

Mechanical Thrombectomy in Anterior Circulation Occlusion Could Be More Effective than Medical Management Even in Low DWI-ASPECTS Patients

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Abstract

The purpose of this study was to investigate whether patients with low preoperative Diffusion-weighted Imaging Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) could benefit from mechanical thrombectomy for acute anterior circulation occlusion. This was a retrospective, non-blinded, cohort study. From September 2012 to August 2016, 83 consecutive patients of acute anterior circulation occlusion were treated with thrombectomy using second-generation devices or medical management. The DWI-ASPECTS was scored after the first MRI. Patient characteristics and clinical outcomes were compared between the treatment groups. Significant dependence was defined as a modified Rankin scale score ≥ 3 at 90 days. As a result, 33 patients underwent mechanical thrombectomy and 50 received medical management. In the mechanical thrombectomy group, the variable of lower DWI-ASPECTS (5, 4–6 vs. 8, 7–8, $P < 0.001$), especially ≤ 6 , was significantly associated with poor prognosis. However, compared with patients of DWI-ASPECTS ≤ 6 who received medical management, there were significantly fewer patients with poor outcomes in thrombectomy (dependent in 11 of 15 vs. 23 of 23, respectively; $P = 0.019$). Although patients with lower pretreatment DWI-ASPECTS could benefit less from thrombectomy, their outcomes were still better than medical management. Therefore, mechanical thrombectomy could be considered in some patients with low pretreatment DWI-ASPECTS.

Key words: interventional neuroradiology, acute stroke, diffusion-weighted imaging, mechanical thrombectomy, proximal anterior circulation occlusion

Introduction

For patients with ischemic stroke caused by a proximal large artery occlusion in the anterior circulation, early treatment with intra-arterial mechanical thrombectomy is recommended.¹⁾ However, about 30–70% of patients who have received mechanical thrombectomy have failed to achieve good outcomes according to the various large trials.^{2–6)} The degree of early ischemic changes on pretreatment imaging studies is often used for the selection of a candidate for mechanical thrombectomy, but their usefulness is unclear because they cannot rule out the possibility that patients diagnosed as lacking significant

salvageable ischemic brain tissue might benefit from mechanical thrombectomy. In this study, we retrospectively compared the functional outcomes of patients with proximal large artery occlusions in the anterior circulation between treatments with and without mechanical thrombectomy. The purpose of the present study was to determine whether early mechanical thrombectomy could be considered even in low preoperative Diffusion-weighted Imaging-Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS).

Materials and Methods

Study purpose, design and eligibility criteria

We tried to determine if preoperative lower DWI-ASPECTS was predictive of poor outcome and, therefore, indicative of the ineffectiveness of mechanical thrombectomy for those patients.

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This was a non-blinded cohort study. All the data were anonymized and retrospectively analyzed. The requirement for a signed informed consent was waived off based on the guideline of our institutional ethics review board that approved that this study presented no more than minimal risk of harm to subjects and involved no procedures for which written consent was normally required outside of the study context (approved number 161043). Of the consecutive series of patients admitted within 4.5 h of ischemic stroke onset between September 2012 and August 2016 at our hospital, those with proximal large artery occlusions in the anterior circulation confirmed by magnetic resonance angiography (MRA) were included in the analysis. A proximal large artery occlusion in the anterior circulation was defined as an occlusion of the distal intracranial internal carotid artery or the middle (M1/M2) cerebral artery.⁵⁾ In this analysis, the cases of mechanical thrombectomy performed with first-generation devices were excluded due to its low efficacy.¹⁾

Test methods, patient characteristics and clinical outcomes

During the study period, we preferentially performed MRI/MRA for the acute ischemic stroke patients because the occlusions of cerebral arteries and acute ischemic changes could be simultaneously evaluated. The DWI-ASPECTS,⁷⁾ which was a modified version of the ASPECTS system evaluated on diffusion-weighted MRI, was scored after the first MRI by each doctor in charge and recorded in a retrospective fashion.

