ORIGINAL RESEARCH

Occurrence and Predictors of Futile Recanalization following Endovascular Treatment among Patients with Acute Ischemic Stroke: A Multicenter Study

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EDITOR'S CHOICES

BACKGROUND AND PURPOSE: Although recanalization is the goal of thrombolysis, it is well recognized that it fails to improve outcome of acute stroke in a subset of patients. Our aim was to assess the rate of and factors associated with "futile recanalization," defined by absence of clinical benefit from recanalization, following endovascular treatment of acute ischemic stroke.

MATERIALS AND METHODS: Data from 6 studies of acute ischemic stroke treated with mechanical and/or pharmacologic endovascular treatment were analyzed. "Futile recanalization" was defined by the occurrence of unfavorable outcome (mRS score of ≥3 at 1–3 months) despite complete angiographic recanalization (Qureshi grade 0 or TIMI grade 3).

RESULTS: Complete recanalization was observed in 96 of 270 patients treated with IA thrombolysis. Futile recanalization was observed in 47 (49%). In univariate analysis, patients with futile recanalization were older (73 ± 11 versus 58 ± 15 years, $P < .0001$) and had higher median initial NIHSS scores (19 versus 14, $P < .0001$), more frequent BA occlusion (17% versus 4%, $P = .049$), less frequent MCA occlusion (53% versus 76%, $P = .032$), and a nonsignificantly higher rate of symptomatic hemorrhagic complications (2% versus 9%, $P = .2$). In logistic regression analysis, futile recanalization was positively associated with age >70 years (OR, 4.4; 95% CI, 1.9–10.5; $P = .0008$) and initial NIHSS score 10–19 (OR, 3.8; 95% CI, 1.7–8.4; $P = .001$), and initial NIHSS score ≥20 (OR, 64.4; 95% CI, 28.8–144; $P < .0001$).

CONCLUSIONS: Futile recanalization is a relatively common occurrence following endovascular treatment, particularly among elderly patients and those with severe neurologic deficits.

ABBREVIATIONS: ACA = anterior cerebral artery; BA = basilar artery; CI = confidence interval; Gp IIb/IIIa = glycoprotein IIb/IIIa; h = hour; IA = intra-arterial; ICA = internal carotid artery; ICH = intracerebral hemorrhage; IMS = Interventional Management of Stroke; IV = intravenous; MCA = middle cerebral artery; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; mRS = modified Rankin Scale; N/A = not applicable; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; OR = odds ratio; PCA = posterior cerebral artery; PROACT = Prolyse in Acute Cerebral Thromboembolism; rtPA = recombinant tissue plasminogen activator; TIMI = Thrombolysis in Myocardial Infarction; VA = vertebral artery

The goal of IV and IA thrombolytic therapy in acute stroke is to recanalize an occluded vessel to salvage ischemic but still-viable brain tissue. Recanalization correlates with good clinical outcome in most, but not all, reported literature.[1] Futile recanalization occurs when successful recanalization fails to improve the functional outcome.

In the IMS II trial, 60% (33/55) of subjects treated with IA rtPA via the MicroLysUS infusion catheter (EKOS, Bothell, Washington) or standard microcatheters had partial or complete reperfusion (TIMI grade 2 and 3). Of those 33 subjects, 15 (55%) had a 3-month favorable outcome as measured by an mRS score of 0–2.[2] Other major studies did not specifically report the rate of futile recanalization. Yet, there was always a mismatch between recanalization and favorable outcome rates, suggesting that futile recanalization occurs in variable proportions regardless of treatment strategy. In the PROACT II trial,[3] the recanalization rate was 66%, while the rate of favorable outcome was 40% (26% mismatch). A similar pattern was documented in the Combined Lysis of Thrombus in Brain Ischemia by Using Transcranial Sonography and Systemic TPA trial (82% recanalization, 51% favorable outcome),[4] the MERCI trial (68% recanalization rate, 34% favorable outcome),[5,6] and the Multi MERCI trial (68% recanalization rate, 32% favorable outcome).[7]

Given the resources required for and risk associated with endovascular treatment,[8-10] it is important to identify the subset of patients who will not benefit from recanalization. The aim of our study was to assess the rate of and factors associated with futile recanalization following endovascular treatment among patients with acute ischemic stroke.

