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REVIEW ARTICLE

Endovascular Approaches to Acute Stroke, Part 2: A Comprehensive Review of Studies and Trials

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SUMMARY: Reperfusion remains the mainstay of acute ischemic stroke treatment. Endovascular therapy has become a promising alternative for patients who are ineligible for or have failed intravenous (IV) thrombolysis. The conviction that recanalization of properly selected patients is essential for the achievement of good clinical outcomes has led to the rapid and widespread growth in the adoption of endovascular stroke therapies. However, comparisons of the recent reperfusion studies have brought into question the strength of the association between revascularization and improved clinical outcome. Despite higher rates of recanalization, the mechanical thrombectomy studies have demonstrated substantially lower rates of good outcomes compared with IV and/or intra-arterial thrombolytic trials. However, such analyses disregard important differences in clot location and burden, baseline stroke severity, time from stroke onset to treatment, and patient selection in these studies. Many clinical trials are testing novel devices and drugs as well as the paradigm of physiology-based stroke imaging as a treatment-selection tool. The objective of this article is to provide a comprehensive review of the relevant past, current, and upcoming data on endovascular stroke therapy with a special focus on the prospective studies and randomized clinical trials.

Mirroring its intravenous (IV) counterpart, much of the early work in endovascular stroke therapy has been reported in nonrandomized case series. Reports of successful intra-arterial thrombolysis (IAT) date back to the late 1950s, when Sussmann and Fitch[1] described the recanalization of an acutely occluded internal carotid artery (ICA) with intra-arterial (IA) injection of plasmin. Although pioneering work continued, it was not until the early 1990s that IAT was studied in a more systematic manner. In 2002, Lisboa et al[2] published a meta-analysis regarding the safety and efficacy of this approach. They performed a meta-analysis of 27 studies (minimum of 10 patients in each) with a total of 852 patients who had received IAT and 100 control subjects, in the era before the mechanical thrombectomy trials.[3-5] There were more favorable outcomes in the IAT group than in the control group (41.5% versus 23%, $P = .002$), with a lower mortality rate for IAT (27.2% versus 40%, $P = .004$). The IAT group had an odds ratio (OR) of 2.4 (95% confidence interval [CI,], 1.45–3.85) for favorable outcome, despite a higher frequency of symptomatic intracranial hemorrhage (SICH; 9.5% versus 3%, $P = .046$). In addition, they found a trend toward better outcomes with combined IV recombinant tissue plasminogen activator (rtPA) and IAT than with IAT alone. They also remarked that IAT-treated supratentorial strokes were more likely to have favorable outcomes than infratentorial ones (42.2% versus 25.6%, $P = .001$; OR, 2.0; 95% CI, 1.33–3.0).

A recent retrospective study compared 144 patients treated with IAT by using urokinase (UK) within 6 hours of symptom onset versus 147 patients treated with aspirin (250–500 mg) immediately after exclusion of intracranial hemorrhage (ICH) by imaging.[6] Patients were matched for age and National Institutes of Health Stroke Scale (NIHSS) scores (median, 14). At 2 years, the IAT-treated patients demonstrated higher rates of functional independence (modified Rankin Scale [mRS] score, ≤2; 56% versus 42%; $P = .037$) and excellent clinical outcomes (mRS score, ≤1; 40% versus 24%; $P = .008$). Mortality was 23% and 24% in the patients treated with IAT and aspirin, respectively. These results likely reflect the higher recanalization rates seen with endovascular treatment compared with medical therapy. Indeed, a single-center review of 350 patients with acute stroke treated with IAT by using UK showed recanalization rates >75% when additional endovascular techniques (such as mechanical fragmentation of the thrombus, thromboaspiration, percutaneous transluminal angioplasty, and implantation of stents) were used.[7] In this analysis, low NIHSS score at admission ($P < .001$), good collateral circulation ($P < .001$), and successful endovascular recanalization ($P < .001$) were found to predict favorable outcome, whereas diabetes mellitus ($P < .001$) and SICH ($P < .001$) predicted unfavorable outcome.

This strong correlation between vessel recanalization and favorable outcomes was further highlighted in a recent meta-analysis performed by Rha and Saver.[8] These authors reviewed the recanalization and outcome data from all articles published between 1985 and 2002 that evaluated vessel recanalization, either spontaneous or therapeutically induced, in acute ischemic stroke. Fifty-three studies encompassing 2066 patients were included. Recanalization rates according to method of intervention were the following: spontaneous (24.1%), IV thrombolysis (46.2%), IAT (63.2%), combined IV/IA thrombolysis (67.5%), and mechanical treatment (83.6%). Clinical outcome data categorized by recanalization status were available from 33 articles encompassing 998 patients. Good functional outcomes at 3 months were more frequent in recanalized versus nonrecanalized patients (OR, 4.43; 95% CI, 3.32–5.91). Three-month mortality was reduced in recanalized patients (OR, 0.24; 95% CI, 0.16–0.35). Rates of

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symptomatic hemorrhagic transformation did not differ between the 2 groups (OR, 1.11; 95% CI, 0.71–1.74). Nonetheless, the relationship between reperfusion after a stroke and clinical outcomes is not necessarily a linear one because other factors, including intensity and duration of the ischemia, baseline stroke severity, collateral circulation, cerebral perfusion pressure, lesion location, and lesion volume, are important in determining clinical outcomes. As such, reperfusion may be followed by different clinical scenarios, including neurologic improvement, worsening, and even death related to reperfusion brain edema and/or ICH.[9]

Overall, the revascularization rates described in the literature are higher with IA than IV thrombolysis.[8,9] In angiographic and transcranial Doppler sonographic controlled trials of IV rtPA, partial or complete recanalization of middle cerebral artery (MCA) occlusions has been reported in approximately one third of the patients[10-13] compared with two thirds of patients with IA recombinant pro-UK (rpro-UK) and IV heparin in the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial.[14] In vertebrobasilar occlusion, recanalization rates are reported to be 53% for IV thrombolysis and 65% for IAT.[15] However, more definite conclusions regarding the superiority of IAT over IV thrombolysis are limited, due to the fact that randomized controlled data comparing these 2 treatments are restricted to a single small study that was prematurely terminated.

Ducrocq et al[16] randomized acute ischemic stroke presenting with moderate-to-severe deficit (Scandinavian Stroke Scale [SSS] score, ≤50) within the first 6 hours from symptom onset to receive 900,000 U UK, via either the IV or IA route. The presence of early ischemic signs on CT involving greater than one third of the MCA territory was not considered an exclusion criterion. No diagnostic procedure was required to assess the presence of an occlusion in the IV group. In the IAT group, angiographic inclusion criteria were complete occlusion or minimal perfusion of either the M1 or M2 MCA segments. Patients who underwent angiography but did not receive UK (because of the absence of occlusion or endovascular procedure failure) were considered in an intent-to-treat analysis. Fourteen patients received IV UK (mean age, 58 years; mean SSS, 20.8) and 13 patients, IA UK (mean age, 59.5 years; mean SSS, 19.6). After these 27 patients were randomized, the study was terminated by the national health authorities because of the seemingly excessive mortality rate. Seven patients (26%) died, 4 in the IV group (edematous infarct in 3 and recurrence in 1) and 3 in the IA group (ICH in 2 and edematous infarct in 1). Patients given IV UK were treated significantly earlier (4 hrs. 16 mins. versus 5 hrs. 24 mins.; $P = .007$). Even though IA patients showed greater and earlier improvement, there was no significant difference in primary (90-day mRS score, ≤2; 4 versus 6 patients; $P = .6$) or secondary outcomes.

Anterior Circulation Thrombolysis

MCA Occlusion: PROACT I-II and Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trials

The safety and efficacy of IAT in patients with proximal MCA (M1 or M2 segments) occlusion treated within 6 hours of symptom onset has been evaluated in 3 multicenter randomized controlled trials. In the PROACT I and II trials, patients were treated with rpro-UK.[14,17] In the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan, patients were treated with UK.[18]

In the PROACT I trial, 26 patients (median NIHSS score, 17) were treated with rpro-UK, and 14 patients (median NIHSS score, 19), with a placebo at a median of 5.5 hours from symptom onset.[17] Patients in the treatment group received 6 mg of IA rpro-UK during 2 hours, and all patients received high- or low-dose IV heparin, given as a bolus followed by a 4-hour infusion at the time of angiography. Mechanical disruption of the clot was not allowed. Both the recanalization rates (Thrombolysis in Myocardial Infarction [TIMI] 2–3: 57.7% versus 14.3%) and the incidence of SICH (15.4% versus 7.1%) were higher in the rpro-UK than in the placebo group. Of note, all patients in the rpro-UK group with early CT changes involving >33% of the MCA territory had ICH. In the rpro-UK group, the rates of recanalization were dependent on the administered dose of heparin. At the end of the 2-hour rpro-UK infusion, 81.8% of the patients treated with high-dose heparin (100-IU/kg bolus followed by 1000-IU/h infusion for 4 hours) demonstrated recanalization, whereas only 40% were recanalized in the low-dose heparin subgroup (2000-IU bolus followed by a 500-IU/h infusion for 4 hours). However, the rate of SICH at 24 hours was also higher in the high-dose heparin group (27.3% versus 6.7%). The overall 90-day cumulative mortality rate was 26.9% in the rpro-UK group and 42.9% in the placebo group. Although the number of patients in this study was too low to allow any definite conclusions regarding efficacy, its results led to the PROACT II trial.

PROACT II was a phase 3 trial designed to assess the clinical efficacy and safety of IA rpro-UK. In this study, 180 patients were enrolled in a 2:1 randomization scheme to receive either IA rpro-UK plus 4 hours of low-dose IV heparin or low-dose IV heparin alone.[14] The rpro-UK and control patients were in general well-matched for baseline characteristics, except for an excess history of diabetes among the control patients (13% versus 31%) and more European Cooperative Acute Stroke Study (ECASS) CT scan protocol violations among rpro-UK patients (10% versus 4%). The median baseline NIHSS score was 17 in both groups. The median time to initiation of rpro-UK treatment was 5.3 hours. As in PROACT I, mechanical disruption of the clot was not allowed. A total of 9 mg of IA rpro-UK was infused during a 2-hour period in all patients, regardless of the angiographic results at 1 hour post-treatment initiation. The primary clinical outcome, the proportion of patients with slight or no disability at 90 days (mRS score, ≤2), was achieved in 40% of the 121 patients in the rpro-UK treatment group, compared with 25% of the 59 patients in the control group (absolute benefit, 15%; relative benefit, 58%; number needed to treat, 7; $P = .043$). Among all randomized patients, 13 patients in the rpro-UK group did not receive any rpro-UK and 5 control patients received thrombolytic. If these 18 patients were excluded from the intention-to-treat analysis, the absolute benefit for the primary outcome would still remain at 15% in favor of rpro-UK (42% versus 27%, $P = .053$).

