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STATE-OF-THE-ART PAPER

Acute Stroke Intervention

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This review summarizes the current state-of-the-art regarding the endovascular management of acute ischemic stroke. Beginning with intravenous tissue plasminogen activator, this paper traces the gradual shift of systemic thrombolysis from a competing to complementary treatment modality. Intra-arterial thrombolysis, mechanical thrombectomy with the Merci (Concentric Medical, Mountain View, California) and Penumbra (Penumbra, Inc., Alameda, California) systems, angioplasty, primary intracranial stenting, and emerging stentriever devices are sequentially reviewed. Ultimately, this paper lays the foundation for current endovascular stroke management and considers future areas of progress and research.
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Stroke Epidemiology

Acute ischemic stroke inflicts tremendous morbidity and mortality. In the United States, 795,000 new and recurrent strokes occur annually, with direct economic costs in excess of $73 billion (1). Over the past decade, mechanical thrombectomy by endovascular means emerged as a complementary treatment to systemic intravenous (IV) tissue plasminogen activator (t-PA). The gradual adoption of perfusion-based imaging modalities has begun to refine patient selection. These dual developments offer great promise in the treatment of large-vessel occlusions, the most severe form of acute ischemic

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stroke. This paper reviews the data underpinning recent progress in the endovascular management of ischemic stroke and ranges from IV t-PA to the advent of stentriever devices.

Patient Selection

Important features of the patient's clinical presentation that bear on endovascular treatment decisions include the following: 1) time since onset of ictus; 2) severity of neurologic deficit quantified by the National Institutes of Health Stroke Scale (NIHSS) (2); 3) age (2); 4) baseline functional status; 5) features of medical history that suggest a potential stroke etiology; and 6) vascular anatomy.

Presentation within 4.5 h offers the patient the possibility of IV t-PA as a definitive therapy or bridge to endovascular intervention (3). Wake-up strokes require the conservative assumption that the ictus coincides with the time that the patient was last seen in a normal state. However, physiologic imaging modalities mitigate against this clinical uncertainty and allow meaningful intervention in select patients beyond 8 h with good clinical outcomes (4).

Patients with an NIHSS score >8 or >5 with a substantial aphasic component receive screening for endovascular intervention. Age and functional status serve as complementary elements of stroke patient evaluation. Generally speaking, patients older than 80 years of age fare more poorly with endovascular therapy, with increasing risks of poor functional outcome and iatrogenic hemorrhage (2). Independent functional status may ultimately qualify patients older than 80 years of age for endovascular evaluation.

After completion of an expedited clinical evaluation, the patient proceeds to noninvasive imaging. At Millard Fillmore Gates Hospital at the University at Buffalo, the computed tomography (CT) imaging stroke protocol includes: 1) a noncontrast cranial CT scan to exclude hemorrhagic conversion or other structural abnormality; 2) CT perfusion (CTP) imaging with special attention to time-to-peak, cerebral blood flow (CBF), and cerebral blood volume (CBV) sequences; and 3) CT angiography of the aortic arch through the intracranial vessels. Perfusion imaging is performed on a 320-slice Aquilon scanner (Toshiba Medical Systems, Tustin, California).

CTP is being evaluated for the assessment of a completed infarct in the vascular distribution of the occluded vessel and estimation of the tissue at risk of becoming an infarct if not reperfused. Perfusion features stratify the patient's risk of hemorrhage after endovascular intervention and potential benefit of mechanical flow restoration. In general terms, when decreased CBF and CBV (findings suggestive of a completed infarct) represent less than one third of the territory exhibiting increased time-to-peak (putative penumbra), we have found that the patient benefits from endovascular intervention and has a lower risk of symptomatic intracerebral hemorrhage (ICH). Early ischemic changes on a noncontrast CT scan that correspond to CBF and CBV deficits solidify the reliability of predicting a completed infarct. Reperfusion of a larger necrotic core is ineffective and would likely increase the risk of hemorrhage (5). Conversely, patients with hyperacute presentations (i.e., <2 h) were found to have salvageable of regions with decreased CBV and CBF after endovascular therapy, even in the face of a poor CTP profile. Finally, occlusion of proximal M1 perforators and attendant basal ganglionic involvement in the infarct core presaged a higher risk of hemorrhage after recanalization and poor clinical outcome (6). The main limitation of CTP in our experience has been that it lacks the ability to accurately differentiate between true penumbra (tissue that will be converted to an infarct if it is not reperfused) and benign oligemia (tissue that is ischemic when compared with surrounding tissue but will survive due to collaterals even if not reperfused). Recent studies suggest that clinical improvement is noted even in late reperfusion patients with large penumbras identified on CTP imaging (4,7). We must emphasize here that the use of CTP as an aid in selecting patients for endovascular therapy is at present purely experimental, and the lessons that we have learned and the measures that we use at our institution need to be studied as part of a multicenter, randomized, prospective, controlled trial.

