Collateral Flow Averts Hemorrhagic Transformation After Endovascular Therapy for Acute Ischemic Stroke

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Background and Purpose—Collaterals sustain the ischemic penumbra to limit growth of the infarct core before revascularization, yet the impact of baseline collateral flow on hemorrhagic transformation (HT) after endovascular therapy remains unknown.

Methods—A collaborative study from 2 stroke centers in distinct geographic regions included 222 consecutive patients who received endovascular therapy for acute cerebral ischemia. The influence of collaterals on HT was analyzed in distinct case scenarios relative to baseline collateral grade at angiography (0 to 1 versus 2 to 4) and recanalization (Thrombolysis in Myocardial Ischemia scale, 0 to 1 versus 2 to 3): good collaterals and successful recanalization (n=98), poor collaterals with successful recanalization (n=43), good collaterals and no recanalization(n=46), and poor collaterals and no recanalization (n=35).

Results—HT after endovascular therapy occurred in 103 (46.4%) patients; 42 (18.9%) were symptomatic. HT was more frequently observed in patients with poor collaterals and recanalization than in other groups (P=0.048). When revascularization was achieved, patients with poorer collaterals were more likely to have symptomatic worsening with HT (r=−0.181, P=0.032). Multiple logistic regression analysis identified aggressive treatment (OR, 2.558 for Merci clot retrieval; 95% CI, 1.153 to 5.678; OR, 3.618 for combined fibrinolytics and mechanical therapy; 95% CI, 1.551 to 8.437; and OR, 2.085 for intravenous thrombolysis before endovascular therapy; 95% CI, 1.096 to 3.969), poor collaterals and recanalization (OR, 2.666; 95% CI, 1.163 to 6.113), and serum glucose levels (OR, 1.007; 95% CI, 1.000 to 1.014) as independent predictors of HT.

Conclusions—Angiographic grade of collateral flow strongly influences the rate of HT after therapeutic recanalization for acute ischemic stroke. Collateral status readily available from baseline angiography may therefore refine therapeutic decision-making in acute cerebral ischemia. **(*Stroke*. 2011;42:2235-2239.)**

Key Words: angiography ■ collaterals ■ hemorrhagic transformation ■ ischemic ■ magnetic resonance imaging ■ stroke ■ thrombolysis

Hemorrhagic transformation (HT) is the most dreaded complication of endovascular therapy for acute ischemic stroke. Relatively sparse attention has been devoted to the role of baseline collateral circulation in patients with acute ischemic stroke who are candidates for revascularization. Previous studies have demonstrated that baseline collateral grade at angiography may predict the success rate of recanalization, resultant infarct volume, and clinical severity after revascularization procedures.[1–3] The relationship of baseline collaterals with respect to occurrence of HT after revascularization therapy remains unknown.

We have previously reported that the extent of angiographic collaterals evident at conventional angiography correlated strongly with the severity of hypoperfusion[4] and that HT was associated with severe hypoperfusion.[5] In the present study, we evaluated whether the baseline collateral grade was an important determinant of HT after therapeutic revascularization, capitalizing on the availability of collateral status before intervention.

Patients and Methods

We analyzed demographic, clinical, laboratory, and radiographic data prospectively collected on consecutive patients who received endovascular therapy (intra-arterial thrombolytic therapy or mechanical therapy such as guidewire manipulation or a mechanical thrombectomy device) for acute cerebral ischemia. This study analyzed consecutive patients encountered at 2 university hospital stroke centers: Los Angeles, CA, from May 2002 through July 2007 and Seoul, South Korea, from July 2005 through October 2009. Patients were included in this study if (1) they presented with symptoms of acute cerebral ischemia within the middle cerebral artery territory;

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and (2) they underwent conventional angiography for endovascular therapy. Institutional Review Board approval was obtained for these analyses.

All patients underwent comprehensive diagnostic cerebral angiography, including injection of both internal carotid arteries and the dominant vertebral artery, with image acquisition into the late venous phase to assess collateral circulation from all possible sources. Angiographic collateral grade was evaluated with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology Collateral Flow Grading System on baseline angiography.[6] This angiographic scale assigns patients to Grade 0 (no collaterals visible to the ischemic site), 1 (slow collaterals to the periphery of the ischemic site with persistence of some of the defect), 2 (rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory), 3 (collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase), and 4 (complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion). Vascular recanalization was based on the Thrombolysis in Myocardial Infarction scale with assignments of 3 (complete recanalization), 2 (partial recanalization), 1 (minimal recanalization), and 0 (no recanalization). Two reviewers blinded to the patient information independently assessed the baseline collateral grade and Thrombolysis in Myocardial Infarction grade. Kappa coefficient for interobserver agreement was 0.896 for collateral grade and 0.79 for Thrombolysis in Myocardial Infarction grade. The opinion of a third neuroradiologist was sought to resolve disagreements.

