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Comparison of Endovascular Treatment with Intravenous Thrombolysis for Isolated M2 Segment of Middle Cerebral Artery Occlusion in Acute Ischemic Stroke

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Abstract

Background—The benefit of endovascular treatment for distal large artery ischemic occlusions such as M2 segment of middle cerebral artery is not clear.

Methods—We retrospectively analyzed data from 51 subjects who had an isolated M2 segment occlusion on baseline computed tomographic (CT) angiogram who were randomized to either intravenous (IV) recombinant tissue plasminogen activator (rt-PA) followed by endovascular treatment or IV rt-PA alone in a multicenter trial. We determined the effect of endovascular treatment on occurrence of excellent [mRS (modified Rankin scale) scores of 0–1] functional outcomes at three months and any death within 3 and 12 months. We also performed proportional odds logistic regression analysis to compare the distribution of mRS scores between the two groups. Each of the analyses was adjusted for age, baseline Alberta stroke program early CT score strata, and baseline National Institutes of Health Stroke scale score strata.

Results—At three months, the rate of excellent functional outcome (38.2% versus 17.6%, unadjusted odds ratio 2.9; 95% confidence interval ; 0.7–12.1; $p = 0.15$) was non-significantly higher among subjects with M2 segment occlusion who were randomized to endovascular treatment. In multivariate analysis, the odds of excellent functional outcome at three months were non-significantly higher among subjects who were randomized to endovascular treatment at three months (OR 2.7; 95% CI; 0.6–13.6; $p = 0.22$). There was a trend toward lower disability grades in subject randomized to endovascular treatment when distribution of the mRS score at three months were compared (common OR 2.6; $p = 0.084$), adjusting for potential confounders. The rates of any death within 3 (adjusted OR 0.1; 95% CI; 0.1–0.8; $p = 0.031$) and within 12 months (adjusted OR 0.1; 95% CI; 0.1–0.7; $p = 0.022$) were significantly lower among those who were randomized to endovascular treatment.

Conclusion—In this post-hoc analysis, acute ischemic stroke subjects who had isolated M2 segment occlusion randomized to endovascular treatment appeared to have lower mortality and a trend toward lower grades of disability.

Introduction

The 2015 American Heart Association (AHA)/American Stroke Association (ASA) focused update of the 2013 guidelines regarding endovascular treatment recommended that acute ischemic stroke patients should receive endovascular treatment with a stent retriever if the causative occlusion is located in the internal carotid artery (ICA) or proximal middle cerebral artery (MCA) (M1) in addition to other criteria (Class I; Level of Evidence A) [1]. The guidelines made the recommendation because a very high proportion of patients in the stent retriever trials had ICA or proximal MCA (M1) segment occlusion with the number of patients with isolated M2 lesions too small for any conclusions. Trials like Endovascular Treatment for Smalll Core and Anterior Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), randomized revascularization with Solitaire device versus best medical therapy in anterior circulation stroke within eight hours (REVASCAT), and stent-retriever thrombectomy after intravenous (IV) t-PA versus t-PA alone in stroke (SWIFT PRIME) excluded patients with isolated M2 segment occlusions, although small numbers of these

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patients were enrolled in multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands and extending the time for thrombolysis in emergency neurological deficits intra-arterial (EXTEND-IA) trials. The relative benefit of angiographic recanalization (compared with lack of recanalization) with endovascular treatment in patients with angiographic occlusion of M2 segment has been determined in subsequent analyses with inconclusive results [2,3]. In addition, the relatively lower magnitude of benefit with endovascular treatment and associated recanalization may be related to high rates of angiographic recanalization and favorable outcomes with treatment with IV recombinant tissue plasminogen activator (rt-PA) alone in patients with M2 segment occlusion [4,5]. The benefit of endovascular treatment in regards higher rates of recanalization and favorable outcomes is more prominent when compared with no IV rt-PA such as in phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute MCA stroke study [6]. The practical management question that remains unanswered is whether an acute ischemic stroke patient who has an isolated occlusion of M2 segment of MCA on computed tomography (CT) angiography and qualifies for IV rt-PA should receive additional endovascular treatment. Although definitive evidence may not be available, data from randomized or nonrandomized observational or registry studies with limitations of design or execution may be used to identify magnitude of benefit with endovascular treatment and assist clinicians in decision making in current practice. Such data are classified as level of evidence C by AHA/ASA, and current guidelines acknowledge the value of such data in absence of level A or B data [1]. We performed this analysis to provide an in-depth comparison between patients with MCA occlusion M2 segment occlusion treated with IV rt-PA and those treated with additional endovascular treatment.