Received April 27, 2009; accepted after revision July 31.

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Previously presented as a poster at: Annual Meeting of the International Stroke Conference, February 17–20, 2009; San Diego, California; and as a platform presentation at: Annual Meeting of the American Academy of Neurology, April 25–May 2, 2009; Seattle, Washington.

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Indicates article with supplemental on-line tables.

DOI 10.3174/ajnr.A2006

Materials and Methods

We combined individual patient data from 6 studies of patients treated with IA thrombolysis in the setting of acute ischemic stroke. All studies were approved by local institutional review boards. The methodology and results of all 6 studies as well as the compilation and patient selection process for current analysis are summarized in Online Tables 1–3, respectively.

Study A. Study A prospectively evaluated the safety of mechanical disruption of thrombus following a full dose of IV rtPA in the setting of acute stroke within 3 hours of symptom onset. Favorable outcome (1–3 months; mRS score, ≤2) was determined by either a clinic visit or a telephone interview.[11]

Study B. Study B was a prospective nonrandomized open-label trial aimed at evaluating the safety of IA reteplase in conjunction with IV abciximab in patients with acute ischemic stroke presenting 3–6 hours after symptom onset. The primary end point was symptomatic ICH at 24–72 hours, and secondary end points were partial or complete recanalization, early neurologic improvement at 24 hours, and favorable outcome at 1 month (mRS score, ≤2). The study was approved by the US Food and Drug Administration and was overseen by an independent data and safety monitoring board.[12]

Study C. Study C prospectively evaluated the safety of the MicroLysUS infusion catheter (EKOS) (a standard microinfusion catheter with a ring sonography transducer tip) for acute embolic stroke treatment. The secondary goal was to assess the efficacy of sonography-accelerated thrombolysis in improving clinical outcomes.[13]

Study D. Study D retrospectively assessed the rate of reocclusion and its effect on clinical outcome after IA thrombolysis for acute ischemic stroke. Favorable outcome (1–3 months; mRS score, ≤2) was determined by either a clinic visit or a telephone interview.[14]

Study E. Study E was a case series of consecutive patients who presented to an academic center with ischemic stroke, had angiographically confirmed arterial occlusion, and were treated with IA thrombolysis. Favorable outcome (1–3 months; mRS score, ≤2) was determined by either a clinic visit or a telephone interview.[15]

Study F. Study F was a case series representing the experience of another academic center. Consecutive patients with acute ischemic stroke treated with IA thrombolysis were included. Functional outcome was assessed 3 months after the index event by using the mRS. Several articles have been published on the basis of these data.[16-20]

In each of the 6 studies, neurologic evaluation including the NIHSS score was documented before the procedure, 24 hours after the procedure, and on day 7 or discharge. Radiologic evaluation with CT scan of the head was performed before the procedure and 24–48 hours after. CT scan was also performed whenever neurologic deterioration occurred. Angiographic occlusion and recanalization were classified by interventional neurologists or neuroradiologists by using either the TIMI grading scale[21] or the Qureshi grading scale.[22] The TIMI is a point scale from 0 (complete occlusion) to 3 (complete recanalization), which was originally developed to assess arterial occlusion and perfusion in patients with myocardial infarction and was later adopted for use in stroke by the PROACT II trial.[2] The TIMI grading system does not account for occlusion location or collateral circulation. The Qureshi grading system is a scale from 0 (best possible score) to 5 (worst possible score), which angiographically classifies arterial occlusion and recanalization. The Qureshi grading system was specifically designed for ischemic stroke to address the limitations of the pre-existing TIMI grading system. The Qureshi grading scale has been validated for use in acute stroke (Table 1).[22,23] Complete recanalization was defined by a posttreatment TIMI grade of 3,[24] which is equivalent to a Thrombolysis in Cerebral Infarction reperfusion grade of 3.[25] Six patients did not have a posttreatment TIMI grade available. In those patients, complete recanalization was defined as a Qureshi grade[22] of 0. All 3 grades represent complete patency with filling of all distal branches. A distinct parameter for recanalization of the primary arterial occlusive lesion independent of global reperfusion[24,25] was not collected. Favorable outcome was defined as mRS[26-28] ≤2 at 1–3 months. "Futile recanalization" was defined as unfavorable outcome despite complete recanalization.

