Supplemental Online Content

Zi W, Qui Z, Li F, et al. Effect of endovascular treatment alone versus intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.23523

This supplemental material has been provided by the authors to give readers additional information about their work.

CONSORT checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	10-12
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	13-14
	2b	Specific objectives or hypotheses	14
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	14, 16
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Summary of Changes of protocol, page 66-68 in Supplement 2
Participants	4a	Eligibility criteria for participants	15
	4b	Settings and locations where the data were collected	15
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	16-17
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	17-19
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Page 66 in the Summary of Changes of trial protocol (Supplement 2)
Sample size	7a	How sample size was determined	19-20

Section/Topic	Item No	Checklist item	Reported on page No
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Page 5-6 in the Statistical Analysis Plan (Supplement 3)
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	16
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	16
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	16
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	16
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Page 7 in the Statistical Analysis Plan (Supplement 3)
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	20
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	20-21
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	22 and Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	22 and Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	22
	14b	Why the trial ended or was stopped	21-22
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	40-42

Section/Topic	Item No	Checklist item	Reported on page No
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	22-24
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	43-45
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	43-45
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	eFigure 6, eFigure 7, eTable 3, eTable 4, and eTable 5 in Supplement 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	46-48
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	28-30
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	30
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	30
Other information			
Registration	23	Registration number and name of trial registry	12
Protocol	24	Where the full trial protocol can be accessed, if available	Supplement 2 Or DOI: 10.1177/1747493020925349
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	32

4. eMethods

4.1. eMethod 1. Inclusion and exclusion criteria

4.1.1. Inclusion criteria

(1) Aged 18 years or older;
(2) Presenting with acute ischemic stroke symptom within 4.5 hours;
(3) Eligible for intravenous alteplase;
(4) Occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery confirmed by CT or MR angiography;
(5) Randomization no later than 4 hours 15 minutes after stroke symptom onset. Time of stroke onset was defined as time last known well;
(6) Informed consent obtained from patients or their legal representatives.

4.1.2. Exclusion criteria

(1) CT or MR evidence of hemorrhage (the presence of micro-bleeds is allowed);
(2) Contraindications of intravenous alteplase;
(3) Pre-morbidity with a modified Rankin scale score of 0 to 2;
(4) Currently in pregnant or lactating or serum beta HCG test is positive on admission;
(5) Contraindication to radiographic contrast agents, nickel, titanium metals or their alloys;
(6) Arterial tortuosity and/or other arterial disease that would prevent the device from reaching the target vessel;
(7) Patients with a preexisting neurological or psychiatric disease that would confound the neurological functional evaluations;
(8) Patients with occlusions in multiple vascular territories (e.g. bilateral anterior circulation, or anterior/posterior circulation);
(9) CT or MR evidence of mass effect or intracranial tumor (except small meningioma);
(10) CT or MR evidence of cerebral vasculitis;
(11) CT or MR angiography evidence of intracranial arteriovenous malformations or aneurysms;
(12) Any terminal illness with life expectancy less than 6 months;
(13) Unlikely to be available for 90-day follow-up;
(14) Current participation in another clinical trial.

4.2 eMethod 2. Early termination of the trial

The first interim analysis of DEVT was scheduled to occur after 194 patients had completed their 90-day clinical outcome. After the publication of the positive findings of the DIRECT-MT study[1] on May 7th, 2020, DEVT had enrolled 235 patients but had not yet arrived at 194 patients with completed 90-day outcomes (the scheduled endpoint for our interim analysis).

The steering committee made a decision to stop enrollment into the trial. After consultation with the Data and Safety Monitoring Board chairman (Dr. Anding Xu, The First Affiliated Hospital of Jinan University, Guangzhou, China) our interim analysis plan was accelerated by several weeks. Thus, the interim analysis was completed on 194 patients with completed 90-day outcomes on May 12th, 2020. The interim analysis was performed according to all prespecified criteria. For details, see Figure S2 in this file. At this point the Data and Safety Monitoring Board recommended to the Steering Committee early stopping of trial enrollment for efficacy. The last patient who completed 90-day follow-up on July 22th, 2020.

4.3. eMethod 3. Assessment of modified Rankin scale score at 90 days

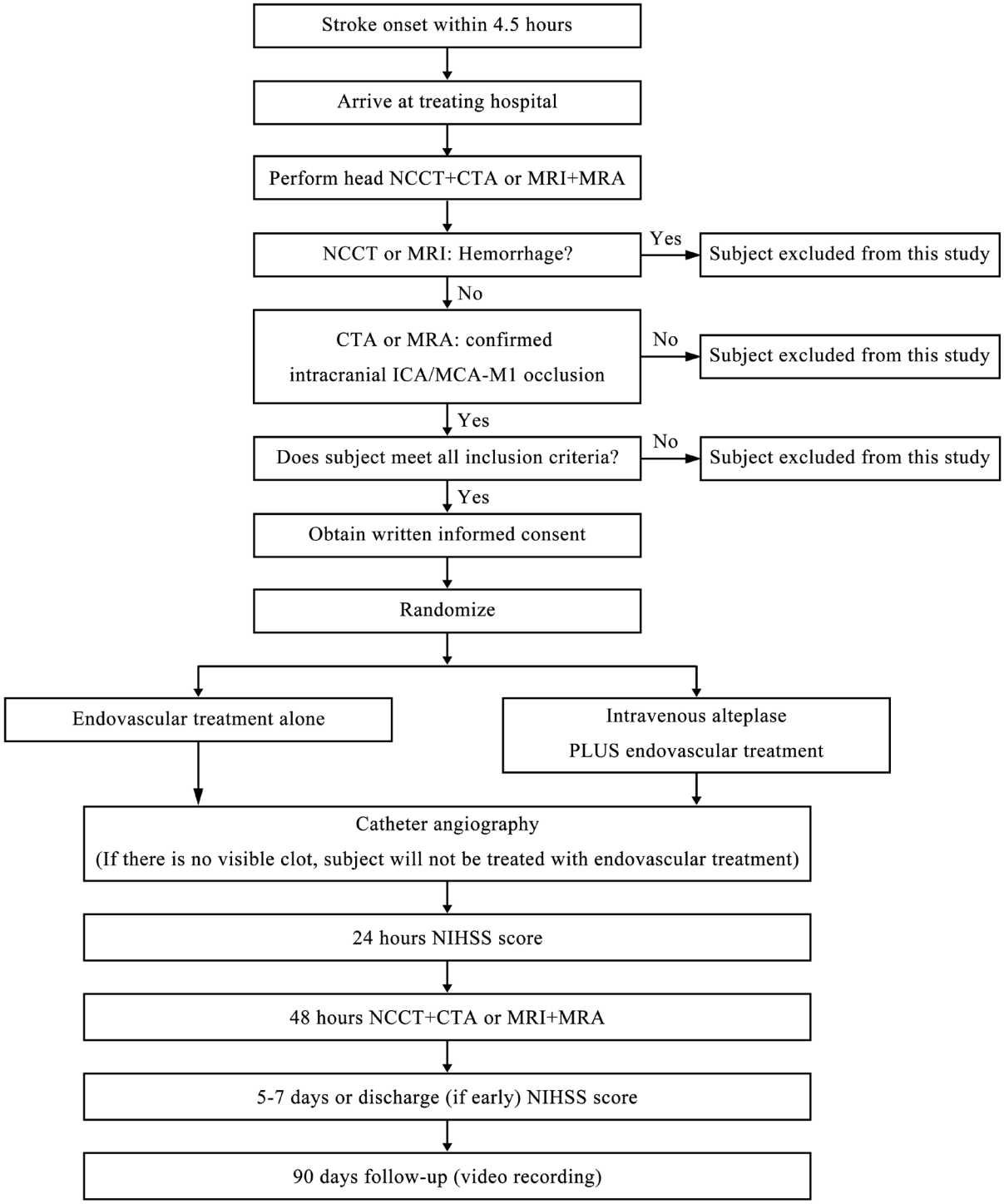
At the 90 days follow-up visits, a local neurologist who was unaware of group assignment recorded the modified Rankin scale score in a face to face structured clinical interview and recorded the interview using a portable camera or voice recorder (in case patient who was unwilling to take video recording). The primary functional outcome was centrally assessed by two independent certified neurologists in a blinded manner by the use of the video or voice recording. Disagreements were resolved by consensus. Electronic Data Capture System did not reveal the group assignment and patients were instructed not to reveal any relevant information that could potentially lead to disclosing their treatment group to the assessors. If video or voice recording is not available, the outcomes determined by the local investigator blindly in person are used as default. It was prespecified that the missing modified Rankin scale scores at 90 days were assumed the worst possible score. If the patient was identified to be alive, we imputed a modified Rankin scale score of 5. Otherwise, we imputed a score of 6.

4.4. eMethod 4. Investigator training

The initiation meeting of the DEVT trial was held in Chongqing on April 21, 2018. The training of DEVT protocol, including the patient selection criteria, periprocedural clinical and imaging assessment, endovascular treatment technique, and the requirement of follow-up at 90 days, were conducted immediately after the initiation meeting. To speed up the enrollment progress, the steering committee recruited 6 more stroke centers and held a program training meeting in Beijing on June 30, 2018. In order to improve the endovascular treatment technique of investigators and ensure the quality of the trial, the training of study protocol and endovascular treatment technique and project promotion meeting was held once about every six months in Chongqing.