Methods

We analyzed data derived from acute ischemic stroke patients with isolated M2 segment of MCA occlusion documented by CT angiogram who were enrolled in the Interventional Management of Stroke (IMS) III trial. This data analysis did not require any Institutional Review Board/Ethics committee approval. The IMS III trial randomized ischemic stroke patients aged 18–82 years who were eligible for IV rt-PA within three hours after symptom onset [7,8]. Patients with early ischemic changes such as large regions of clear hypodensity on CT scan, which involved greater than one-third of the MCA, were excluded. CT angiography was not required to determine eligibility for the trial enrollment in the first part of the trial, but was performed at a number of centers routinely as part of standard clinical care. In the second part of the trial, CT angiography was required to determine eligibility in patients with lower baseline National Institutes of Health Stroke Scale (NIHSS) scores (scores 8–9) by identifying a proximal arterial occlusion [7,8]. In the third part of the trial, absence of a visible intracranial occlusion served as an exclusion from eligibility in clinical sites where baseline CT angiography was performed. All the CT angiographic images were submitted and analyzed at the central core laboratory. Each segment of the extracranial and intracranial arterial vasculature was assessed in CT angiographic study by a consensus panel of two readers for the presence of contrast material within the lumen, and was graded for any stenosis or occlusion [9]. The trial required follow-up (24-hour) CT angiography or magnetic resonance (MR) angiography to evaluate recanalization rates for all subjects in both treatment arms.

Once enrolled, the subjects were randomized in 1:2 ratio to either receive a standard dose of IV rt-PA (0.9 mg per kilogram) or endovascular treatment following IV rt-PA (referred to endovascular treatment here after). Subjects randomized to endovascular treatment underwent catheter-based angiography and those with a treatable arterial occlusion received intra-arterial rt-PA at site of occlusion (maximum 22 mg) by means of the Micro-Sonic SV infusion system [EKOS] or a standard microcatheter. Mechanical thrombectomy was performed as considered appropriate by treating physician using the Merci retriever [Concentric Medical], Penumbra System [Penumbra], or Solitaire FR revascularization device [Covidien]. IV heparin infusion was given as a 2000-unit bolus at initiation of procedure, followed by an infusion of 450 units per hour. The recommended time interval from symptom to initiation and completion of procedure were five and seven hours, respectively. The NIHSS score assessment was performed in every subject immediately prior to initiation of IV rt-PA and at 24 (±6) hours, and CT scans were performed at baseline, at 24 (±6) hours, and if there was a neurologic decline. The 24-hour NIHSS score assessed by an examiner was blinded to the 24-hour CT scan results.

Post-procedure recanalization was assessed from images acquired during catheter-based angiograms that were submitted to central core laboratory and reviewed by two independent raters in stepwise manner, and any difference was resolved by consensus. Angiographic outcome was evaluated for both recanalization of the original primary arterial occlusive lesion during and after

therapy, as well as for global perfusion post-treatment using the thrombolysis in cerebral infarction (TICI) score. All disagreements in the location of arterial occlusion and recanalization were resolved by consensus. Near complete or complete recanalization were defined based on the post-treatment TICI scores of 2b and 3, respectively [7]. CT angiogram was performed 24 hours after randomization, and was coded on a five-grade scale accounting the patency of target vessel (1: complete occlusion, 2: hairline lumen, 3: >50% stenosis but not hairline lumen, 4: ≤50% stenosis, and 5: normal).

The outcomes of interest included—excellent and good functional outcomes: mRS score of 0–1 and 0–2 at 90 (±14) days, respectively, determined by a study investigator who was blinded to the treatment assignment. The outcome was also assessed at 366 (±30) days. Other outcomes of interest included: (1) minimal impairment in activities of daily living (ADLs): Barthel index of 95 or 100 at three months [7]; (2) good quality of life: EQ-5D index score of 0.6 or more at 3 and 12 months [10] (imputing "0" for death); and (3) any death: death regardless of cause within 3- and 12-month post-randomization.