Table 1: Qureshi grading scheme for stratification of patients with acute ischemic stroke based on initial site of occlusion and collateral supply

Grade	Qureshi Grading Scheme
0	No occlusion
1	MCA occlusion (M3 segment), ACA occlusion (A2 or distal segments), 1 BA/VA branch occlusion
2	MCA occlusion (M2 segment), ACA occlusion (A1 or A2 segments), ≥2 BA/VA branch occlusions
3	MCA occlusion (M1 segment)
3A	Lenticulostriate arteries spared and/or leptomeningeal collaterals visualized
3B	No sparing of lenticulostriate arteries or leptomeningeal collaterals visualized
4	ICA occlusion (collaterals present), BA occlusion (partial filling direct or via collaterals)
4A	Collaterals fill MCA, anterograde filling[a]
4B	Collaterals fill ACA, retrograde filling[a]
5	ICA occlusion (no collaterals), BA occlusion (complete)

Note:—The interobserver variability and correlation with recanalization and short-term favorable outcome and mortality have been previously described in patients with acute ischemic stroke undergoing intra-arterial thrombolysis.[22,23]
[a] The predominant pattern of filling.

Statistical Analysis

Patient characteristics were descriptively compared across studies. The study sample was dichotomized on the basis of favorable outcome into futile and nonfutile recanalization groups. Univariate analysis was performed to compare the 2 groups with respect to demographic, clinical, and radiologic variables, as well as rates of outcome events. The exact χ^2 test was used for categoric data; analysis of variance, for continuous data; and the Kruskal-Wallis test, for nonparametric variables. We performed the test for heterogeneity to identify the possibility of 1 study skewing the results of the combined analysis. There was statistically significant heterogeneity between the studies. Multivariate analysis was performed to study predictors of futile recanalization by using the generalized linear model with logit link, which takes into account the structure of the data (patients within study) and provides more conservative estimates of association. Variables selected for the multivariate analysis were age, initial NIHSS score, initial severity of arterial occlusion defined by Qureshi grade, and time to treatment. Selection was based on clinical rather than statistical significance. A test for interaction was performed for statistically significant main effect predictors. A P value $< .05$ was considered significant. All analyses were performed by using SAS statistical software (SAS, Cary, North Carolina).

Results

The initial compilation resulted in a sample of 270 patients treated with pharmacologic and/or mechanical IA thrombolysis. Sixteen patients were excluded for the following reasons: lack of initial occlusion ($n = 11$), lost to follow-up ($n = 3$), age

<18 years ($n = 1$), and undocumented time of symptom onset ($n = 1$) (On-line Table 3). Complete recanalization was observed in 96 (38%) of the remaining 254 patients.

Patients with complete recanalization had a mean age of 65 ± 15 years; 39 (40%) were women. The median initial NIHSS score was 16 (range, 4–42). The median initial Qureshi grade was 3 (range, 1–5). The occlusion was located in the MCA (64%), ICA (18%), BA (11%), VA (6%), and PCA (1%). Median time to treatment was 256 minutes (range, 60–780 minutes). Five patients (5%) developed symptomatic ICH. Some of the patients' characteristics were different across studies, reflecting the differences in the inclusion/exclusion criteria. For example, study C was the only study to have an upper limit for age (77 years); thus, it had the youngest cohort of patients. Study D inclusion criteria required an initial NIHSS score of ≥16 and had the highest initial NIHSS score, while study B inclusion criteria required NIHSS scores of 4–23 and had the lowest initial NIHSS score (On-line Tables 1 and 2). Patients with complete recanalization were further divided on the basis of their functional outcome. Favorable outcome (1–3 months; mRS score, ≤2) was observed in 49 patients (51%), while 47 patients (49%) had futile recanalization.