Recently, there has been interest in estimating CTP thresholds and using quantitative and automated CTP maps to estimate core and penumbra to aid in choosing patients for reperfusion beyond traditional therapeutic windows or when time of onset of stroke is not known (8,9). Differences in CTP hardware and software can affect quantified metrics (10,11), and clearly defined thresholds for guiding therapy have yet to be standardized (12). Some studies suggest the use of CBF thresholds for defining areas of infarct, specifically CBF <25 ml/100 g/min (13). In an analysis of 130 patients with acute stroke, Wintermark et al. (14) suggested using absolute CBV <2 ml/100 g to define core infarct, and

Abbreviations and Acronyms

CBF = cerebral blood flow
CBV = cerebral blood volume
CT = computed tomography
CTP = computed tomography perfusion
FDA = U.S. Food and Drug Administration
IA = intra-arterial
ICH = intracerebral hemorrhage
IMS = Interventional Management of Stroke
IV = intravenous
MCA = middle cerebral artery
mRS = modified Rankin scale
NIHSS = National Institutes of Health Stroke Scale
NINDS = National Institute of Neurological Disorders and Stroke
OR = odds ratio
r-proUK = recombinant pro-urokinase
rt-PA = recombinant tissue plasminogen activator
TCD = transcranial Doppler
TIBI = Thrombolysis in Brain Ischemia
TIMI = Thrombolysis In Myocardial Infarction
t-PA = tissue plasminogen activator
UK = urokinase

a relative mean transit time increase >145% of normal to define penumbra. Murphy et al. (13) studied 30 patients and demonstrated CBF × CBV as the best predictor for differentiating core infarct and penumbra, better than CBF or CBV thresholds alone. Specific thresholds are also specific to the perfusion software platform being used and may not be automatically transferable to other vendors, scanners, and even software versions. At this time, much work remains to standardize quantitative methods of CTP interpretation, which, in the future, may be addressed by a proposed consortium for acute stroke imaging (12).

Attention should be paid to technical aspects of data acquisition and post-processing, including placement of regions of interest and selecting an appropriate volume of imaging for the patient's clinical syndrome (15). Entities such as chronic infarct, severe microvascular ischemia, and seizure can be mistaken for acute infarct. Vascular stenoses can mimic and overestimate areas of ischemic penumbra; therefore, CTP should always be performed and interpreted in conjunction with CT angiography (5).

CT angiography, although not essential at institutions proceeding directly to the performance of catheter angiography for diagnostic purposes, provides critical information for endovascular planning. First and foremost, the target vessel occlusion (identified mostly by clinical correlation with symptoms) responsible for the patient's presentation is confirmed with the corresponding CTP data. Additionally, CT angiography allows us to determine the length of the occlusion, identify the presence of tandem occlusions, and plan macrovascular access.

IV Thrombolysis

In acute ischemic stroke, IV thrombolytic therapy remains the standard of care for qualifying patients (16). In 1996, the U.S. Food and Drug Administration (FDA) approved the use of IV recombinant tissue plasminogen activator (rt-PA), based largely on the results of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study (17). In 2008, the European Cooperative Acute Stroke Study III trial (3) demonstrated a statistically significant benefit of IV t-PA administered within the 3- to 4.5-h treatment window. The DEFUSE (Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution) study evaluated 74 patients with a perfusion-diffusion mismatch on magnetic resonance imaging as a surrogate for ischemic penumbra (18). The assumption was that these patients would benefit from IV thrombolysis in an extended time window of 3 to 6 h after onset. A target-mismatch profile was defined as a perfusion-weighted imaging lesion that was ≥10 ml and ≥120% of the diffusion-weighted imaging lesion without a malignant profile; a malignant profile was defined as a baseline diffusion-weighted imaging lesion ≥100 ml and/or a perfusion-weighted imaging lesion of ≥100 ml. Early reperfusion was associated with favorable clinical response in patients with a perfusion-diffusion mismatch (odds ratio [OR]: 5.4; $p = 0.039$) and an even more favorable response in patients with the target-mismatch profile (OR: 8.7; $p = 0.011$). Patients with the no-mismatch profile (i.e., perfusion-weighted imaging corresponded to diffusion-weighted imaging) did not appear to benefit from early reperfusion. In patients with the malignant profile, early reperfusion was associated with 50% symptomatic ICH. Early reperfusion was associated with symptomatic ICH in 50% of patients with the malignant profile compared with 6.7% with the target-mismatch profile. This study suggested that perfusion imaging may stratify patients who stand to benefit from IV thrombolysis during a 3- to 6-h window versus patients for whom IV t-PA presents a higher hemorrhagic risk.

The technical success of IV t-PA in achieving revascularization was well characterized by a study using transcranial Doppler (TCD) imaging. In 109 patients, TCD imaging allowed classification of waveforms into Thrombolysis In Brain Ischemia (TIBI) tiers (19). The recanalization (TIBI 4 or 5) rate was 35% for patients who presented with minimal to no initial flow (TIBI 0 or 1) and 52% for patients with initial partial occlusion (TIBI 2 or 3). TIBI flow recovery correlated with NIHSS score improvement; technical outcomes, therefore, corresponded to clinical results. At 24-h, NIHSS scores were higher in patients with TIBI flow grade 0 or 1 than those with TIBI flow grade 4 or 5. Lack of flow recovery predicted worsening or lack of improvement and a high mortality rate (71%) for patients with posterior circulation occlusions. Additional TCD studies supported the need for adjunctive methods in cases of failed IV t-PA revascularization (20,21). In large-vessel occlusive strokes, a high percentage of vessels did not completely recanalize after IV thrombolysis. Failed revascularization rates corresponded to the occlusion site: 67% middle cerebral artery (MCA), 25% basilar artery, and 100% internal carotid artery (Thrombolysis In Myocardial Infarction [TIMI] [22] flow grades 0 to 2); this correlated with significant neurologic deficits at 24 h (20,21).