In a subsequent multivariate analysis, the OR associated with treatment (after adjustment for other important prog-

Table 1: Summary of the major endovascular stroke therapy trials

Trial	Design	Baseline NIHSS		Recanalization Rates		Good Clinical Outcome (90-day mRS ≤ 2)		Mortality		SICH	
		Rx	Ctrl	Rx	Ctrl	Rx	Ctrl	Rx	Ctrl	Rx	Ctrl
PROACT II*(n = 180) (IAT, 121)	RCT, IA pro-UK + IV heparin vs IV heparin	17	17	66%	18%	40%	25%	25%	27%	10%	2%
MELT Japan† (n = 114), (IAT, 57)	RCT, IA UK vs medical treatment	14	14	73.7%	–	49.1%	38.6%	5.3%	3.5%	9%	2%
IMS I (n = 80), (IAT, 62)	POL, IV rtPA + IA rtPA	18	–	56%	–	43%	–	16%	–	6.3%	–
IMS II (n = 81) (IAT, 55)	POL, IV rtPA + IA rtPA/EKOS	19	–	58%	–	46%	–	16%	–	9.9%	
MERCI (n = 141)	POL, IA MERCI, IA lytics allowed, IV disallowed	20	–	60.3% 48%‡	–	27.7%	–	43.5%	–	7.8%	–
Multi MERCI (n = 164)	POL, IA MERCI, IA + IV lytics allowed	19	–	68% 55%‡	–	36%	–	34%	–	9.8%, PH-2: 2.4%	–
Penumbra (n = 125)	POL, IA Penumbra, IA lytics allowed	17	–	81.6%‡	–	25%	–	32.8%	–	11.2%, PH-2: 1.6%	–

Note:—Rx indicates treatment; Ctrl, control; RCT, randomized controlled trial; EKOS, EKOS MicroLysUS infusion catheter; PH, parenchymal hematoma; POL, prospective open-label study; IAT: number of patients treated with IAT; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SICH, symptomatic intracranial hemorrhage; IA, intra-arterial; IV, intravenous; UK, urokinase; rtPA, recombinant tissue plasminogen activator.
* Primary end point (90-day mRS ≤2) was reached (P = .04).
† Secondary end point (90-day mRS ≤1) was reached (42.1% vs 22.8%, P = .045).
‡ Device alone.

Table 2: Impact of revascularization on clinical outcomes

Trial and Clinical Outcomes at 90 days	Recanalized Patients (%)	Nonrecanalized Patients (%)	P Value
MERCI			
mRS ≤2	46	10.4	<.0001
Mortality	31.8	54.2	.0101
Multi MERCI			
mRS ≤2	49.1	9.6	<.001
Mortality	24.8	51.9	<.001
Penumbra			
mRS ≤2	29	9	.0596
Mortality	29	48	.1384
IMS I-II			
mRS ≤2	45.6	6.9	.0004
Mortality	10.9%	34.5	.01

nostic variables) was 2.49 (P = .022), which was greater than the OR obtained from the original PROACT II analysis of 2.13 (P = .043). This analysis also demonstrated that age >68 years (OR, 0.23; 95% CI, 0.11–0.48), NIHSS score (NIHSS score, 11–20: OR, 0.36; 95% CI, 0.13–1.00; NIHSS score, >20: OR 0.085; 95% CI, 0.022–0.33), and CT hypoattenuation >5.25 mL (OR, 0.47; 95% CI, 0.23–0.96) were the most important predictors of outcome.[19] A more-detailed evaluation of the radiographic data showed that patients with a baseline Alberta Stroke Program Early CT (ASPECT) score of >7 were 3 times more likely to achieve the primary clinical outcome with IA rpro-UK compared with controls, whereas patients with a baseline ASPECT score of ≤7 were less likely to benefit from treatment.[20] Post hoc analysis also demonstrated that women benefited more from treatment than men (absolute benefit: 20% versus 10%), despite similar rates of recanalization.[21] This difference in treatment effect is likely related to the fact that untreated women fared worse than untreated men (90-day mRS score, ≤2: 17% versus 31%). In other words, women do worse after ischemic stroke than men, but this sex difference in natural history is nullified with IA rpro-UK, a phenomenon that has also been documented with IV rtPA.[22]

The overall 2-hour recanalization rate (TIMI 2–3) in PROACT II was 66% for the rpro-UK group and 18% for the control group (P < .001). Complete (TIMI 3) recanalization rates were 19% and 2%, respectively (P < .003). SICH within 24 hours occurred in 10% of rpro-UK patients and 2% of control patients (P = .06). ICH symptoms in rpro-UK–treated patients developed at a mean of 10.2 ± 7.4 hours after the start of treatment. All SICHs occurred in patients with a baseline NIHSS score of ≥11 (NIHSS score, 11–20, 11%; NIHSS score >20, 13%). Mortality after SICH was 83% (10/12). Elevated serum glucose was significantly associated with SICH in the rpro-UK–treated patients (patients with baseline glucose level >200 mg/dL experienced a 36% risk of SICH compared with 9% for those with ≤200 mg/dL).[23] Mortality was 25% for the rpro-UK group and 27% for the control group, despite the higher incidence of ICH in the rpro-UK patients.

Secondary clinical outcomes at 90 days included the percentage of patients with an NIHSS score <1, ≥50% reduction from baseline NIHSS score, and a Barthel index score of ≥60 or ≥90. Despite a trend in favor of the rpro-UK group, none of these secondary functional or neurologic outcome measures achieved statistical significance. Although encouraging, the results of PROACT-II were insufficient in the view of the US Food and Drug Administration (FDA) and international regulatory agencies to grant approval for a stroke label for IA rpro-UK, and another larger trial was requested. This confirmatory trial was judged too expensive and, to date, has not been undertaken.

The MELT trial was designed to establish the safety and clinical efficacy of IA infusion of UK in patients with acute stroke treated within 6 hours of symptom onset. As in PROACT I and II, only patients displaying angiographic occlusions of the M1 or M2 MCA segments were randomized. Mechanical thrombus disruption was permitted only with a microguidewire. No other mechanical techniques were allowed. IA infusion of UK (120,000 U for 5 minutes) was performed and repeated until the total dose reached 600,000 U, 2 hours had passed after starting infusion, or complete recanalization was achieved. The trial was aborted prematurely by the steering committee after the approval of IV rtPA in Japan. At that time,

a total of 114 patients (57 patients in each group) had undergone randomization. Baseline characteristics were similar in the 2 groups. The median baseline NIHSS score was 14 in both groups. The primary end point (90-day mRS score, ≤2) was more frequent in the UK group than in the control group (49.1% versus 38.6%; OR, 1.54; 95% CI, 0.73–3.23), but this difference did not reach significance ($P = .345$). However, 2 preplanned secondary end points reached statistical significance at a conventional level (unadjusted for multiple comparisons). The rate of excellent functional outcome (90-day mRS score, ≤1) was significantly more frequent in the UK group compared with the control group (42.1% versus 22.8%; $P = .045$; OR, 2.46; 95% CI, 1.09–5.54). In addition, there were significantly more patients with NIHSS scores of 0–1 at 90 days in the UK group than in the control group (35.1% versus 14.0%, $P = .017$). Partial or complete recanalization was achieved in 42 of 57 of the patients (73.7%) treated with IA UK. Mechanical thrombus disruption was performed in 39 of the 57 patients (68%). Recanalization was complete in 3 patients; partial ≥50%, in 27; partial <50%, in 12; and not achieved in 15. There was no significant difference in the 90-day cumulative mortality (5.3% versus 3.5%, $P = 1.00$) or ICH rate within 24 hours of treatment (9% versus 2%, $P = .206$).

The patient cohorts in MELT and PROACT II were reasonably comparable in age and sex but differed in several other key aspects, including NIHSS scores (14 versus 17), early infarct signs on CT (47% versus 76%), and time to initiation of IA treatment (3.8 versus 5.3 hours). With these more favorable baseline characteristics, it is not surprising that the MELT control group had superior rates of good clinical outcome compared with the PROACT II control group (mRS score, ≤2: 38.6% versus 25%). This very favorable control group in MELT obviously had a negative impact on the chances of showing a benefit with IAT. Despite the lack of a positive primary end point, the MELT trial provided significant additional data to support IAT. Indeed, a meta-analysis of PROACT I, PROACT II, and MELT trials, including 204 patients treated with IAT and 130 controls, showed a lower rate of death or dependency at long-term follow-up with IAT compared with controls (58.5% versus 69.2%; $P = .03$; OR, 0.58; 95% CI, 0.36–0.93).[24]

ICA Occlusion

Acute strokes due to distal ICA occlusion usually carry a much worse prognosis than do MCA occlusions. In addition, ICA occlusions appear to have poorer response to IV thrombolysis compared with MCA occlusions.[11] To date, to our knowledge, there have been no randomized controlled trials that have included ICA occlusion. Thus, all data regarding its natural history and endovascular treatment results are derived from small case series. Arnold et al[25] analyzed 24 consecutive patients (median NIHSS score, 19) presenting with ICA T occlusions who were treated by IAT by using UK at an average of 237 minutes from symptom onset. Only 4 patients (16.6%) had a favorable outcome at 3 months. The mortality rate was 41.7% (10/24). Partial recanalization of the intracranial ICA was achieved in 15 (63%), of the MCA in 4 (17%), and of the anterior cerebral artery (ACA) in 8 patients (33%). Complete recanalization did not occur. The presence of good leptomeningeal collaterals and age <60 years were the only predictors of a favorable clinical outcome.

Jansen et al[26] reported a series of 32 patients (mean age, 56 years) with acute intracranial ICA occlusions who were treated with IV rtPA ($n = 16$), IA rtPA ($n = 8$), or IA UK ($n = 8$). Only 16% of the patients achieved moderate or good clinical outcomes. Successful recanalization occurred in only 4 patients (12.5%). Death occurred in 53% of the patients. Zaidat et al[27] described a series of 18 patients with acute stroke and occlusion of the distal ICA treated with IAT ± IV rtPA. The mortality rate was 50% despite high rates of complete angiographic recanalization (80% in the combined IV/IA thrombolysis group and in 62% with IAT alone group). Patients with occlusions extending to the MCAs and ACAs (T occlusions) were the least likely to respond to thrombolysis. SICH occurred in 20% of the patients receiving IV/IA therapy and in 15% of the IAT-only group. Moderate-to-good outcomes (90-day mRS score, ≤3) were seen in 38.9% of the patients (7/18). Sorimachi et al[28] reported better outcomes with IAT for proximal MCA occlusion ($n = 12$; mRS score, ≤2, 75%) than for distal ICA occlusions ($n = 11$; mRS score, ≤2, 36.4%), despite similar recanalization rates (100% versus 91%).

The ability to recanalize appears to have improved with the advent of modern thrombectomy devices. Flint et al[29] reported 80 patients (mean age, 67 ± 16 years; mean NIHSS score, 20 ± 5; mean time from stroke onset to treatment, 4.1 ± 1.6 hours) with angiographically proved intracranial ICA occlusion who were enrolled in the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Part I trials. Eleven patients (14%) also received IV rtPA. Recanalization of the intracranial ICA was achieved in 53% of the patients with the Merci retriever (Concentric Medical, Mountain View, Calif) alone (42/80) and in 63% (50/80) with the Merci retriever plus adjunctive endovascular treatment. Overall, 25% of the patients (20/79) had a good neurologic outcome at 90 days (39% of the recanalized patients versus 3% of the nonrecanalized patients, $P < .001$). The overall 90-day mortality rate was 46% (30% in the recanalized patients versus 73% of the nonrecanalized patients, $P < .001$). The rate of SICH was 10% (8/80).

Acute strokes related to isolated proximal (extracranial) ICA occlusions typically have a better prognosis, given the compensatory collateral flow at the level of the external carotid artery−ICA anastomosis (eg, ophthalmic artery) and/or circle of Willis. However, patients with an incomplete circle of Willis or with tandem occlusions of the intracranial ICA/MCA often present with severe strokes and are potential candidates for emergent revascularization. Jovin et al[30] reported a series of 25 patients (mean age, 62 ± 11 years; median NIHSS score, 14) who presented with neurologic deterioration in the setting of extracranial ICA occlusion. Successful revascularization was achieved in 92% (23/25) of the patients after carotid artery stent placement. There were 2 clinically insignificant adverse events (1 asymptomatic ICH and 1 non-flow-limiting dissection).

Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) is a relatively rare disorder with a frequency of approximately 1 per 10,000 ophthalmology outpatient visits in the United States.[31] CRAO typ-

ically causes acute and severe visual loss with <10% of patients reporting any meaningful spontaneous visual recovery. Acute thrombosis or embolism or both are thought to represent the underlying pathology in cases of nonarteritic CRAO. Treatment options are varied and include ocular massage, paracentesis, carbogen (mixture of 95% oxygen and 5% carbon dioxide) inhalation, topical β-blocker and acetazolamide, aspirin, IV heparin, and isovolemic hemodilution. All of these treatments share a limited efficacy. In view of the poor natural history and limitations of conventional therapy, a powerful rationale exists for using IAT in patients with CRAO.

Arnold et al[32] compared the visual outcomes of 37 patients with CRAO who underwent IAT with UK within 6 hours from symptom onset with a control group of 19 patients who were also evaluated within 6 hours but did not undergo thrombolytic treatment. In both groups, some patients were treated by paracentesis and/or acetazolamide. The median time to treatment was 240 minutes (mean, 240 minutes) in the IAT group and 240 minutes (mean, 221 minutes) in the conventional treatment group ($P > .05$). Visual acuity before treatment did not significantly differ between the 2 groups. Visual improvement was more likely with IAT ($P = .01$). In the IAT group, 8 of 37 patients (22%) regained visual acuity of >0.6 compared with none (0/19) in the control group ($P = .04$). Acetazolamide and/or paracentesis, in addition to antithrombotic therapy, did not improve visual acuity in the IAT group. Minor treatment-related complications were seen in 3 patients; 2 had transient ischemic attacks and 1, a minor stroke. There were no hemorrhagic complications.

Similarly, Aldrich et al[31] conducted a single-center nonrandomized study of acute CRAO. The authors compared 21 patients treated with IAT with another 21 patients treated with standard therapy. Visual acuity at presentation was 20/400 or worse in all patients. There was no statistically significant difference in the visual acuity at presentation between the 2 groups. IAT patients presented within 15 hours of symptom onset. The mean time from onset of visual loss to IAT was 9.3 ± 2.9 hours. Vasculitis was excluded by clinical and laboratory (eg, erythrocyte sedimentation rate) assessment and hypoperfusion of the ipsilateral ICA by angiography or duplex ultrasonography. IAT was performed after microcatheterization of the ipsilateral ophthalmic artery by using rtPA to a maximum of 20 mg (mean dose, 11.25 ± 3.5 mg). Seventy-six percent of subjects in the IAT group had a visual acuity improvement of 1 line or more, compared with 33% in the standard therapy group ($P = .012$). Multivariate analysis, controlling for sex, history of prior stroke/transient ischemic attack, and history of hypercholesterolemia showed that patients who received IAT were 36 times more likely to have improvement in visual acuity ($P = .0001$). In addition, IAT-treated patients were 13 times more likely to have improvement in visual acuity of 3 lines or more ($P = .03$) and 4.9 times more likely to have a final visual acuity of 20/200 or better ($P = .04$). There were 2 groin hematomas in the IAT group. No ischemic strokes or retinal or intracerebral hemorrhages occurred.

The aforementioned results are consistent with a recent meta-analysis performed by Noble et al.[33] This study included a total of 158 patients with CRAO derived from 8 different reports, each containing at least 5 patients. Treatment was initiated within an average of 8.4 ± 4 hours of symptom onset. Visual improvement occurred in 93% of patients, with 13% achieving 20/20 or better, 25% achieving 20/40 or better, and 41% achieving 20/200 or better. Complications were seen in 4.5% of patients. A randomized multicenter study comparing conservative management with IAT in patients with CRAO who presented within 20 hours of symptom onset and with a visual acuity <0.32 was started by the European Assessment Group for Lysis in the Eye (EAGLE) in 2002.

Posterior Circulation Thrombolysis

There are 2 essential considerations when discussing the treatment and prognosis of basilar artery occlusion (BAO). The first is that this term has been used loosely in the literature. For instance, many series have established the diagnosis of BAO by using flow-based studies such as time-of-flight MR angiography or transcranial Doppler sonography, which can be relatively insensitive to low residual flow and, therefore, may overdiagnose occlusion. The second consideration is the clinical pleomorphism of BAO, ranging from relatively mild fluctuating symptoms all the way to "locked-in" syndrome or coma. These facts obviously have an impact on the treatment expectations and natural history of the disease and may explain the heterogeneity in the literature regarding the natural history of BAO. Indeed, some studies have reported favorable outcomes in 30%–67% of these patients, whereas others have described poor outcome rates in the 60%–90% range.[34] In fact, both the mechanism and the severity of the basilar disease have been shown to predict outcome. An analysis of the New England Medical Center Posterior Circulation Registry, a prospectively collected series of 407 consecutive patients with posterior circulation ischemia, identified 55 patients with moderate (50%–70%) or severe (>70%) basilar stenosis and 32 patients with BAO as documented by MR angiography, conventional angiography, or transcranial Doppler sonography. Patients with basilar artery (BA) embolism had a 2.4-fold higher risk of poor outcome compared with patients with diffuse or localized atherosclerosis (58.3% versus 24% [remodeling ratio (RR), 2.43; 95% CI, 1.30–4.54; $P = .03$]). Not surprisingly, patients with BAO had a significantly higher risk of poor outcome than individuals with basilar stenosis, regardless of the stroke mechanism (atherosclerosis, 40% versus 16% [RR, 2.5; 95% CI, 1.13–5.54; $P = .02$]; embolism, 40.6% versus 21.8% [RR, 1.86; 95% CI, 0.97–3.58; $P = .06$]).

Acute thromboembolic occlusion of the BA is a relatively rare entity accounting for only 6%–10% of large-vessel strokes in humans.[35] Indeed, the infrequency of BAO is reflected by the paucity of prospective data and controlled trials regarding this ruthless disease. Randomized controlled data for IAT in BAO are limited to a single small study that was prematurely terminated.[36] In this study, 16 patients were randomized to receive IAT with UK or anticoagulation alone within 24 hours of stroke-symptom onset and angiographic evidence of posterior circulation vascular occlusion. All patients received IV heparin (activated partial thromboplastin time [PTT] goal, 60–80 seconds) for at least 2 days and then oral warfarin. Clinical outcomes were determined by the 6-month Barthel and Rankin scales. The study was terminated early because of slow recruitment and withdrawal of UK from the Australian market. The mortality rate was 50% in both groups (4/8 patients). Among the survivors, the median mRS score was 1 in

the IAT group and 3 in the control group. Good outcome occurred in 4 of 8 patients in the IAT group compared with 1 of 8 patients in the control group ($P = .28$), despite the fact that there were more severe strokes in the IAT arm. Even though this study suggests a potential benefit for IAT in BAO, its sample size was obviously too small and the results are insufficient to provide randomized-level evidence for the general use of IAT in BAO. Most of the rationale for the application of IAT in BAO is, therefore, based on the favorable reports of uncontrolled case series compared with the severity of the underlying disease.

Since the first series of IAT for BAO by Zeumer et al in 1983,[37] Furlan and Higashida[38] have demonstrated that >278 cases have been reported, with an overall recanalization rate of 60% and a mortality rate of 90% in nonrecanalized patients versus 31% in at least partially recanalized patients. Similar findings were reported in another meta-analysis that incorporated 10 studies including 316 patients.[35] This study reported an overall recanalization rate of 64% and overall mortality rate of 56%. The mortality rate was 87% in nonrecanalized patients versus 37% in recanalized patients, resulting in a 48% absolute risk reduction of death ($P < .001$). The rate of SICH in this analysis was only 7%.

In yet another meta-analysis of published case series, Lindsberg and Mattle[15] studied the outcomes of BAO after IAT or IV thrombolysis. In 420 patients with BAO treated with IV thrombolysis ($n = 76$) or IAT ($n = 344$), death or dependency was equally common, 78% (59/76) and 76% (260/344). Recanalization was achieved more frequently with IAT (225/344, 65%) than with IV thrombolysis (40/76, 53%, $P = .05$), but survival rates after IV thrombolysis (38/76, 50%) and IAT (154/344, 45%) were similar ($P = .48$). A total of 24% of patients treated with IAT and 22% treated with IV thrombolysis reached good outcomes ($P = .82$). Without recanalization, the likelihood of good outcome was close to nil (2%). The authors concluded that recanalization occurs in more than half of patients with BAO treated with IAT or IV thrombolysis, and 45%–55% of survivors regain functional independence. They advised that hospitals not equipped for IAT should consider setting up specific protocols for IV thrombolysis in BAO because in their analysis, the effect of IVT did not appear to be much different from that of IAT. However, this analysis had many limitations, including the fact that most the patients with IV thrombolysis were evaluated by time-of-flight MR angiography, which is less sensitive to low-flow states.[39]

The Basilar Artery International Cooperation Study (BASICS) was a prospective observational multicenter international registry of consecutive patients presenting with a symptomatic and radiologically confirmed BAO (by CT angiography, MR angiography, or conventional angiography) and represents the largest data base on BAO to date.[40] The registry was started in November 2002 and was completed in September 2007, with a total of 624 patients enrolled at 49 centers worldwide. An interim analysis of the first 592 patients has been completed.[41] A total of 183 (31%) patients were treated with antithrombotics (heparin and/or aspirin) alone, 121 (21%) patients received IV thrombolysis (alone, $n = 80$; or in combination with IAT, $n = 41$), and 288 (48%) underwent endovascular treatment alone (IAT alone, $n = 179$; IAT and mechanical, $n = 79$; mechanical alone, $n = 30$). The mean age in the antithrombotics, IV thrombolysis (alone or IAT bridging), and endovascular treatment groups was 64, 65, and 62 years, respectively. The median NIHSS scores (interquartile range, [IQR]) were 15 (6–28), 21 (11.5–28), and 25(15–30) respectively. Patients in the IV thrombolysis (alone or IAT bridging) group were treated earlier than the patients in the endovascular treatment−alone group (0–3 hours, 55.4% versus 23.3%; 3–6 hours, 26.4% versus 41.3%; 6–9 hours, 5.8% versus 17%; >9 hours, 12.4% versus 18.3%). There was a discrepancy between the severity of the deficits and the treatment type, with more patients with mild-to-moderate deficits receiving antithrombotics and more patients with severe deficits receiving endovascular treatment.

Overall outcomes in this study varied according to the severity of deficits on presentation. The rates of favorable outcomes (mRS score, 0–3) in patients presenting with mild-to-moderate deficits ($n = 239$) versus severe deficits ($n = 347$) were 53% versus 17%, respectively. Conversely, mortality rates were 17% versus 50%, respectively. Clinical outcomes were further stratified according to the severity of deficits on presentation and treatment type. The rates of favorable outcome in patients presenting with mild-to-moderate deficits were 58% in the antithrombotics group, 62% in the IV thrombolysis (alone or IAT bridging) group, and 44% in the endovascular treatment-alone group, whereas the mortality rates were 13%, 16%, and 23%, respectively. In patients presenting with severe deficits, the rates of favorable outcome were 7% in the antithrombotics group, 27% in the IV thrombolysis (alone or IAT bridging) group, and 18% in the endovascular treatment−alone group, whereas the mortality rates were 54%, 46%, and 49%, respectively. The overall rates of SICH were 0.6% in the antithrombotics group, 5% in the IV thrombolysis alone group, 7% in the IV/IAT bridging group, and 12% in the endovascular treatment−alone group, whereas the rates of fatal ICH were 0.6%, 1.3%, 2.4%, and 4%, respectively. All 41 patients with severe deficits who were treated with IV and/or IAT beyond 9 hours from symptom onset had poor outcomes. After adjusting for age, NIHSS score, time to treatment, location of the occlusion, and history of diabetes or prior stroke, endovascular treatment alone did not show any superiority over IV thrombolysis (alone or in combination with IAT) in terms of mortality or dependency. The authors concluded that a randomized trial is, therefore, required to establish the best therapeutic approach to BAO.