In univariate analysis (On-line Table 4), patients with futile recanalization were older (73 ± 11 versus 58 ± 15 years, $P <$ .0001) and had higher initial median NIHSS scores (19 versus 14, $P <$ .0001), more frequent basilar artery occlusion (17% versus 4%, $P = .049$), and less frequent MCA occlusions (64% versus 76%, $P = .032$). The symptomatic hemorrhagic complication rate was nonsignificantly higher in the futile recanalization group (9% versus 2%, $P = .2$). Time to treatment was not significantly different, with a median of 263 minutes (range, 60–540 minutes) for the futile recanalization group versus 240 minutes (60–780 minutes) for the nonfutile recanalization group ($P = .38$). There was no correlation between time to treatment and initial NIHSS score based on the Spearman rank correlation (−0.113, $P = .27$). Occlusion severity was not significantly associated with futile recanalization in the univariate analysis but was highly correlated with NIHSS score ($P = .0024$).

Rates of futile recanalization were significantly different across source studies ($P = .01$, On-line Table 3); therefore, study variation was incorporated in the multivariate model by using a generalized linear model. In the multivariate analysis, age >70 years was independently associated with futile recanalization ($P = .0008$). Both NIHSS score strata (NIHSS score, >10 and NIHSS score, >20) were independent predictors, with a statistically significant trend ($P = .0001$). Interaction between age and NIHSS strata was not significant.

Time to treatment stratum 3–6 hours was associated with futile recanalization compared with the time stratum <3 hours ($P = .045$). However, time stratum ≥6 hours was not associated with futile recanalization ($P = .27$). Overall, there was no significant trend across the 3 time strata. We also studied the association between time to treatment (as a continuous variable) and clinical outcome to avoid diluting the effect by limiting the analysis to only the trichotomized variable. Time to treatment as a continuous variable had no effect on clinical outcome. Initial occlusion as measured by Qureshi grade was not significantly associated with futile recanalization (Table 2). Multiple models were subsequently created to assess the predictive value of circulation type (anterior versus posterior circulation) and MCA occlusion sites, but no association was found.

Table 2: Multivariate analysis determining the predictors of futile recanalization

Variable	OR (95% CI)	*P* Value for Difference	*P* Value for Trend
Age strata			N/A
≤70 years	Reference		
>70 years	4.4 (1.9–10.5)	.0008	
NIHSS score strata			<.0001
0–9	Reference		
10–19	3.8 (1.7–8.4)	.001	
≥20	64.4 (28.8–144.4)	<.0001	
Time to treatment strata			.38
≤3 hours	Reference		
3–6 hours	2.5 (1.3–4.8)	.0049	
>6 hours	1.3 (0.8–2.2)	.27	
Occlusion severity strata (Qureshi: grade)			N/A
Mild (grade 0–2)	Reference		
Severe (grade 3–5)	0.4 (0.1–2.6)	.37	

Discussion

In this pooled analysis of patients with acute ischemic stroke treated with IA thrombolysis, almost half of the patients who had complete recanalization of a visualized arterial occlusion met our definition of futile recanalization. This does not preclude the benefit of partial recanalization. In the IMS II trial, 45% of the patients who had partial or complete reperfusion (TIMI 2 and 3) had poor outcome (ie, futile recanalization).[4] Other major studies did not report the outcome of recanalized patients; therefore, futile recanalization rate cannot be calculated.

Predictors of Futile Recanalization

Our analysis showed that futile recanalization was associated with age of >70 years and NIHSS score of >10. In the NINDS trial, all age groups benefited from treatment, but patients <75 years of age and patients with an NIHSS score of <20 had the greatest potential for a favorable response.[29] In a post hoc analysis of the PROACT II trial, age >68 years and NIHSS score of <20 were predictors of good outcome in multivariate analysis.[30] Other case series reported age <60 years and NIHSS score of <10 as predictors of good outcome.[31] Current thrombolysis guidelines by the American Stroke Association recommend caution when dealing with "severe" strokes, without specifying a threshold NIHSS score,[8] because of the increased risk of symptomatic hemorrhagic complications.