Statistical Analysis

We compared the baseline demographic and clinical characteristics of subjects who were randomized to endovascular treatment with those who had received IV rt-PA alone. We used chi-square and analysis of variance (ANOVA) tests for categorical and continuous variable comparisons, respectively. We performed nine different logistic regression analyses to determine the effect of endovascular treatment on occurrence of outcomes of interest: (1) excellent and good functional outcomes at 3 and 12 months;(2) any death within 3 and 12 months; (3) independence in ADLs at three months; and (4) good quality of life at 3 and 12 months. We also performed proportional odds logistic regression analysis to compare the distribution of mRS between subjects randomized to endovascular treatment to those randomized to IV rt-PA alone. Each of the analysis was adjusted for age (continuous variable), baseline Alberta stroke program early CT score (ASPECTS) strata (0–7 and 8–10), and baseline NIHSS score strata (≤9, 10–19, and ≥20). All analyses were performed using IBM SPSS STATISTICS Version 20 (IBM Corp, Armonk, NY).

Results

A total of 51 subjects (mean age±SD; 68.3±11.7; 28 were men) had a documented isolated M2 segment occlusion on CT angiography among 306 subjects who underwent a CT angiogram in IMS III trial. The mean time interval (±SD) between symptom onset and initiation of IV rt-PA in the 51 subjects was 125.5(±32.1) min, and that between symptom onset and CT angiography was 93.1(±30.4) min. Of these 51 subjects (mean age±SD; 68.3±11.7 years) with M2 segment occlusion, 34 and 17 subjects received IV rt-PA followed by endovascular treatment and IV rt-PA alone, respectively. Of the 34 patients randomized to endovascular treatment, 28 (82.4%) received endovascular treatment and 6 (17.6%) underwent a catheter-based angiogram, but did not have an occlusion that required endovascular treatment. The mean time interval (±SD) between symptom onset and initiation of catheter-based angiogram in 34 subjects was 219.8(±56.7) min, and that between baseline CT scan and the initiation of catheter-based angiogram was 134.9(±45.6) min. The endovascular treatment consisted of intra-arterial thrombolytic administration (n = 25), EKOS catheter (n = 1), Merci concentric retriever (n = 6) [+standard microcatheter], Penumbra aspiration catheter and system (n = 3) (system only), and Solitaire stent retriever (n = 1). Near complete and complete recanalization were seen in 7 (20.6%) and 13 (38.2%) patients, respectively. Device/procedure-related complications were observed in 6 of 34 subjects which included groin hematoma (n = 3), arterial dissection (n = 1), and embolus in previously uninvolved distribution (n = 2).

The comparison of demographic and clinical characteristics of subjects who were randomized to endovascular treatment and those to IV rt-PA alone are presented in Table 1. There were no differences in regards to age, gender, and race/ethnicity distribution between the two groups. Although not significant, there were some imbalances with higher proportion of subjects in NIHSS score strata ≥20 among those who were randomized to IV rt-PA alone and lower proportion of subjects with ASPECTS of 8–10 on baseline CT scan among those who were randomized to endovascular treatment. There was a non-significantly lower rate of neurological deterioration (14.7% versus 23.5%) and symptomatic intracranial hemorrhages (5.9% versus 11.8%) among subjects who were randomized to endovascular treatment.

At three months, the rate of excellent functional outcome (mRS 0–1) (38.2% versus 17.6%, unadjusted odds ratio [OR] 2.9; 95% confidence interval [CI]; 0.7–12.1; p = 0.15) was non-significantly higher among subjects with M2 segment occlusion who were randomized to endovascular treatment (see Table 2). After adjusting for age, initial NIHSS score strata, and ASPECTS strata, the

Table 1:

Demographic and clinical characteristics of the acute ischemic stroke subjects based on the randomized treatment arm