The addition of novel pharmacologic approaches and mechanical devices may lead to higher rates of recanalization and favorable outcomes than what has been previously described. Nagel et al[42] recently reported the results of an observational longitudinal single-center study comparing rtPA IAT alone with IV abciximab followed by rtPA IAT (bridging therapy) in 75 patients with acute BAO (median age, 67.5 years; 35.8% women). IV abciximab was given as an initial bolus of 0.25 mg/kg followed by 0.125 μg/kg/min for 12 hours. IA rtPA was infused up to a maximum dose of 0.9 mg/kg. In both groups, mechanical disruption of the thrombus was performed and atherothrombotic lesions were treated with additional percutaneous transluminal angioplasty/stent placement as needed. Baseline parameters, including age, sex, risk factors, Glasgow coma scale score at presentation, occlusion type, and time to IA treatment, did not differ significantly between the 2 groups.

However, patients in the bridging group were more frequently treated with percutaneous transluminal angioplasty/stent placement (10 versus 1, $P = .02$) and received lower doses of rtPA (median, 40 mg versus 47.5 mg; $P < .01$). Patients in the bridging group ($n = 43$) had higher recanalization rates (TIMI 2–3, 83.7% versus 62.5%; $P = .03$), improved survival rates (58.1% versus 25%; $P = .01$), and higher rates of favorable clinical outcomes (mRS score, 0–3; 34.9% versus 12.5%; $P = .02$) compared with patients with IAT only ($n = 32$). SICH rates were similar in both groups (14% versus 18.8%, $P = .41$). Independent predictors for recanalization included age (OR, 0.95; 95% CI, 0.91–0.99), atrial fibrillation (OR, 6.53; 95% CI, 1.14–37.49), and bridging therapy (OR, 3.37; 95% CI, 1.02–11.18). Independent predictors for outcome included Glasgow coma scale score at presentation (OR, 1.24; 95% CI, 1.03–1.45) and the combination of bridging therapy with successful recanalization (OR, 3.744; 95% CI, 1.04–13.43). Similarly improved outcomes were seen in a pooled analysis of the patients with BAO enrolled in the MERCI and Multi MERCI trials.[43] These patients were treated with the Merci retriever within 8 hours after symptom onset. Recanalization occurred in 21 of 27 (78%) patients. Mortality was 44% and favorable outcomes (mRS score, 0–3) were seen in 41%.

Factors predicting outcomes after IAT in patients with BAO have also been established. Levy et al[44] performed a meta-analysis of all case series involving ≥10 patients with BAO who underwent IAT with UK and/or rtPA during the period from January 1987 to November 1997. A total of 164 patients were reviewed. The authors found that both failure to recanalize (RR, 2.34; 95% CI, 1.48–3.71; $n = 126$) and the presence of coma on presentation (RR, 1.95; 95% CI, 1.26–2.99; $n = 145$) were associated with higher mortality rates, whereas thrombus location in the distal one third of the BA, compared with the proximal and/or middle portions of the BA, was associated with a lower mortality rate (RR, 0.52; 95% CI, 0.31–0.86; $n = 126$). The level of occlusion also appears to impact the chances of recanalization. In general, distal occlusions, which are usually embolic in etiology, have higher recanalization rates than proximal occlusions, which are more commonly atherothrombotic in nature. Most stroke experts agree that the time window for IAT in the posterior circulation should be longer than the 6- to 8-hour window typically used for strokes in the carotid circulation, though no consensus guidelines exist to define this interval. The underlying rationale for the longer time window in patients with BAO includes not only the dire prognosis of untreated lesions but also a lower rate of hemorrhagic transformation with IAT in this vascular territory. Indeed, many centers base their treatment decisions on the total stroke burden and symptoms at presentation rather than on time. The evolution of patients with BAO is, nonetheless, difficult to predict as shown in a recent report of 2 patients with BAO who, despite successful IAT, still evolved with large bilateral pontine infarcts and locked-in states but, following aggressive supportive care and rehabilitation, became fully independent (mRS score, 2).[45]

Combined IV and IA Thrombolysis

Several studies have evaluated the feasibility, safety, and efficacy of combined IV rtPA with IAT in patients with acute stroke. This approach has the potential of combining the advantages of IV rtPA (fast and easy to use) with the advantages of IAT (directed therapy, titrated dosing, mechanical aids to recanalization, and higher rates of recanalization), thus improving the speed and frequency of recanalization.

Adjusted-Dosage IV Thrombolysis Followed by IAT (Bridging Approach) Versus Primary IAT Alone. The Emergency Management of Stroke (EMS) Bridging Trial was a double-blind randomized placebo-controlled multicenter phase 1 study of IV rtPA (0.6 mg/kg) or IV placebo followed by immediate IAT with rtPA.[46] Seventeen patients were randomly assigned to the IV/IA group and 18, to the placebo/IA group. Clot was found in 22 of 34 patients. TIMI 3 recanalization occurred in 6 of 11 IV/IA patients versus 1 of 10 placebo/IA patients ($P = .03$) and correlated with the total dose of rtPA ($P = .05$). However, no difference in the 7- to 10-day or 3-month outcomes was found, and there were more deaths in the IV/IA group. Eight intraparenchymal hemorrhages (IPHs) occurred. SICH occurred in 1 placebo/IA patient and 2 IV/IA patients. Life-threatening extracranial bleeding complications occurred in 2 patients, both in the IV/IA group.

Wolfe et al[47] compared the safety and efficacy of combined rtPA IV/IAT (0.6 mg/kg IV to a maximum of 60 mg, followed by 0.3 mg/kg IA to a maximum of 30 mg) versus primary IAT in patients with stroke presenting within 6 hours from symptom onset. A total of 41 patients were treated with IV/IAT versus 55 patients with primary IAT. There were significant differences in terms of mean time to treatment (151 versus 261 minutes, respectively; $P < .0001$) and IA rtPA dose (17.5 versus 22.8 mg, respectively; $P = .05$). Propensity score matching yielded 25 patients in each group. The rates of recanalization were 64% with IV/IAT versus 48% with primary IAT (OR, 1.9; 95% CI, 0.5–7.0, $P = .3$). The rate of SICH was 12% in each group. More patients in the IV/IAT group achieved an mRS score of ≤2 at 90 days, but the difference was not statistically significant (OR, 1.6; 95% CI, 0.5–5.8; $P = .3$). The mortality rate was 20% in the IV/IAT group versus 16% in the primary IAT group (RR, 1.3; 95% CI, 0.4–4.1; $P = .7$)

Noncomparative Studies of Adjusted-Dosage IV Thrombolysis Followed by IAT (Bridging Approach). Ernst et al[48] performed a retrospective analysis of 20 consecutive patients (median NIHSS score, 21) who presented within 3 hours of stroke symptoms and were treated by using IV rtPA (0.6 mg/kg) followed by IA rtPA (≤0.3 mg/kg or 24 mg, whichever was less, for a maximum of 2 hours) in 16 of the 20 patients. Despite a high number of ICA occlusions (8/16), TIMI 2–3 recanalization rates were obtained in 50% (8/16) and 19% (3/16) of the patients, respectively. One patient (5%) developed a fatal ICH. Ten patients (50%) recovered to an mRS score of 0–1; 3 patients (15%), to an mRS score of 2; and 5 patients (25%), to an mRS score of 4–5.

Suarez et al[49] studied bridging therapy in 45 patients by using IV rtPA at 0.6 mg/kg within 3 hours of stroke onset. Patients exhibiting evidence of perfusion-weighted imaging/diffusion-weighted imaging (DWI) mismatch on MR imaging underwent subsequent IAT. Eleven patients received IAT with rtPA (maximum dose, 0.3 mg/Kg), and 13 patients received IAT with UK (maximum dose, 750,000 U). SICH occurred in 2 of the 21 patients in the IV rtPA−only group but in none of the patients in the IV rtPA/IAT group. Of the 24 patients in the IV rtPA/IAT group, 21 had MCA occlusions, 2 had ACA oc-

clusions, and 1 had a posterior cerebral artery (PCA) occlusion. Complete recanalization occurred in 5 of the 13 IV rtPA/IA UK−treated patients and 4 of the 11 IV rtPA/IA rtPA−treated patients. Partial recanalization occurred in 5 of the 13 IV rtPA/IA UK−treated patients and 4 of the 11 IV rtPA/IA rtPA−treated patients. Favorable outcomes (Barthel index, ≥95) were seen in 92%, 64%, and 66% of the IV rtPA/IA UK, IV rtPA/IA rtPA, and IV rtPA-only−treated patients, respectively.

Full Dosage IV Thrombolysis Followed by IAT. In a prospective, open-label study, Hill et al[50] assessed the feasibility of a bridging approach by using full-dose IV rtPA. Following IV infusion of 0.9-mg/kg rtPA, 6 patients underwent IAT with rtPA (maximum dose, 20 mg), and 1 additional patient underwent intracranial angioplasty. TIMI 2–3 recanalization was achieved in 3 of these patients. There were no SICHs. Similarly, Shaltoni et al[51] revised the outcomes of IAT after 0.9-mg/kg IV rtPA in a single center during a 7-year interval period. A total of 69 patients (mean age, 60 ± 13 years; range, 26–85 years; 55% male) with a median baseline NIHSS score of 18 (range, 6–39) were included. IV rtPA was initiated at 124 ± 32 minutes (median, 120 minutes), and IAT, at 288 ± 57 minutes (median, 285 minutes). IA thrombolytics included reteplase ($n = 56$), alteplase ($n = 7$), and UK ($n = 6$), with an average total dosage of 2.8 U, 8.6 mg, and 700,000 U, respectively. Mechanical disruption of the clot with a microguidewire and/or balloon angioplasty was used in 52 patients (75%). The Merci retriever was not used. Carotid artery stent placement was performed in 3 patients. SICH occurred in 4 of 69 (5.8%, all patients with parenchymal hematomas type 2 [PH-2]), 3 of which were fatal. Overall, there were 24 ICHs, including 5 hemorrhagic infarctions type 1 (HI-1), 6 HI-2s, 7 PH-1s, 5 PH-2s, and 1 subarachnoid hemorrhage (SAH). Thrombolysis in Cerebral Infarction (TICI) 2–3 recanalization was achieved in 50 (72.5%), and a favorable outcome (home or inpatient rehabilitation), in 38 (55%). The mortality rate was 17% (12/69).

In another series, Burns et al[52] performed a retrospective case-control study to establish whether endovascular interventions after full-dosage IV rtPA are superior to IV rtPA alone. These authors compared the outcomes of 33 consecutive patients treated with a combination of 0.9-mg/kg IV rtPA and endovascular interventions, at a tertiary care facility with a control cohort of 30 consecutive patients treated with IV rtPA only at a comparable facility where endovascular interventions were not available. Baseline parameters were similar in the combined IV/IAT and IV rtPA−only groups: mean age, 66.6 ± 12.0 versus 66.4 ± 17.4 years; mean baseline NIHSS score, 15.8 ± 3.5 versus 16.0 ± 3.5; mean time to IV rtPA, 118 ± 27.4 versus 103.1 ± 37.1 minutes, respectively. The mean time to IAT in the combined therapy group was 239.9 ± 61.6 minutes.

Endovascular interventions consisted of IA reteplase infusion ($n = 14$) and mechanical devices, including the Merci retriever ($n = 8$), snares ($n = 15$), and balloon angioplasty ($n = 10$, including 1 stent placement). IAT led to complete recanalization in 40% of cases, partial recanalization in 33%, and no recanalization in 27%. The rates of SICH were 12.1% in the combined IV/IAT group and 3.3% in the IV rtPA−only group. The combined IV/IAT group experienced significantly lower mortality at 90 days (12.1% versus 40.0%, $P = .019$) with a significantly greater improvement in NIHSS scores by the time of discharge or follow-up ($P = .025$). In the combined IV/IAT group, patients with admission NIHSS scores between 10 and 15 and age ≤80 years showed the greatest improvement, with a significant change of the NIHSS scores from admission ($P = .00015$ and $P = .013$, respectively). The safety of full-dosage IV rtPA followed by thrombectomy was tested in the Multi MERCI trial[4] and will be discussed in later in this article. Overall, the aforementioned studies support the safety of IAT after the administration of full-dose IV rtPA.