Intra-Arterial (IA) Thrombolysis

Although IV thrombolysis represents the standard of care for eligible patients and t-PA is the only drug to receive FDA approval for treatment of ischemic stroke, it offers only marginal efficacy in large-vessel occlusions. Overall, in most cases, IV t-PA–induced recanalization occurs during the first hour after treatment (complete in 31% and partial in 22%), by TCD monitoring. The probability of recanalization after the first 60 min drops significantly (OR for delayed/early recanalization: 0.16 [95% confidence interval: 0.085 to 0.304; $p < 0.001$]) (23).

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Theoretically, IA thrombolysis may offer a higher dose of thrombolytic drug delivery to the clot with fewer systemic complications and higher recanalization rates (24). IA treatment may also facilitate extension of the therapeutic window and provide an option for patients with contraindications to systemic thrombolysis (i.e., postoperative stroke) or patients in whom IV thrombolysis has failed. Angiographic precision confers the following advantages: 1) gold standard characterization of the obstructive lesion; 2) imaging of collateral flow anatomy; 3) confirmation and exact degree and timing of recanalization; and 4) combination with mechanical thrombectomy methods. Conversely, disadvantages of IA treatment include delay in treatment, risks of catheter manipulation, and the need for skilled endovascular facilities and personnel (24).

The PROACT (Prolyse in Acute Cerebral Thromboembolism) studies evaluated IA thrombolysis with recombinant pro-urokinase (r-proUK) in patients within 6 h of an MCA (M1 or M2 segment) occlusion stroke (25,26). The PROACT-II study (a phase III prospective, randomized, placebo-controlled study) enrolled 180 patients with a median NIHSS score of 17 (range 4 to 30) (26). A favorable outcome (modified Rankin scale [mRS] score of 0 to 2 at 90 days) was achieved in 40% of patients treated with IA r-proUK (9 mg; plus low-dose heparin) versus only 25% of control subjects (low-dose heparin only) ($p = 0.04$). The recanalization rate was significantly higher in the r-proUK group (66%) than in the control group (18%) ($p < 0.001$). Although the symptomatic ICH rate was higher in r-proUK patients (10%) than in control patients (2%) ($p = 0.06$), no difference in mortality rate was observed. Although only IA r-proUK was used in the PROACT study of thrombolysis because of the unavailability of this drug, rt-PA is used for IA thrombolysis (r-proUK was used in PROACT but is not available at present, so rt-PA is used). However, the FDA has not yet approved rt-PA for IA thrombolysis.

Two studies in Japan evaluated IA-UK treatment. Using data from Japan's J-MUSIC (Multicenter Stroke Investigator's Collaboration), an initial case-control analysis assessed the effects of IA-UK thrombolysis in 91 patients with acute cardioembolic stroke and presentation NIHSS score of 5 to 22 (median NIHSS score, 14) who were treated within 4.5 h of symptom onset (27). Favorable outcomes (mRS score of 0 to 2) occurred in 50.5% of the UK group and 34.1% of the control group ($p = 0.0124$), with no differences in mortality rate.

The MELT (Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial) represents the second Japanese study (28). Approval of IV infusion of rt-PA in Japan prompted early termination of this trial. This randomized trial enrolled 57 patients to IA-UK versus 57 patients to placebo within 6 h of MCA (M1 or M2 segment) stroke. No significant advantages were observed for IA treatment with respect to favorable outcome (mRS score of 0 to 2) at 90 days. Excellent functional outcomes at 90 days (mRS score of 0 to 1) were present in 42.1% of the IA group and in 22.8% of the placebo group ($p = 0.045$; OR: 2.46, 95% confidence interval: 1.09 to 5.54), with a significantly higher incidence of NIHSS 0 to 1 scores in the IA group compared with the control group ($p = 0.017$). No significant difference was observed in mortality or ICH rate.

From these Japanese IA thrombolysis studies, it is apparent that the recanalization rate may differ with occlusion site and stroke etiology. Consideration of the occlusion pathology may therefore inform endovascular planning. Lower recanalization rates were observed in patients with thromboembolic carotid-terminus occlusion (30%) relative to MCA M1-segment (50%) or M2-segment (90%) occlusions (29).