5. eFigures

5.1. eFigure 1. Overview of the DEVT trial

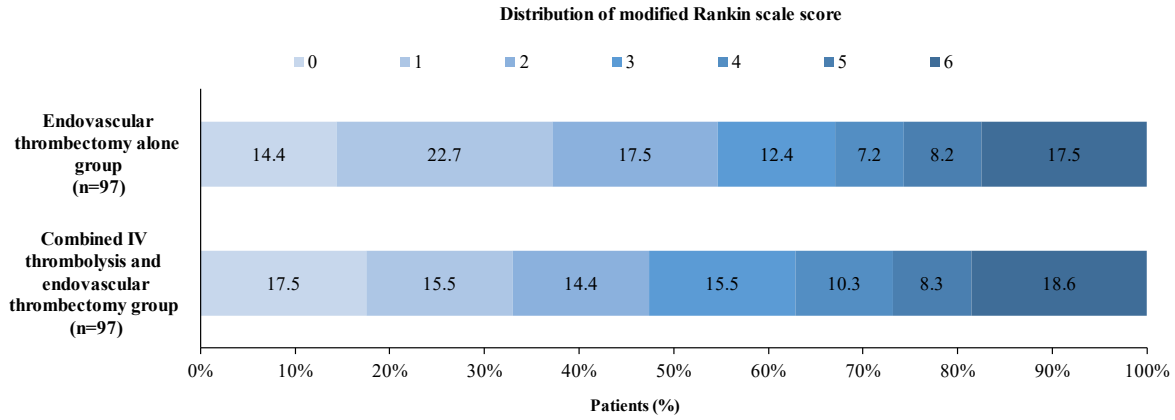


MRI denotes magnetic resonance imaging, NCCT non-contrast computed tomography.

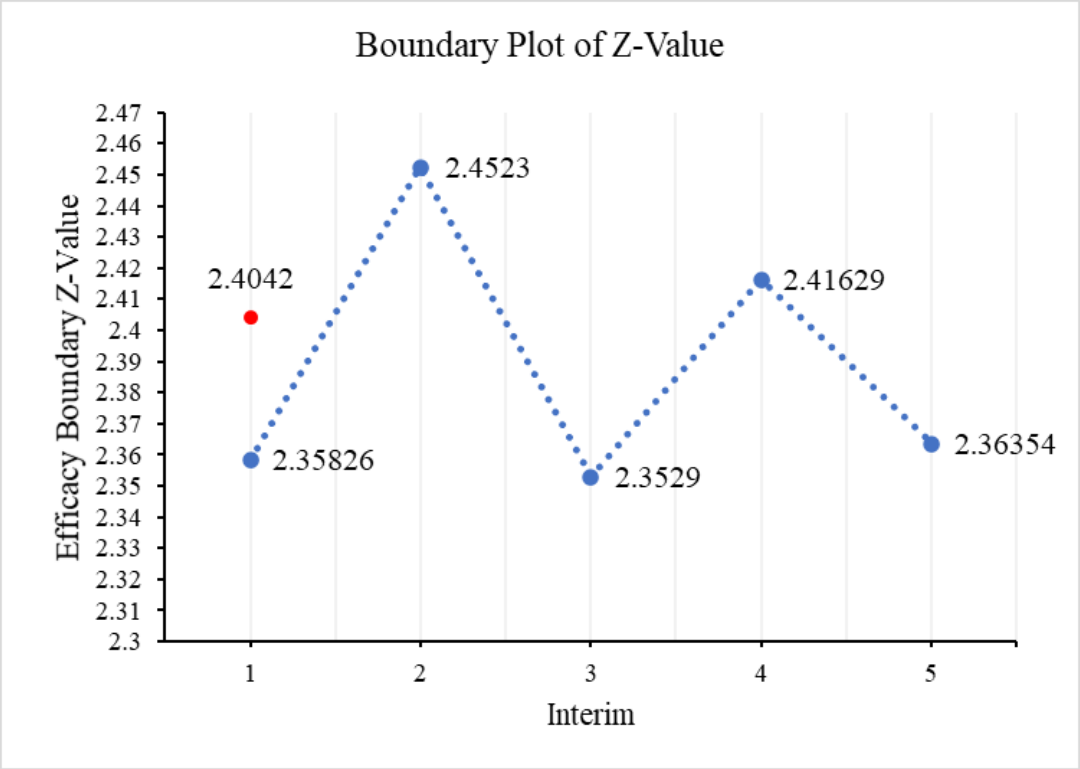
5.2. eFigure 2. Analysis of the primary outcome in the first interim analysis (n=194) used by the DSMB to take the decision to stop the trial

Distribution of the modified Rankin scale scores at 90 days was shown in eFigure2A. First interim analysis according to central evaluation through video (152 evaluations), voice (6 evaluations) recording or local investigators as default (1 evaluation); thirty-five patients died before 90 days.

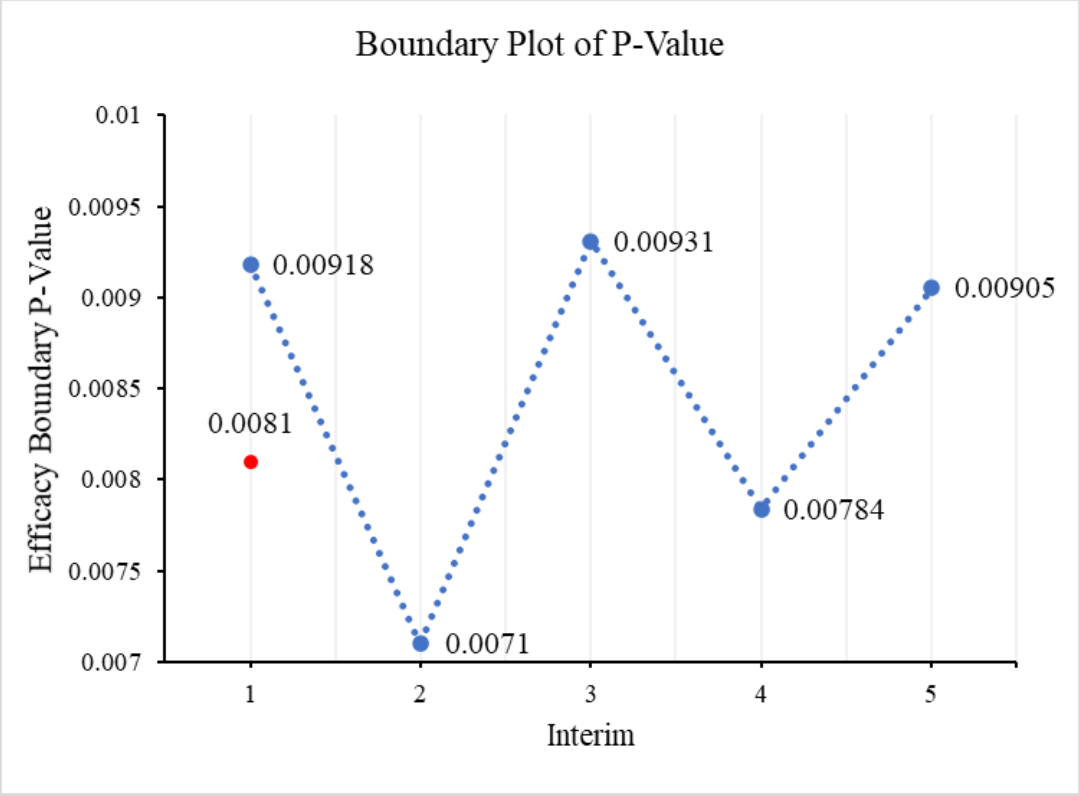
Efficacy Boundary Z-Value and P-Value Scale are the values such that statistics and P-Value outside this boundary at the corresponding interim indicate termination of the study and rejection of the null hypothesis, respectively. The proportion of functional independence for the endovascular thrombectomy alone group (54.64%) exceeded that of the combined IV thrombolysis and endovascular thrombectomy group (47.42%) by 7.2% (1-sided 97.5% CI, -6.8% to ∞). The non-inferiority test results demonstrated that the endovascular thrombectomy alone group was not inferior to the combined IV thrombolysis and endovascular thrombectomy group (Z=2.4042, $P_{non\text{-}inferiority}$=0.0081), which had crossed the efficacy boundary (Z=2.35826, $P_{non\text{-}inferiority}$=0.00918) that was prespecified for early termination (eFigure 2B~C).