IAT Followed by IV Thrombolysis. A "reversed bridging" approach has been proposed by Keris et al.[53] In this study, 12 patients (3 ICA and 9 MCA occlusions) of the 45 enrolled (all with NIHSS scores of >20) were randomized to receive an initial IA infusion of 25 mg of rtPA for 5–10 minutes, followed by IV infusion of another 25 mg for 60 minutes, within 6 hours of stroke onset (total combined dose, 50 mg; with a maximum dose of 0.7 mg/kg). The remaining 33 patients were assigned to a control group and did not undergo any thrombolysis. TIMI 2–3 recanalization occurred in one twelfth and five twelfths of the thrombolysis-treated patients, respectively. There were no SICHs. At 12 months, 83% of the patients in the thrombolysis group were functionally independent, whereas only 33% of the control subjects had a good outcome. The mortality rates at 12 months were 17% and 64%, respectively.

Interventional Management of Stroke Study I and II. The Interventional Management of Stroke (IMS I) Study was a multicenter open-label single-arm pilot study with the aim of investigating the feasibility and safety of a combined IV and IA approach to recanalization in patients with ischemic stroke.[54] A total of 80 patients (mean age, 64 ± 13.0 years; mean NIHSS score, 18 ± 4.5) were enrolled and received IV rtPA (0.6 mg/kg, 60 mg maximum, 15% of the dose as a bolus with the remainder administered for 30 minutes) within 3 hours of stroke onset (mean time from stroke onset to IV rtPA, 136 ± 30.2 minutes). Cerebral angiography was subsequently performed. If a thrombus was identified in an appropriate intracranial artery such as the MCA, ACA, PCA, or BA, then additional rtPA was infused via a microcatheter at the site of the thrombus up to a total dose of 22 mg during a 2-hour period or until complete recanalization. A 2,000-U bolus of IV heparin was administered once the thrombus was visualized and the decision was made to infuse IA rtPA. A heparin infusion was maintained at 450 U per hour during the IA rtPA infusion and was discontinued at the end of the procedure. In addition, a heparin flush solution (approximately 40 U of heparin per hour) was administered via access sheath and the guide catheter during the angiographic procedure. If the patient did not have an angiographic occlusion in the vascular territory appropriate for the patient's symptoms, then no IA rtPA was administered and the procedure was concluded. Termination of the IA treatment was also mandated in the following cases: 1) angiographic mass effect not explained by early edema; 2) suspicion of extravasation of contrast suggesting vessel rupture, 3) CT evidence of hemorrhage (ie, for a patient whose condition deteriorates and the procedure is interrupted for a CT, the procedure could be re-started if the CT shows no ICH), 4) worsening of clinical deficit that was not explained by angiographic findings, 5) seizure, 6) achievement of TIMI 3

reperfusion, or 7) 120 minutes of IA infusion of rtPA had occurred or >7 hours had elapsed since symptom onset. No angioplasty or stent placement procedure was allowed.

A total of 62 of the 80 patients received IA rtPA (mean time from stroke onset to IA rtPA, 217 ± 46.7 minutes). Primary comparisons were with similar subsets of the placebo and rtPA−treated subjects from the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Trial.[55] The 90-day mortality rate in IMS I subjects (16%) was numerically lower but not statistically different from the mortality rate of the placebo (24%) or rtPA−treated subjects (21%) in the NINDS rtPA Stroke Trial. The rate of SICH (6.3%) in IMS I subjects was similar to that of the rtPA−treated subjects (6.6%) but higher than the rate in the placebo-treated subjects (1.0%, $P = .018$) in the NINDS rtPA Stroke Trial. The small number of SICHs ($n = 5$) in IMS I precluded any meaningful analysis of its risk factors. However, the presence of ICA (versus MCA) occlusion (OR, 3.00; 95% CI, 1.03–8.73) and a history of atrial fibrillation (OR, 4.08; 95% CI, 1.30–12.84) were found to predict independently the occurrence of any ICH.[56] IMS I subjects had a significantly better outcome at 90 days than NINDS placebo-treated subjects for all outcome measures (OR, ≥2). Thirty-four of the 80 patients (43%) achieved an mRS ≤2 at 90 days. For the 62 subjects who received IA rtPA in addition to IV rtPA, the rate of complete recanalization (TIMI 3) was 11% (7/62) and the rate of partial or complete recanalization (TIMI 2–3) was 56% (35/62). Subsequent reanalysis of 61 angiograms from IMS I, with a comparison between recanalization (arterial occlusive lesion [AOL] grading) and reperfusion (TIMI grading) scores demonstrated only a modest agreement between these 2 grading systems (κ, 0.30; 95% CI, 0.16–0.44).[57] Good clinical outcome occurred in 49% of patients with AOL II/III scores ($P = .055$) and in 54% with TIMI 2–3 scores ($P = .019$). The 2 methods did not significantly differ in their ability to predict outcome ($P = .13$).

A pooled analysis of the baseline CT scans in the IMS I ($n = 80$) and the NINDS rtPA Stroke Trial ($n = 380$) demonstrated no relationship between the baseline ASPECT score and onset-to-treatment time or age.[58] This study also indicated that after adjustment for baseline NIHSS score, age, glucose level, and onset-to-treatment time, the chances of patients with an ASPECT score of >7 achieving a 90-day mRS of ≤1 were higher with combined IV/IA rtPA (39.2%) than with IV rtPA (29.2%) or placebo (22.5%). However, this apparent superiority of IV/IA therapy was not seen in patients with unfavorable baseline CT scan appearance (ASPECT score, ≤7). In this group, the rates of good outcome (90-day mRS score, ≤1) were 23.4%, 32.5%, and 18.9% in the combined IV/IA rtPA, IV rtPA, and placebo-treated patients, respectively.

The IMS II objective was to continue investigating the feasibility of the combined IV and IA approach to restore cerebral blood flow in patients with acute stroke.[59,60] The main difference between IMS I and IMS II is that IMS II used the MicroLysUS infusion catheter (EKOS, Bothell, Wash) (see Part 1 of this review)[61] to deliver the rtPA into the clot, by using microcatheter sonography technology. The rationale was that the sonography energy delivered in the clot loosens the fibrin strands, increasing the permeability and penetration of the thrombolytic agents. As in IMS I, patients 18–80 years of age with a baseline NIHSS score of ≥10 were given IV rtPA (0.6 mg/kg, 60 mg maximum for 30 minutes) within 3 hours of stroke onset. Patients with occlusive clots involving the ICA, MCA (M1 or M2 segments), vertebral artery, or BA were subsequently administered ≤22-mg IA rtPA and low-energy sonographic energy at the clot site by using the MicroLysUS infusion catheter (EKOS) for a maximum of 2 hours of infusion or until thrombolysis was achieved. If the catheter could not access the clot, standard microcatheters were used as per the IMS I protocol. IAT had to be initiated within 5 hours of symptom onset and terminated by 7 hours of onset. The total maximum dose of rtPA (both IV and IA) in the study was 82 mg compared with a maximum dose of 90 mg in the NINDS rtPA Stroke Trial. As in IMS I, angioplasty and/or stent placement was not allowed per protocol. The periprocedural anticoagulation scheme was also similar to that in IMS I. In the absence of a treatable occlusion in the vascular territory appropriate for the patient's symptoms, no IAT was administered and the angiographic procedure was terminated.

Primary comparisons were made with similar subsets of placebo and rtPA−treated subjects from the NINDS rtPA Stroke Trial and subjects from IMS I. Eighty-one subjects (mean age, 64 ± 11.5 years; mean baseline NIHSS score, 19 ± 5.3; median time from symptom onset to initiation of IV rtPA, 142 minutes) were enrolled. Twenty-six patients received IV rtPA only. The remaining 55 patients received both IV and IA rtPA via either the MicroLysUS infusion catheter (EKOS) ($n = 36$) or a standard microcatheter ($n = 19$). Forty-six percent of patients achieved an mRS score of ≤2 at 90 days compared with 39% and 28% of the patients in the rtPA and placebo arms of the NINDS IV rtPA Stroke Trial, respectively. After adjustment for baseline NIHSS score, age, and time to treatment, the ORs of IMS II subjects attaining an mRS score of ≤2 at 90 days were 1.74 (95% CI, 0.95–3.19) and 2.82 (95% CI, 1.54–5.16) compared with rtPA- and placebo-treated subjects in the NINDS rtPA Stroke Trial, respectively. The 90-day mortality rate in IMS II (16%) was numerically lower than that of placebo- (24%) or rtPA–treated subjects (21%) in the NINDS rtPA Stroke Trial.

The rate of SICH in IMS II subjects (9.9%) did not significantly differ from that for rtPA−treated subjects in the NINDS rtPA Stroke Trial (6.6%). IMS II patients had significantly improved outcomes at 90 days compared with the NINDS placebo-treated subjects for all end points (OR, ≥2.7) and better outcomes than NINDS rtPA–treated patients as measured by the Barthel Index and global test statistic. IMS II subjects treated with IA rtPA ± MicroLysUS infusion catheter had a 4% (2/55) TICI/TIMI 3 and a 60% (33/55) TICI/TIMI 2–3 reperfusion flow after conclusion of the IA procedure. Of the 33 subjects with TICI/TIMI 2–3 reperfusion, 15 (55%) achieved favorable outcomes at 90 days (mRS score, ≤2) compared with only 6 (27%) of the 22 subjects with TICI/TIMI 0–1 ($P = .046$). In the sonographic catheter–treated group, complete recanalization was achieved in 12 of 29 (41.4%) occlusions at 60 minutes and 20/29 (68.9%) occlusions at 2 hours or procedure end, resulting in final TICI 2–3 reperfusion grades of 62.0% (18/29). An analysis of 75 of 81 patients in IMS II who had anterior circulation strokes and underwent angiography and/or intervention demonstrated that the use of heavy sedation/pharmacologic paralysis as opposed to no/

mild sedation (OR, 7.0; 95% CI, 2.0–24.5; $P = .002$) and female sex (OR, 5.5; 95% CI, 1.7–17.2; $P = .004$) were independently associated with poor clinical outcomes. The use of heavy sedation/pharmacologic paralysis was also found to be an independent predictor of death (OR, 5.0; 95% CI, 1.34–18.7; $P = .02$).[62]

Pooled analysis of the IMS I-II data demonstrated that partial or complete recanalization (AOL 2–3) occurred in 74.6% (56/75) and good reperfusion (TICI 2–3) occurred in 61.3% (46/75) of ICA T and M1 occlusions. Revascularization correlated with good outcome for TICI 2–3 reperfusion ($P = .0004$), TICI 2B-3 reperfusion ($P = .0002$), and AOL 2–3 recanalization ($P = .03$).[60] Another analysis of the IMS I-II cohort was performed to establish the frequency and clinical importance of ACA emboli during IAT in patients undergoing the bridging approach.[63] This study demonstrated that ACA embolism rarely occurs during IAT procedures to treat M1/M2 occlusions (1/60 patients, 1.7%). However, distal embolic events were identified in 3 of 20 (15%) ICA T occlusions before IAT and in another 3 ICA T occlusions after IAT.

Evidence of ACA territory infarct on the 24-hour follow-up CT was demonstrated in 8/25 (32%) ICA T occlusions. These events were less common with the use of the MicroLysUS infusion catheter (EKOS) compared with standard microcatheter thrombolysis ($P = .05$). Despite the relatively small volume of these infarcts, lower extremity weakness was present in 9 of 10 patients at 24 hours. Good outcomes were achieved in 4 of 25 (16%) patients with ICA T occlusion overall but in zero of 10 patients with distal ACA emboli or ACA CT infarcts ($P = .07$).