A retrospective study of 62 patients treated with IA-UK within 6 h of stroke onset evaluated whether recanalization differs among different types of thromboembolic occlusions (29). Treatment of carotid territory occlusions resulted in an overall 53% recanalization efficacy: 28% of carotid-terminus, 55% of M1-segment, 74% of distal M1-segment, and 60% of M2-segment occlusions. Regression analysis revealed that only the recanalization rate correlated with occlusion site ($p = 0.010$). The recanalization rate was not influenced by stroke etiology (large-artery atherosclerosis, cardioembolism without transesophageal echocardiography findings, or stroke of undetermined etiology); a subgroup of patients with cardiac thrombus confirmed by transesophageal echocardiography had significantly lower recanalization rates and were the lone exception ($p = 0.017$). In summary, IA recanalization success of thromboembolic carotid territory occlusions corresponded to thromboembolus location but not stroke etiology.

Combined IV and IA Thrombolysis

The IMS (Interventional Management of Stroke) studies aimed to investigate the feasibility and safety of a combined IV and IA approach to thrombolysis. In IMS-I, 80 patients were enrolled within 3 h of stroke onset; the median baseline NIHSS score was 18 (30). The patients received IV t-PA at 0.6 mg/kg followed by 22 mg IA via a 2-h infusion or until thrombolysis. Outcome was compared with that in the NINDS rt-PA stroke trial (17). IMS subjects had a significantly better outcome at 3 months than NINDS placebo-treated subjects for all outcome measures (OR: ≥ 2) but not beyond the benefit conferred to the IV thrombolysis group.

IMS-II was a continuous, nonrandomized, safety and feasibility pilot study to evaluate the efficacy and safety of reduced-dose IV rt-PA (0.6 mg/kg), followed by IA rt-PA coupled with low-energy sonography to theoretically in-

crease fluid permeation and thrombolytic infusion within the clot (via the EKOS Primo Micro-Infusion Catheter [EKOS Corporation, Bothell, Washington]) (31). IMS-II subjects had significantly better outcomes at 3 months than NINDS placebo-treated subjects for all end points (OR: ≥2.7) and better outcomes than NINDS rt-PA–treated subjects as measured by the Barthel Index and Global Outcome Test.

Pooled IMS I and II data showed that partial or complete recanalization occurred in 74.6% of internal carotid artery–terminus and MCA-M1 occlusions, with good reperfusion (Thrombolysis In Myocardial Infarction [TIMI] flow grade 2/3) in 61.3% (31,32). Revascularization correlated strongly with good outcome for TIMI flow grade 2 or 3 reperfusion ($p = 0.0004$). Compared with the NINDS t-PA stroke trial, 3-month mortality was nonsignificantly lower in IMS-II (16%) compared with placebo-treated patients (24%) or rt-PA–treated patients (21%). The rate of symptomatic ICH was higher in IMS-II (9.9%) but not significantly different from that in the NINDS t-PA stroke trial (6.6%). The definitive trial, IMS-III, is ongoing, and the results will likely provide class I evidence of the concept of IV-IA therapy.

Mechanical Thrombectomy

IV t-PA results in early recanalization in only 30% to 50% of patients, with even lower rates of revascularization in larger vessel occlusions and is associated with a reocclusion rate as high as 17% (33–36). Mechanical revascularization for acute stroke may be considered for intracranial large-vessel occlusions in patients presenting with acute stroke. Clot perturbation may be achieved with common devices such as microwires, snares, and angioplasty balloons, although these techniques have not been evaluated in prospective trials.

Two FDA-approved devices are available specifically for mechanical thrombectomy: the Merci retriever (Concentric Medical, Mountain View, California) and the Penumbra (Penumbra, Inc., Alameda, California). The Merci retriever, FDA approved in 2004, is a corkscrew-shaped device consisting of a flexible nitinol wire in 5 helical loops. Designed for placement distal to the thrombus, retrieval allows en bloc thrombus removal (Fig. 1). The penumbra device (Fig. 2), by contrast, works proximally to disrupt and aspirate the thrombus. Both devices are designed for thrombectomy in carefully selected acute stroke patients with large-vessel intracranial occlusions.

The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) and Multi-MERCI trials evaluated the safety and efficacy in the setting of acute stroke within 8 h of onset (37–39). The primary end points were successful revascularization in all treatable vessels and major device-related

Figure 1. The Merci Retriever

The Merci retriever is a corkscrew-shaped device that consists of a flexible nitinol wire in 5 helical loops (courtesy of Concentric Medical, Mountain View, California).

complications. The control arm was the spontaneous recanalization rate of 18% from the PROACT II (26) trial. In the Multi-MERCI Part I, 111 patients with an average baseline NIHSS score of 19 underwent thrombectomy with the newer generation L5 retriever device (37). Thirty patients received IV t-PA before intervention. Treatment with the retriever alone resulted in revascularization in 60 of 111 vessel (54%) and in 77 of 111 vessels (69%) after additional therapy (IA t-PA, mechanical clot disruption). Ten of 111 patients (9.0%) had a symptomatic ICH; of these 10 patients, 2 received IV t-PA and 8 did not. The rate of clinically significant device-related complications was 4.5%. Among patients in whom revascularization was achieved, there was a 2-fold survival advantage, and a significantly higher proportion of patients lived without significant disability. Multi-MERCI Part II included an additional 52 patients with 3-month outcome of 39% of patients with an mRS score of <2, symptomatic ICH rate of 7.99%, asymptomatic ICH rate of 28.9%, and mortality in 30% (38). This trial was important in establishing that mechanical thrombectomy could be safely and effectively performed in patients who received IV t-PA as well as those who are not candidates for IV thrombolytic agents.