Variables, such as sex, age, occluded artery, various vascular risk factors, neurological status, laboratory data, intravenous alteplase and DWI-ASPECTS results, were included in the analysis. Glasgow Coma Scale⁸⁾ and National Institutes of Health Stroke Scale (NIHSS) scores⁹⁾ were evaluated on admission. Symptomatic intracranial hemorrhage was defined as any hemorrhagic transformation temporally related to worsening of neurological condition with an increase of ≥ 4 points on the NIHSS.¹⁰⁾ Hypertension, hypercholesterolemia, diabetes mellitus and atrial fibrillation were defined according to self-reported history or the standard definitions of blood pressure as $>160/90$ mmHg,¹¹⁾ low-density lipoprotein cholesterol as >4.1 mmol/L,¹²⁾ NGSP standards for glycated hemoglobin as $>6.5\%$,¹³⁾ and electrocardiographic findings, respectively. Patients who had a ≤ 5 -year history of smoking before admission were classified as smokers.¹⁴⁾ Alcohol consumer was defined as those consuming >7 standard drinks per week on an average.¹⁵⁾

Patient characteristics and clinical outcomes were compared between the treatment groups. Dependent was defined as modified Rankin scale¹⁶⁾ score of ≥ 3 at 90 days after the event.⁵⁾ Modified Rankin scale scoring was according to the report from the transferred hospital or at our outpatient visit. Predictors of dependency were analyzed in the mechanical thrombectomy group and compared with the resembling patients of the medical management group.

Treatment selection

Treatment selection varied depending on the study period. From September 2012 to December 2014, mechanical thrombectomy was discreetly selected for patients with proximal large artery occlusions in the anterior circulation.¹⁷⁻¹⁹⁾ For example, before December 2014, mechanical thrombectomy was often avoided if the attending doctor believed that patients were too old and/or ill. After the publication of the index report in January 2015,⁵⁾ mechanical thrombectomy was aggressively performed unless considerable early ischemic changes on baseline imaging studies were apparent. Even after that, medical management was often selected in cases of low DWI-ASPECTS, such as DWI-ASPECTS ≤ 4 ;²⁰⁾ however, no apparent threshold was determined, and the indication of mechanical thrombectomy was left to the discretion of attending physicians. Accordingly, medical management was often preferred before December 2014 and mechanical thrombectomy after January 2015.

Treatment details

The medical management group received the standard care as described in the guidelines for the management of acute stroke.²¹⁾ The mechanical thrombectomy group received the medical management plus endovascular treatment. The initial goal of mechanical thrombectomy was to achieve a significant recanalization, defined by a thrombolysis in cerebral infarction (TICI)²²⁾ grade 2b or 3, as early as possible.¹⁾ The TICI grade was scored by an attending doctor at the time of treatment and recorded in a retrospective fashion. The treatment method was left to the discretion of each interventionist and involved thrombus aspiration or use of a retrievable stent. Mechanical thrombectomy was performed with second-generation devices.¹⁾ Intra-arterial thrombolysis using alteplase or urokinase was not performed. All procedures were performed by endovascular specialists qualified by the Japanese Society for Neuroendovascular Therapy. Stroke onset to recanalization or completion of procedure was defined as the time from onset to recanalization \geq TICI 2b or final angiography in case of \leq TICI 2a.⁶⁾

Participants in both groups received intravenous alteplase within 4.5 h after stroke onset at the discretion of each stroke specialist.

Statistical analysis

Dichotomous categorical data, such as sex ratio, presence of various vascular risk factors, angiographic outcome, preceding intravenous alteplase and prehospital functional independence, were analyzed by Fisher's exact test. The Mann-Whitney *U*-test was used for ordinal or ratio data, such as NIHSS score, age, onset to reperfusion time and glucose level. Values for non-categorical data were presented as the median and 25–75% interquartile range. Odds ratio with 95% confidence interval was calculated for variables showing significant association with poor outcome. The optimal cutoff values for the significant variables were determined using receiver-operating characteristic curve analysis; i.e., values nearest to the upper left corner of the curve graph. Because the regression coefficients would be biased in both positive and negative directions if the number of the cases belonging to the less frequent category is about 10,²³⁾ we did not perform multiple logistic regression analysis. The threshold for statistical significance was $P < 0.05$. If the P value was < 0.001 , it was expressed as $P < 0.001$. All statistical analyses were performed using EZR

(Saitama Medical Center, Jichi Medical University, Saitama, Japan) version 1.27.²⁴⁾

Results

Participants (Fig. 1)

Of the consecutive 376 patients admitted within 4.5 h of ischemic stroke onset, 83 with proximal large artery occlusions in the anterior circulation were included in the analysis. Patients without occlusion ($n = 252$), those already dependent prior to the event ($n = 18$), those who had not undergone MRI ($n = 5$), those already dependent without undergoing MRI ($n = 2$), or those who underwent mechanical thrombectomy with first-generation devices ($n = 16$) were excluded from the study (Fig. 1).