eFigure 2A



eFigure 2B

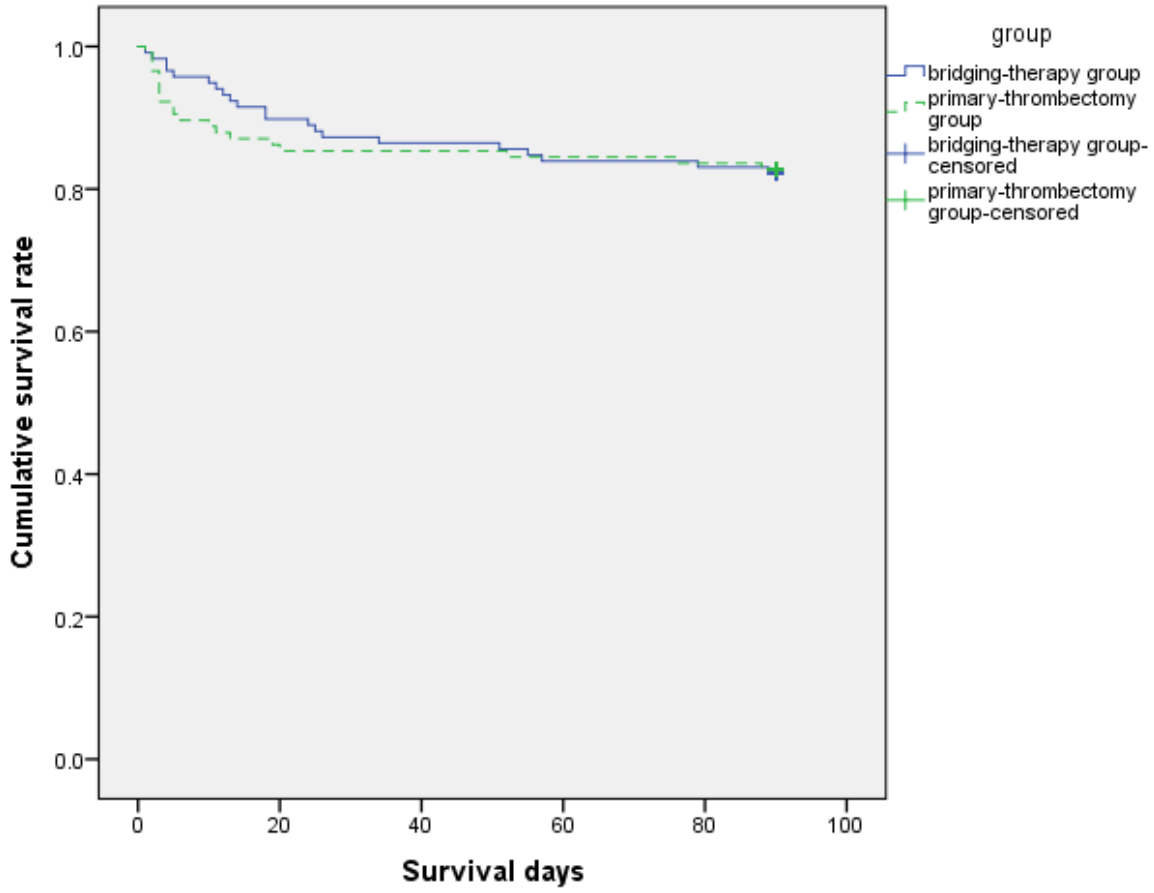


eFigure 2C

5.3. eFigure 3. Distribution of participating centers on the map of China

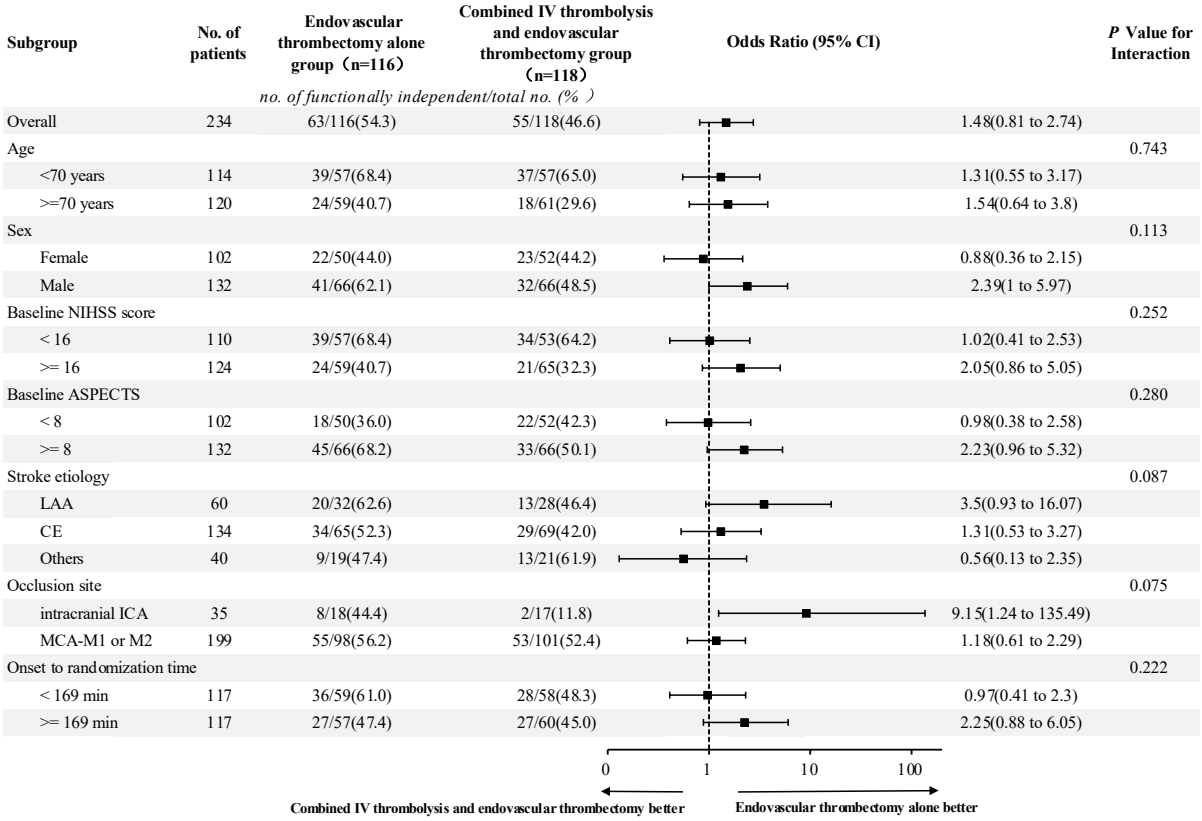
5.4. eFigure 4. Number of patients recruited by each center.

5.5. eFigure 5. Kaplan-Meier estimates of the probability of death in patients



Log-Rank test: P = 0.998

5.6. eFigure 6. Analysis of functional independence at 90 days in prespecified subgroups.



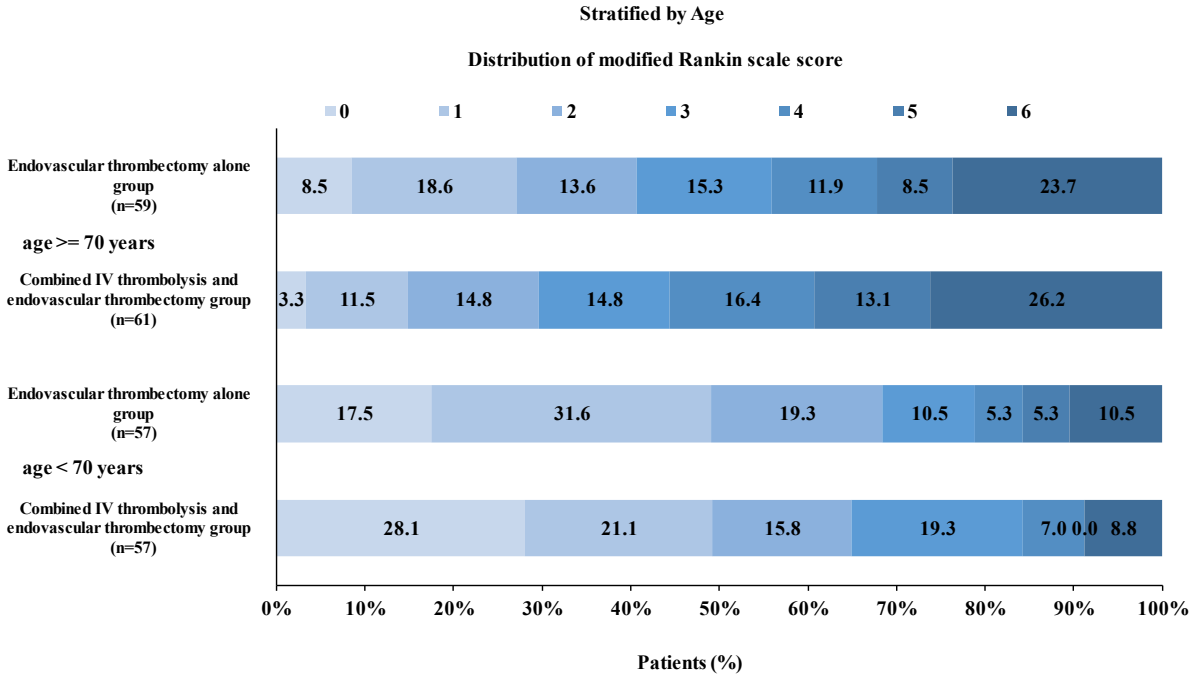
This forest plot shows that there was no evidence of heterogeneity of treatment effect across in most prespecified subgroups. The odds ratio was calculated by using logistic regression taking the following variables into account: age, baseline NIHSS score, baseline ASPECTS, occlusion site, and time from onset to randomization. Time of stroke onset was defined as time last known well. The thresholds for age, baseline NIHSS score, baseline ASPECTS, and onset to randomization time were chosen at the median. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core. CE denotes cardioembolism, CI confidence interval, ICA internal carotid artery, LAA large artery atherosclerosis, MCA-M1 or M2 the first or second segment of middle cerebral artery.