The integral components of the Merci Retrieval System include the Merci retriever, Merci microcatheter, and the Merci balloon guide catheter (balloon guide). The Merci procedure is performed after femoral artery access is obtained with the Merci balloon guide, which comes in both 8- and 9-F outer diameters. Once the balloon guide is in the conduit vessel of interest, a medium-sized catheter (4.2- and 5.3-F outer diameters), the distal access catheter (used for triaxial support), and microcatheter of choice are advanced over the microwire to the clot under direct fluoroscopic guidance. The microwire is then exchanged for the Merci retriever system with placement distal to the clot (Fig. 3). The balloon guide is then inflated. Using a slow, steady pulling motion, the retriever engages the clot while the distal access catheter position is maintained. Then, as the

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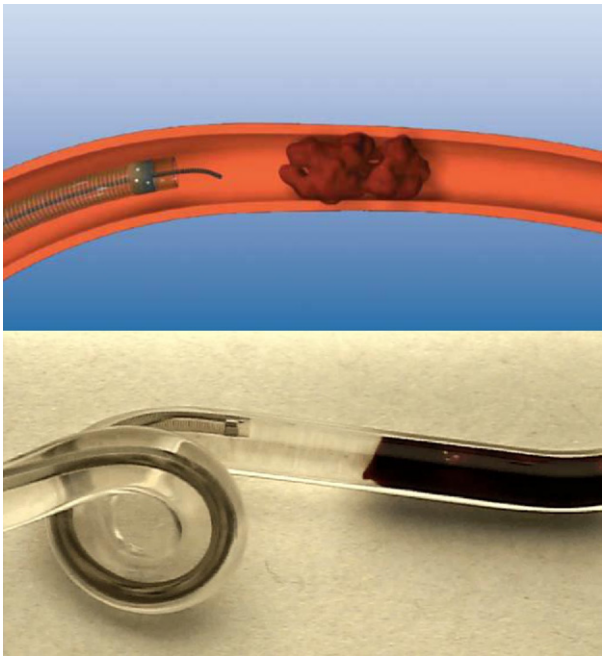

Figure 2. Penumbra Thrombus Perturbation and Aspiration System

(Top) Schematic representation. **(Bottom)** Model of Penumbra aspiration catheter and separator proximal to intraluminal thrombus (courtesy of Penumbra, Inc., Alameda, California).

clot moves more proximally, the distal access catheter, microcatheter, and retriever are moved toward the guide while aggressive aspiration is performed from the guide. The retriever can be resheathed and the steps repeated.

The Penumbra Pivotal Stroke Trial also showed that the Penumbra device was safe and effective for revascularization in patients with acute intracranial large-vessel occlusion (40). This prospective, multicenter, single-arm study included 125 patients with an NIHSS score of at least 8, presenting within 8 h of symptom onset, and ineligible for or with an occlusion refractory to IV t-PA. TIMI flow grade 2 or 3 revascularization was obtained in 81.6% of patients. ICH was seen in 28% of patients, 11% of whom were symptomatic. Overall mortality was 32.8% from all causes.

The Penumbra system has 3 main components: a reperfusion catheter, separator, and a thrombus removal ring. The Penumbra procedure is performed after arterial access is obtained and usually after systemic heparinization. All components of the Penumbra system are deliverable through a 6-F standard guide catheter, but an 070 Neuron catheter (Penumbra, Inc.) is the guide designed for the system. The reperfusion catheter is then advanced past the guide catheter over a guidewire and placed proximal to the clot. The catheters and separators are available in different sizes for various arterial diameters (Fig. 4). The guidewire is then removed from the reperfusion catheter, and the penumbra separator is advanced through the reperfusion catheter. The aspiration pump is then started and a continuous aspiration, clot disruption-debulking process is performed with the separator. In general, the Penumbra device works better in straight arterial segments than around curves or at branch points because the separator may cause arterial perforation. In addition, the largest catheter possible should be used to allow for the greatest amount of aspiration because suction decreases dramatically with decreasing vessel diameter.

In general, mechanical thrombectomy has been proven safe and effective for removal of clots in large vessels after acute ischemic stroke in multiple nonrandomized, prospective trials. Mechanical thrombectomy requires the knowledge and skills of trained neurointerventionists with experience in the use of these devices who can choose patients best suited for this treatment.