	Subjects randomized to endovascular treatment N=34	Subjects randomized to IV rt-PA treatment alone N=17	P value
Age in years [median (range)]	71 (23-81)	73 (53-81)	0.35
Gender			
Men	16 (47.1)	12 (70.6)	0.12
Women	18 (52.9)	5 (29.4)	
Race or ethnic group			0.20
African-American	7 (20.6)	1 (5.9)	
White	24 (70.6)	13 (76.5)	
Others	3 (8.8)	3 (17.6)	
Baseline NIHSS score [median (range)]	16 (7-25)	14 (8-24)	0.85
Baseline NIHSS score strata			0.48
<10	1 (2.9)	1 (5.9)	
10-19	29 (85.3)	12 (70.6)	
>=20	4 (11.8)	4 (23.5)	
ASPECTS 8,9 or 10	20 (58.8)	13 (76.5)	0.27
Time interval between symptom onset to emergency department arrival (minutes ±SD)	84.6±22.7	85.4±35.6	0.48
Time interval between symptom onset to randomization (minutes ±SD)	146.8±30.8	141.6±37.1	0.60
Time interval between emergency department arrival to IV rt-PA initiation (minutes ±SD)	107.7±30.3	109.6±43.5	0.86
Vascular risk factors			
Hypertension	30 (88.2)	13 (76.5)	0.28
Diabetes mellitus	10 (29.4)	7 (41.2)	0.40
Congestive heart failure	8 (23.5)	0	0.03
Coronary artery disease	6 (17.6)	5 (29.4)	0.34
Cigarette smoking	8 (23.5)	5 (29.4)	0.74
Atrial fibrillation	15 (44.1)	6 (35.3)	0.55
Hyperlipidemia	12 (35.3)	11 (64.7)	0.10
Previous stroke	3 (8.8)	3 (17.6)	0.36
History of myocardial infarction	2 (5.9)	1 (5.9)	0.67
Modified Rankin scale (status prior to stroke)			1.00
0	31 (91.2)	16 (94.1)	
1	2 (5.9)	1 (5.9)	
2	1 (2.9)	0	
Baseline INR [median (range)]	1.0 (0.8-1.1)	1.0 (0.8-1.1)	0.18
Baseline serum glucose (mmol/liter ±SD)	7.2±2.6	7.9±4.0	0.48
Baseline systolic blood pressure (mm Hg ±SD)	149.8±20.3	154.7±23.8	0.46
Current antiplatelet use	11 (32.0)	9 (52.9)	0.17
Current statin use	11 (32.4)	6 (35.3)	0.83
Procedural complications	6 (17.6)	0 (0)	0.16
Hospital stay in days [median (range)]	7 (2-26)	6 (1-39)	0.98
Intubation anytime during 7 hours from stroke onset	13 (38.2)	4 (23.5)	0.35
Neurological deterioration	5 (14.7)	4 (23.5)	0.39
Symptomatic intracranial hemorrhage	2 (5.9)	2 (11.8)	0.47
Partial or complete recanalization at 24 hours	23/26 (67.6)	10/13 (58.8)	0.35

Abbreviations used: NIHSS National Institutes of Health Stroke Scale; ASPECTS Alberta Stroke Program Early CT Score; SD standard deviation; rt-PA recombinant tissue plasminogen activator; IV intravenous; INR international normalized ratio

odds of excellent functional outcome at three months were non-significantly higher among subjects who were randomized to endovascular treatment at three months (OR 2.7; 95% CI; 0.6–13.6; $p = 0.22$). The distribution of the mRS scores at three months is presented in Figure 1. There was a trend toward lower disability grades in subject randomized to endovascular treatment in unadjusted (common OR 2.7; $p = 0.063$) and adjusted (common OR 2.6; $p = 0.084$) analyses. The rate of any death within three months was significantly lower among those who were randomized to endovascular treatment (5.9% versus 35.3%, adjusted OR 0.1; 95% CI; 0.1–0.8; $p = 0.031$). The odds of any death within 12 months remained significantly lower in subjects randomized to endovascular treatment (adjusted OR 0.1; 95% CI; 0.1–0.7; $p = 0.022$). The rates of good functional outcome (mRS 0–2) was higher among patients randomized to endovascular treatment at three months (52.9% versus 41.2%; adjusted OR 1.1; 95% CI; 0.3–4.7; $p = 0.85$). The rates of good quality of life and independence in ADLs at three months, although higher in subjects randomized to endovascular treatment, did not reach statistical significance (see Table 2).