5.7. eFigure 7. Distribution of modified Rankin scale scores at 90 days in prespecified subgroups

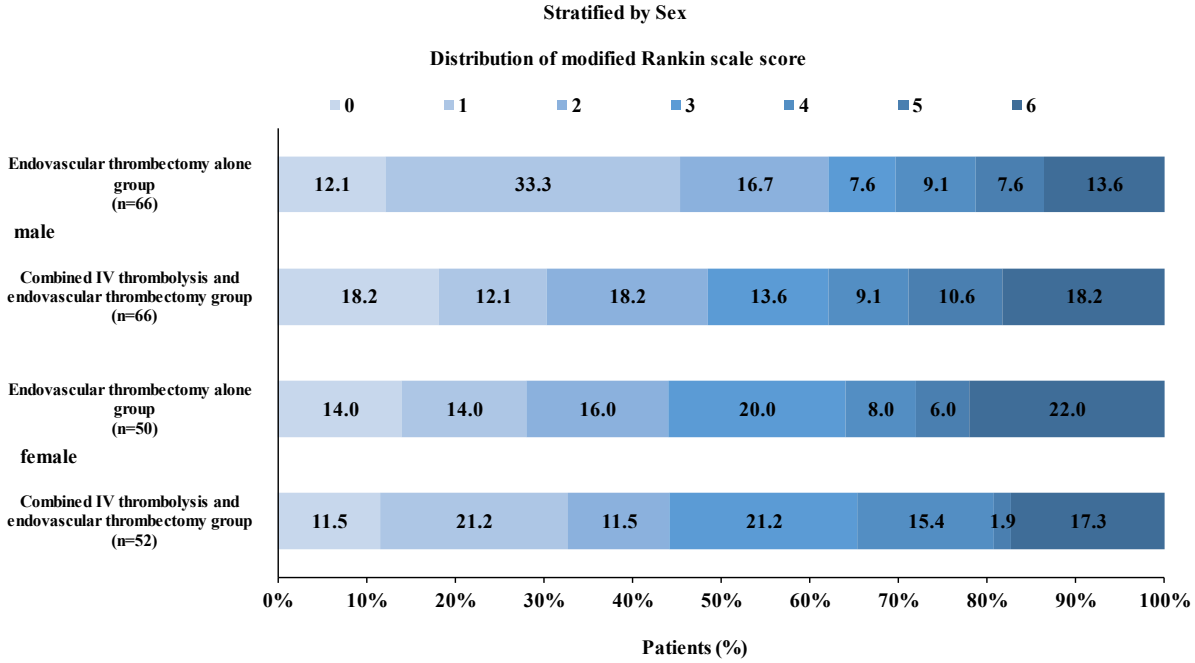
These figures show the distribution of modified Rankin scale score at 90 days among the 7 prespecified subgroups. These groups and cut-points are:

- age (< 70 or ≥ 70 years)
- sex (female or male)
- baseline NIHSS score (< 16 or ≥ 16)
- baseline ASPECTS (< 8 or ≥ 8)
- stroke etiology (large artery atherosclerosis, cardioembolism, or others)
- occlusion site (intracranial internal carotid artery or not)
- onset to randomization time (< 169 or ≥ 169 minutes)

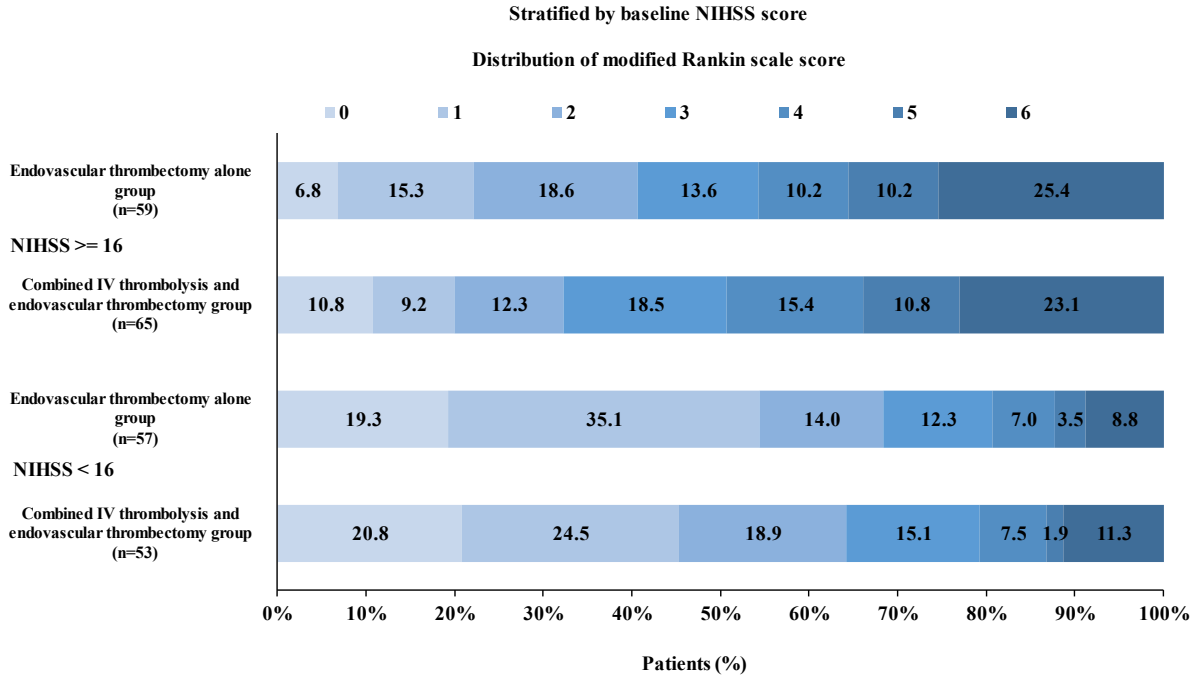
eFigure 7A: Distribution of modified Rankin scores at 90 days in the two groups in patients stratified by age. There is no evidence of heterogeneity of treatment effect between these subgroups ($P_{interaction}$=0.29, Breslow-Day test).



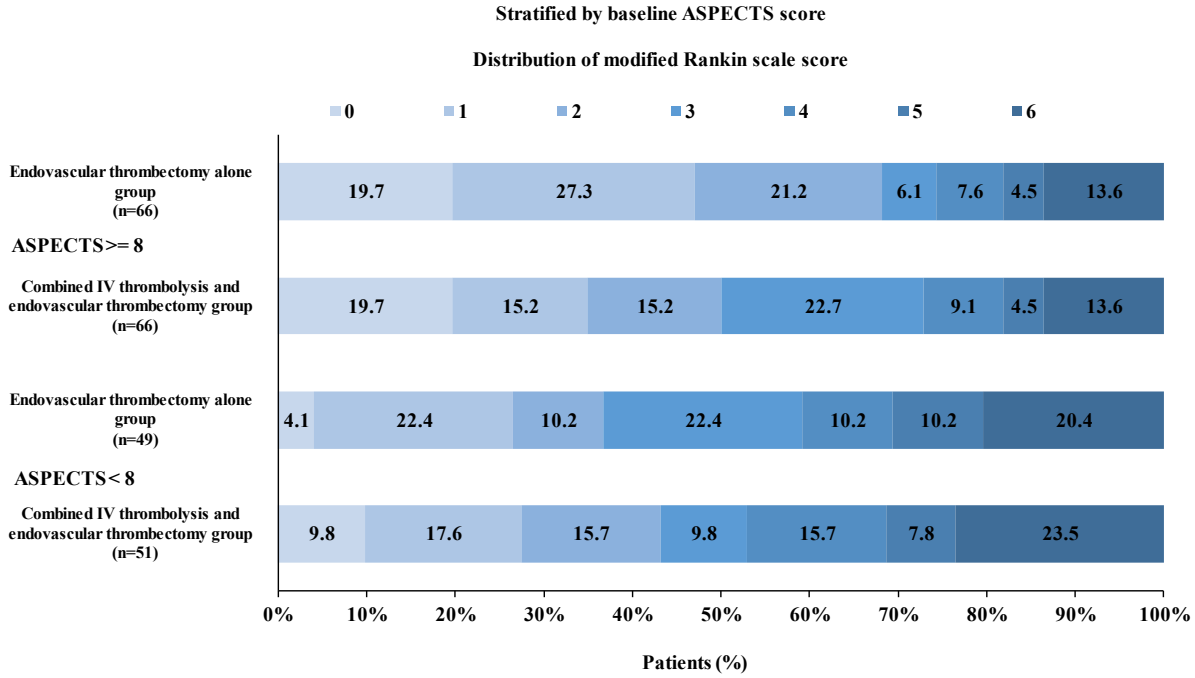
eFigure 7B: Distribution of modified Rankin scores at 90 days in the two groups in patients stratified by sex. There is no evidence of heterogeneity of treatment effect between these subgroups ($P_{interaction}$=0.14, Breslow-Day test).