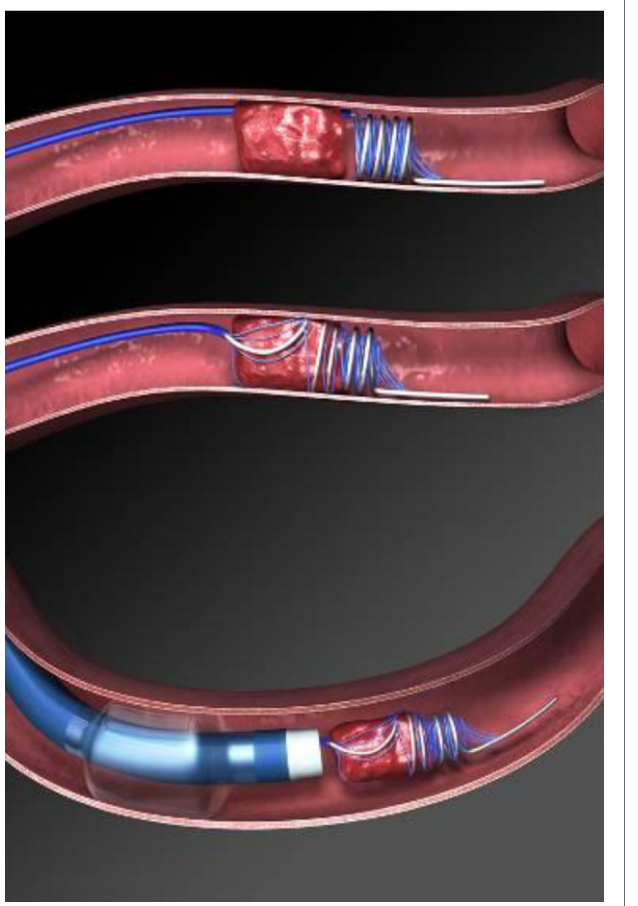

Figure 3. The Merci Retriever

The device is placed distal to the clot **(top)**, engages the clot **(middle)**, and then pulls the clot back into the guide catheter **(bottom)** (courtesy of Concentric Medical).

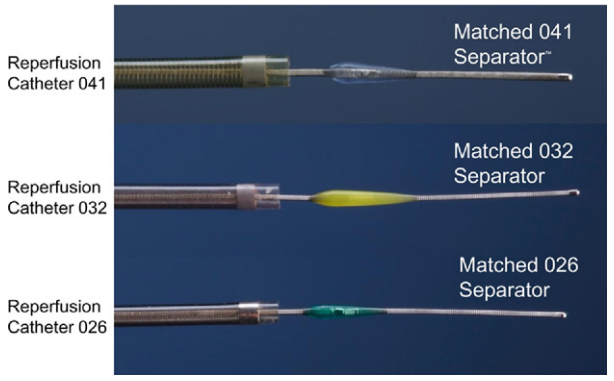

Figure 4. The Penumbra Aspiration System

Shown are matching catheters and separators 041, 032, and 026 (courtesy of Penumbra, Inc.).

Stent-Assisted Revascularization for Acute Ischemic Stroke

Several retrospective case series reported successful use of self-expanding stents for acute stroke treatment, with higher rates of recanalization than those obtained with other recanalization modalities (41–43). A multicenter retrospective review of prospectively collected data for 20 acute ischemic stroke patients (mean presentation NIHSS score of 17) treated with Enterprise stent (Codman Neurovascular, Raynham, Massachusetts) placement as a bail-out procedure after current embolectomy options had been used showed TIMI flow grade 2 or 3 recanalization in all patients (100%) and improvement in NIHSS score of ≥4 points at discharge in 75% of patients (44). Adjunctive therapy included Merci retrieval (n = 12), angioplasty (n = 7), glycoprotein IIb/IIIa inhibition (n = 12), IA nitroglycerin administration (n = 1), Wingspan stent (Boston Scientific, Natick, Massachusetts) deployment (n = 3), and Xpert stent (Abbott Laboratories, Abbott Park, Illinois) deployment (n = 1). The authors 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 3 cases of failed Wingspan stenting.

On the basis of these preliminary data, we received FDA approval for a pilot study, SARIS (Stent-Assisted Recanalization in acute Ischemic Stroke), to evaluate the Wingspan stent for revascularization in patients who did not improve after or had a contraindication to IV thrombolysis (45). The mean time interval from stroke onset to intervention was 5 h 13 min. Total time from procedure onset to vessel recanalization was 45 min. The average presenting NIHSS score was 14. Seventeen patients presented with a TIMI score of 0 and 3 patients with a TIMI score of 1. Occluded vessels included the right MCA (n = 11), left MCA (n = 5), basilar artery (n = 3), and right carotid terminus (n = 1). Intracranial stents 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 2 patients, the tortuous vessel did not allow tracking of the Wingspan stent. The more navigable Cordis Enterprise stent (Cordis Neurovascular, Inc., Miami Lakes, Florida) was used in both these cases. Twelve patients had other adjunctive therapies: IA eptifibatide (n = 10), IA rt-PA (n = 2), angioplasty (n = 8), and IV rt-PA (n = 2). TIMI flow grade 2 or 3 recanalization was achieved in 100% of patients; 65% of patients improved >4 points in the NIHSS score after treatment. One patient (5%) had symptomatic ICH and 2 had asymptomatic ICH. At the 1-month follow-up evaluation, 12 of 20 patients (60%) had a mRS score of ≤2 and 9 (45%) had an mRS score of ≤1. Mortality at 1 month was 25% (n = 5). 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.