In most IA trials, inclusion criteria are an upper limit for age, again because of safety reasons.[9] This is usually set at 80 years,[4,32-34] though 75[35] and 85 years[2,36] have also been used. In a pooled analysis of 101 patients from 4 prospective studies, patients ≥80 years had a lower likelihood of favorable outcome (OR, 0.34; 95% CI, 0.1–1.1; $P = .07$) and higher mortality rates (OR, 3.62; 95% CI, 1.15–11.36; $P = .027$) following IA thrombolysis for acute stroke after adjusting for recanalization.[37] In another retrospective analysis, patients ≥80 years had significantly lower survival rates (57% versus 80%, $P =$

.01) and lower excellent functional outcome rates, defined as an mRS score of 0–1 (26% versus 40%, $P = .02$).[38] In both studies, initial stroke severity, time to treatment, and rate of symptomatic ICH were similar in both age groups.

In our analysis, time to treatment stratum 3–6 hours was associated with futile recanalization, but there was no overall association between outcome and time to treatment as a continuous or trichotomized variable. The effect of time to treatment was studied in the NINDS trial. Patients treated within 90 minutes benefited more than those treated in 90–180 minutes.[29] A pooled analysis of 3 major IV thrombolysis trials showed a correlation between time to treatment and favorable outcome but also showed that the upper limit of the treatment window may be as late as 5–6 hours.[39] In IA thrombolysis, the current recommended time window is 6 hours based on the PROACT II data.[2] Other studies showed that IA thrombolysis benefit can be extended beyond that window, particularly in the posterior circulation.[40-42] This is supported by perfusion-diffusion MR imaging studies showing that mismatch (potentially salvageable tissue) does exist even beyond 24 hours.[43]

The lack of effect of time to treatment as seen in previous studies may be related to greater severity of neurologic deficit in patients presenting early after symptom onset and a greater level of caution used in treating patients who present late after symptom onset.[44] We did not see any correlation between time to treatment and initial NIHSS score (Spearman rank correlation, -0.113; $P = .27$). However, we cannot exclude the possibility that outcomes may be inadvertently biased to better outcomes by a more careful selection of patients who present later after symptom onset, and thus obscuring the effect of time to treatment (cherry-picking phenomenon).[45] It is also possible that the heterogeneity of treatment protocols has influenced the exact time to recanalization as opposed to time to initiation of treatment.

There was a trend toward more hemorrhagic complication in the patients with futile recanalization, who were also significantly older than those in the nonfutile recanalization group. It is possible that the overall neurologic and medical complications rate was higher in the futile recanalization group and led to poor functional outcome.

Possible Mechanisms of Futile Recanalization

Good collateral circulation can sustain tissue viability until recanalization occurs, and it was shown to influence outcome.[46,47] Proximal occlusion affects larger areas of brain tissue compared with distal occlusion and, subsequently, is associated with poor outcome.[22,48] Reocclusion of a revascularized vessel can occur immediately,[14,49] several hours after thrombolysis,[50-52] or within the first 24 hours after thrombolysis.[53] Subacute reocclusion was angiographically demonstrated in 9% of patients with acute stroke treated with IA thrombolysis and was associated with a trend toward a higher rate of neurologic deterioration.[53]

The existence and the extent of salvageable penumbra can conceivably affect outcome.[54] Hypoperfusion volumes predicted final infarct volume in 1 study.[55] In another study, hypoperfusion was observed in 42% of patients several hours after IA recanalization for acute stroke (median time to recanalization, 5 hours; range, 4–8 hours). Most hypoperfused tissue demonstrated infarction on day 7. Selective neuronal loss in rescued penumbra has been reported and linked to initial hypoperfusion.[56] Microvascular compromise (also termed the "no reflow phenomenon") is another important factor that can prevent effective tissue perfusion at the capillary level despite macrovascular patency. This is secondary to plugging of microvessels by leukocytes and platelets due to activation of endothelial receptors.[57] Microvascular compromise has been associated with poor outcome after percutaneous transluminal coronary angioplasty for a first acute myocardial infarction.[58,59] To our knowledge, this issue has not been studied in the setting of acute stroke.