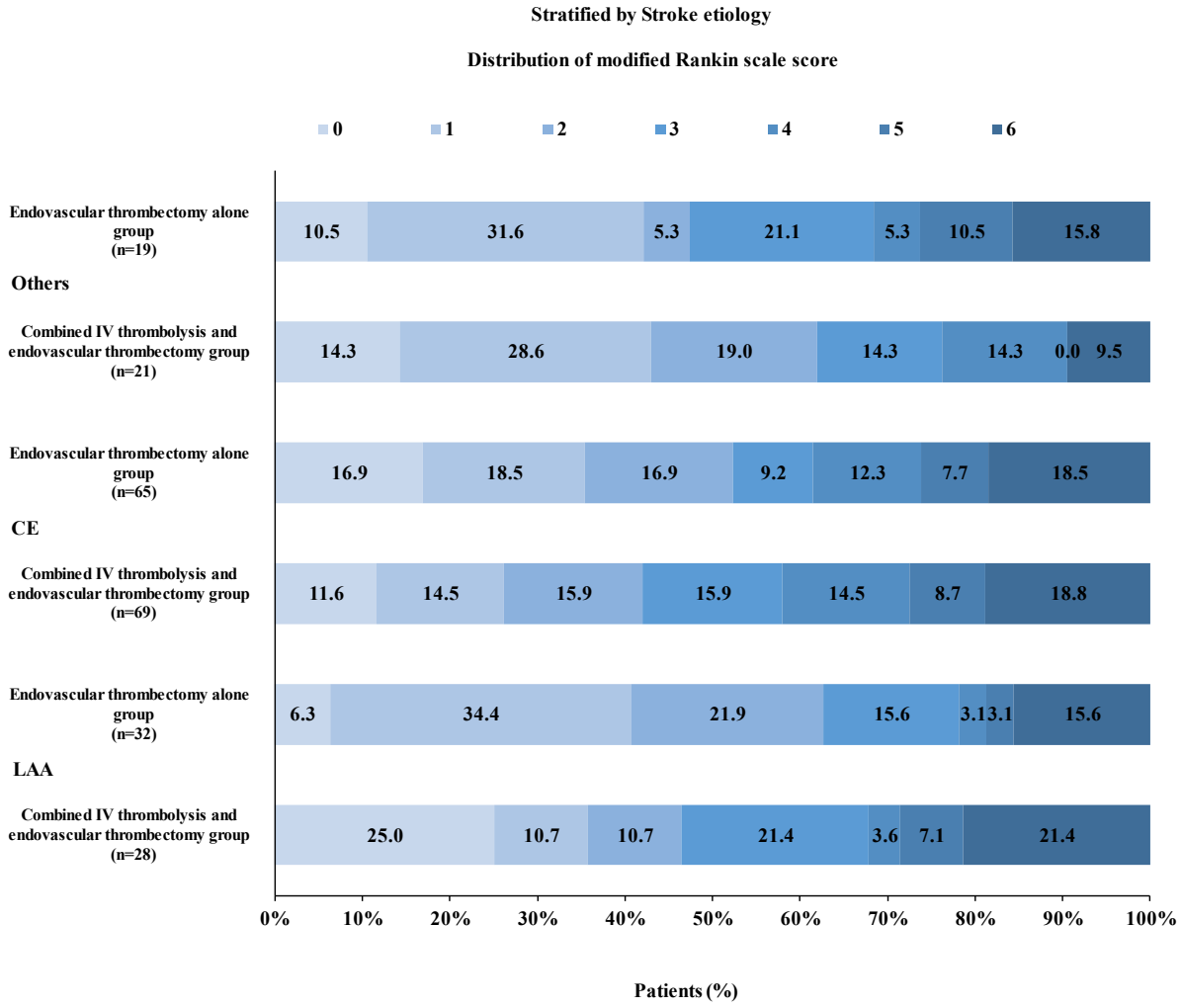
eFigure 7C: Distribution of modified Rankin scores at 90 days in the two groups in patients stratified by baseline NIHSS score. There is no evidence of heterogeneity of treatment effect between these subgroups ($P_{interaction}$=0.91, Breslow-Day test).



eFigure 7D: Distribution of modified Rankin scores at 90 days in the two groups in patients stratified by baseline ASPECTS. There is no evidence of heterogeneity of treatment effect between these subgroups ($P_{interaction}$=0.09, Breslow-Day test).

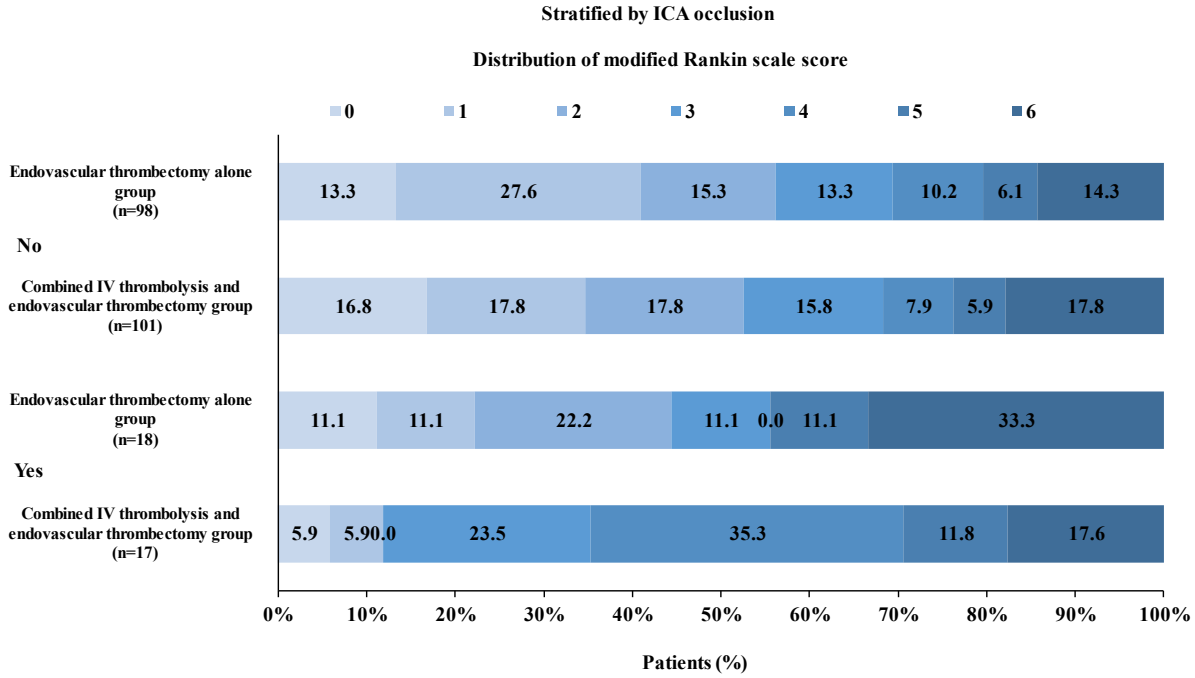


eFigure 7E: Distribution of modified Rankin scores at 90 days in the two groups in patients stratified by stroke etiology. There is no evidence of heterogeneity of treatment effect between these subgroups ($P_{interaction}$=0.82, Breslow-Day test).



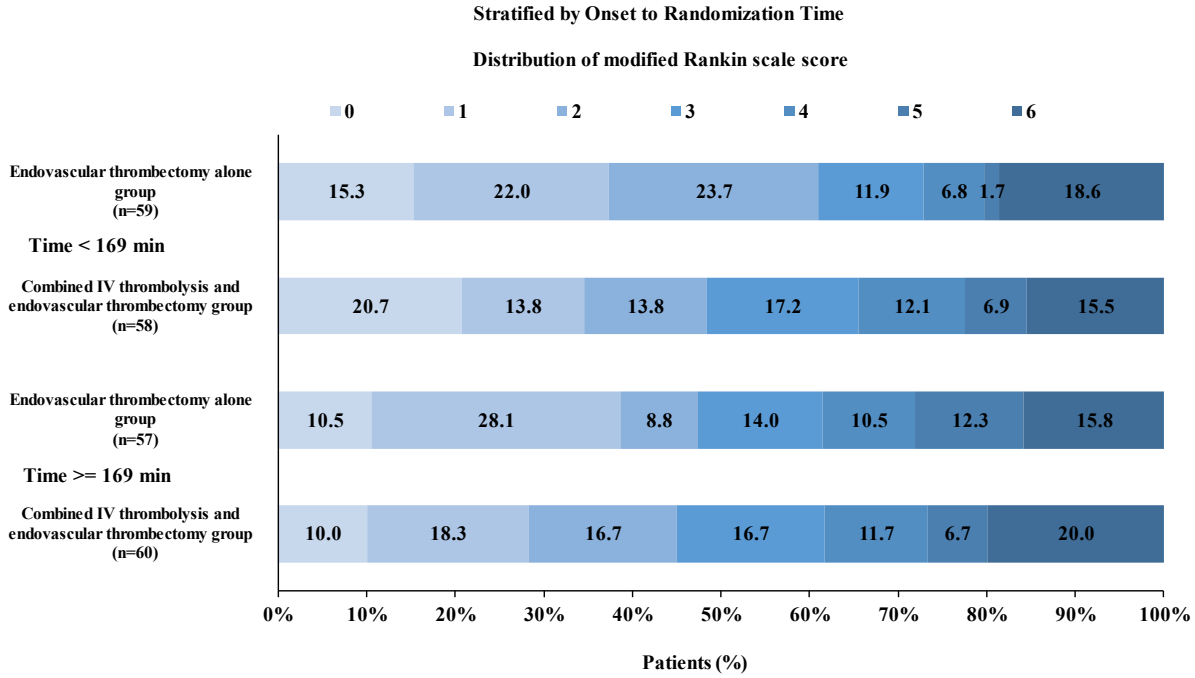
Others type contained stroke of undetermined cause and stroke of other determined cause.
LAA denotes large artery atherosclerosis, CE cardioembolism.

eFigure 7F: Distribution of modified Rankin scores at 90 days in the two groups in patients stratified by occlusion site (intracranial internal carotid artery occlusion or not). There is no evidence of heterogeneity of treatment effect between these subgroups ($P_{interaction}$=0.06, Breslow-Day test).



