Original Paper

European Neurology

Eur Neurol 2015;74:315–321
DOI: 10.1159/000441445

Received: June 24, 2015
Accepted: October 4, 2015
Published online: December 18, 2015

Occlusion Location of Middle Cerebral Artery Stroke and Outcome after Endovascular Treatment

Marcel Arnold[a] Agnieszka Slezak[a] Marwan El-Koussy[b] Rudolf Lüdi[a] Oliver Findling[a] Marie-Luise Mono[a] Mirjam Rachel Heldner[a] Urs Fischer[a] Pasquale Mordasini[b] Gerhard Schroth[b] Heinrich P. Mattle[a] Jan Gralla[b] Simon Jung[a, b]

Departments of [a]Neurology and [b]Diagnostic and Interventional Neuroradiology, Inselspital, University Hospital Bern and University of Bern, Bern, Switzerland

Key Words
Intra-arterial thrombolysis · Mechanical thrombectomy · Middle cerebral artery · Outcome

Abstract
Background: The aim of this study was to analyze the influence of the location of middle cerebral artery (MCA) occlusion on recanalization, complications and outcome after endovascular therapy. ***Methods:*** Four-hundred sixty-four patients with acute MCA occlusions were treated with endovascular therapy. ***Results:*** Two-hundred ninety-three patients had M1 occlusions, 116 had M2, and 55 had M3/4 occlusions. Partial or complete recanalization was more frequently achieved in M1 (76.8%) than in M2 (59.1%) or M3/4 (47.3%, $p < 0.001$) occlusions, but favorable outcome (modified Rankin Scale 0–2) was less frequent in M1 (50.9%) than M2 (63.7%) or M3/4 (72.7%, $p = 0.018$) occlusions. Symptomatic intracerebral hemorrhage (ICH) did not differ between occlusion sites, but asymptomatic ICH was more common in M1 (22.6%) than in M2 occlusions (8.6%, $p = 0.003$). Recanalization was associated with favorable outcome in M1 ($p < 0.001$) and proximal M2 ($p = 0.003$) but not in distal M2 or M3/4 occlusions. ***Conclusions:*** Recanalization with endovascular therapy was more frequently achieved in patients with proximal than distal MCA occlusions, but recanalization was associated with favorable outcome only in M1 and proximal M2 occlusions. Outcome was better with distal than proximal occlusions. This study shows that recanalization can be used as a surrogate marker for clinical outcome only in patients with proximal occlusions.

Introduction

Since the first successful local intra-arterial thrombolysis (IAT) in a patient with basilar artery occlusion in 1981 [1], several randomized trials showed a benefit of intravenous thrombolysis (IVT) or IAT [2–11]. The efficacy of IVT or IAT in dependence of the occluded vessel has not been addressed in major IVT trials like Atlantis, European Cooperative Acute Stroke Study (ECASS) and National Institutes of Neurological Disorders and Stroke (NINDS). In a majority of IAT trials, the occlusion loca-

J.G. and S.J. contributed equally to this work.

KARGER 125 YEARS

0014–3022/15/0746–0315$39.50/0

E-Mail karger@karger.com
www.karger.com/ene

Marcel Arnold, MD
Department of Neurology, University of Bern, Inselspital
Freiburgstrasse 10
CH–3010 Bern (Switzerland)
E-Mail marcel.arnold@insel.ch

tion was categorized into the major vessel territories: basilar artery, internal carotid or middle cerebral artery (MCA). Several studies found differences in recanalization and clinical outcome between patients with occlusions of these territories [12–15].

Until now, no large randomized IVT trial and only a small number of observational IVT studies analyzed the occlusion site along the MCA with regard to outcome. These studies found poorer outcomes in proximal occlusions and better recanalization in distal occlusions [15–18]. Four recent randomized controlled trials showed a clear superiority of endovascular treatment over standard treatment; these studies mainly included patients with ICA- and M1-occlusions, and the proportion of patients with M2 occlusion was small (4–14%). There is ongoing debate whether endovascular treatment is also efficacious in M2-occlusions or more in distal occlusions [19–31].