Another analysis of the IMS I-II dataset compiling 98 cases of proximal anterior circulation occlusions (M1, M2, and ICA T) suggested that microcatheter contrast injections (MCIs) during combined IV/IA rtPA therapy may be associated with an increased risk of ICH.[64] In this patient group, the rates of any ICH and PH-2 were 58% (57/98) and 10% (10/98), respectively. More MCIs were seen in the ICH compared with the non-ICH group (median, 2 versus 1; $P = .04$). Despite a higher number of MCIs, the presence of edema/mass effect on baseline CT, atrial fibrillation, time to IV rtPA initiation and TICI reperfusion score were independent predictors of ICH in a multivariable analysis. The authors hypothesized that contrast toxicity or pressure transmission by the injections likely accounted for this increase in ICH risk and advised that MCIs during IAT should be minimized whenever possible.

An exploratory analysis of the clinical effect of mild hemorrhagic transformation after IAT in the IMS I-II patients found no association between HI-1 or combined HI-1 and HI-2 with clinical outcome. However, asymptomatic hemorrhagic transformation (which also includes asymptomatic PH-1 and PH-2) was associated with poor clinical outcome (OR, 2.57; 95% CI, 1.07–6.19), as were sex (OR, 2.72; 95% CI, 1.16–6.45), baseline glucose level (OR, 1.01; 95% CI, 1.00–1.02; $P = .03$), and infarct volume (OR, 1.02; 95% CI, 1.01–1.03).[65] A subsequent analysis limited to the ICA T and M1 occlusions treated with combined IV/IA therapy demonstrated that HIs were not a marker of early successful reperfusion as had been previously suggested by a study of IV thrombolysis in patients with proximal MCA occlusions.[66] In fact, this study indicated that both HIs (OR, 0.11; 95% CI, 0.02–0.68; $P = .02$) and PHs (OR, 0.11; 95% CI, 0.020–0.67; $P = .02$) were inversely associated with early revascularization success.[67]

Another pooled analysis of the IMS I-II dataset was performed with the aim to investigate the impact of time from symptom onset to vessel recanalization (time to reperfusion) on clinical outcomes. In this study, Khatri et al[68] carefully analyzed 54 cases of proximal intracranial anterior circulation occlusions (ICA T, $n = 8$ or MCA M1, $n = 46$) that were successfully reperfused (TICI 2–3) by IAT within 7 hours of stroke onset (range, 208–395 minutes). After adjustments were made for age, baseline NIHSS score, sex, and baseline glucose level, this group was compared with 38 cases without reperfusion (TICI 0–1). Only time from symptom onset to reperfusion (OR, 0.981; 95% CI, 0.967–0.995) and age (OR, 0.949; 95% CI, 0.903–0.998) independently predicted good clinical outcomes (90-day mRS score, ≤ 2) after reperfusion. On the basis of these observations, the authors concluded that outcomes after recanalization of intracranial occlusions is time-dependent and that, at later times, reperfusion may be associated with a poor risk-benefit ratio. However, these findings have been contested by a recent analysis of the pooled dataset of the MERCI and Multi MERCI trials, which demonstrated no association between time to reperfusion and clinical outcomes in patients treated with thrombectomy within 8 hours of stroke onset.[69]

Thrombectomy/Thromboaspiration Trials

The MERCI and Multi MERCI Trials. The Merci retriever was the first stroke device to be approved by the FDA and thus started the era of mechanical thrombectomy. The device was initially approved in August 2004 and is currently labeled under the following indication: "To restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke. Patients who are ineligible for treatment with IV rtPA or who fail IV t-PA therapy are candidates for treatment." The Merci retriever was initially studied in a small phase-1 multicenter trial that enrolled 30 patients with NIHSS scores of ≥ 10 in the setting of angiographic occlusion of a major cerebral artery.[70] Twenty-eight patients (mean age, 68 years; median baseline NIHSS score, 22; range, 12–39) were treated. The occlusion sites were the intracranial ICA in 5 (18%), MCA in 18 (64%), both ICA and MCA in 3 (11%), and vertebrobasilar artery in 2 (7%) patients. Median time from onset to completion of treatment was 6 hours 15 minutes. Successful recanalization (TIMI 2–3) with the retriever alone was achieved in 12 (43%) patients and with additional IA rtPA in 18 (64%) patients. There was 1 procedure-related technical complication, with no clinical consequence. There were 12 asymptomatic ICHs (43%), but no SICH occurred. At 1 month, 9 of 18 revascularized patients and zero of 10 nonrevascularized patients had achieved significant recovery (mRS score, ≤ 3). Ten patients (36%) died during the 30-day follow-up period. None of the deaths were related to the study device.

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial was a prospective single-arm multicenter trial designed to test the safety and efficacy of the Merci clot retrieval device to restore the patency of intracranial arteries in the first 8 hours of an acute stroke.[3] All patients were ineligible

for IV rtPA. Main inclusion criteria were age ≥18 years, stroke signs/symptoms with baseline NIHSS score of ≥8, stroke symptom duration between 3 and 8 hours or duration between zero and 3 hours and a contraindication for IV rtPA, and occlusion of a treatable vessel on angiography. Patients were excluded from the study if their CT scan revealed ICH, significant mass effect with midline shift, or hypoattenuation involving greater than one third of the MCA territory (sulcal effacement and/or loss of gray-white differentiation alone was allowed). Patients with >50% stenosis of the artery proximal to the target vessel were also excluded. If the treatable vessel was not opened to at least TIMI 2 flow with a maximum of 6 passes with the device, it was considered a treatment failure for the device. IA thrombolytics were allowed in cases of device failure or to treat distal embolus not accessible to the device after successful proximal embolectomy. Periprocedural use of IV heparin was allowed at the discretion of the investigator. Primary outcomes were recanalization and safety, and secondary outcomes were neurologic outcomes at 90 days in recanalized versus nonrecanalized patients. From May 2001 to December 2003, 1809 patients were screened and 151 patients were enrolled in the trial. The mean age was 67.0 ± 15.5 years. The mean baseline NIHSS score was 20.1 ± 6.6. Forty-six percent of patients were women. The mean time from symptom onset to groin puncture was 4.3 ± 1.7 hours, and the mean procedure duration was 2.1 ± 1.0 hours. The occlusion sites were the ICA (19%), ICA terminus (14%), M1 or M2 MCA branches (57%), intracranial vertebral artery (1%), and BA (9%). TIMI 2–3 recanalization was achieved in 46% (69/151) of patients in the intention-to-treat analysis and in 48% (68/141) of patients in whom the device was deployed. This rate is significantly higher than that expected by using the control arm of the PROACT II trial (18%) as an historical control ($P < .0001$).

After adjunctive therapy (IA rtPA/UK, angioplasty, snare), the rate of recanalization increased to 60.3%. Clinically significant procedural complications occurred in 10 of 141 (7.1%) patients. Three cases of embolization of a previously uninvolved vascular territory occurred (all ACA after MCA embolectomy), 1 of which was clinically significant. SICH was observed in 11 of 141 (7.8%) patients. Five of these were SAHs, and 6 were IPHs, including 2 PH-2s. The overall rates of good outcome (mRS score, ≤2) and mortality at 90 days were 27.7% and 43.5%, respectively. Good neurologic outcomes at 90 days were more frequent (46% versus 10%; RR, 4.41; 95% CI, 2.08–9.33), and mortality rates were lower (32% versus 54%; RR, 0.59; 95% CI, 0.39–0.89) with successful compared with unsuccessful recanalization. In a multivariate logistic regression analysis, successful revascularization (OR, 12.82; 95% CI, 2.95–55.75; $P < .0001$), age (OR, 0.94; 95% CI, 0.90–0.98; $P = .0009$), and baseline NIHSS score (OR, 0.78; 95% CI, 0.67–0.89; $P = .0007$) were the strongest predictors of good outcome at 90 days. Alternatively, the absence of recanalization, higher age, and higher NIHSS scores were independently associated with 90-day mortality.

The Multi MERCI trial was an international multicenter single-arm trial with the following 3 objectives: to gain greater experience with the first-generation Merci retrievers (X5 and X6) in patients ineligible for IV rtPA, to explore the safety and technical efficacy of the retriever in patients treated with IV rtPA who failed to recanalize, and to collect safety and technical efficacy data on a second-generation retriever (L5).[4,71] The inclusion/exclusion criteria, techniques, and measures of outcome were otherwise similar to the ones used in the MERCI trial. From January 2004 to July 2006, 1088 patients were screened and 177 patients were enrolled in the study. The device was deployed in 164 patients who served as the cohort for the study analysis. The mean age was 68.1 ± 16.0 years. The median (IQR) baseline NIHSS score was 19 (range, 15–23). Fifty-seven percent of the patients were women. The median (IQR) time from symptom onset to groin puncture was 4.3 hours (range, 3.2–5.3 hours), and the median (IQR) procedure duration was 1.6 hours (1.2–2.3 hours). The occlusion sites were the ICA/ICA terminus (32%), M1 or M2 MCA branches (60%), and posterior circulation (8%). Forty-eight patients (29.3%) received IV rtPA before intervention, and 57 patients received intraprocedural IA lytics.

Treatment with the retriever alone resulted in successful (TIMI 2–3) recanalization in 55% of treatable vessels and in 68% after adjunctive therapy (IA rtPA, mechanical). Clinically significant procedural complications occurred in 5.5% of the patients. SICH occurred in 9.8% of patients; however, the rate of symptomatic PH-2 was only 2.4%. There were no significant differences in the rates of SICH (10% versus 9.5%, $P = .99$), use of IA lytics (35% versus 34%, $P = .99$), or clinically significant procedure complications (4.2% versus 6%, $P = .99$) between those patients treated with IV rtPA and those who did not receive IV rtPA. The overall rates of good outcome (36%) and mortality (34%) at 90 days were substantially improved in comparison with those in the MERCI trial. As in the MERCI trial, good neurologic outcomes at 90 days were more frequent (49% versus 9.6%), and mortality rates were lower (25% versus 52%) with successful compared with unsuccessful recanalization. The authors concluded that mechanical thrombectomy after IV rtPA seems as safe as mechanical thrombectomy alone and that thrombectomy with both first- and second-generation retrievers is efficacious in opening intracranial vessels during acute strokes in patients who are either ineligible for IV rtPA or who have failed to recanalize with IV rtPA.

Two single-center studies reflecting the "real-world" experience with the Merci retriever have been published. The results were essentially comparable with those of the trials. Devlin et al[72] treated 25 consecutive patients with stroke (median age, 63 years; median baseline NIHSS score, 18) according to the MERCI/Multi MERCI protocol, except that patients with tandem proximal carotid and intracranial lesions were also treated with carotid angioplasty and stent placement. Isolated M1 or M2 MCA lesions occurred in 52%; ICA T lesions, in 8%, and vertebrobasilar lesions, in 8%. Tandem lesions involving proximal ICA and proximal intracranial vessels occurred in 32%, requiring emergent carotid stent placement. Median time from symptom onset to angiography was 4.3 hours. TIMI 2–3 recanalization was achieved in 56% of patients. Asymptomatic ICH occurred in 28%, and SICH, in 4% of the patients. The rate of good outcome (mRS score, ≤2) at 90 days was 24%. The 90-day mortality rate was 36%. Successful recanalization was directly associated with good outcomes and inversely associated with mortality at 90 days ($P < .001$).