ICA denotes internal carotid artery.

eFigure 7G: Distribution of modified Rankin scores at 90 days in the two groups in patients stratified by onset to randomization time. There is no evidence of heterogeneity of treatment effect between these subgroups ($P_{interaction}$=0.34, Breslow-Day test).



6. eTables

6.1. eTable 1. Additional baseline characteristics

	Endovascular thrombectomy alone group (N=116)	Combined IV thrombolysis and endovascular thrombectomy group (N=118)
Coronary heart disease - no./total no. (%)	30 (25.9)	19(16.1)
Smoking - no./total no. (%)	28 (24.1)	29(24.6)
Median platelet count in blood routine test (IQR), 10^9/L[a]	185(146-224)	180(148-217)
Median international normalized ratio (IQR) [b]	1.00(0.95-1.11)	1.02(0.95-1.10)
Location of stroke in right hemisphere - no./total no. (%)	58 (50.0)	61 (51.7)
Location of the atherosclerotic lesion - no./total no. (%)		
Intracranial	28 (24.1)	23 (19.5)
Extracranial	4 (3.4)	5 (4.2)
Collateral status, no./total no. (%) [c]		
ASITN/SIR grade 0	14/116(12.1)	8/118(6.8)
ASITN/SIR grade 1	24/116(20.7)	28/118(23.7)
ASITN/SIR grade 2	47/116(40.5)	48/118(40.7)
ASITN/SIR grade 3	31/116(26.7)	34/118(28.8)
ASITN/SIR grade 4	0	0

IQR denotes interquartile range, and ASITN/SIR American Society of Interventional and Therapeutic Neuroradiology / Society of Interventional Radiology.

[a] Data were missing for 5 patients (3 in the endovascular thrombectomy alone group and 2 in the combined IV thrombolysis and endovascular thrombectomy group).

[b] Data were missing for 6 patients (3 in the endovascular thrombectomy alone group and 3 in the combined IV thrombolysis and endovascular thrombectomy group).

[c] The ASITN/SIR collateral flow grading system is a 5-point scale: with 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 the 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 late venous phase; and 4=complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion.

6.2. eTable 2. Additional workflow metrics and procedural characteristics

	Endovascular thrombectomy alone group (N=116)	Combined IV thrombolysis and endovascular thrombectomy group (N=118)
Workflow times		
Onset to hospital arrival[a]	90 (57-126)	100 (60-135)
Hospital arrival to imaging	22 (16-32)	25 (15-32)
Imaging to randomization	38 (27-56)	33 (25-60))
Onset to reperfusion[a]	289 (231-329)	285 (239-342)
Onset to start of intravenous alteplase[a]	NA	176 (153-225)
Imaging to start of intravenous alteplase	NA	40 (34-68)
Randomization to start of intravenous alteplase	NA	7 (5-10)
Randomization to groin puncture	32 (17-50)	34 (20-53)
Randomization to reperfusion or procedure completion[b]	111 (84-150)	106 (75-154)
Groin puncture to reperfusion or procedure completion[b]	72 (45-113)	68 (43-107)
Hospital arrival to start of intravenous alteplase, no./total no. (%)		
0-90 min	NA	99 (83.9)
90-180 min	NA	18 (15.3)
180-270 min	NA	1 (0.8)
Total number of stent retriever passes (Median IQR)	1 (1-2)	1 (0-2)
Total number of aspiration device passes (Median IQR)	0 (0-1)	0 (0-1)
Procedures performed with stent-retriever only - no./total no. (%)	61 (52.6)	57 (48.3)
Procedures performed with local aspiration only - no./total no. (%)	17 (14.7)	18 (15.3)
Procedures performed with stent-retriever and local aspiration - no./total no. (%)	17 (14.7)	16 (13.6)
Procedures performed with neither stent-retriever nor local aspiration - no./total no. (%)	7 (6)	11 (9.3)
Intraarterial thrombolysis - no./total no. (%)		
Alteplase	2 (1.7)	5/116 (4.2)
Urokinase	3 (2.6)	1 (0.8)
Intraarterial tirofiban - no./total no. (%)	19 (16.4)	15 (12.7)
Extracranial stenting - no./total no. (%)	0 (0.0)	1 (0.8)
First pass effect - no./total no. (%)	51(44.0)	51 (43.2)
Rescue therapy - no./total no. (%)	31(26.7)	33 (28.0)

Balloon guide catheter - no./total no. (%)	1(0.9)	1 (0.8)
eTICI Grade, no./total no. (%)[c]		
0	1/113 (0.9)	3/117 (2.6)
1	0	2/117 (1.7)
2a	12/113 (10.6)	10/117 (8.6)
2b	35/113 (31.0)	31/117 (26.5)
2c	21/113 (18.6)	21/117 (17.9)
3	44/113 (38.9)	50/117 (42.7)

[a] Time of stroke onset was defined as time last known well.

[b] Revascularization was defined as the first visualization of successful reperfusion, as indicated by an extended Thrombolysis in Cerebral Infarction (eTICI) score of 2b, 2c, or 3 (on a scale from 0 [no reperfusion] to 3 [complete reperfusion]). End of time interval is time of first visualization of successful reperfusion (eTICI 2b-3) in patients with reperfusion and time of the last contrast bolus in patients without reperfusion (eTICI 0-2a).

[c] The eTICI reperfusion grading system is a 6-point scale: with 0 = no reperfusion noted; 1 = reduction in thrombus without filling of distal arterial branches, 2a = reperfusion of < 50% of the territory, 2b = a reperfusion of ≥ 50% of the territory, 2c = near-complete perfusion with distal slow flow or presence of small cortical emboli, and 3 is a complete reperfusion.3 Data were missing for 4 patients (3 in the endovascular thrombectomy alone group and 1 in the combined IV thrombolysis and endovascular thrombectomy group).

6.3. eTable 3. Primary and secondary outcomes in per-protocol analysis

	Endovascular thrombectomy alone group (N=111)	Combined IV thrombolysis and endovascular thrombectomy group (N=113)	Unadjusted Difference (95% CI)	Adjusted Odds Ratios (95% CI) [b]
Primary efficacy outcome [a]				
Functional independence (mRS 0-2) at 90 days - no./total no. (%)	59 (53.2)	52 (46.0)	7.1 (-5.9 to ∞)[a]	1.49(0.80-2.80)
Secondary efficacy outcomes				
Excellent outcome (mRS 0-1) at 90 days - no./total no. (%)	43 (38.7)	35 (31.0)	7.8 (-4.7 to 20.2)	1.55(0.82-2.94)
Disability level (median mRS score) at 90 days (IQR)	2(1-5)	3(1-4)	0 (-1 to 0)	1.15(0.72-1.84) [c]
eTICI level of 2b, 2c or 3 at final angiogram - no./total no. (%)[d]	95/108(88.0)	97/112(86.6)	1.4 (-7.4 to 10.2)	1.15(0.51-2.64)
Reperfusion on follow-up CTA or MRA within 48 hours - no./total no. (%)[e]	91/94(96.8)	89/96(92.7)	4.1 (-2.2 to 10.4)	2.41(0.64-11.55)
				Adjusted Beta Coefficient (95% CI) [f]
Median NIHSS score change from baseline at 24 hours (IQR)[g]	-4(-9 to 0)	-3(-6 to -1)	-1(-2 to 1)	-0.38(-2.24 to 1.48)
Median NIHSS score change from baseline at 5~7 days or early discharge (IQR)[g]	-7(-11 to -0)	-6(-10 to -2)	0(-2 to 2)	0.88(-1.97 to 3.72)
Median EQ-5D-5L scale score at 90 days (IQR)[h]	0.89(0.19-1.00)	0.91(0.62-1.00)	0(0 to 0.05)	0.03(-0.05 to 0.12)

Patients achieved successful reperfusion before intervention assessed on initial digital substraction angiography (n=5, 2 in the endovascular thrombectomy alone group and 3 in the combined IV thrombolysis and endovascular thrombectomy group), and patients with occlusion in the second segment of middle cerebral artery (n=5, 3 in the endovascular thrombectomy alone group and 2 in the combined IV thrombolysis and endovascular thrombectomy group) had been removed from the per-protocol analysis.