The aim of this study was to analyze the impact of the MCA occlusion site on recanalization and outcome after endovascular therapy for acute ischemic stroke.

Patients and Methods

Patients

From May 1992 to May 2011, we prospectively acquired data of 464 patients with acute ischemic stroke with occlusions of the MCA who received endovascular treatment at our center. During the same period, 103 patients with occlusions of the MCA were treated with IVT. Some data from these patients were previously reported [24–26, 32].

All patients were examined by a neurologist immediately after admission to the emergency room. Neurologic deficits were scored using the National Institutes of Health Stroke Scale (NIHSS) [33]. Demographic and clinical data were recorded (age, gender, premedication, time of symptom onset, coronary artery disease, atrial fibrillation, hypertension, diabetes, current cigarette smoking, hypercholesterolemia, history of transient ischemic attack (TIA) or ischemic stroke, family history of TIA and stroke). The decision for treating with IVT and/or endovascular therapy was made on an individual basis. In general, within 4.5 h of symptom onset IVT was performed followed by IAT in the case of persisting vessel occlusion; after 4.5 h direct IAT was performed if: (1) diagnosis of ischemic stroke was established; (2) baseline NIHSS score was ≥4 points or isolated aphasia or hemianopia was present, or in case of recurrent neurological deficits with a persistent major vessel occlusion; (3) hemorrhage on cranial CT or MRI was excluded; (4) MCA occlusion correlated with the neurological deficit; (5) MCA occlusion was judged to be endovascularly accessible; (6) symptom duration was not longer than 6 h; or (7) no individual clinical or premorbid conditions or laboratory findings advised against thrombolysis. Digital subtraction angiography was performed via a transfemoral approach using a biplane, high-resolution angiography system and all patients underwent complete 4-vessel cerebral angiography. All procedures were performed by 4 fully trained interventional neuroradiologists. The site of the artery occlusion was categorized. Collaterals were classified as: none; moderate if minimal leptomeningeal anastomoses were visualized and no or minimal filling of the occluded vessel territory was seen; good, if leptomeningeal anastomoses filled the occluded vessel territory by more than half. The interventional neuroradiologist and neurologist decided on the use of urokinase and or mechanical intervention. At the end of angiography, recanalization was classified by the treating neuroradiologist according to thrombolysis in myocardial infarction (TIMI) grades [34] and was prospectively assessed and entered into our database. Since the introduction of the thrombolysis in cerebral infarction (TICI) score, all recanalization results are also assessed according to TICI grades, but were not used for evaluation in this long-term study.

A repeat CT or MRI scan was generally obtained after 24 h but never later than 72 h after treatment, and was performed again in cases of clinical deterioration. Symptomatic and asymptomatic intracerebral hemorrhages (ICH) were graded according to the PROACT II criteria [35]. Secondary preventive treatment was given according to current evidence and European guidelines [36, 37]. Clinical outcome was assessed 3 months after the stroke using the modified Rankin Scale (mRS) [38].

Statistical Analysis

Statistical analyses were performed using SPSS 21 (SPSS Inc., Chicago, Ill., USA). Categorical variables were compared with χ^2 and Fisher's exact test as appropriate, and continuous variables were analyzed with the Mann–Whitney test. Outcome was dichotomized into favorable (mRS 0–2) or poor (mRS 3–6) clinical outcome. Recanalization was dichotomized into poor (TIMI 0–1) or good (TIMI 2–3). Forward stepwise logistic regression including all variables with $p < 0.2$ in univariate analyses (age, gender, NIHSS score on admission, time from symptom onset to treatment, atrial fibrillation, diabetes, hypertension, hypercholesterolemia, previous stroke, smoking, TOAST (the Trial of Org 10172 in Acute Stroke Treatment), occlusion site as categorical variable, recanalization, symptomatic ICH) were used to determine the predictors of bleeding complications and outcome. A p value of <0.05 was considered significant.