Baseline clinical characteristics and outcomes of patients with acute proximal large artery occlusion in the anterior circulation (Table 1)

The patient characteristics and outcomes of both groups are presented in Table 1. In the mechanical thrombectomy group, stroke onset to hospital arrival (minutes) was significantly shorter (81, 60–115 vs. 102, 71–150, $P = 0.043$) and more patients received intravenous alteplase ($P < 0.001$) than medical management group. About 14 of 33 patients who underwent mechanical thrombectomy and 35 of 50

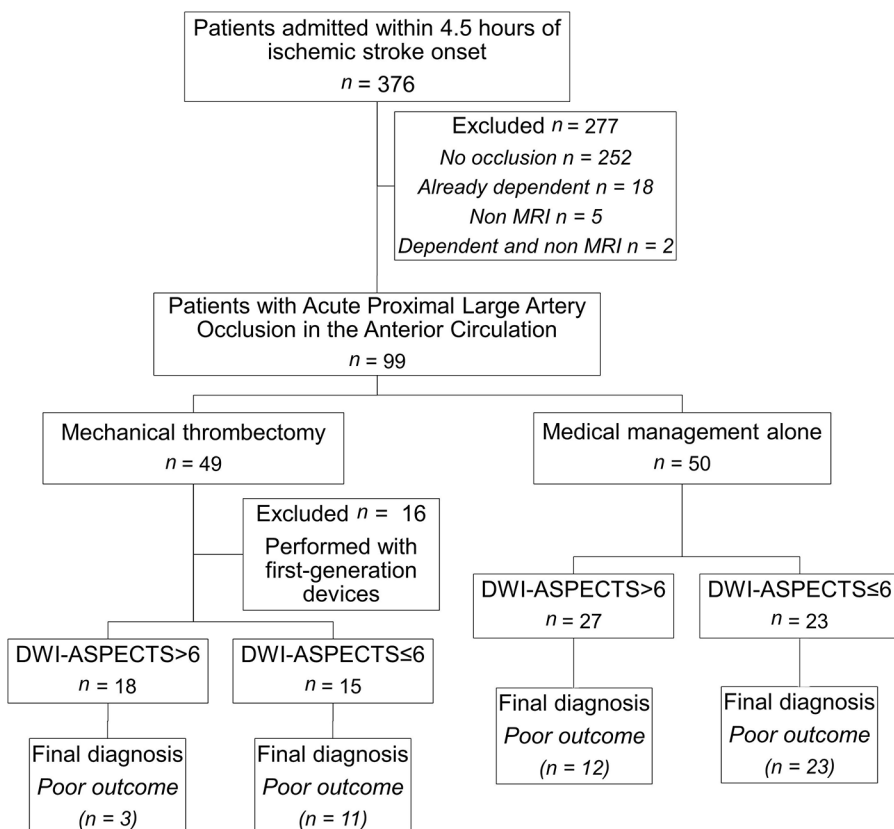


Fig. 1 Flow of participants through the study.

Table 1 Patient characteristics and outcomes of each treatment group

Factors	Mechanical thrombectomy (<i>n</i> = 33)	Medical management (<i>n</i> = 50)	<i>P</i>
Age (years)	79, 73–88	83, 73–87	0.63
Sex (male), <i>n</i> (%)	18 (55)	22 (44)	0.38
Stroke onset to hospital arrival (minutes)	81, 60–115	102, 71–150	0.043
Systolic blood pressure (mmHg)	144, 118–164	148, 128–174	0.30
Glucose level (mmol/L)	6.7, 5.8–7.6	6.6, 6.0–7.9	0.69
Occluded artery (ICA:MCA)	7:26	14:36	0.61
Lesion side (right), <i>n</i> (%)	19 (58)	24 (48)	0.50
Glasgow Coma Scale score	13, 10–14	12, 9–14	0.53
NIHSS on admission	16, 13–21	16, 9–20	0.20
Atrial fibrillation	25	32	0.34
Hypertension	27	36	0.43
Diabetes mellitus	7	12	>0.99
Hyperlipidemia	6	14	0.43
Previous ischemic stroke	4	10	0.39
Alcohol	14	14	0.24
Smoking	15	15	0.24
Premorbid modified Rankin scale 2	4	2	0.21
Intravenous alteplase	30	32	<0.001
DWI-ASPECTS	7, 5–8	7, 4–9	0.83
Poor prognosis	14	35	0.022