All patients underwent routine blood tests, electrocardiography, cardiac telemetry for at least 24 hours, and echocardiography. All patients underwent MRI before revascularization therapy if not contraindicated. Diffusion-weighted imaging lesion volume measurements were performed by 1 of the authors blinded to the clinical information using a computer-assisted volumetric analysis program (Medical Image Processing Analysis and Visualization, Version 2.1, Center for Information Technology, National Institutes of Health).

HT was defined and classified into 4 subtypes: hemorrhagic infarct Type 1, small petechiae along the margins of the infarct; hemorrhagic infarct Type 2, more confluent petechiae within the infarcted area but without a space-occupying effect; a parenchymal hematoma Type 1, defined as a hematoma in <30% of the infarcted area with some space-occupying effect; and a parenchymal hematoma Type 2, a hematoma in >30% or the infarcted area with a substantial space-occupying effect. The clinical categories for HTs were defined as follows: asymptomatic HT (no clinical worsening on the National Institutes of Health Stroke Scale score despite HTs), minor symptomatic HT (a 1- to 3-point increase in the National Institutes of Health Stroke Scale score), and major symptomatic HT (a ≥4-point increase in the National Institutes of Health Stroke Scale score).

We analyzed the differences between the groups using Pearson χ^2 test or linear-by-linear association for categorical variables, and a Student *t* test, a 1-way analysis of variance, or Kruskal-Wallis test for continuous variables. Spearman correlation coefficient was used to analyze the association of collateral grade with the degree of infarct growth. In addition, independent factors for HT were evaluated using logistic regression. In this study, a score of 0 to 1 was designated as poor and 2 to 3 as good (successful therapeutic) recanalization. Variables from univariate analyses at $P<0.2$ were considered to represent explanatory variables and were evaluated together in subsequent multivariate analyses. All statistical analyses were performed using commercially available software (SPSS for Windows, Version 13.0; SPSS Inc, Chicago, IL). $P<0.05$ was considered statistically significant.

Results

A total of 222 patients were included; 138 from the United States and 84 from South Korea. Baseline characteristics for patients are listed in Table 1. HT was noted in 103 (46.4%) patients; 42 (18.9%) were symptomatic. Postprocedure imaging was performed in all patients (gradient echo MRI in 173 and CT in 49) at 24.9±29.3 hours after endovascular therapy.

Table 1. Patients' Characteristics

Female gender (%)	103 (46.4)
Age, y	65.2±16.4
Atrial fibrillation (%)*	86 (40.2)
Initial NIHSS score	16.6±6.6
Mode of endovascular therapy (%)	
IA fibrinolysis alone	62 (27.9)
Mechanical alone	
Merci clot retrieval	79 (35.6)
Other mechanical methods†	27 (12.2)
Mechanical+IA fibrinolysis	54 (24.3)‡
Time from onset to endovascular therapy, h	5.3±2.2
IV tissue-type plasminogen activator prior to endovascular therapy (%)	80 (36.0)

NIHSS indicates National Institutes of Health Stroke Scale; IA, intra-arterial; IV, intravenous.

*Excluding 8 patients who did not undergo either echocardiogram or cardiac telemetry for at least 24 hours.

†Including mechanical clot disruption and angioplasty with or without stent.

‡Including 14 patients who received Meci clot retrieval.

Patient characteristics depending on the baseline collateral grade and recanalization (Thrombolysis in Myocardial Infarction) are illustrated in Table 2. HT were more frequently observed in patients with poor collaterals and therapeutic recanalization than in other groups ($P=0.048$). Other characteristics were similar among these groups, except that baseline National Institutes of Health Stroke Scale scores were higher and diffusion-weighted imaging lesion volumes were larger in those patients with poor collaterals. Symptomatic HT were more frequently observed in patients who had poor collaterals and achieved therapeutic recanalization (Group 2) than in those with good collaterals (Group 1; $P=0.023$). Spearman correlation analysis showed that patients with poorer collaterals were more likely to have symptomatic worsening with HT in patients who showed therapeutic recanalization (Thrombolysis in Myocardial Infarction 2 to 3; $r=-0.181$, $P=0.032$), but such correlation was not observed in those without therapeutic recanalization ($r=0.041$, $P=0.715$; Figure).