Results

Of 464 patients with MCA occlusions, 293 had an occlusion in the M1, 116 in the M2 and 55 in the M3/4 segment. Of the patients with M2 occlusions, 83 had a proximal and 14 a distal occlusion of the M2 segment. A second vessel occlusion was found in 7.8% of the M1 occlusions (4 patients with additional distal MCA occlusions, 17 with ACA occlusions, one with vertebral artery and one with posterior cerebral artery occlusion), 6% of the M2 occlusions (6 with ACA occlusions, one with vertebral artery occlusion) and 7.3% of the M3/4 occlusions (one with additional distal MCA occlusion, 3 with ACA occlusions).

Baseline characteristics, risk factors and treatment details are given in table 1. Median baseline NIHSS in M1 occlusions was 16, which was significantly higher than in

Table 1. Baseline characteristics of 464 patients treated with IAT

	M1	M2	M3/4
Number	293	116	55
Age, years, SD	64.9 (13.8)	63.7 (13.6)	65.2 (12.4)
Female, sex, mean	50.2	38.8	43.6
Vascular risk factors, % (n/N)			
Diabetes mellitus	14.0 (41/293)	23.5 (27/115)	5.5 (3/55)
Hypertension	58 (179/293)	64.3 (74/115)	67.3 (37/55)
Current smoking	16.5 (48/291)	27 (31/115)	25.5 (14/55)
Hypercholesterolemia	50.3 (147/292)	54.4 (62/114)	38.2 (21/55)
Coronary artery disease	25 (73/292)	14.9 (17/114)	16.4 (9/55)
Atrial fibrillation	41.3 (116/283)	37.7 (43/114)	29.1 (16/55)
Previous stroke	7.8 (23/293)	9.6 (11/115)	12.7 (7/55)
Baseline NIHSS, median, range	16 (3–36)	12 (0–25)	10 (3–22)
Second occlusion site, %, range	7.8 (23/293)	6 (7/116)	7.3 (4/55)
IAT type, %, range			
Urokinase only	59.4 (174/293)	77.6 (90/116)	100 (55/55)
Mechanical only	9.6 (28/293)	6 (7/116)	0
Both	31.1 (91/293)	16.4 (19/116)	0
Minutes from symptom onset to treatment, median (range)	249 (16–943)	275 (19–610)	278 (77–408)
Urokinase dose, median IE, range	10^6 (0–10^6)	10^6 (0–10^6)	8×10^5 (2.5×10^4–8×10^5)
Collaterals none or bad (0), %, range	16.5 (47/284)	15 (17/113)	28.3 (15/53)
Middle (1), %, range	42.6 (121/284)	68.1 (77/113)	50.9 (27/53)

Table 2. Recanalization, outcome and complications (p values: results of multivariable regression analysis, NS: not significant)

	M1	M2	M3/4	p value
Recanalization TIMI 2–3	76.8 (225/293)	59.1 (68/115)	47.3 (26/55)	**<0.001**
Outcome mRS 0–2	50.9 (145/285)	63.7 (72/113)	72.7 (40/55)	**0.018**
Survival	82.5 (235/285)	84.1 (95/113)	96.4 (53/55)	NS
Symptomatic ICH	4.5 (13/292)	6.9 (8/116)	3.6 (2/55)	NS
Asymptomatic ICH	22.6 (66/292)	8.6 (10/116)	9.1 (5/55)	**0.003**

M2 (12, p < 0.001) or M3/4 (10, p < 0.001) occlusions, whereas NIHSS in M2 and M3/4 occlusions did not differ significantly. There was a trend toward a higher median baseline NIHSS in proximal compared to distal M2 segment occlusions (12 vs. 7, p = 0.067). Collateral circulation in M1 occlusions was better than in M2 (p < 0.001) or M3/4 (p = 0.012) occlusions (table 1). Mechanical techniques were more often used in proximal occlusions and M3 occlusions were only treated medically (p < 0.001). Recanalization rates, outcome and bleeding complications for the different vessel segments are listed in table 2 and illustrated in figure 1.

Successful recanalization (TIMI 2–3) was more frequently observed in M1 occlusions (76.8%) than in M2 (59.1%, p = 0.001) or M3/4 (47.3%, p < 0.001) occlusions. The occlusion site was the only independent predictor of successful recanalization in multivariable regression analysis (p < 0.001).