Values for non-categorical data are presented as the median and 25–75% interquartile range. DWI-ASPECTS: Diffusion-weighted Imaging Alberta Stroke Program Early Computed Tomography Score, ICA: internal carotid artery, MCA: middle cerebral artery, NIHSS: National Institute of Health Stroke Scale.

patients who received medical management alone were functionally dependent at 90 days ($P = 0.022$).

Variables associated with poor outcome after mechanical thrombectomy

In the mechanical thrombectomy group, TICI 2b or 3 was achieved in 31 (94%) cases. On univariate analysis, higher age (years) (83, 79–90 vs. 74, 68–84, $P = 0.024$), lower Glasgow Coma Scale score (10, 9–12 vs. 14, 12–15, $P < 0.001$), and lower DWI-ASPECTS (5, 4–6 vs. 8, 7–8, $P < 0.001$) were significantly associated with poor outcome. The variables of TICI 2a or lower (odds ratio, Infinite; 95% confidence interval, 0.26–Infinite; $P = 0.17$), male sex (odds ratio, 0.27; 95% confidence interval, 0.046–1.4; $P = 0.085$), past history of diabetes mellitus (odds ratio, 0.17; 95% confidence interval, 0.0034–1.8; $P = 0.20$), onset to successful recanalization or completion of procedure (249, 206–325 vs. 210, 175–266, $P = 0.074$),^{1,17,25,26} and use of intravenous alteplase (odds ratio, 0.34; 95% confidence interval, 0.0054–7.3; $P = 0.56$) were not significantly associated with poor outcome. On receiver-operating characteristic curve analysis, DWI-ASPECTS ≤ 6 (area under the

curve, 0.84; sensitivity, 79%; and specificity, 87.9%) was the optimal cutoff value.

Benefit of mechanical thrombectomy on patients with low DWI-ASPECTS (Table 2 and Fig. 2)

To evaluate the benefit of mechanical thrombectomy on patients with low DWI-ASPECTS, the outcomes of patients with DWI-ASPECTS ≤ 6 were compared between the treatment groups (Table 2). Symptomatic intracranial hemorrhage occurred significantly more in medical management patients ($P = 0.027$). Eleven of 15 mechanical thrombectomy patients and 23 of 23 medical management patients were dependent at 90 days, and the difference was significant ($P = 0.019$). The DWI-ASPECTS were not significantly different between the treatment groups (5, 4–6 vs. 4, 1–5, $P = 0.092$); however, lower DWI-ASPECTS, such as 0 and 1 were only included in the medical management group (Fig. 2). For 17 patients with DWI-ASPECTS of 5 or 6, 5 of 8 mechanical thrombectomy patients and 9 of 9 medical management patients were dependent at 90 days (odds ratio, 0; 95% confidence interval, 0–1.9; $P = 0.082$). To exclude the patients with palliative treatment,

Table 2 Patient characteristics and outcomes of each treatment group of DWI-ASPECT ≤ 6