ASPECTS denotes Alberta Stroke Program Early CT Score, CI confidence interval, CTA computed tomography angiography, EQ-5D-5L European Quality of Life Five-Dimension Five-Level Self-Report Questionnaire, MRA magnetic resonance angiography, NA not applicable, and NIHSS National Institutes of Health Stroke Scale.

[a] The confidence interval non-inferiority approach was used for the analysis of primary efficacy outcome. The absolute difference between the two groups was 0.071 (1-sided 97.5% CI, -0.059 to ∞). The lower boundary of 97.5% confidence interval was -0.059, and was greater than the non-inferiority margin -0.10 as prespecified. In addition, the non-inferiority test demonstrated that Z value and P value was 2.5711 and 0.0051, respectively, which had crossed the first-interim efficacy boundaries (Z-value Scale=2.3526, P-Value Scale=0.00918). Therefore, it could be concluded that endovascular treatment alone is non-inferior to intravenous alteplase plus endovascular treatment and the trial could be terminated early.

[b] Values were adjusted for age, baseline NIHSS score, baseline ASPECTS, occlusion site, and time from Onset to randomization, as prespecified in the protocol and statistical analysis plan.

[c] Common odds ratio: the analysis involved 116 patients in endovascular thrombectomy alone group and 118 patients in combined IV thrombolysis and endovascular thrombectomy group. The common odds ratio was estimated from an ordinal logistic regression model and indicates the odds of improvement of 1 point on the mRS, with a common odds ratio greater than 1 favoring the endovascular thrombectomy treatment alone.

[d] The eTICI grade was determined at the final angiogram and ranged from 0 (no reperfusion) to 6 (completed reperfusion). An eTICI of 2b-3 indicates successful reperfusion. Four data were missing (3 in the endovascular thrombectomy alone group and 1 in the combined IV thrombolysis and endovascular thrombectomy group). A complete list of eTICI grade was provided in eTable 2 in the Supplement.

[e] Data for follow-up CTA or MRA were not available for 23 patients (12 in the endovascular thrombectomy alone group and 11 in the combined IV thrombolysis and endovascular thrombectomy group). 11 patients failed in reperfusion (5 in the endovascular thrombectomy alone group and 6 in the combined IV thrombolysis and endovascular thrombectomy group). Vessel patency was adjudicated by two blinded independent neuro-radiologists in imaging core laboratory. Disagreements were resolved through consensus.

[f] The Beta coefficient was estimated from a multivariable linear regression model.

[g] Scores on NIHSS range from 0 to 42, with less scores indicating less severe neurologic deficits.

[h] Scores on the EQ-5D-5L range from -0.39 (where 0 is the value of a health state equivalent to dead; negative values representing values as worse than dead) to 1 (full health), with higher scores indicating a better quality of life.

6.4. eTable 4. Safety outcomes in per-protocol analysis

	Endovascular thrombectomy alone group (N=111)	Combined IV thrombolysis and endovascular thrombectomy group (N=113)
Severe adverse events - no./total no. (%)		
Mortality at 90 days	20 (18.0)	20 (17.7)
All intracranial hemorrhage[a]		
Symptomatic intracerebral hemorrhage	7/110(6.4)	7/112(6.3)
Asymptomatic intracranial hemorrhage	18/110(16.4)	29/112(25.9)
Other adjudicated severe adverse events within 90 days - no./total no. (%)		
Large or malignant middle cerebral artery stroke	13 (11.7)	9(8.0)
Hemicraniectomy[b]	3(2.7)	5(4.4)
Acute respiratory failure	14(12.6)	12(10.6)
Acute heart failure	12(10.8)	9(8.0)
Procedure associated complications - no./total no. (%)[c]		
Arterial perforation	2(1.8)	6(5.3)
Arterial dissection[d]	0/108(0)	1/112(0.9)
Clot migration [d]	20/108(18.5)	28/112(25.0)
Distal occlusion(s) present at procedure end[e]	19/108(17.6)	21/112(18.8)
Contrast extravasation[f]	16/110(14.5)	17/112(15.2)
Puncture access complications		
Groin hematoma	1(0.9)	1(0.9)
Groin pseudoaneurysm	1(0.9)	5(4.4)

[a] Symptomatic intracerebral hemorrhage was assessed by a clinical events committee according to the Heidelberg criteria.4 Data were not available for 2 patients (1 in the endovascular thrombectomy alone group and 1 in the combined IV thrombolysis and endovascular thrombectomy group).

[b] The indication of hemicraniectomy procedure was large or malignant middle cerebral artery stroke.

[c] All procedural-associated complications were reported by the clinical events committee.

[d] Data were not available for 4 patients (3 in the endovascular thrombectomy alone group and 1 in the combined IV thrombolysis and endovascular thrombectomy group).

[e] This item was defined as after Reperfusion of the primary occlusion site, any vessel occlusions distal from the primary occlusion site were considered emboli due to periprocedural thrombus fragmentation. Data were not available for 4 patients (3 in the endovascular thrombectomy alone group and 1 in the combined IV thrombolysis and endovascular thrombectomy group).

[f] Data for follow-up computed tomography or magnetic resonance were not available for 2 patients (1 in the endovascular thrombectomy alone group and 1 in the combined IV thrombolysis and endovascular thrombectomy group).

6.5. eTable 5. The hierarchical modeling and sensitivity analyses for assessment of site effects (post hoc analysis)

eTable 5-A. The hierarchical modeling analysis for site effects (post hoc analysis)

Parameter	Wald Chi-Square	Pr > ChiSq	Estimate	95% Confidence Limits of Estimate	
Intercept	2.2766	0.1313	2.4788	-0.7411	5.6987
group	0.6291	0.4277	0.3694	-0.5434	1.2822
group*affiliation	0.0039	0.9503	0.00250	-0.0761	0.0811
affiliation	0.7616	0.3828	0.0242	-0.0301	0.0785
age	11.4139	0.0007	-0.0491	-0.0776	-0.0206
Baseline NIHSS	22.6831	<.0001	-0.1803	-0.2546	-0.1061
Baseline ASPECTS	6.5452	0.0105	0.2119	0.0496	0.3742
Occlusion site	3.3123	0.0688	0.7579	-0.0583	1.5741
Time from onset to randomization	0.3565	0.5504	0.00192	-0.00439	0.00824

eTable 5-B. The sensitivity analysis for site effects after eliminating the affiliation with the largest number of enrolled patients (post hoc analysis)

Parameter	Wald Chi-Square	Pr > ChiSq	Estimate	95% Confidence Limits of Estimate	
Intercept	2.9608	0.0853	3.0440	-0.4233	6.5112
group	1.7720	0.1831	0.7281	-0.3439	1.8000
group*affiliation	0.1124	0.7374	-0.0146	-0.0998	0.0706
affiliation	0.7056	0.4009	0.0255	-0.0341	0.0852
age	9.0360	0.0026	-0.0482	-0.0796	-0.0168
Baseline NIHSS	22.7705	<.0001	-0.2067	-0.2917	-0.1218
Baseline ASPECTS	6.5362	0.0106	0.2315	0.0540	0.4090
Occlusion site	2.3640	0.1242	0.6740	-0.1852	1.5333
Time from onset to randomization	0.0314	0.8594	0.000624	-0.00628	0.00752

In this sensitivity analysis, the center (The 904th Hospital of CPLA) with the largest number (39 cases) of enrolled cases was eliminated.

eTable 5-C. The sensitivity analysis for site effects after merging the affiliations with a small number of enrolled patients (post hoc analysis)

Parameter	Wald Chi-Square	Pr > ChiSq	Estimate	95% Confidence Limits of Estimate	
Intercept	2.2146	0.1367	2.4503	-0.7768	5.6774
group	0.4636	0.4959	0.3389	-0.6366	1.3143
group*affiliation	0.0168	0.8969	0.00633	-0.0894	0.1021
affiliation	0.4880	0.4848	0.0239	-0.0432	0.0911
age	11.2405	0.0008	-0.0487	-0.0771	-0.0202
Baseline NIHSS	22.6271	<.0001	-0.1800	-0.2541	-0.1058
Baseline ASPECTS	6.5561	0.0105	0.2123	0.0498	0.3747
Occlusion site	3.3178	0.0685	0.7572	-0.0576	1.5719
Time from onset to randomization	0.3807	0.5372	0.00198	-0.00432	0.00828

We merged 5 centers with only one patient into 1 center, 5 centers with 2 patients into 1 center, 3 centers with 3 patients into 1 center, and 4 centers with 4 patients were merged into two centers, respectively.