Stent-Assisted Revascularization: Durability, Late Outcomes, and the Rise of Stentrievers

The main limitation of current stent-assisted revascularization, as reported in the literature, is the theoretical risk of acute and mid-term stent failure (within 6 months of stent deployment), based on the Wingspan registries. Currently, there are no large studies that assess stent patency and complications related to placement of a permanent implant in an acute ischemic stroke patient beyond 1 month of stent placement. Mid-term results from SARIS are currently under review. Zaidat et al. (42) reported 1 case (11%) of immediate in-stent restenosis after acute stroke treatment. The risk of in-stent stenosis may be higher in the setting of symptomatic intracranial stenosis or acute stroke compared with the "natural history" of intracranial stents placed for other pathologic indications, such as aneurysm treatment (46).

The need for aggressive antiplatelet and/or anticoagulant therapy associated with intracranial stent placement (42,47–53) is a second major disadvantage if stent placement is used as a treatment technique in the setting of acute stroke. Zaidat et al. (42) reported an 11% hemorrhage rate associated with stent placement for acute stroke. Moreover, Levy et al. (41) reported an identical 11% incidence of lethal hemorrhages in patients treated with stent placement for acute stroke.

Stentriever designs attempt to maintain the advantages of a stent platform, namely, navigability, fast device delivery, and quick flow restoration, without condemning the patient to the disadvantages of a permanent intracranial implant. We have reported the feasibility of using the Solitaire FR device (ev3, Irvine, California; now Covidien Vascular Therapies, Mansfield, Massachusetts) in a canine stroke model with soft and hard clots in the intracranial circulation

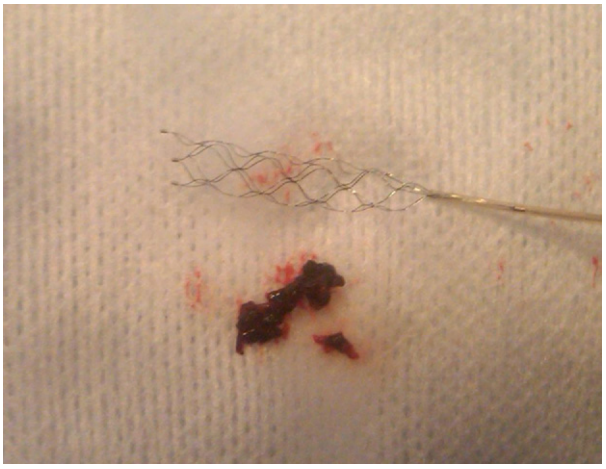

Figure 5. The Solitaire FR Device

Solitaire FR device (ev3, Irvine, California; now Covidien Vascular Therapies, Mansfield, Massachusetts). Device with retrieved clot. Reprinted, with permission, from Natarajan et al. (54).

(Fig. 5) (54). Current ongoing clinical trials include SWIFT (Solitaire FR With the Intention For Thrombectomy), a multicenter study to test the safety and efficacy of the Solitaire FR stent platform based clot retriever and compare it with the FDA-approved Merci clot retriever, and SARIS-II, a study of another 20 prospective patients treated with Wingspan stent–assisted recanalization for stroke.

Conclusions

Tremendous progress in the endovascular management of acute ischemic stroke lends great optimism to ongoing research efforts. As perfusion imaging and technical advancements in mechanical thrombectomy expand the number of candidates for meaningful endovascular intervention, it becomes our collective responsibility to ensure patient access to these advancements. Although much work remains to prospectively validate the results presented in this paper, momentum in the field augurs the prospect of continued advancement.

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REFERENCES

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010;121:e46–215.
2. Nogueira RG, Liebeskind DS, Sung G, Duckwiler G, Smith WS. Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials. Stroke 2009; 40:3777–83.
3. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317–29.
4. Natarajan SK, Snyder KV, Siddiqui AH, Ionita CC, Hopkins LN, Levy EI. Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes. Stroke 2009;40: 3269–74.
5. Lui YW, Tang ER, Allmendinger AM, Spektor V. Evaluation of CT perfusion in the setting of cerebral ischemia: patterns and pitfalls. AJNR Am J Neuroradiol 2010;31:1552–63.
6. Loh Y, Towfighi A, Liebeskind DS, et al. Basal ganglionic infarction before mechanical thrombectomy predicts poor outcome. Stroke 2009; 40:3315–20.
7. Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. Stroke 2010;41:1996–2000.
8. Hellier KD, Hampton JL, Guadagno JV, et al. Perfusion CT helps decision making for thrombolysis when there is no clear time of onset. J Neurol Neurosurg Psychiatry 2006;77:417–9.
9. Wintermark M, Fischbein NJ, Smith WS, Ko NU, Quist M, Dillon WP. Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke. AJNR Am J Neuroradiol 2005;26: 104–12.
10. Eastwood JD, Lev MH, Azhari T, et al. CT perfusion scanning with deconvolution analysis: pilot study in patients with acute middle cerebral artery stroke. Radiology 2002;222:227–36.
11. Miles KA, Griffiths MR. Perfusion CT: a worthwhile enhancement? Br J Radiol 2003;76:220–31.
12. Wintermark M, Albers GW, Alexandrov AV, et al. Acute stroke imaging research roadmap. Stroke 2008;39:1621–8.
13. Murphy BD, Fox AJ, Lee DH, et al. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion-derived blood flow and blood volume measurements. Stroke 2006;37: 1771–7.
14. Wintermark M, Flanders AE, Velthuis B, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke 2006;37:979–85.
15. Sanelli PC, Lev MH, Eastwood JD, Gonzalez RG, Lee TY. The effect of varying user-selected input parameters on quantitative values in CT perfusion maps. Acad Radiol 2004;11:1085–92.
16. Adams HP, Jr., del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation 2007;115:e478–534.
17. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–7.
18. Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study. Ann Neurol 2006;60:508–17.
19. Demchuk AM, Burgin WS, Christou I, et al. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. Stroke 2001;32:89–93.