Multiple regression analysis was performed to further evaluate independent predictors for HT (Table 3). Aggressive treatment (OR, 2.558 for Merci clot retrieval; 95% CI, 1.153 to 5.678; OR, 3.618 for combined fibrinolytics and mechanical therapy; 95% CI, 1.551 to 8.437; and OR, 2.085 for intravenous thrombolysis before endovascular therapy; 95% CI. 1.096 to 3.969), poor collaterals and recanalization (OR, 2.666; 95% CI, 1.163 to 6.113), and serum glucose levels (OR, 1.007; 95% CI, 1.000 to 1.014) were independently associated with HT after adjusting for all other variables.

Discussion

The principal finding of this novel analysis on collaterals and HT is that poor baseline collaterals and successful therapeutic recanalization may result in clinically significant hemor-

Table 2. Hemorrhagic Transformation Depending on Collaterals and TIMI Score

	Group 1 (n=98)	Group 2 (n=43)	Group 3 (n=46)	Group 4 (n=35)	*P* (Among Groups)	*P* (Group 1 vs 2)
Angiographic finding						
Pretreatment collateral grading	2–4	0–1	2–4	0–1		
Recanalization (TIMI) scale score	2–3	2–3	0–1	0–1		
Female gender (%)	43 (43.9)	21 (48.8)	25 (54.3)	14 (40.0)	0.552	0.586
Age, y (SD)	65.4 (17.7)	65.6 (13.8)	62.0 (19.0)	68.5 (11.1)	0.366	0.940
Atrial fibrillation (%)	35 (37.6)	18 (41.9)	16 (36.4)	17 (50.2)	0.587	0.638
S-glucose, mg/dL, mean (SD)	127.7 (40.6)	137.6 (46.1)	126.2 (38.1)	142.3 (71.2)	0.315	0.211
NIHSS score, mean (SD)	15.8 (6.7)	19.1 (5.0)	13.8 (7.2)	19.2 (5.2)	<0.001	0.002
Initial DWI, mean (SD)	25.1 (37.2)	52.2 (44.9)	28.7 (39.8)	66.0 (62.7)	<0.001	0.001
Site of occlusion (%)					0.514	0.254
Carotid bifurcation	8 (8.2)	8 (18.6)	3 (6.5)	6 (17.1)		
Carotid intracranial	16 (16.3)	9 (20.9)	11 (23.9)	8 (22.9)		
Proximal M1	41 (41.8)	16 (37.2)	19 (41.3)	10 (28.6)		
Distal M1	16 (16.3)	3 (7.0)	4 (8.7)	3 (8.6)		
Distal MCA	17 (17.3)	7 (16.3)	9 (19.6)	8 (22.9)		
Mode of endovascular treatment (%)					0.165	0.086
IA fibrinolytics alone	26 (26.5)	10 (23.3)	14 (30.4)	12 (34.3)		
Mechanical	5 (5.1)	8 (18.6)	10 (21.7)	4 (11.4)		
Merci clot retrieval	38 (38.8)	15 (34.9)	14 (30.4)	12 (34.3)		
Combined IA fibrinolytics and endovascular therapy	29 (29.6)	10 (23.3)	8 (17.4)	7 (20.0)		
IV tPA before endovascular therapy (%)	38 (38.8)	16 (37.2)	13 (28.3)	13 (37.1)	0.666	0.860
Onset to endovascular therapy, min (SD)	332.7 (112.6)	320.6 (169.8)	295.3 (90.2)	305.4 (178.7)	0.606	0.714
Follow-up CT or gradient echo						
No HT (%)	56 (57.1)	15 (34.9)	26 (56.5)	22 (62.9)		
Radiological HT (%)	42 (42.9)	28 (65.1)	20 (43.5)	13 (37.1)	0.048	0.015
HI-1	7	7	3	1		
HI-2	12	10	11	4		
PH-1	12	7	3	5		
PH-2	11	4	3	3		
Symptomatic HT (%)	14 (14.3)	13 (30.2)	8 (17.4)	7 (20.0)	0.168	0.027
Minor	5	5	6	5		
Major	9	8	2	2		