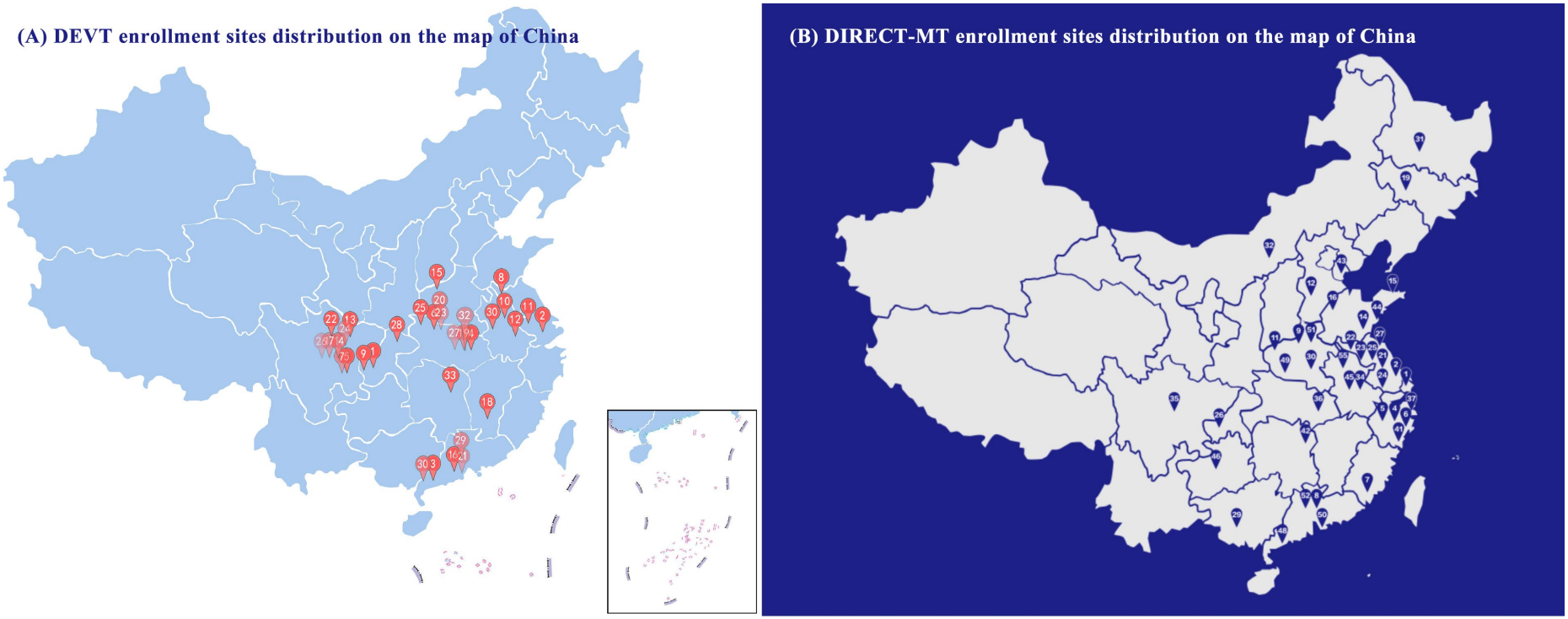
6.6. eTable 6. Differences between DEVT, DIRECT-MT, and SKIP trial

	DEVT	DIRECT-MT	SKIP
Trial design	Non-inferiority	Change from superiority to non-inferiority	Non-inferiority
Sample size calculation	● assuming that the proportion of mRS score 0 to 2 at 90 days of the endovascular treatment alone group and alteplase plus endovascular treatment group are 43% ● non-inferiority margin is -10% ● two-sided α=0.05，power=0.8 ● ratio between the two groups is 1:1 ● 5-interim group-sequential trial, Pocock function to determine α spending and Z and P value boundary ● attrition rate = 5% 97 cases/arm/interim，in total of 970 cases of all five interims	● assuming the proportion of mRS score 0 to 2 at 90 days of the endovascular treatment alone group and alteplase plus endovascular treatment group is 37% and 33% ● non-inferiority margin odds ratio is 0.8 ● two-sided α=0.05，power=0.8 ● ratio between the two groups is 1:1 ● 710 cases. 15% reduction in the sample size because of adjustment for major prognostic variables ● dropout rate = 5% 318 cases/arm, 636 cases in total	● assuming the proportion of mRS score 0 to 2 at 90 days of the endovascular treatment alone group and alteplase plus endovascular treatment group is 48.6% and 35.2% ● non-inferiority margin odds ratio is 0.74 ● two-sided α=0.05，power=0.8 ● ratio between the two groups is 1:1 ● 178 cases. 100 cases/arm, 200 cases in total
Inclusion criteria	Age ≥ 18 years old mRS of 0 or 1 before onset[a] ICA or MCA-M1 occlusion on CTA or MRA NIHSS: no limit ASPECTS: no limit Onset to randomization ≤ 4 hours 15 minutes	Age ≥ 18 years old mRS of 0 or 2 before onset[a] ICA, MCA-M1 or M2 occlusion on CTA NIHSS ≥ 2 ASPECTS: no limit Onset to intravenous rt-PA ≤ 4 hours 30 minutes	Age ≥ 18 and < 86 years old mRS of 0 or 2 before onset[a] ICA or MCA-M1 occlusion on CTA or MRA NIHSS ≥ 6 ASPECTS: DWI ≥ 5 or CT ≥ 6 Onset to puncture < 4 hours
Dose of intravenous alteplase	0.9 mg per kilogram of body weight	0.9 mg per kilogram of body weight	0.6 mg per kilogram of body weight
Participation hospital	Academic tertiary hospital (9/33=27.3%) Municipal tertiary hospital (21/33=63.6%）	Academic tertiary hospital (41/41=100%)	Unknown

	County tertiary hospital (3/33=9.1%)		
Participation department	Neurology (32/33=97%） Neurosurgery (1/33=3%)	Neurology (30/41=73.2%) Neurosurgery (8/41=19.5%) Radiology (3/41=7.3%)	Unknown
Geographical distribution	Mainly in central and western China (see eFigure 8 next to this table)	Mainly in eastern China	Japan
Primary endpoint	Proportion of mRS score of 0-2 at 90 days	mRS score at 90 days	Proportion of mRS score of 0-2 at 90 days

DIRECT-MT denotes Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke1, DWI diffusion weighted imaging, ICA internal carotid artery, MCA-M1 the first segment of middle cerebral artery, MCA-M2 the second segment of middle cerebral artery, NIHSS National Institutes of Health Stroke Scale, and SKIP The randomized study of endovascular therapy with versus without intravenous tissue plasminogen activator in acute stroke with ICA and M1 occlusion.5,6

[a] Time of stroke onset was defined as time last known well.



eFigure 8. Comparison of enrollment sites geographic distribution between DEVT and DIRECT-MT on the map of China.

6.7. eTable 7. Assessment of intracranial hemorrhage based on Heidelberg classification

Class type description[4]	Endovascular thrombectomy alone group	Combined IV thrombolysis and endovascular thrombectomy group
Hemorrhagic transformation of infarcted brain tissue, no (%)		
HI1 Scattered small petechiae, no mass effect	5(20.0)	7(18.4)
HI2 Confluent petechiae, no mass effect	11(44.0)	19(50.0)
PH1 Hematoma within infarcted tissue, occupying<30%, no substantive mass effect	3(12.0)	2(5.3)
Intracerebral hemorrhage within and beyond infarcted brain tissue, no (%)		
PH2 Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect	1(4.0)	2(5.3)
Intracerebral hemorrhage outside the infarcted brain tissue or intracranial–extracerebral hemorrhage, no (%)		
SAH Subarachnoid hemorrhage	2(8.0)	2(5.3)
rPH Parenchymal hematoma remote from infarcted brain tissue	1(4.0)	1(2.6)
IVH Intraventricular hemorrhage	0	0
SDH Subdural hemorrhage	0	0
Combined hemorrhage of the above types, no (%)	2(8.0)	6(13.0)
Total, no (%)	**25(100)**	**38(100)**

HI denotes hemorrhagic infarction, PH parenchymatous hematoma. Data for intracranial hemorrhage were not available for 2 patients (1 in the endovascular thrombectomy alone group and 1 in the combined IV thrombolysis and endovascular thrombectomy group).

eTable 8. Definitions of Symptomatic Intracerebral Hemorrhage

	Clinical	Radiographic	Causality of Neurological Deterioration	Time Frame
NINDS[7] definition	Any clinical suspicion of hemorrhage or any decline in neurological status	Any hemorrhage on CT	Regardless of causal relationship	CT required at 24 h and 7–10 d after stroke onset and with any clinical change suggestive of hemorrhage; primary analysis evaluated hemorrhage within 36 h
ECASS II[8] definition	Clinical deterioration or adverse events indicating clinical worsening (eg, drowsiness, increase of hemiparesis) or causing an increase in NIHSS score of ≥4 points	Any hemorrhage on CT	Regardless of causal relationship	CT done at 22–36 h and 7 d after stroke onset
ECASS III[9] definition	Clinical deterioration defined by an increase of ≥4 points in NIHSS score or that led to death	Any hemorrhage	Hemorrhage as the predominant cause of the neurological deterioration	CT/MRI required at 22–36 h after stroke onset
SITS-MOST[10] definition	Neurological deterioration indicated by an NIHSS score that was ≥4 points higher than the baseline value or the lowest value between baseline and 24 h or hemorrhage leading to death	Local or remote PH-2	Regardless of causal relationship	CT/MRI 22–36 h after stroke onset

CT indicates computed tomography; NINDS, National Institute of Neurological Diseases and Stroke; ECASS, European Cooperative Acute Stroke Study; NIHSS, National Institutes of Health Stroke Scale; MRI, magnetic resonance imaging; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke: Monitoring Study.

7. eReferences

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