foundation. He has previously received a one-time honorarium from Cordis Corporation.

L. Nelson Hopkins, MD, FACS, is Professor and Chairman of Neurosurgery, Professor of Radiology, and Director of the Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York in Buffalo, New York; and Chairman, Department of Neurosurgery, Millard Fillmore Gates Hospital, Kaleida Health in Buffalo, New York. He has disclosed that he receives research support from Toshiba; serves as a consultant to Abbott Vascular, Boston Scientific Corporation, Cordis Corporation, Micrus Endovascular, and W. L. Gore. He has further disclosed that he has a financial interest in AccessClosure, Boston Scientific Corporation, and Micrus Endovascular; serves as a board member, trustee, or holds an officer position in AccessClosure and Micrus Endovascular; and receives honoraria from Bard Peripheral Vascular, Boston Scientific Corporation, and Cordis Corporation.

1. Levy EI, Siddiqui AH, Crumlish A, et al. First Food and Drug Administration-approved prospective trial of primary intracranial stenting for acute stroke. SARIS (Stent-Assisted Recanalization in Acute Ischemic Stroke) (doi 10.1161/STROKEAHA.109.561274). Stroke. Published online August 20, 2009.
2. Hacke W, Brott T, Caplan L, et al. Thrombolysis in acute ischemic stroke: controlled trials and clinical experience. Neurology. 1999;53:S3-14.
3. Hacke W, Kaste M, Fieschi C, et al. for the ECASS Study Group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017-1025.
4. Hacke W, Kaste M, Fieschi C, et al. Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet. 1998;352:1245-1251.
5. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke. 2005;36:1432-1438.
6. Versnick EJ, Do HM, Albers GW, et al. Mechanical thrombectomy for acute stroke. AJNR Am J Neuroradiol. 2005;26:875-879.
7. Zaidat OO, Suarez JI, Sunshine JL, et al. Thrombolytic therapy of acute ischemic stroke: correlation of angiographic recanalization with clinical outcome. AJNR Am J Neuroradiol. 2005;26:880-884.
8. Humpich M, Singer OC, du Mesnil de Rochemont R, et al. Effect of early and delayed recanalization on infarct pattern in proximal middle cerebral artery occlusion. Cerebrovasc Dis. 2006;22:51-56.
9. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. 2007;38:967-973.
10. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke. 2008;39:1205-1212.
11. Tomsick T, Broderick J, Carrozella J, et al. Revascularization results in the Interventional Management of Stroke II trial. AJNR Am J Neuroradiol. 2008;29:582-587.
12. Wolpert SM, Bruckmann H, Greenlee R, et al. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. AJNR Am J Neuroradiol. 1993;14:3-13.
13. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke. 2007;38:948-954.
14. Fischer U, Arnold M, Nedeltchev K, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke. 2005;36:2121-2125.
15. Lincoff AM, Topol EJ. Illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction? Circulation. 1993;88:1361-1374.
16. Grotta JC, Welch KM, Fagan SC, et al. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. Stroke. 2001;32:661-668.
17. Qureshi AI, Siddiqui AM, Kim SH, et al. Reocclusion of recanalized arteries during intra-arterial thrombolysis for acute ischemic stroke. AJNR Am J Neuroradiol. 2004;25:322-328.

18. Bose A, Henkes H, Alfke K, et al. The Penumbra System: a mechanical device for the treatment of acute stroke due to thromboembolism. AJNR Am J Neuroradiol. 2008;29:1409-1413.

19. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999;282:2003-2011.

20. Natarajan SK, Siddiqui AH, Hopkins LN, et al. Endovascular thrombolysis: pharmacologic and mechanical. In: Bendok BR, Batjer HH, Naidech AM, et al, eds. Hemorrhagic and Ischemic Stroke: Surgical, Interventional, Imaging, and Medical Approaches. New York, NY: Thieme Publishers. In press.

21. Natarajan S, Karmon Y Siddiqui AH, et al. Intracranial stent-assisted revascularization for acute ischemic stroke. Vascular Disease Management. In press.

22. The Penumbra Pivotal Stroke Trial Investigators. The Penumbra Pivotal Stroke Trial. Safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. (doi 10.1161/STROKEAHA.108.544957). Stroke. Published online ahead of print July 11, 2009.

23. Brekenfeld C, Schroth G, Mattle HP, et al. Stent placement in acute cerebral artery occlusion: use of a self-expandable intracranial stent for acute stroke treatment. Stroke. 2009;40:847-852.

24. Levy EI, Mehta R, Gupta R, et al. Self-expanding stents for recanalization of acute cerebrovascular occlusions. AJNR Am J Neuroradiol. 2007;28:816-822.

25. Zaidat OO, Wolfe T, Hussain SI, et al. Interventional acute ischemic stroke therapy with intracranial self-expanding stent. Stroke. 2008;39:2392-2395.