TIMI indicates Thrombolysis in Myocardial Infarction; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging; MCA, middle cerebral artery; IA, intra-arterial; IV, intravenous; tPA, tissue-type plasminogen activator; HT, hemorrhagic transformation; PH, parenchymal hematoma; CT, computed tomography; SD, standard deviation.

rhagic complications. Although recanalization to restore antegrade flow may be crucial to achieve favorable outcome in patients undergoing revascularization therapy, our data revealed that therapeutic recanalization in the setting of poor collaterals resulted in a high frequency of HT with worsened clinical neurological status. Poor collateral status at baseline may limit effective reperfusion, even when recanalization is successful. Recanalization upstream from regions of severe

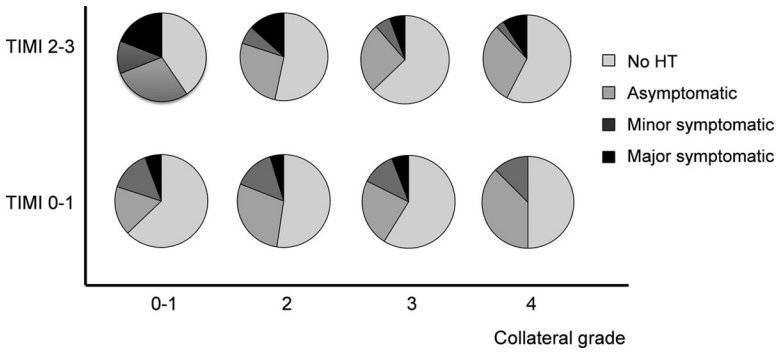

Figure. Relationship between clinical categories of hemorrhagic transformation with pretreatment collateral grading (x-axis) and the degree of recanalization (y-axis). TIMI indicates Thrombolysis in Myocardial Infarction; HT, hemorrhagic transformation.

Table 3. Factors Associated With Hemorrhagic Transformation After Endovascular Therapy

	Hemorrhagic Transformation			Estimated OR		
	Present (n=103)	Absent (n=119)	*P*	Crude	Adjusted (95% CI)	*P*
Female gender (%)	50 (48.5)	53 (44.5)	0.551			
Age, y (SD)	65.0 (16.1)	65.4 (16.7)	0.866			
Atrial fibrillation (%)	47 (47.5)	39 (33.6)	0.044	1.599	…	
S-glucose on admission, mg/dL (SD)	140.6 (52.4)	123.6 (40.9)	0.010	1.007	1.007 (1.000–1.014)	0.046
NIHSS score on admission (SD)	17.2 (6.6)	16.0 (6.5)	0.179	1.002	…	
DWI lesion volume, mL (SD)*	38.7 (51.6)	38.6 (45.7)	0.989			
Site of occlusion (%)			0.441			
Carotid bifurcation	11 (10.7)	14 (11.8)				
Carotid intracranial	22 (21.4)	22 (18.5)				
Proximal M1	45 (43.7)	41 (34.5)				
Distal M1	10 (9.7)	16 (13.4)				
Distal MCA	15 (14.6)	26 (21.8)				
Mode of endovascular treatment (%)			0.015			
IA fibrinolytics alone	20 (19.4)	42 (35.3)		Reference	Reference	
Mechanical†	10 (9.7)	17 (14.3)		1.241	1.159 (0.414–3.242)	0.779
Merci clot retrieval	41 (39.8)	38 (31.9)		2.496	2.558 (1.153–5.678)	0.021
Combined IA fibrinolytics and endovascular therapy	32 (31.1)	22 (18.5)		3.710	3.618 (1.551–8.437)	0.003
IV tPA before endovascular therapy (%)	44 (42.7)	36 (30.3)	0.054	1.942	2.085 (1.096–3.969)	0.025
Time from onset to endovascular therapy, min (SD)	320.3 (137.7)	317.7 (132.3)	0.904			
Collateral grading and TIMI status (%)			0.022			
Nonrecanalized	33 (32.0)	48 (40.3)		Reference	Reference	
Good collateral and recanalized	42 (40.8)	56 (47.1)		0.975	0.939 (0.479–1.839)	0.854
Poor collateral and recanalized	28 (27.2)	15 (12.6)		2.735	2.666 (1.163–6.113)	0.021

NIHSS indicates National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging; MCA, middle cerebral artery; IA, intra-arterial; IV, intravenous; tPA, tissue plasminogen activator; TIMI, Thrombolysis in Myocardial Infarction; OR, odds ratio; CI, confidence interval; SD, standard deviation.