Favorable 3-month outcome was achieved in 145 of 285 (50.9%) M1 occlusions, 72 of 113 (63.7%) M2 and 40 of 55 (72.7%) M3/4 occlusions indicating that 3-month favorable outcome was worse in M1 compared to M2 (p = 0.025) or M3/4 (p = 0.003) occlusions. The occlusion site was an independent predictor of favorable outcome in multivariable regression analysis (p = 0.019; other predictors: age: p < 0.001, OR 0.954, 95% CI 0.936–0.972; baseline NIHSS: p < 0.001, OR 0.879, 95% CI 0.839–0.921); diabetes mellitus: p = 0.005, OR 0.392, 95% CI 0.205–0.751; hypercholesterolemia: p = 0.001, OR 2.229, 95% CI 1.400–3.547; recanalization: p < 0.001, OR 4.051, 95% CI 2.414–6.799; collaterals: p = 0.021, OR 1.490, 95% CI 1.062–2.091; symptomatic ICH: p = 0.001, OR 0.027, 95% CI 0.003–0.223).

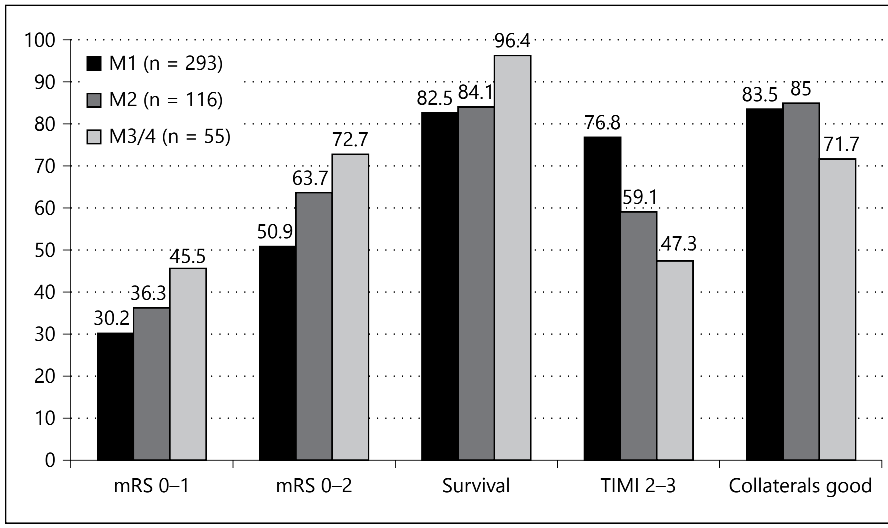

Fig. 1. Collaterals, recanalization rate and clinical outcome at 3 months.

Two hundred thirty-five of 285 (82.5%) patients with M1 occlusions, 95 of 113 (84.1%) patients with M2, and 53 of 55 (96.4%) patients with M3/4 occlusions survived. Survival at 3 months differed significantly between M1 and M3 ($p = 0.007$) but not between M1 and M2 ($p = 0.769$) occlusions. The occlusion site was not an independent predictor of survival ($p = 0.124$; predictors: age: $p < 0.001$, OR 0.928, 95% CI 0.901–0.957; baseline NIHSS: $p = 0.001$, OR 0.923, 95% CI 0.880–0.968: collaterals: $p < 0.001$, OR 2.200, 95% CI 1.457–3.321; symptomatic ICH: $p < 0.001$; OR 0.063, 95% CI 0.021–0.188; diabetes mellitus: $p = 0.047$, OR 0.507, 95% CI 0.259–0.992). Symptomatic ICH was noted in 13 of 292 (4.5%) M1, 8 of 116 (6.9%) M2 and 2 of 55 (3.6%) M3/4 occlusions and there was no significant difference of the ICH rates among the occlusion sites ($p = 0.526$). Asymptomatic ICH was more frequently seen in M1 (22.6%) than in M2 (8.6%, $p = 0.001$) and in M3/4 (9.1%, $p = 0.027$) occlusions. The occlusion site was an independent predictor of asymptomatic ICH in multivariable regression analysis ($p = 0.003$; other predictors: atrial fibrillation: $p = 0.017$, OR 1.849, 95% CI 1.117–3.061; smoking: $p = 0.014$, OR 0.332, 95% CI 0.138–0.801). The rate of asymptomatic ICH did not differ significantly between proximal (9.6%) or distal (7.1%) M2 occlusions.