Factors	Mechanical thrombectomy ($n = 15$)	Medical management ($n = 23$)	<i>P</i>
Age (years)	85, 78–90	84, 67–86	0.34
Sex (male), n (%)	6 (40)	11 (48)	0.74
Stroke onset to hospital arrival (minutes)	90, 65–125	89, 68–141	0.75
Systolic blood pressure (mmHg)	133, 117–164	144, 124–171	0.38
Glucose level (mmol/L)	6.7, 5.8–7.2	7.0, 6.3–7.9	0.37
Occluded artery (ICA:MCA)	4:11	13:10	0.1
Lesion side (right), n (%)	8 (53)	12 (52)	>0.99
Glasgow Coma Scale score	11, 10–14	10, 9–12	0.26
NIHSS on admission	18, 14–22	19, 16–24	0.53
Atrial fibrillation	15	15	0.013
Hypertension	12	14	0.29
Diabetes mellitus	2	6	0.44
Hyperlipidemia	3	3	0.66
Previous ischemic stroke	2	3	>0.99
Alcohol	4	8	0.72
Smoking	3	8	0.47
Premorbid modified Rankin scale 2	3	0	0.054
Intravenous alteplase	15	9	<u><0.001</u>
Any intracranial hemorrhage	4	11	0.18
Symptomatic intracranial hemorrhage	0	7	<u>0.027</u>
Death	2	9	0.15
DWI-ASPECTS	5, 4–6	4, 1–5	0.092
Poor prognosis	11	23	<u>0.019</u>

Values for non-categorical data are presented as the median and 25–75% interquartile range. *P* value of < 0.05 is underlined. DWI-ASPECTS: Diffusion-weighted Imaging Alberta Stroke Program Early Computed Tomography Score, ICA: internal carotid artery, MCA: middle cerebral artery, NIHSS: National Institute of Health Stroke Scale.

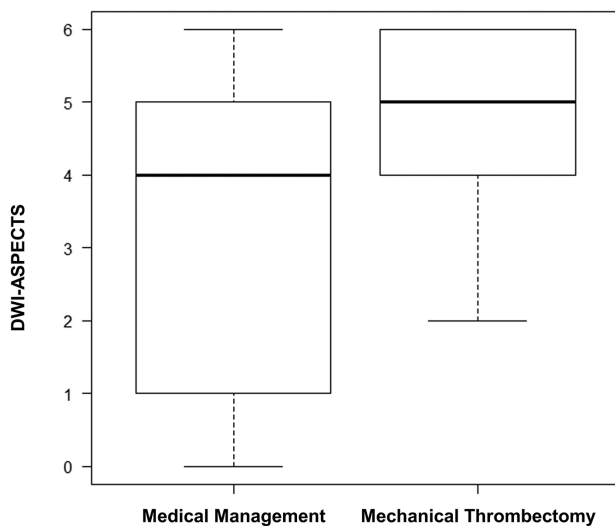


Fig. 2 Box-and-whisker plot comparing the distribution of Diffusion-weighted Imaging Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) between the treatment groups which included the patients of DWI-ASPECTS ≤ 6 .

the patients treated with intravenous alteplase were compared between the groups. As a result, 11 of 15 mechanical thrombectomy patients and 9 of 9 medical management patients were dependent at 90 days (odds ratio, 0; 95% confidence interval, 0–2.4; $P = 0.26$).

Discussion

Implications for practice

Our study demonstrated that a lower DWI-ASPECTS, especially of ≤ 6 , was predictive of poor prognosis after mechanical thrombectomy. Nevertheless, favorable outcome was achieved in significantly more patients who underwent mechanical thrombectomy than in patients who received medical management alone.

Various factors affecting outcome after mechanical thrombectomy

Various factors affecting outcome after mechanical thrombectomy have been advocated. The increasing time from stroke onset to angiographic reperfusion

following mechanical thrombectomy has been found to be associated with an increased rate of mortality and a decreased rate of good outcomes.²⁵⁾ Effective recanalization of TICI grade 2b or 3 has been shown to reflect better functional outcome than that of partial recanalization.^{17,26)} Hyperglycemia (glucose ≥ 8.3 mmol/L) has been found to be significantly more frequent in patients who deteriorated despite angiographic recanalization treated with intra-arterial thrombolysis and urokinase or alteplase.²⁷⁾

Patients with acute stroke treated with alteplase were susceptible to symptomatic intracerebral hemorrhage if recanalization therapy was applied too late²⁸⁾ or if their DWI-ASPECTS were ≤ 5 .²⁰⁾ However, the proportion of parenchymal hematoma with considerable mass effect did not differ from the perspective of recanalization status after mechanical thrombectomy.²⁹⁾ In this study, symptomatic intracranial hemorrhage occurred significantly more in medical management patients, suggesting that the utility of mechanical thrombectomy might partially depend on the reduction of symptomatic intracranial hemorrhage. However, inclusion of the extremely low DWI-ASPECTS such as 0–1 in the medical management group might affect the result. Earlier recanalization with mechanical thrombectomy might reduce the hemorrhagic risk.³⁰⁾