*Baseline MRI findings.

†Including mechanical clot disruption and angioplasty with or without stent.

hypoperfusion may augment hemorrhagic conversion. There may also be several explanations for the low frequency of HT in patients with good collaterals. During focal cerebral ischemia, cerebral blood vessel damage occurs early and in a progressive fashion.[7] The degree of ischemic vascular injury can be minimized by collateral supply to vessels as well as brain tissue within the oligemic regions. In addition, it was very recently reported that perfusion status (severe time-to-maximum delay and low cerebral blood volume) rather than diffusion-weighted imaging lesion volume was associated with HT after revascularization therapy.[5,8] Moreover, a higher rate of HT and infarct growth in patients with poor collaterals in whom therapeutic recanalization was achieved may support the concept of reperfusion injury.[3]

Collateral status differs among patients with acute ischemic stroke.[2,4] In clinical practice, stroke neurologists or interventionalists do not pay attention to the baseline collateral status or they may try to restore antegrade flow more aggressively if patients have poor retrograde filling through collaterals. Our present and earlier results showed that recanalization despite poor collaterals may result in unexpected results in terms of infarct growth, recanalization rate, and HT.[2,3] A recent guideline for the early management of ischemic stroke recommended that unlike the routine use of intravenous tissue-type plasminogen activator in patients within a defined therapeutic time window, the use of intra-arterial fibrinolytics or endovascular therapy should be used only in selected patients.[9] Our data raise the possibility that although patients who showed baseline poor collateral status are expected to have an unfavorable outcome, the efforts to achieve revascularization may not be beneficial and may possibly even be harmful.

We have recently reported that pretreatment angiographic collateral grade determines the results of endovascular therapy in terms of revascularization rate as well as tissue fate after therapeutic revascularization.[2,3] Patients with greater extent of pretreatment collaterals more frequently achieved therapeutic recanalization.[3] The higher rate of HT in patients with poor collaterals may be the result of more aggressive revascularization strategies in patients with poor collaterals. Our present results showed that aggressive treatment (ie, combined fibrinolytics and mechanical/Merci clot retrieval therapy) was associated with HT. However, when we analyzed patients restricted to those who received Merci clot retrieval, poor collaterals and therapeutic recanalization predicted HT, although patients received the

same endovascular therapy (Supplemental Tables I and II; http://stroke.ahajournals.org).

The results of this study should be interpreted with caution because this study is not a randomized controlled trial. Patients were treated with a variety of revascularization therapies, including fibrinolytics and differing types of endovascular therapy. Our findings should be confirmed by the results from larger ongoing studies such as the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) registry or Interventional Management of Stroke (IMS) III trial. The nature of this study did not mandate prospective postprocedure CT and therefore we must assume that there may be differences in HT detection and timing relating to differences in imaging acquisition. In addition, our data do not provide the answer to the question about what we should do for patients with poor collaterals. In cases in which collateral flow is marginal, evolving hemodynamic strategies to improve ischemia through augmentation of collateral perfusion may be warranted.[10] Collateral therapeutics may entail use of readily available hemodynamic manipulations such as head positioning, hypervolemia, hypertensive therapy, or partial aortic obstruction in selected cases.[10] In addition, the importance of pharmacological agents designed to protect the vasculature has been suggested.[11] Further studies about the role of collaterals on vascular protection are warranted.

Our data indicate that a tailored approach is needed to maximize the beneficial effects of endovascular therapy. Angiographic collaterals should be considered individually in these patients, and the decision for more aggressive endovascular treatment should be refined with the information on collaterals readily available from baseline angiography.

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Disclosures

None.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Hemorrhagic transformation depending on collaterals and TIMI score among patients who received Merci Clot Retrieval.