Recanalization was associated with favorable outcome in M1 ($p < 0.001$) and proximal M2 occlusions ($p = 0.003$) but not in distal M2 ($p = 0.505$) or M3/4 ($p = 1.0$) occlusions.

Finally, the influence of stroke etiology based on the TOAST classification was not significantly different with regard to outcome, recanalization or bleeding complications.

Discussion

The main finding of this study is that recanalization and outcome of MCA occlusions after endovascular therapy critically depend upon the occlusion site within the vessel. In our series, best recanalization rates were observed in proximal (M1) and worst rates in distal (M3/4) MCA occlusions. Nevertheless, 3-month clinical outcome was worse in M1 compared to M2 or M3/4 occlusions. Recanalization was associated with favorable outcome in M1 and proximal M2 occlusions but not in distal M2 or M3/4 occlusions.

We treated 293 patients with M1, 116 patients with M2, and 55 patients with M3/4 occlusions with endovascular procedures. NIHSS scores were significantly different for different occlusion sites. In M1 occlusions, we found a median NIHSS of 16, in M2 of 12, and in M3/4 of 10 points. Collaterals were generally better in proximal than in distal occlusions, most likely because only few leptomeningeal collaterals can supply blood to the non-perfused tissue in peripheral occlusions and more collateral systems can compensate for proximal occlusions.

Recanalization

Some trials using IVT reported recanalization rates according to occlusion sites ranging from 30 to 65% for M1 and 32 to 76% for M2 occlusions [15–18]. One study found a recanalization rate of 66% in M3/4 occlusions [16]. In endovascular treatment, only a few authors reported recanalization rates for different sites of MCA occlusions. In the MERCI and Multi-MERCI trials, better recanalization rates were reported in M2 compared to M1 occlusions (82.1 vs. 60%) [19].

In contrast to these reports of better recanalization in distal occlusions, in our cohort, we observed a TIMI 2–3 recanalization more frequently in M1 (76.8%) than in M2 (59.1%) or M3/4 occlusions (47.3%). The occlusion site was the only factor associated with recanalization in multivariable regression analysis ($p < 0.001$). The techniques used in our series might account for this difference. When thrombus aspiration techniques and stent retrievers are used as in our series, proximally occluding thrombi are more easily accessible for extraction than distally located clots. Comparison of the favorable recanalization rates in proximal occlusions in our series with published rates after IVT support the proposal that endovascular therapy might be advantageous over IVT, especially in proximal occlusions. The poorer outcome in patients with proximal vessel occlusion despite higher recanalization rates in our study may be due to the fact that more proximal occlusions lead to larger areas of hypoperfused tissue and higher NIHSS scores. All reperfusion treatments require time for complete recanalization; the affected tissue may either recover or be irreversibly damaged.

Outcome and Complications

Several trials reported outcome after IVT according to the MCA occlusion site [15–18, 39]. mRS 0–1 outcome at 3 months ranged from 24% with proximal to 52% with distal occlusions [15]. Bhatia et al. [39] found favorable outcomes (mRS 0–2) at 3 months in 60% of M1 and/or proximal ICA occlusions and in 77% of M2 occlusions. For endovascular treatment, the MERCI and multi MERCI trials achieved 33.3% favorable outcomes (mRS 0–2) with M1 and 40.7% with M2 occlusions [19]. In SWIFT PRIME, only 6 of 94 patients (6%) treated with IVT had M2 occlusion and 13 of 93 patients (14%) treated with stent retriever plus IVT had M2 occlusion [27]. In this small subgroup of M2 occlusions, the authors reported a trend toward a more favorable clinical outcome in the stent retriever group (RR 1.35, 95% CI 0.41–4.41). In the larger subgroup with M1 occlusions ($n = 133$), there was a significantly better clinical outcome in the endovascular group RR 1.74, 95% CI 1.23–2.46) in favor of the endovascular group [27]. In MR CLEAN, EXTEND-IA, ESCAPE and REVASCAT, outcome and complications were not separately reported for M2 occlusion because of the small sample sizes of this subgroup [28–31].

