# Supplementary information

**Supplementary Table 1. Baseline characteristics and procedural details for the per-protocol population.**

| Characteristics | ED Group (n=79) | Control Group (n=79) | P value |
|---|---|---|---|
| Age, mean (SD), years | 63.76 (9.77) | 62.78 (10.93) | 0.555 |
| Gender, No. (%) | | | |
| Male | 58 (73.4) | 57 (72.2) | 0.858 |
| Female | 21 (26.6) | 22 (27.8) | |
| Weight, mean (SD), kg [#] | 70.31 (10.77) | 70.73 (13.11) | 0.826 |
| BMI, mean (SD), $kg/m^2$ [#] | 24.53 (2.79) | 24.98 (3.82) | 0.397 |
| Medical History, n (%) [a] | | | |
| Previous ischemic stroke | 14 (17.7) | 18 (22.8) | 0.428 |
| Hypertension | 31 (39.2) | 38 (48.1) | 0.262 |
| Hyperlipidemia | 1 (1.3) | 0 | 0.316 |
| Diabetes | 13 (16.5) | 10 (12.7) | 0.499 |
| Cardiac disease | 10 (12.7) | 13 (16.5) | 0.499 |
| Atrial fibrillation | 22 (27.8) | 14 (17.7) | 0.129 |
| Medications, n (%) [a] | | | |
| Antihypertensive drugs | 23 (29.1) | 20 (25.3) | 0.592 |
| Statin or other lipid-lowering drug | 5 (6.3) | 2 (2.5) | 0.246 |
| Aspirin or other antiplatelet drug | 6 (7.6) | 5 (6.3) | 0.755 |
| Anticoagulation drug | 9 (11.4) | 6 (7.6) | 0.416 |
| Currently smokes tobacco, No./total (%) | 28/78 (35.9) | 22/79 (27.8) | 0.279 |
| Currently drinks alcohol, No./total (%) [b] | 15/79 (19.0) | 17/79 (21.5) | 0.692 |
| Breath at baseline, median (IQR), per minute | 18 (18-18) | 18 (18-18) | 0.438 |
| HR at baseline, median (IQR), per minute | 69 (61-83) | 73 (60-80) | 0.861 |
| Blood pressure at baseline, mean (SD), mm Hg | | | |
| Systolic | 140.8 (23.4) | 141.1 (25.4) | 0.938 |
| Diastolic | 82.2 (14.3) | 82.0 (15.5) | 0.958 |
| Blood-glucose at baseline, median (IQR) [¥] | 6.99 (5.83-8.29) | 7.11 (6.14-9.10) | 0.253 |
| ASPECTS score at baseline, median (IQR) [c] | 8 (7-9.5) | 8.5 (7-9) | 0.950 |

| | | | |
|---|---|---|---|
| NIHSS score at baseline, median (IQR) [d] | 14 (10-17) | 14 (11-16) | 0.972 |
| Pre-stroke score on the modified Rankin Scale, n (%) [e] | | | |
| mRS 0 | 73 (92.4) | 68 (86.1) | 0.199 |
| mRS 1 | 6 (7.6) | 11 (13.9) | |
| Median duration, median (IQR), min | | | |
| Onset to puncture * | 303 (217-392) | 314 (241-387) | 0.647 |
| Onset to recanalization | 369 (280-440) | 385 (322-465) | 0.162 |
| Groin puncture to recanalization * | 48 (35-70) | 65 (44-99) | 0.004 |
| Onset to randomization | 396 (317-487) | 416 (357-505) | 0.109 |
| Cause of large-vessel occlusion, n (%) | | | |
| Intracranial atherosclerosis | 25 (31.6) | 21 (26.6) | 0.484 |
| Extracranial atherosclerosis | 16 (20.3) | 21 (26.6) | 0.348 |
| Cardioembolism | 33 (41.8) | 32 (40.5) | 0.872 |
| Other cause | 5 (6.3) | 5 (6.3) | 1.000 |
| Intravenous alteplase, n (%) [f] | 19 (24.1) | 21 (26.6) | 0.714 |
| mTICI score at the end of the procedure, n (%) | | | |
| 2b | 12 (15.2) | 19 (24.1) | 0.073 |
| 2c | 1 (1.3) | 5 (6.3) | |
| 3 | 66 (83.5) | 55 (69.6) | |
| Location of responsible vessel, n (%) | | | |
| MCA-M1 | 40 (50.6) | 42 (53.2) | 0.750 |
| MCA-M2 | 2 (2.5) | 2 (2.5) | 1.000 |
| ICA | 23 (29.1) | 30 (38.0) | 0.238 |
| MCA-M1+ICA | 14 (17.7) | 5 (6.3) | 0.028 |
| Cerebral collateral circulation grade, n (%) [g] | | | |
| 0 | 12 (17.1) | 20 (27.0) | 0.407 |
| 1 | 18 (25.7) | 12 (16.2) | |
| 2 | 22 (31.4) | 19 (25.7) | |
| 3 | 11 (15.7) | 15 (20.3) | |
| 4 | 7 (10.0) | 8 (10.8) | |

Data are No. (%) or No./total (%), mean (SD), or median (IQR). Abbreviation: ED, edaravone dexborneol; BMI, body mass index; HR, heart rhythm; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; mTICI, modified thromboysis in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery.

[a] Comorbidities based on family or patient report.

[b] Currently drinks alcohol means consuming alcohol at least once a week within one year prior to the onset of the disease.

[c] ASPECTS scores determine extent of ischemic tissue based on CT imaging. Scores range from 0 to 10 with higher scores indicating less infarct volume. Data missing for 3 participants for ASPECTS score at baseline.