Discussion

In a post-hoc analysis of a randomized trial, acute ischemic stroke subjects who had isolated M2 segment occlusion randomized to endovascular treatment appeared to have lower mortality at 3 and 12 months, and a trend

Table 2:
Multivariate analysis of outcomes

	Subjects randomized to endovascular treatment N=34	Subjects randomized to IV rt-PA treatment alone N=17	Unadjusted OR (95% CI); p-value	Adjusted OR (95% CI) *: p-value
Excellent functional outcome at 3 months (mRS 0 or 1)	13 (38.2)	3 (17.6)	2.9 (0.7-12.1); p=0.15	2.7 (0.6-13.6); p=0.22
Good functional outcome at 3 months (mRS 0-2)	18 (52.9)	7 (41.2)	1.6 (0.5-5.2); p=0.43	1.1 (0.3-4.7); p=0.85
Any death within 3 months	2 (5.9)	6 (35.3)	0.1 (0.1-0.7); p=0.020	0.1 (0.1-0.8); p=0.031
Good quality of life at 3 months (EQ-5D) ‡	23/32 (71.9)	10/17 (58.8)	1.8 (0.5-6.2); p=0.36	1.2 (0.3-4.9); p=0.75
Independence in activities of daily living at 3 months (Barthel index score 95-100	17 (50.0)	6 (35.3)	1.8 (0.5-6.0); p=0.32	1.9 (0.3-5.6); p=0.65
Excellent functional outcome at 12 months (mRS 0 or 1)	11 (32.4)	5 (29.4)	1.2 (0.3-4.1); p=0.83	0.8 (0.2-3.3); p=0.77
Good functional outcome at 12 months (mRS 0-2)	16 (47.1)	6 (35.3)	1.6 (0.5-5.4); p=0.43	1.1 (0.3-4.3); p=0.90
Any death within 12 months	3 (8.8)	7 (41.2)	0.1 (0.1-0.6); p=0.011	0.1 (0.1-0.7); p=0.022
Good quality of life at 12 months (EQ-5D) †	23/33 (67.6)	10/17 (58.8)	1.6 (0.5-5.5); p=0.44	1.2 (0.3-5.2); p=0.77

Abbreviations: rt-PA recombinant tissue plasminogen activator; IV intravenous; INR international normalized ratio; OR odds ratio; CI confidence interval; mRS, modified Rankin scale.

* Model adjusted for age, baseline National Institutes of Health Stroke Scale score strata, and Alberta Stroke Program Early CT (ASPECTS) Score strata

‡ In our cohort, two subjects had missing EQ-5D assessment at 3 months

† In our cohort, one subject had missing EQ-5D assessment at 12 months

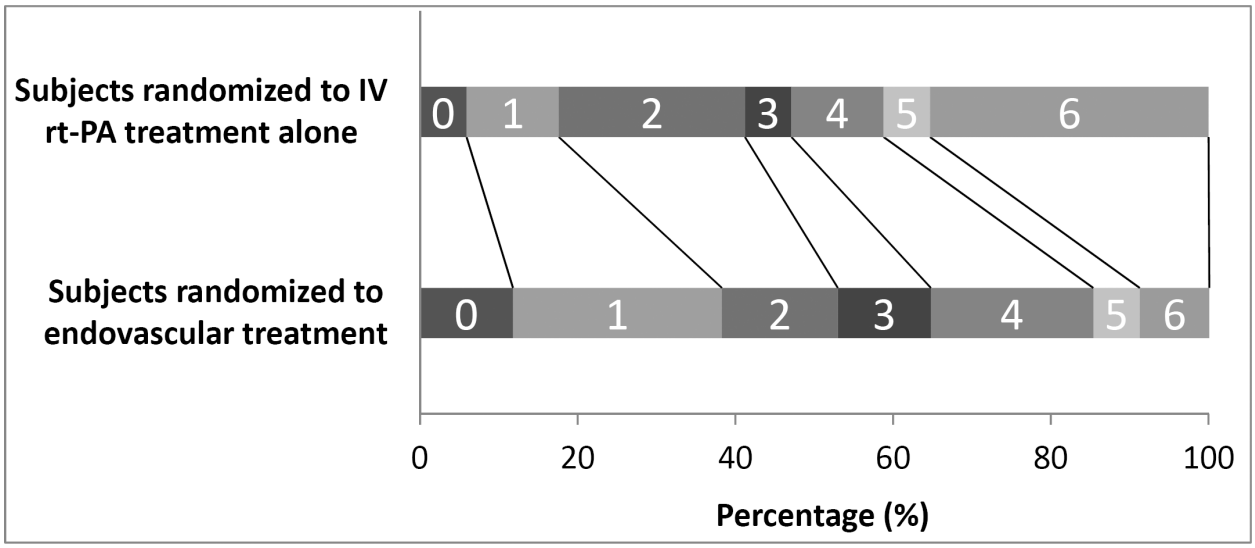

Figure 1:Distribution of the modified Rankin scale scores of the acute ischemic stroke subjects at 3 months based on the randomized treatment arm Abbreviations: IV Intravenous; rt-PA: recombinant tissue plasminogen activator