Limitations of the Study

Study limitations include the retrospective nature of the analysis, the heterogeneity in methodology and results of the source studies, and the lack of adjustment for medical comorbidities. The potential benefit from partial recanalization was not explored. There is an undefined component of variability in categorizing angiographic severity and recanalization response in patients included in the study, due to interpretation by multiple readers. We dichotomized the grades of the angiographic scales used to reduce interoberserver variability. Defining favorable outcome by an mRS score of ≤ 2 may not detect minor clinical benefit related to recanalization (eg, a shift in mRS score from 5 to 3). However, mRS grades of >2 have been consistently used to define poor outcomes in trials evaluating endovascular treatment in patients with acute ischemic stroke.[2,4] Finally, the findings on the initial CT scan, which is an important factor in clinical decision making, were not collected consistently and, therefore, are not included in the present analysis. Serial diffusion and perfusion MR imaging data were not available, which would have allowed us to mechanistically define the role of microvascular compromise and reocclusion. While there is a possibility that the quantitative estimates of futility may have been different with greater standardization, we do not think that the basic findings of the study would have been affected.

Conclusions

In a large pooled analysis, we observed that futile recanalization is a relatively common occurrence following endovascular treatment, particularly among elderly patients and those with severe neurologic deficits. Further studies need to explore the mechanisms underlying futile recanalization and develop methods to effectively exclude such patients from receiving endovascular treatment in various protocols.

References

1. Rha JH, Saver JL. **The impact of recanalization on ischemic stroke outcome: a meta-analysis.** *Stroke* 2007;38:967–73
2. IMS II Trial Investigators. **The Interventional Management of Stroke (IMS) II study.** *Stroke* 2007;38:2127–35. Epub 2007 May 24
3. Furlan A, Higashida R, Wechsler L, et al. **Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study—a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism.** *JAMA* 1999;282:2003–11
4. Alexandrov AV, Molina CA, Grotta JC, et al. **Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke.** *N Engl J Med* 2004;351:2170–78
5. Smith WS, Sung G, Starkman S, et al. **Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial.** *Stroke* 2005;36:1432–38. Epub 2005 Jun 16
6. Smith WS. **Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke: results of the Multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I.** *AJNR Am J Neuroradiol* 2006;27:1177–82
7. Smith WS, Sung G, Saver J, et al. **Mechanical thrombectomy for acute ischemic**