Kim et al[73] reported their experience with the Merci re-

triever in 24 patients, 4 of whom had time to treatment of >8 hours. The mean age was 64 years (range, 14–89 years; 42% women). The median NIHSS score was 21 (range, 11–30). Median symptoms-to-procedure-start time was 303 minutes (range, 85–2385 minutes). TIMI 2–3 recanalization was achieved in 63% (15/24) of patients. Recanalization was achieved in 33% of the ICA occlusions, 60% of the MCA occlusions, and 100% of the BAOs. In patients with device only, recanalization occurred in 10 of 16. Four of the 5 patients who had failed IV rtPA were successfully recanalized. Three patients unresponsive to device therapy received rescue IA rtPA/abciximab, and 2 recanalized. Recanalization was achieved in 3 of 4 patients in whom treatment was started >8 hours after symptom onset. Overall, asymptomatic ICH occurred in 38%, and SICH, in 8% of the patients. The rate of good functional outcome at 90 days was 25% (6/24). The 90-day mortality rate was 29%.

By eliminating the need for thrombolytics, mechanical thrombectomy has made endovascular treatment feasible in many circumstances in which IAT had been previously judged unsafe. These situations were not infrequent and included recent surgery, contralateral strokes, or significant hemorrhage. Specifically, patients with significantly abnormal hemostasis at stroke onset, including international normalized ratio (INR) >1.7, elevated PTT, or platelet count <100,000/μL are not considered candidates for thrombolysis with IV rtPA or IAT. However, given the unique nature of thrombectomy, the MERCI and Multi MERCI trials enrolled patients who were on anticoagulation as long as their INR was <3.0 and their PTT was <2 times that of the controls. In addition, the platelet count thresholds used in these trials were substantially lower than those stipulated in previous trials (>50,000/μL in MERCI Part I and >30,000/μL in MERCI Part II and Multi MERCI). Indeed, a recent pooled analysis of the MERCI and Multi MERCI trials led to the identification of 35 patients with significantly abnormal hemostasis (INR > 1.7, $n = 20$; PTT > 45 seconds, $n = 11$; platelet count < 100,000/μL, $n = 6$; INR > 1.7 and PTT > 45 seconds, $n = 2$). These patients were compared with 270 patients with normal hemostasis parameters. No significant difference in the rates of major SICH (8.6% versus 8.5%) was found, supporting the safety of thrombectomy in patients with abnormal hemostasis. Similarly, there was no significant difference in the rates of revascularization (TIMI 2–3, 60% versus 65%) or mortality (40% versus 38%). However, patients with normal hemostasis had a higher rate of good clinical outcomes (9% versus 35%; $P = .002$). In patients with abnormal hemostasis, successful revascularization was associated with improved outcomes ($P = .015$) and lower mortality rates (24% versus 64%; $P = .033$).[74]

The Penumbra Stroke System Trials. The results of the initial feasibility pilot trial with the Penumbra System (Penumbra, Alameda, Calif) were summarized in the Part 1 of this article series.[61] In short, 21 vessel occlusions (7 ICAs; 5 MCAs; 9 BAs) were treated in 20 patients (mean NIHSS score, 21 ± 8) ≤8 hours after symptom onset. Recanalization before IA lysis was achieved in all treated cases (48% TIMI 2; 52% TIMI 3), and favorable outcome at 30 days, in 45% of the patients. The mortality rate was 45%.[75] This study was followed by a larger prospective single-arm multicenter trial (the Penumbra Stroke Trial) conducted at 24 international centers in the United States and Europe.[5] Inclusion/exclusion criteria were roughly similar to the ones used in the MERCI and Multi MERCI trials, including stroke signs/symptoms with baseline NIHSS score, ≥8; symptom duration between zero and 8 hours; and occlusion of a treatable vessel on angiography. A total of 125 patients were enrolled (mean age, 63.5 ± 13.5 years; mean baseline NIHSS score, 17.3 ± 5.2; 49% female; median time from stroke onset to procedure, 4.1 hours). The occlusion sites were the ICA (18%), M1 or M2 MCA branches (70%), vertebrobasilar arteries (9%), and other (3%).

Complete or partial revascularization (TIMI 2–3) occurred in 81.6% of the occluded vessels. The rate of procedural serious adverse events (SAEs) was 3.2%, none of which were device-related. SICH occurred in 14 of 125 patients (11.2%), and asymptomatic ICH, in 21 of 125 patients (16.8%). At discharge, 57.8% of patients had achieved ≥4-point improvement in NIHSS scores. Good outcomes (mRS score, ≤2) at 90 days were achieved by 25% of patients. The 90-day mortality rate was 32.8%. As in the MERCI and Multi MERCI trials, good neurologic outcomes at 90 days were more frequent (29% versus 9%, $P = .0596$) and mortality rates were lower (29% versus 48%, $P = .1384$) with successful compared with unsuccessful recanalization. The results of this study, which led to the FDA approval of the Penumbra device in December 2007, were well duplicated in a postmarket retrospective review of 139 patients who were treated with the device at 7 international centers, reflecting a favorable safety and effectiveness profile in a real-world setting.[76]

Patients were treated according to the device-approval indication (ie, NIHSS score, ≥8; presentation within 8 hours of symptom onset; and an occlusion [TIMI 0–1] of a treatable intracranial vessel). The mean age was 64 years. The mean baseline NIHSS score was 16. The average time from symptom onset to initiation of therapy was 4.5 hours. Most target vessels (96%) had TIMI scores of zero or 1 at the site of primary occlusion before treatment. Eighty patients (57.6%) also received IA adjunctive thrombolytic therapy. After use of the Penumbra System, 84% of the treated vessels were revascularized to TIMI 2 (46%) or 3 (38%). At discharge, 56% of patients had an NIHSS improvement of at least 4 points. Eight procedural SAEs occurred in the 139 patients (5.8%), none of which were attributed to device malfunction or breakage. A total of 18 patients (13%) were found to have ICH at 24 hours, of whom 10 (7.2%) were symptomatic. To date, the all-cause mortality rate is 22% (31/139). Of the patients who have reached the 90-day follow-up, 40% had an mRS score of ≤2.

Issues in Comparing Different Reperfusion Trials. Given the relative paucity of controlled data in the stroke field, many stroke researchers have tried to compare different reperfusion studies in an attempt to better understand the advantages and limitations of the currently available treatment options. The results of these analyses, however, are limited by the significant differences in methodology and patient selection used in the respective studies. As an example, the mechanical revascularization trials have been criticized for their high rates of mortality and relatively low rates of good outcomes despite high rates of successful recanalization. In fact, one might argue that the rates of good outcome (at 90 days) have been substantially higher in studies that have used IV or IA thrombolytics such as the NINDS rtPA,[55] ECASS III (52.4%),[77] Combined Lysis of

Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST, 51%),[78] IMS I (43%),[54] IMS II (46%),[59] and the PROACT II (40%)[14] trials than in mechanical revascularization studies such as the MERCI (27.7%),[3] Multi MERCI (36%),[4] and Penumbra (25%)[5] trials, notwithstanding the significantly higher recanalization rates seen in the mechanical studies. There are several potential explanations for the apparent disconnect between recanalization and clinical outcomes, including differences in clot location and burden, baseline stroke severity, and time from symptom onset to treatment in these studies. Parenthetically, patients could have been harmed by the interventional procedures and that outcome could have nullified any benefit from recanalization, though the relatively low rates of SICH and SAEs reported in the thrombectomy trials make this possibility unlikely.

Another important consideration is the asymmetry of the underlying patient population inherent to the study design. Thrombolytic trials are typically outcome studies and, as such, exclude patients with poor baseline functional status. Mechanical revascularization studies have used recanalization as their primary end point and have not excluded patients with poor functional baseline. Indeed, 23 (14%) of the patients treated in the Multi MERCI study had a baseline pre-stroke mRS score of $\geq$1 (including 13 patients with mRS score of $>$2). The simple exclusion of these patients would have increased the rates of good outcome in Multi MERCI from 36% to 39.4%.[4] These results are very similar to those seen in PROACT II, despite the fact that Multi MERCI also treated patients with ICA and basilar occlusions who typically have a higher morbidity/mortality risk.

Therefore, comparisons among different studies would require, at the very least, adequate matching of the baseline variables. With that in mind, Josephson et al[79] compared the results of mechanical thrombectomy (MERCI and Multi MERCI) and IAT (PROACT II) in patients with acute stroke. The authors identified patients in the MERCI and Multi MERCI trials who would have been eligible for PROACT II. Rates of good outcome (mRS score, $\leq$2) and mortality at 90 days were subsequently compared, adjusting for differences in baseline NIHSS score and age. Sixty-eight patients enrolled in MERCI and 81 enrolled in Multi MERCI were eligible for PROACT II. In both unadjusted and adjusted analyses, PROACT II−eligible patients with thrombectomy showed a trend toward better clinical outcomes compared with the PROACT II control arm (adjusted analysis: MERCI, 35.4% [P = not significant]; Multi MERCI, 42.8% [P = .048]; PROACT II control, 25.4%). In both unadjusted and adjusted analyses, mortality rates did not significantly differ between thrombectomy patients and PROACT II control patients (adjusted analysis: MERCI 29, 1%; Multi MERCI, 18.0%; PROACT II control, 27.1%). Compared with the PROACT II treatment group, thrombectomy patients showed similar rates of good outcome and mortality. The authors concluded that the differences in the rates of mortality and good outcome between the MERCI/Multi MERCI trials and the PROACT II trial are explained by differences in study design and baseline patient characteristics.

Finally, end points also need to be adjusted when comparing different studies. As an example, the MERCI and Multi MERCI trials used a very unique recanalization grading system, which required TIMI 2 or 3 flow in all treatable vessels. Therefore, a successful recanalization for the MCA required all M1 and M2 segments to be at least TIMI 2, and a successful recanalization for the ICA required the ICA, M1, and both M2 branches to be at least TIMI 2. This is a much more rigid scale than the more commonly used TIMI or TICI reperfusion scales that have been used in most of the other studies. For instance, a patient with an ICA occlusion who recanalizes the ICA, M1, and the superior division M2 posttreatment would have been a failure in MERCI if the inferior division had remained completely occluded. This same patient would have been considered a TIMI 2 (success) in the IMS I-II and Penumbra trials.

Ongoing and Upcoming Studies

Interventional Management of Stroke Study III (IMS III). The ongoing IMS III trial is a phase 3 randomized multicenter open-label clinical trial continuing the investigation into the efficacy of the combined IV and IA approach to treat acute stroke.[80] Main inclusion criteria are the following: 1) age $\geq$18 and $\leq$80 years; 2) baseline NIHSS score, $\geq$10; and 3) initiation of IV rtPA within 3 hours from stroke onset. The exclusion criteria are, in general, similar to those of the NINDS rtPA trial exclusions. The CT exclusion criteria include hemorrhage of any degree, significant mass effect with midline shift, large hypoattenuation (more than one third of the MCA territory or ASPECTS $\leq$4), and CT evidence of intraparenchymal tumor. Sulcal effacement and/or loss of gray-white differentiation alone are not contraindications for treatment. Patients are randomized to receive IV rtPA followed by IA therapy or standard-dose (0.9 mg/kg) IV rtPA alone in a 2:1 ratio. Patients in the IV/IA group receive a lower dose of rtPA (0.6 mg/kg, 60 mg maximum) for 40 minutes followed by immediate angiography. If a treatable thrombus is not visualized, no IA therapy is administered. If an appropriate thrombus is identified, the neurointerventionalist may select either the MicroLysUS infusion catheter (EKOS) standard microcatheter to infuse rtPA or select the Merci retriever per user preference. The investigators are currently exploring incorporation of the Penumbra System as another mechanical option. A maximum dose of 22 mg of rtPA may be administered intraarterially. IA treatment must begin within 5 hours and must be completed within 7 hours of stroke onset. The primary outcome measure is the rate of good clinical outcomes (mRS score, $\leq$2) at 90 days. The primary safety measure is mortality at 3 months and SICH within the 24 hours of randomization. Trial enrollment began in July 2006. The planned sample size is 900 patients. As of February 2009, 240 subjects have been enrolled in 39 sites across the United States, Canada, and Australia.