	Group 1 (n=47)	Group 2 (n=16)	Group 3 (n=17)	Group 4 (n=13)	*P (among groups)*	*P (group 1 vs. 2)*
Angiographic finding						
Pretreatment collateral grading	2-4	0-1	2-4	0-1		
Recanalization (TIMI) scale score	2-3	2-3	0-1	0-1		
Female gender (%)	25 (53.2)	9 (56.3)	8 (47.1)	6 (46.2)	*.939*	*.533*
Age, year (SD)	67.3 (20.6)	67.0 (14.3)	63.1 (17.9)	70.5 (12.3)	*.734*	*.954*
Atrial fibrillation (%)	22 (52.4)	6 (37.5)	4 (26.7)	6 (50.0)	*.341*	*.385*
s-glucose (mg/dl), mean (SD)	130.1 (39.3)	151.1 (61.0)	127.7 (25.1)	158.9 (87.8)	*.215*	*.127*
NIHSS score, mean (SD)	18.4 (6.4)	21.5 (5.3)	18.5 (6.7)	21.2 (4.8)	*.193*	*.081*
Initial DWI, mean (SD)	38.7 (49.9)	46.7 (40.8)	51.5 (54.3)	76.1 (53.2)	*.234*	*.622*
Site of occlusion (%)					*.380*	*.133*
Carotid bifurcation	0 (0.0)	2 (22.2)	0 (0.0)	1 (12.5)		
Carotid intracranial	9 (28.1)	3 (33.3)	2 (18.2)	2 (25.0)		
Proximal M1	12 (37.5)	3 (33.3)	6 (54.5)	2 (25.0)		
Distal M1	10 (31.3)	1 (11.1)	2 (18.2)	3 (37.5)		
Distal MCA	1 (3.1)	0 (0.0)	1 (9.1)	0 (0.0)		
IV tPA prior to endovascular therapy (%)	11 (23.4)	0 (0.0)	4 (23.5)	1 (7.7)	*.097*	*.052*
Onset to endovascular therapy, min (SD)	368.0 (113.9)	402.5 (191.2)	344.2 (95.0)	416.3 (174.4)	*.516*	*.427*
Follow up CT or gradient echo						
No HT (%)	22 (46.8)	4 (25.0)	10 (58.8)	7 (53.8)		
Radiological HT (%)	25 (53.2)	12 (75.0)	7 (41.2)	6 (46.2)	*.231*	*.126*
HI-1	3	3	1	1		
HI-2	9	5	4	1		
PH-1	5	3	1	2		
PH-2	8	1	1	2		
Symptomatic HT (%)	11 (23.4)	8 (53.2)	3 (17.6)	4 (30.8)	*.120*	*.051*
Minor	3	4	3	3		
Major	8	4	0	1		

Supplementary Table 2. Factors associated with hemorrhagic transformation after endovascular therapy in patients who received Merci Clot Retrieval.

	Hemorrhagic transformation			Estimated OR		
	Present (n=50)	Absent (n=43)	*P*	Crude	Adjusted (95% CI)	*P*
Female gender (%)	25 (50.0)	23 (53.5)	*.737*			
Age, year (SD)	65.2 (18.7)	69.0 (17.2)	*.322*			
Atrial fibrillation (%)	24 (52.2)	14 (35.9)	*.133*	2.034	…	
s-glucose on admission, mg/dl (SD)	141.7 (48.2)	132.3 (54.7)	*.406*			
NIHSS score on admission (SD)	19.6 (6.3)	19.0 (6.0)	*.605*			
DWI lesion volume, ml (SD) *	46.9 (48.7)	49.6 (53.0)	*.828*			
Site of occlusion (%)			*.267*			
Carotid bifurcation	2 (5.9)	1 (3.8)				
Carotid intracranial	9 (26.5)	7 (26.9)				
Proximal M1	16 (47.1)	7 (26.9)				
Distal M1	7 (20.6)	9 (34.6)				
Distal MCA	0 (0)	2 (7.7)				
IV tPA prior to endovascular therapy (%)	10 (20.0)	6 (14.0)	*.584*			
Time from onset to endovascular therapy, min (SD)	384.9 (147.4)	367.9 (122.5)	*.588*			
Collateral grading and TIMI status (%)			*.126*			
Non-recanalized	13 (26.0)	17 (39.5)		Reference	Reference	
Good collateral and recanalized	25 (50.0)	22 (51.2)		1.603	1.761 (0.479-1.839)	*.257*
Poor collateral and recanalized	12 (24.0)	4 (9.3)		4.523	4.364 (1.112-17.13)	*.035*

* baseline MRI findings