In our series, results ranged from 51% favorable outcomes with M1 occlusions, 64% with M2, and 73% with M3/4 occlusions (table 2). The occlusion site was an independent predictor of outcome also in multivariable regression analysis ($p = 0.018$). Additionally, we observed a trend toward favorable outcome in distal compared to proximal M2 occlusions (85.7 vs. 64.4%).

The observed survival rates are similar to those reported by Shi et al. [19] (67.1% in M1 and 74.1% in M2 occlusions), when taking into consideration the higher NIHSS baseline in their cohort. Survival at 3 months differed significantly between M1 and M3, but not between M1 and M2 occlusions, and not between the different M2 occlusion locations.

This study showed an association of outcome with successful recanalization in M1 and proximal M2 occlusions but not in distal M2 or M3/4 occlusions. This result is in line with 2 other trials, which found a significant association between recanalization and outcome in M1 but not M2 occlusions [13, 19]. To our knowledge, differences between proximal and distal M2 occlusions have not been previously reported. That recanalization was not associated with outcome in distal M2 or M3/4 occlusions might be attributable to a methodological problem. Patients with distal M2 or M3/4 occlusions frequently show only minor neurological deficits, and the mRS may not be sensitive enough to detect these minor deficits. Changes in the NIHSS score might detect differences in outcome in patients with minor neurological deficits. However, we did not assess NIHSS score at 3 months in all patients.

Complications

Symptomatic ICH did not differ between the occlusion sites. However, the number of patients with ICH was quite small in each group, making final conclusions difficult. Asymptomatic ICH was more frequent in M1 (22.6%) than in M2 (8.6%) occlusions ($p = 0.003$). The existence of atrial fibrillation and non-smoking were independent predictors of asymptomatic ICH. The size of the infarct and a larger territory of reperfusion are possible explanations for the association of an ICH with proximal occlusions. It appears that there might be a protective effect of smoking against an ICH, which could be explained by increased plasminogen activator inhibitor-1 production in smokers [40].

Limitations

Our study has the inherent limitations of selection bias of a non-randomized single center study. In addition our data were analyzed retrospectively, though prospectively collected and recorded in our database. The data were collected over 2 decades and the evolution of mechanical recanalization techniques and general acute care (like stroke unit treatment, early rehabilitation, fast etiological workup) of stroke patients might have influenced our results. In addition, patients' selection for endovascular treatment was made on an individual basis, which might contribute to a selection bias.

Conclusions

Our results suggest that recanalization, outcome and complications depend critically upon the occlusion site within the MCA. Successful recanalization seems to be decisive for reaching favorable outcome, especially in M1 and proximal M2 occlusions, which may be predominantly explained by the less severe pre-treatment neurological deficits in more distal occlusions.

Therefore, results of revascularization studies may be influenced by summarizing all MCA occlusion types in one group, as was performed in most previous IAT trials (e.g. Melt, PROACT 1–2, Penumbra Pivotal Trial). Future trials of endovascular treatment of MCA occlusions should take these differences between recanalization and clinical outcome according to the MCA vessel segments into account for patient selection and stratified randomization. Analyses of the location of MCA occlusions are especially crucial when recanalization is used as a surrogate marker for clinical outcome.

Disclosure Statement

J.G. was the global principle investigator of the STAR trial. MA received honoraria for lectures and advisory boards from Bayer, Boehringer Ingelheim, Bristol Meyer Squibbs, Pfizer and Covidien.