26. Henkes H, Miloslavski E, Lowens S, et al. Treatment of intracranial atherosclerotic stenoses with balloon dilatation and self-expanding stent deployment (WingSpan). Neuroradiology. 2005;47:222-228.

27. Levy EI, Sauvageau E, Hanel RA, et al. Self-expanding versus balloon-mounted stents for vessel recanalization following embolic occlusion in the canine model: technical feasibility study. AJNR Am J Neuroradiol. 2006;27:2069-2072.

28. Abou-Chebl A, Bajzer CT, Krieger DW, et al. Multimodal therapy for the treatment of severe ischemic stroke combining GPIIb/IIIa antagonists and angioplasty after failure of thrombolysis. Stroke. 2005;36:2286-2288.

29. Nogueira RG, Schwamm LH, Buonanno FS, et al. Low-pressure balloon angioplasty with adjuvant pharmacological therapy in patients with acute ischemic stroke caused by intracranial arterial occlusions. Neuroradiology. 2008;50:331-340.

30. Qureshi AI, Siddiqui AM, Suri MF, et al. Aggressive mechanical clot disruption and low-dose intra-arterial third-generation thrombolytic agent for ischemic stroke: a prospective study. Neurosurgery. 2002;51:1319-1329.

31. Ringer AJ, Qureshi AI, Fessler RD, et al. Angioplasty of intracranial occlusion resistant to thrombolysis in acute ischemic stroke. Neurosurgery. 2001;48:1282-1290.

32. Fitzsimmons BF, Becske T, Nelson PK. Rapid stent-supported revascularization in acute ischemic stroke. AJNR Am J Neuroradiol. 2006;27:1132-1134.

33. Sauvageau E, Levy EI. Self-expanding stent-assisted middle cerebral artery recanalization: technical note. Neuroradiology. 2006;48:405-408.

34. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med. 1985;312:932-936.

35. Hauck EF, Mocco J, Snyder KV, et al. Temporary endovascular bypass: a novel treatment for acute stroke (doi 10.3174/ajnr.A1536). AJNR Am J Neuroradiol. Published online March 13, 2009.

36. Mocco J, Hanel RA, Sharma J, et al. Enterprise vascular reconstruction device to salvage acute ischemic occlusions refractory to traditional endovascular recanalization methods. J Neurosurg. In press.

37. Natarajan SK, Snyder KV, Siddiqui AH, et al. Interventional management of acute ischemic stroke. In: Haase J, Schafers H-J, Sievert H, et al, eds. Cardiovascular Interventions in Clinical Practice. Oxford, UK: Wiley Blackwell. In press.

38. Bose A, Hartmann M, Henkes H, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. Stroke. 2007;38:1531-1537.

39. Fiorella D, Levy EI, Turk AS, et al. US multicenter experience with the Wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. Stroke. 2007;38:881-887.

40. Zaidat OO, Klucznik R, Alexander MJ, et al. The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis. Neurology. 2008;70:1518-1524.

41. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001;345:1444-1451.

42. Aronow HD, Steinhubl SR, Brennan DM, et al. Bleeding risk associated with 1 year of dual antiplatelet therapy after percutaneous coronary intervention: insights from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Am Heart J. 2009;157:369-374.

43. Flaherty ML, Tao H, Haverbusch M, et al. Warfarin use leads to larger intracerebral hematomas. Neurology. 2008;71:1084-1089.

44. Kjaer J, Larsen CH, Poulsen TS, et al. Bleeding complications after treatment with clopidogrel and acetylsalicylic acid after acute coronary syndrome. Ugeskr Laeger. 2006;168:3209-3214.

45. Reaume KT, Regal RE, Dorsch MP. Indications for dual antiplatelet therapy with aspirin and clopidogrel: evidence-based recommendations for use. Ann Pharmacother. 2008;42:550-557.

46. Albuquerque FC, Levy EI, Turk AS, et al. Angiographic patterns of Wingspan in-stent restenosis. Neurosurgery. 2008;63:23-28.

47. Levy EI, Turk AS, Albuquerque FC, et al. Wingspan in-stent restenosis and thrombosis: incidence, clinical presentation, and management. Neurosurgery. 2007;61:644-651.

48. Turk AS, Levy EI, Albuquerque FC, et al. Influence of patient age and stenosis location on Wingspan in-stent restenosis. AJNR Am J Neuroradiol. 2008;29:23-27.

49. Fiorella DJ, Levy EI, Turk AS, et al. Target lesion revascularization after Wingspan: assessment of safety and durability. Stroke. 2009;40:106-110.

50. Cha SH, Han MH, Choi YH, et al. Vascular responses in normal canine carotid arteries: comparison between various self-expanding stents of the same unconstrained size. Invest Radiol. 2003;38:95-101.

51. Kelly ME, Furlan AJ, Fiorella D. Recanalization of an acute middle cerebral artery occlusion using a self-expanding, reconstrainable, intracranial microstent as a temporary endovascular bypass. Stroke. 2008;39:1770-1773.