MR Imaging and Recanalization of Stroke Clots Using Embolectomy. MR Imaging and Recanalization of Stroke Clots Using Embolectomy (MR Rescue) is a National Institutes of Health−funded multicenter randomized controlled trial of patients with ischemic stroke with large-vessel occlusions located in the anterior circulation. A total of 120 patients will be randomized to treatment with the Merci retriever or medical therapy (including antithrombotic treatment), with randomization stratified by MR imaging pattern (penumbral

versus nonpenumbral) and automated image processing in real time. The primary hypothesis is that the presence of substantial penumbral tissue on MR imaging predicts patients most likely to respond to mechanical thrombectomy. A nested hypothesis seeks to demonstrate that patients having undergone thrombectomy have improved functional outcome compared with randomized controls, though this is a secondary goal and the trial may not have enough power to show statistically significant differences across these 2 groups. The main inclusion criteria are the following: 1) NIHSS score, ≥6; 2) age, ≥18 and ≤85 years; 3) procedure able to be initiated within 8 hours from stroke onset; 4) intracranial ICA or proximal MCA (M1 or M2) occlusion on MR angiography; and 5) premorbid mRS score of 0–1. The main exclusion criteria are the following: 1) NIHSS score, ≥30; 2) acute ICH, coma, rapidly improving neurologic signs before randomization; 3) patient meeting the criteria for IV tPA; 4) pre-existing medical, neurologic, or psychiatric disease that would confound the neurologic, functional, or imaging evaluations; 5) pregnancy, renal failure, contrast allergy; 6) proximal ICA occlusion, carotid stenosis >67%, or dissection; and 7) INR > 3.0; PTT > 3 times normal. Patients treated with IV rtPA with persistent target occlusion on posttreatment MR imaging performed at the completion of drug infusion are also candidates for the trial. Trial enrollment started in May 2004, and as of January 2009, a total of 61 of the 120 planned patients have been enrolled at 27 centers. The investigators are actively exploring incorporation of multimodal CT as an alternative to MR imaging (Chelsea Kidwell, personal communication, February 2009).

SYNTHESIS and SYNTHESIS Expansion Trials. SYNTHESIS was a multicenter randomized controlled trial that aimed to compare the functional outcomes after IV versus IA thrombolysis. Evaluation of clinical outcomes was blinded. Eligible patients were randomized to receive either IV rtPA (0.9 mg/kg; maximum, 90 mg) or IAT (rtPA at a rate of 90 mg/h up to 0.9 mg/Kg; maximum, 90 mg). Except for intraprocedural heparin, antithrombotics were not allowed during the first 24 hours. The main inclusion criterion was a clearly defined time of stroke onset, allowing initiation of IV treatment within 3 hours of symptom onset and IAT within 6 hours of symptom onset. The exclusion criteria largely followed the NINDS rtPA trial exclusions. Recruitment started in January 2004 and was stopped prematurely after the randomization of 54 patients in February 2008. The Italian Agency of Drugs requested an interim analysis of the data to expand the study. The trial protocol was modified and re-launched by using the name SYNTHESIS Expansion (SE).

SE is a phase 3 randomized controlled trial comparing IV versus IA thrombolysis and/or IA mechanical treatment. The main inclusion criteria are a clearly defined time of stroke onset, age ≥18 and ≤80 years, and time allowing initiation of IV treatment within 4.5 hours of symptom onset (as per ECASS III) and IAT with rtPA and/or mechanical devices within 6 hours of symptom onset, when uncertainty about appropriateness between the 2 approaches exists as established by the treating physician. Exclusion criteria are the same as in SYNTHESIS. The primary outcome is the rate of survival free of disability (mRS score, 0–1) at 3 months. The planned sample size is 350 subjects. As of February 2009, 58 subjects have been enrolled in 18 Italian centers (Alfonso Ciccone, personal communication, February 2009). No interim analyses have yet been undertaken; the first will be provided at 100 patients.

Randomized Trial of Endovascular Treatment of Acute Ischemic Stroke Versus Medical Management. The Randomized Trial of Endovascular Treatment of Acute Ischemic Stroke Versus Medical Management (RETRIEVE) study is a multicenter international prospective randomized controlled trial that aims to compare mechanical thrombectomy by using the Merci retriever with best medical therapy (with or without IV thrombolysis) in patients with acute stroke who can be treated within 8 hours from stroke onset. The study will be funded by Concentric Medical, the manufacturer of the Merci retriever. The exact protocol details are currently being defined. Enrollment is expected to begin later this year.

Pragmatic Ischemic Stroke Thrombectomy Evaluation. The Pragmatic Ischemic Stroke Thrombectomy Evaluation (PISTE) is a pilot prospective randomized controlled trial with independent blinded measurement of outcome that aims to compare mechanical thrombectomy (by using an approved device with or without IA thrombolytics) with the best medical therapy (with or without IV thrombolysis) in selected patients with acute stroke.[81] The trial is planned to start in the United Kingdom in mid 2009 and will enroll >200 patients. The primary hypothesis is that mechanical revascularization reduces the rate of death or dependency (mRS score, 3–6) at 3 months compared with standard medical therapy alone in patients with MCA or ICA occlusion in an intention-to-treat analysis. The secondary hypotheses include the following: 1) thrombectomy improves vessel recanalization rates at 7 days, 2) thrombectomy reduces the size of infarct on follow-up imaging, 3) thrombectomy improves quality of life, 4) thrombectomy reduces overall cost of care and societal costs, and 5) CT perfusion (CTP) or MR imaging findings are predictors of outcome. The main inclusion criteria are the following: 1) acute ischemic stroke; 2) age, ≥18 years; 3) baseline NIHSS score cutoff yet to be defined; 4) occlusion of the main MCA trunk, MCA bifurcation, or intracranial ICA on CT angiography or MR angiography; 5) interventional treatment that can start within 6 hours of stroke onset; 6) informed consent; 7) functional independence before the stroke; and 8) absence of several medical comorbidities, peripheral vascular disease, or arch anatomy, which would preclude safe cerebral angiography. CTP or MR imaging perfusion will be performed in all patients before the enrollment, but the findings will not be used for eligibility (data will be used in the secondary analysis of the trial). The main exclusion criteria are the following: 1) CT evidence of ICH, 2) stroke >6 hours before start time of possible intervention, 3) mRS score of ≥2 before the current stroke, 4) any stroke or hemorrhage within 3 months, 5) vascular access contraindications, and 6) seizures at onset.

DWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention Trial. The main hypothesis of the DWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial is that MR perfusion/CTP−based endovascular treatment in patients with wake-up and late-presenting strokes is at least as safe and effective as standard endovascular treatment performed within 8 hours of symptom onset (phase I "Lead-in"/prospective single-arm

phase) and leads to improved outcomes when compared with the best medical treatment (phase II, randomized controlled trial).[82] The main inclusion criteria are the following: 1) age, ≥18 and ≤85 years; 2) witnessed or nonwitnessed (including wake-up) strokes with "last time seen well" between 7–23 hours (treatment initiation between 8 and 24 hours); 3) new focal neurologic deficit with an NIHSS score of ≥10 and/or sudden deterioration with ≥4-point increase from the initial presentation with a minimum NIHSS score of 6; 4) premorbid mRS score of 0–1; 5) ICA and/or MCA M1 segment occlusion on MR/CT angiography; and 6) ASPECTS ≥ 7 on CTP−cerebral blood volume map or MR imaging−DWI sequence. The primary end point is the rate of good clinical outcomes (mRS score, ≤2) at 90 days. Patient recruitment is planned to start by mid 2009.

Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke. The Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS) trial is a prospective randomized single-blind multicenter study of NeuroFlo (CoAxia, Maple Grove, Minn) treatment plus standard medical management versus standard medical management alone. Trial design includes a 1:1 randomization of ≤488 patients with acute stroke (NIHSS score, 5–18) at approximately 80 sites worldwide, with a primary end point of 90-day neurologic and functional assessments. Treatment may begin ≤14 hours' postsymptom onset. Preliminary safety data on the first 50 patients enrolled revealed no apparent increased risk of hemorrhagic transformation or of other SAEs, including cardiac or renal events. To date, nearly 300 patients have been enrolled, and enrollment is expected to be completed by January 2010. The SENTIS Data and Safety Monitoring Board conducts ongoing review of all adverse events and, to date, has recommended no changes to the trial.

Safety and Efficacy of NeuroFlo in 8–24 Hour Stroke Patients. The Safety and Efficacy of NeuroFlo in 8–24 Hour Stroke Patients (FLO-24) trial was a prospective single-arm treatment feasibility trial aimed at determining the baseline safety and feasibility of the NeuroFlo device in patients with acute ischemic stroke (age, 18–85 years; NIHSS score, 4–20) whose last known time symptom-free was between 8 and 24 hours.[83] Only patients with discernible perfusion-diffusion mismatch on MR imaging were enrolled. The primary end point was all adverse events occurring from baseline through 30 days post-treatment. Enrollment closed in October 2008 with 26 patients enrolled at 9 sites worldwide. Preliminary data suggest that treatment with the NeuroFlo catheter in this later time window is safe, with no increased risk of ICH compared with historical data. One patient of the 25 treated experienced a hemorrhagic transformation, which was classified as a PH-1 by the Core Laboratory (4%).

Feasibility and Safety of NeuroFlo in Stroke Patients Receiving rtPA. The Feasibility and Safety of NeuroFlo in Stroke Patients Receiving rtPA is a prospective single-arm treatment study aimed at determining the safety and feasibility of using the NeuroFlo device in patients with acute ischemic stroke who have minimal clinical improvement following initiation of IV rtPA. The patient population includes patients with acute ischemic strokes who qualify for and have undergone IV rtPA therapy, whose NIHSS score is between 5 and 22, and who can begin the NeuroFlo procedure within 3 hours of initiation of IV rtPA. Approximately 26 patients will be enrolled at 4 sites worldwide. To date, 22 patients have been enrolled, and enrollment is expected to be completed by May 2009. Of the 13 patients in whom preliminary data are available, none have experienced SICH, suggesting that treatment with the NeuroFlo catheter is safe following administration of IV rtPA.

Registries. The MERCI Registry is a phase IV prospective open-label competitive-enrollment multicenter study that aims to assess the real world use of the Merci retriever in acute ischemic stroke. The Registry started in June 2007 and will involve ≤50 centers worldwide. There are no exclusion criteria, and subjects are followed for 90 days. Primary outcome measures include 90-day rates of good outcome (mRS score, ≤2) and mortality as well as the rates of postprocedural revascularization. Secondary outcomes include NIHSS change from baseline to 24 hours and discharge disposition. There is no predefined sample size, though the registry is projected to enroll at least 1000 subjects. As of February 2009, a total of 478 patients have been enrolled. The Interventional Stroke Therapy Outcomes Registry II (INSTOR II) is a prospective multicenter observational outcomes data base designed to collect data on the demographics, presentation, diagnosis, treatment, resource use, and outcomes of hospitalized patients with stroke. There are no predefined interventions and limited restrictive exclusion criteria. The primary end points for data collection are outcomes at hospital discharge and at 3 months.

Conclusions

The preponderance of the data indicates that reperfusion should represent the near-term treatment goal in stroke. The review presented above demonstrates the logic behind that thesis, as well as the challenges. At times, in the spirit of academic clarity, we have sought to compare results dispassionately from different trials to address core challenges to the question of the need to reperfuse. Finally, the multiple articles, case series, postmarket registries, and initiated and then halted studies point to the continuing need for large randomized controlled studies as have been undertaken with IMS III, MR Rescue, and SYNTHESIS. These and many of the upcoming studies will hopefully provide level 1A data for the overall benefit of neuroendovascular care in acute ischemic stroke.

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