20. Christou I, Burgin WS, Alexandrov AV, Grotta JC. Arterial status after intravenous TPA therapy for ischaemic stroke. A need for further interventions. Int Angiol 2001;20:208–13.
21. Saqqur M, Molina CA, Salam A, et al. Clinical deterioration after intravenous recombinant tissue plasminogen activator treatment: a multicenter transcranial Doppler study. Stroke 2007;38:69–74.
22. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985;312:932–6.
23. Ribo M, Alvarez-Sabin J, Montaner J, et al. Temporal profile of recanalization after intravenous tissue plasminogen activator: selecting patients for rescue reperfusion techniques. Stroke 2006;37:1000–4.
24. Meyers PM, Schumacher HC, Higashida RT, et al. Indications for the performance of intracranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Interdisciplinary Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation 2009;119:2235–49.
25. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. Stroke 1998;29:4–11.
26. 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;282:2003–11.
27. Inoue T, Kimura K, Minematsu K, Yamaguchi T. A case-control analysis of intra-arterial urokinase thrombolysis in acute cardioembolic stroke. Cerebrovasc Dis 2005;19:225–8.
28. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. Stroke 2007;38:2633–9.
29. Urbach H, Hartmann A, Pohl C, et al. Local intra-arterial thrombolysis in the carotid territory: does recanalization depend on the thromboembolus type? Neuroradiology 2002;44:695–9.
30. IMS Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke 2004;35:904–11.
31. IMS II Investigators. The Interventional Management of Stroke (IMS) II Study. Stroke 2007;38:2127–35.
32. Tomsick T, Broderick J, Carrozella J, et al. Revascularization results in the Interventional Management of Stroke II trial. AJNR Am J Neuroradiol 2008;29:582–7.
33. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997;28:2109–18.
34. Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. Neurology 2002; 59:862–7.
35. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32:78–86.
36. Grotta JC, Welch KM, Fagan SC, et al. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. Stroke 2001;32:661–8.
37. Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. AJNR Am J Neuroradiol 2006;27:1177–82.
38. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke 2008;39:1205–12.
39. 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;36:1432–8.
40. 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. Stroke 2009;40:2761–8.
41. Levy EI, Mehta R, Gupta R, et al. Self-expanding stents for recanalization of acute cerebrovascular occlusions. AJNR Am J Neuroradiol 2007;28:816–22.
42. Zaidat OO, Wolfe T, Hussain SI, et al. Interventional acute ischemic stroke therapy with intracranial self-expanding stent. Stroke 2008;39: 2392–5.
43. 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;40:847–52.
44. Mocco J, Hanel RA, Sharma J, et al. Use of a vascular reconstruction device to salvage acute ischemic occlusions refractory to traditional endovascular recanalization methods. J Neurosurg 2010;112:557–62.
45. 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). Stroke 2009;40:3552–6.
46. Fiorella D, Albuquerque FC, Woo H, Rasmussen PA, Masaryk TJ, McDougall CG. Neuroform in-stent stenosis: incidence, natural history, and treatment strategies. Neurosurgery 2006;59:34–42.
47. 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;38:1531–7.
48. Chiam PT, Samuelson RM, Mocco J, et al. Navigability trumps all: stenting of acute middle cerebral artery occlusions with a new self-expandable stent. AJNR Am J Neuroradiol 2008;29:1956–8.
49. 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;38:881–7.
50. Hahnel S, Ringleb P, Hartmann M. Treatment of intracranial stenoses using the Neuroform stent system: initial experience in five cases. Neuroradiology 2006;48:479–85.
51. Kurre W, Berkefeld J, Sitzer M, Neumann-Haefelin T, du Mesnil de Rochemont R. Treatment of symptomatic high-grade intracranial stenoses with the balloon-expandable Pharos stent: initial experience. Neuroradiology 2008;50:701–8.
52. Sauvageau E, Levy EI. Self-expanding stent-assisted middle cerebral artery recanalization: technical note. Neuroradiology 2006;48:405–8.
53. 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;70:1518–24.
54. Natarajan SK, Siddiqui AH, Hopkins LN, Levy EI. Retrievable, detachable stent-platform-based clot-retrieval device (SolitaireFR) for acute stroke revascularization: first demonstration of feasibility in a canine stroke model. Vasc Dis Manage 2010;7:E120–5.

Key Words: acute ischemic stroke ■ angioplasty ■ endovascular therapy ■ mechanical thrombectomy ■ stent-assisted revascularization ■ thrombolysis.