toward lower grades of mRS at three months when mRS was analyzed as an ordinal variable. There were non-significantly higher odds (adjusted OR 2.7) of achieving excellent functional outcome in subjects randomized to endovascular treatment. The analysis was underpowered to demonstrate a significant difference in rates of excellent functional outcome between subjects randomized to IV rt-PA alone compared with those randomized to endovascular treatment. If we assume that the rate of excellent functional outcome was 17.6% in patients treated with IV rt-PA alone at three months and an absolute increase in functional independence of 20.6% is expected with endovascular treatment, a total of 142 (71 in each group) patients will be required to demonstrate a difference with a beta of 80% and alpha of 0.05. The rates of good functional outcome, good quality of life, and independence in ADLs at three months were consistently higher in subjects randomized to endovascular

treatment, although none of these comparisons achieved statistical significance. The difference appeared predominantly in odds of achieving excellent functional outcome (OR 2.7) rather than good functional outcome (OR 1.1). Furthermore, a review of Figure 1 suggests that most prominent differences in the mRS distribution between the two groups were related to mRS score of 1 and 6.

The IMS III trial had very limited use of stent retrievers as these devices were not approved for use in United States during the early part of the trial. The rate of near complete or complete recanalization was 58.8% in 28 subjects who received endovascular treatment. If we include the six patients who did not have any arterial occlusion on catheter-based angiogram, the rate of near complete or complete recanalization was 76.5% in those randomized to endovascular treatment. The rates of recanalization are expected to be higher with the use of stent retrievers. Solitaire FR with the intention for thrombectomy (SWIFT) trial randomized acute ischemic stroke patients who were eligible for thrombectomy to receive thrombectomy treatment with either Solitaire stent retriever or Merci retriever device [11]. The rates of recanalization as assessed by thrombolysis in myocardial ischemia scale 2 or 3 flow in all treatable vessels without symptomatic intracranial hemorrhage were 37/55 (67%) and 48/54 (89%) in patients with M2 segment occlusion randomized to Merci retriever and Solitaire stent retriever, respectively. A pooled analysis was performed on four trials which used the Solitaire stent retriever [12], which included SWIFT PRIME, ESCAPE, EXTEND-IA, and REVASCAT. A total of 56 subjects in the pooled analysis had an occlusion of M2 segment of MCA; of those 23 and 33 were randomized to control group (includes IV rt-PA alone) and endovascular treatment. The treatment effect was in favor of endovascular treatment (OR 1.77; 95% CI; 0.55–5.65; $p = 0.18$) when mRS was analyzed as an ordinal variable. The treatment effect of endovascular treatment reported above appeared similar to the effect seen in our post hoc analysis of M2 segment occlusions comparing mRS as ordinal variable (OR 2.6) despite all subjects in control group had received and benefited from IV rt-PA administration in IMS III trial unlike the pooled analysis mentioned above.

The analysis provides estimates of magnitude and characteristics of differences between acute ischemic stroke subjects with M2 segment occlusion who are randomized to endovascular treatment and those to IV rt-PA. There are some limitations that need to be considered prior to interpretation of the analysis in addition to the limitations posed by small sample size and limited use of stent retrievers during endovascular treatment. Although the study was randomized, the randomization process was not stratified by presence of M2 segment occlusion. Therefore, there may unmeasured differences in regards to prognostic variables between the two groups. The practical implications of the current data require some consideration, particularly whether the trend toward benefit seen with endovascular treatment is considered adequate to consider endovascular treatment in all acute ischemic stroke patients with M2 segment occlusions. An alternate approach may be to exclude patients in whom endovascular treatment is expected to be complex such as those with severe aortic tortuosity and calcification, severe peripheral arterial disease, or M2 segments with morphological characteristics prone to procedural complications on a case by case decision [13]. Another approach may require a randomized clinical trial comparing endovascular treatment with best medical treatment in acute ischemic stroke patients with M2 segment occlusions on CT angiography.

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