stroke: final results of the Multi MERCI trial. *Stroke* 2008;39:1205–12. Epub 2008 Feb 28
8. Adams HP Jr, del Zoppo G, Alberts MJ, et al. **Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.** *Stroke* 2007;38:1655–711. Epub 2007 Apr 12
9. Higashida RT, Furlan AJ, Roberts H, et al. **Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke.** *Stroke* 2003;34:e109–37
10. Qureshi AI, Abou-Chebl A, Jovin TG. **Qualification requirements for performing neurointerventional procedures: a report of the practice guidelines committee of the American Society of Neuroimaging and the Society of Vascular and Interventional Neurology.** *J Neuroimaging* 2008;18:433–47
11. Qureshi AI, Janjua N, Kirmani JF, et al. **Mechanical disruption of thrombus following intravenous tissue plasminogen activator for ischemic stroke.** *J Neuroimaging* 2007;17:124–30
12. Qureshi AI, Harris-Lane P, Kirmani JF, et al. **Intra-arterial reteplase and intravenous abciximab in patients with acute ischemic stroke: an open-label, dose-ranging, phase I study**. *Neurosurgery* 2006;59:789–96, discussion 96–97
13. Mahon BR, Nesbit GM, Barnwell SL, et al. **North American clinical experience with the EKOS MicroLysUS infusion catheter for the treatment of embolic stroke.** *AJNR Am J Neuroradiol* 2003;24:534–48
14. Qureshi AI, Siddiqui AM, Kim SH, et al. **Reocclusion of recanalized arteries during intra-arterial thrombolysis for acute ischemic stroke.** *AJNR Am J Neuroradiol* 2004;25:322–28
15. Miley JT, Memon MZ, Hussein HM, et al. **A multicenter analysis of "time to microcatheter" for endovascular therapy in acute ischemic stroke.** *J Neuroimaging* 2009 Oct 7. [Epub ahead of print]
16. Christoforidis GA, Mohammad Y, Avutu B, et al. **Arteriographic demonstration of slow antegrade opacification distal to a cerebrovascular thromboembolic occlusion site as a favorable indicator for intra-arterial thrombolysis.** *AJNR Am J Neuroradiol* 2006;27:1528–31
17. Slivka AP, Notestine MA, Li J, et al. **Clinical predictors of cerebrovascular occlusion for patients presenting with acute stroke.** *J Stroke Cerebrovasc Dis* 2006;15:30–33
18. Christoforidis GA, Slivka A, Mohammad Y, et al. **Size matters: hemorrhage volume as an objective measure to define significant intracranial hemorrhage associated with thrombolysis.** *Stroke* 2007;38:1799–804
19. Mohammad YM, Christoforidis GA, Bourekas EC, et al. **Qureshi grading scheme predicts subsequent volume of brain infarction following intra-arterial thrombolysis in patients with acute anterior circulation ischemic stroke.** *J Neuroimaging* 2008;18:262–67. Epub 2008 Apr 7
20. Christoforidis GA, Karakasis C, Mohammad Y, et al. **Predictors of hemorrhage following intra-arterial thrombolysis for acute ischemic stroke: the role of pial collateral formation.** *AJNR Am J Neuroradiol* 2009;30:165–70
21. **The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings—TIMI Study Group.** *N Engl J Med* 1985;312:932–36
22. Qureshi AI. **New grading system for angiographic evaluation of arterial occlusions and recanalization response to intra-arterial thrombolysis in acute ischemic stroke.** *Neurosurgery* 2002;50:1405–14, discussion 14–15
23. Mohammad Y, Xavier AR, Christoforidis G, et al. **Qureshi grading scheme for angiographic occlusions strongly correlates with the initial severity and in-hospital outcome of acute ischemic stroke.** *J Neuroimaging* 2004;14:235–41
24. Khatri P, Neff J, Broderick JP, et al. **Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I.** *Stroke* 2005; 36:2400–03. Epub 2005 Oct 13
25. Tomsick T, Broderick J, Carrozella J, et al. **Revascularization results in the Interventional Management of Stroke II trial.** *AJNR Am J Neuroradiol* 2008;29:582–87
26. Rankin J. **Cerebral vascular accidents in patients over the age of 60. II. Prognosis.** *Scott Med J* 1957;2:200–15
27. van Swieten JC, Koudstaal PJ, Visser MC, et al. **Interobserver agreement for the assessment of handicap in stroke patients.** *Stroke* 1988;19:604–07
28. Wolfe CD, Taub NA, Woodrow EJ, et al. **Assessment of scales of disability and handicap for stroke patients.** *Stroke* 1991;22:1242–44
29. **Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA stroke trial.** *Stroke* 1997;28:2119–25
30. Wechsler LR, Roberts R, Furlan AJ, et al. **Factors influencing outcome and treatment effect in PROACT II.** *Stroke* 2003;34:1224–29
31. Arnold M, Schroth G, Nedeltchev K, et al. **Intra-arterial thrombolysis in 100 patients with acute stroke due to middle cerebral artery occlusion.** *Stroke* 2002;33:1828–33
32. IMS Study Investigators. **Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study.** *Stroke* 2004;35:904–11. Epub 2004 Mar 11
33. Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS EXP). http://clinicaltrials.Gov/ct2/show/nct00640367? Term=nct00640367&rank=1. Accessed March 2009
34. Khatri P, Hill MD, Palesch YY, et al. **Methodology of the Interventional Management of Stroke III trial.** *Int J Stroke* 2008;3:130–37
35. Feltgen N, Neubauer A, Jurklies B, et al. **Multicenter study of the European Assessment Group for Lysis in the Eye (EAGLE) for the treatment of central retinal artery occlusion: design issues and implications—EAGLE Study report no. 1: EAGLE Study report no. 1.** *Graefes Arch Clin Exp Ophthalmol* 2006; 244:950–56. Epub 2005 Dec 22
36. Lewandowski CA, Frankel M, Tomsick TA, et al. **Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial.** *Stroke* 1999;30:2598–605
37. Qureshi AI, Suri MF, Georgiadis AL, et al. **Intra-arterial recanalization techniques for patients 80 years or older with acute ischemic stroke: pooled analysis from 4 prospective studies.** *AJNR Am J Neuroradiol* 2009;30:1184–89. Epub 2009 Apr 2
38. Kim D, Ford GA, Kidwell CS, et al. **Intra-arterial thrombolysis for acute stroke in patients 80 and older: a comparison of results in patients younger than 80 years.** *AJNR Am J Neuroradiol* 2007;28:159–63
39. Hacke W, Donnan G, Fieschi C, et al. **Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials.** *Lancet* 2004;363:768–74
40. Flint AC, Duckwiler GR, Budzik RF, et al. **Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials.** *Stroke* 2007;38:1274–80. Epub 2007 Mar 1
41. Macleod MR, Davis SM, Mitchell PJ, et al. **Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke.** *Cerebrovasc Dis* 2005;20:12–17. Epub 2005 May 30
42. Penumbra I. www.Penumbrainc.Com. Accessed January 20, 2009
43. Staroselskaya IA, Chaves C, Silver B, et al. **Relationship between magnetic resonance arterial patency and perfusion-diffusion mismatch in acute ischemic stroke and its potential clinical use.** *Arch Neurol* 2001;58:1069–74
44. Qureshi AI, Kirmani JF, Sayed MA, et al. **Time to hospital arrival, use of thrombolytics, and in-hospital outcomes in ischemic stroke.** *Neurology* 2005;64:2115–20
45. Qureshi AI, Hutson AD, Harbaugh RE, et al. **Methods and design considerations for randomized clinical trials evaluating surgical or endovascular treatments for cerebrovascular diseases.** *Neurosurgery* 2004;54:248–64, discussion 64–67
46. von Kummer R, Holle R, Rosin L, et al. **Does arterial recanalization improve outcome in carotid territory stroke?** *Stroke* 1995;26:581–87
47. Tariq N, Khatri R. **Leptomeningeal collaterals in acute ischemic stroke.** *J Vasc Interv Neurol* 2009;1:91–95
48. Eckert B, Kucinski T, Neumaier-Probst E, et al. **Local intra-arterial fibrinolysis in acute hemispheric stroke: effect of occlusion type and fibrinolytic agent on recanalization success and neurological outcome.** *Cerebrovasc Dis* 2003;15:258–63
49. Janjua N, Alkawi A, Suri MF, et al. **Impact of arterial reocclusion and distal fragmentation during thrombolysis among patients with acute ischemic stroke.** *AJNR Am J Neuroradiol* 2008;29:253–58
50. Alvarez-Sabin J, Molina CA, Ribo M, et al. **Impact of admission hyperglycemia on stroke outcome after thrombolysis: risk stratification in relation to time to reperfusion.** *Stroke* 2004;35:2493–98
51. Humpich M, Singer OC, du Mesnil de Rochemont R, et al. **Effect of early and delayed recanalization on infarct pattern in proximal middle cerebral artery occlusion.** *Cerebrovasc Dis* 2006;22:51–56
52. Molina CA, Alvarez-Sabin J, Montaner J, et al. **Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion.** *Stroke* 2002;33:1551–56
53. Qureshi AI, Hussein HM, Abdelmoula M, et al. **Subacute recanalization and reocclusion in patients with acute ischemic stroke following endovascular treatment.** *Neurocrit Care* 2009;10:195–203. Epub 2008 Dec 3
54. Ebinger M, De Silva DA, Christensen S, et al. **Imaging the penumbra: strategies to detect tissue at risk after ischemic stroke.** *J Clin Neurosci* 2009;16:178–87
55. Karonen JO, Vanninen RL, Liu Y, et al. **Combined diffusion and perfusion MRI with correlation to single-photon emission CT in acute ischemic stroke: ischemic penumbra predicts infarct growth.** *Stroke* 1999;30:1583–90
56. Guadagno JV, Jones PS, Aigbirhio FI, et al. **Selective neuronal loss in rescued penumbra relates to initial hypoperfusion.** *Brain* 2008;131:2666–78
57. Janardhan V, Qureshi AI. **Mechanisms of ischemic brain injury.** *Curr Cardiol Rep* 2004;6:117–23
58. Morishima I, Sone T, Okumura K, et al. **Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction.** *J Am Coll Cardiol* 2000;36:1202–09
59. Gibson CM, Cannon CP, Murphy SA, et al. **Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs.** *Circulation* 2000;101:125–30