References

1 Zeumer H, Hacke W, Kolmann HL, Poeck K: [Local fibrinolysis in basilar artery thrombosis (author's transl)]. Dtsch Med Wochenschr 1982;107:728–731.
2 del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M: PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT investigators. Prolyse in acute cerebral thromboembolism. Stroke 1998;29:4–11.
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;282:2003–2011.
4 Ogawa A, Mori E, Minematsu K, et al: Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. Stroke 2007;38:2633–2639.
5 Penumbra Pivotal Stroke Trial Investigators: The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. Stroke 2009;40:2761–2768.
6 Smith WS, Sung G, Saver J, et al: Mechanical thrombectomy for acute ischemic stroke: final results of the multi MERCI trial. Stroke 2008;39:1205–1212.
7 Albers GW, Clark WM, Madden KP, Hamilton SA: ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. Stroke 2002;33:493–495.
8 Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581–1587.
9 Hacke W, Kaste M, Fieschi C, et al: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245–1251.
10 IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RI, et al: The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet 2012;379:2352–2363.
11 Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators: Thrombolysis with alteplase 3–4.5 h after acute ischemic stroke. N Engl J Med 2008;359:1317–1329.
12 Zaidat OO, Suarez JI, Sunshine JL, et al: Thrombolytic therapy of acute ischemic stroke: correlation of angiographic recanalization with clinical outcome. AJNR Am J Neuroradiol 2005;26:880–884.
13 Tomsick T, Broderick J, Carrozella J, et al; Interventional Management of Stroke II Investigators: Revascularization results in the Interventional Management of Stroke II trial. AJNR Am J Neuroradiol 2008;29:582–587.
14 Linfante I, Llinas RH, Selim M, et al: Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous tissue plasminogen activator. Stroke 2002;33:2066–2071.
15 Saqqur M, Uchino K, Demchuk AM, et al; CLOTBUST Investigators: Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007;38:948–954.
16 del Zoppo GJ, Poeck K, Pessin MS, et al: Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32:78–86.
17 Derex L, Hermier M, Adeleine P, et al: Influence of the site of arterial occlusion on multiple baseline hemodynamic MRI parameters and post-thrombolytic recanalization in acute stroke. Neuroradiology 2004;46:883–887.
18 Seitz RJ, Sondermann V, Wittsack HJ, Siebler M: Lesion patterns in successful and failed thrombolysis in middle cerebral artery stroke. Neuroradiology 2009;51:865–871.
19 Shi ZS, Loh Y, Walker G, Duckwiler GR; MERCI and Multi-MERCI Investigators: Clinical outcomes in middle cerebral artery trunk occlusions versus secondary division occlusions after mechanical thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials. Stroke 2010;41:953–960.
20 Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al: A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11–20.
21 Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al: Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019–1030.

22 Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al: Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009–1018.
23 Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al: Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285–2295.
24 Gönner F, Remonda L, Mattle H, et al: Local intra-arterial thrombolysis in acute ischemic stroke. Stroke 1998;29:1894–1900.
25 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;33:1828–1833.
26 Jung S, Mono ML, Findling O, et al: White matter lesions and intra-arterial thrombolysis. J Neurol 2012;259:1331–1336.
27 Saver JL, Goyal M, Bonafe A, et al; SWIFT PRIME Investigators: Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285–2295.
28 Campbell BC, Mitchell PJ, Kleinig TJ, et al; EXTEND 1A Investigators: Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009–1018.
29 Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators: Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019–1030.
30 Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators: A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11–20.
31 Jovin TG, Chamorro A, Cobo E, et al; REVASCAT Trial Investigators: Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296–2306.
32 Jung S, Galimanis A, Mono ML, et al: Intra-arterial thrombolysis in 623 patients with acute anterior circulation stroke. Stroke 2012;43:1052–1057.
33 Brott T, Adams HP Jr, Olinger CP, et al: Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864–870.
34 The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med 1985;312:932–936.
35 Kase CS, Furlan AJ, Wechsler LR, et al: Cerebral hemorrhage after intra-arterial thrombolysis for ischemic stroke: the PROACT II trial. Neurology 2001;57:1603–1610.
36 European Stroke Initiative Executive Committee; EUSI Writing Committee, Olsen TS, Langhorne P, Diener HC, et al: European stroke initiative recommendations for stroke management-update 2003. Cerebrovasc Dis 2003;16:311–337.
37 European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee: Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457–507.
38 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.
39 Bhatia R, Hill MD, Shobha N, et al: Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke 2010;41:2254–2258.
40 Zidovetzki R, Chen P, Fisher M, Hofman FM, Faraci FM: Nicotine increases plasminogen activator inhibitor-1 production by human brain endothelial cells via protein kinase C-associated pathway. Stroke 1999;30:651–655.