Regarding imaging factors, an absence of large ischemic-core lesions has been advocated.^{2–4,6)} Early ischemic changes on computed tomography (CT) are highly specific for irreversible ischemic brain damage if detection occurs within the first 6 h.³¹⁾ ASPECTS is a quantitative score for assessing early ischemic change on CT, and an ASPECTS score >7 has been associated with functional independence at 3 months in patients with ischemic stroke treated with intravenous alteplase within 3 h.³²⁾ For mechanical thrombectomy, the treatment effect has been found to be lower in patients with ASPECTS scores of 0–4,⁵⁾ and patients with ASPECTS ≤ 5 were excluded from the ESCAPE trial.²⁾

Prediction using DWI

Increasing pretreatment DWI lesion volumes have been associated with a growing risk for poor outcome and symptomatic intracerebral hemorrhage.^{33,34)} However, measurement of DWI lesion volumes required specially designed software, which was unavailable at our institution. The DWI-ASPECTS is a modified version of the ASPECTS that adds 1 area in the corona radiata evaluated on DWI.⁷⁾ The DWI-ASPECTS ≥ 7 has been associated with modified Rankin scale scores of 0–2 at 3 months²⁰⁾ and short-term recovery in patients with middle cerebral artery trunk occlusion³⁵⁾ following intravenous alteplase.

For endovascular treatment, DWI-ASPECTS ≥ 5 has been presented as the optimal threshold for prediction of favorable outcomes among patients undergoing endovascular reperfusion within 6 h.³⁶⁾ In our study, lower DWI-ASPECTS, especially ≤ 6 , was associated with poor outcome at 3 months. However, 27% of the patients who underwent mechanical thrombectomy and none in the medical management group achieved functional independence. Previous reports also have proposed a benefit of endovascular treatment even for low DWI-ASPECTS or high DWI volume,^{37,38)} but comparisons with medical management alone were not performed. Our study, which compared the two groups, showed that significantly more patients who underwent mechanical thrombectomy than who received medical management alone achieved good clinical outcomes. However, the superiority of mechanical thrombectomy was not established because of the selection bias, such as significantly lower proportion of intravenous alteplase in the medical management group, which might reflect the inclusion of the patients with extremely low DWI-ASPECTS and other clinical severity.

The DWI can detect acute changes due to cerebral ischemia.³⁹⁾ However, DWI hyperintensity did not represent irreversibly infarcted tissue in the setting of acute stroke with a high mean rate (24%) of DWI lesion reversal.⁴⁰⁾ It is unknown that patients with lower DWI-ASPECTS have reversible early ischemic changes and can benefit from mechanical thrombectomy. It might be important to evaluate the apparent diffusion coefficient values on DWI because they could distinguish between infarct and reversible areas.⁴¹⁾ From the technical aspect, significant recanalization in a shorter time might be important, as suggested in our study. The investigation to determine the utility of mechanical thrombectomy should be concise not to delay the significant recanalization.

Study limitations

Our study had several limitations. Although the various patient characteristics and laboratory and imaging findings were not significantly different between the groups, selection bias was inevitable because of the retrospective nature of the study. A second limitation is the small size of the study sample. To achieve a faster recanalization, we do not perform MRI before mechanical thrombectomy anymore, so we could not collect further cases. In this study, the patients with extremely low DWI-ASPECTS, such as 0 or 1 were only included in the medical management group, which might affect the result. Lower limit of DWI-ASPECTS which has a chance of good outcome was not determined. We could not clarify the factors which affect the outcome

in patients with low DWI-ASPECTS, such as large mismatch profiles.⁴²⁾ Our results must be confirmed in larger multicenter trials.

Conclusions

Although patients with lower pretreatment DWI-ASPECTS could benefit less from thrombectomy than those with higher DWI-ASPECTS, their outcomes were still better than those who received medical management alone. Therefore, mechanical thrombectomy can be performed in patients with acute proximal large artery occlusion in the anterior circulation even in those with low pretreatment DWI-ASPECTS.

Conflicts of Interest Disclosure

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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