[d] Scores on National Institutes of Health Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit; A mean NIHSS of 8-9 means moderate neurological deficit.

[e] Scores on the modified Rankin Scale (mRS) of functional disability range from 0 (no symptoms) to 6 (death).

[f] Defined as half or more than standard alteplase dose (0.9 mg/kg).

[g] The ASITN/SIR collateral circulation assessment system based on DSA examination. Grades range from 0 to 4 with higher grades indicating better collateral circulation. Grade 0-1 indicates poor collateral circulation; Grade 2 indicates moderate collateral circulation; and Grade 3~4 indicates better collateral circulation. Data missing for 14 participants for cerebral collateral circulation grade.

[#] Data missing for 2 participants for weight and BMI.

[¥] Data missing for 3 participants for blood-glucose at baseline.

***** Data missing for 2 participants for time from onset to puncture and groin puncture to recanalization.

**Supplementary Table 2. Primary and secondary outcomes and safety outcomes in the per-protocol population.**

| Outcome | ED Group (n=79) | Control Group (n=79) | Treatment Effect Metric | Unadjusted | | Adjusted [a] | |
|---|---|---|---|---|---|---|---|
| | | | | Treatment Difference (95% CI) | P Value | Treatment Difference (95% CI) | P Value |
| Primary outcome | | | | | | | |
| mRS score 0-2 at 90±7 days, No. (%) [b] | 53 (67.1) | 47 (59.5) | OR | 1.39 (0.73 to 2.66) | 0.32 | 1.30 (0.64 to 2.67) | 0.47 |
| Secondary outcomes | | | | | | | |
| mRS score 0-1 at 90±7 days, No. (%) [b] | 40 (50.6) | 37 (46.8) | OR | 1.16 (0.62 to 2.17) | 0.63 | 1.07 (0.54 to 2.10) | 0.85 |
| mRS score distribution at 90±7 days [b] | | | OR [c] | 0.68 (0.39 to 1.19) | 0.18 | 0.75 (0.42 to 1.33) | 0.32 |
| Change in NIHSS score from baseline, median (IQR) [d] | | | | | | | |
| at 24 hours | -5 (-8 to -1) | -3 (-7.5 to 0) | GMR | -0.05 (-0.13 to 0.03) | 0.22 | -0.04 (-0.11 to 0.04) | 0.35 |
| at 48 hours | -6 (-10 to -2) | -5 (-9.5 to -2) | | -0.07 (-0.16 to 0.02) | 0.15 | -0.05 (-0.14 to 0.04) | 0.24 |
| at 2 weeks | -9 (-13 to -4) | -8 (-12 to -5) | | -0.11 (-0.23 to 0.01) | 0.07 | -0.09 (-0.21 to 0.03) | 0.14 |
| Infarct volume at 1 week, median (IQR)[e] | 15.24 (3.74 to 51.7) | 20.50 (6.36 to 46.52) | GMR | 0.06 (-0.13 to 0.25) | 0.51 | 0.05 (-0.13 to 0.22) | 0.61 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| All-cause mortality within 90±7 days, No. (%) | 4 (5.1) | 5 (6.3) | HR [f] | 0.82 (0.22 to 3.05) | 0.77 | 1.21 (0.28 to 5.20) | 0.80 |
| Safety Outcomes | | | | | | | |
| sICH at 48 hours, No. (%) [g] | 4 (5.1) | 7 (8.9) | OR | 0.55 (0.15-1.95) | 0.35 | 0.60 (0.13 to 2.76) | 0.51 |
| Intracerebral hemorrhage at 48 hours, No. (%) [g] | | | | | | | |
| PH-1 | 2 (2.5) | 8 (10.1) | OR | 0.23 (0.05 to 1.12) | 0.07 | 0.21 (0.04 to 1.21) | 0.08 |
| PH-2 | 3 (3.8) | 1 (1.3) | OR | 3.08 (0.31 to 30.26) | 0.34 | 0.13 (0.00 to 7.27) | 0.32 |
| HI-1 | 2 (2.5) | 1 (1.3) | OR | 2.03 (0.18 to 22.81) | 0.57 | 0.19 (0.00 to 20.88) | 0.49 |
| HI-2 | 4 (5.1) | 10 (12.7) | OR | 0.37 (0.11 to 1.23) | 0.10 | 0.30 (0.08 to 1.16) | 0.08 |
| SAE within 90 days, No. (%) | 9 (11.4) | 11 (13.9) | HR [f] | 0.84 (0.35 to 2.03) | 0.70 | 1.11 (0.43 to 2.86) | 0.82 |

Data are No. (%), median (IQR). Abbreviation: ED, edaravone dexborneol; CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; GMR, geometric mean ratio; HR, hazard ratio; sICH, symptomatic intracranial hemorrhage; PH, parenchymal hemorrhage; HI, hemorrhagic infarct; SAE, serious adverse events.

a Adjusted for key prognostic covariates (age, sex, pre-stroke score on the modified Rankin Scale, NIHSS score at baseline, previous ischemic stroke, time from onset to recanalization, cerebral collateral circulation grade, number of thrombectomy device passes, and Intravenous thrombolysis).

[b] mRS scores range from 0 to 6: 0, no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe

disability, 5 = severe disability; and 6 = death.

[c] Calculated with Ordinal regression analysis.

[d] NIHSS scores range 0–42, with higher scores indicating greater stroke severity. The log (NIHSS+1) was analyzed using a generalized linear model. Data missing for 3 participants at 2 weeks.

[e] Determined by brain CT or MRI. The log (Infarct volume +1) was analyzed using a generalized linear model. Data missing for 3 participants for infarct volume at 1 week

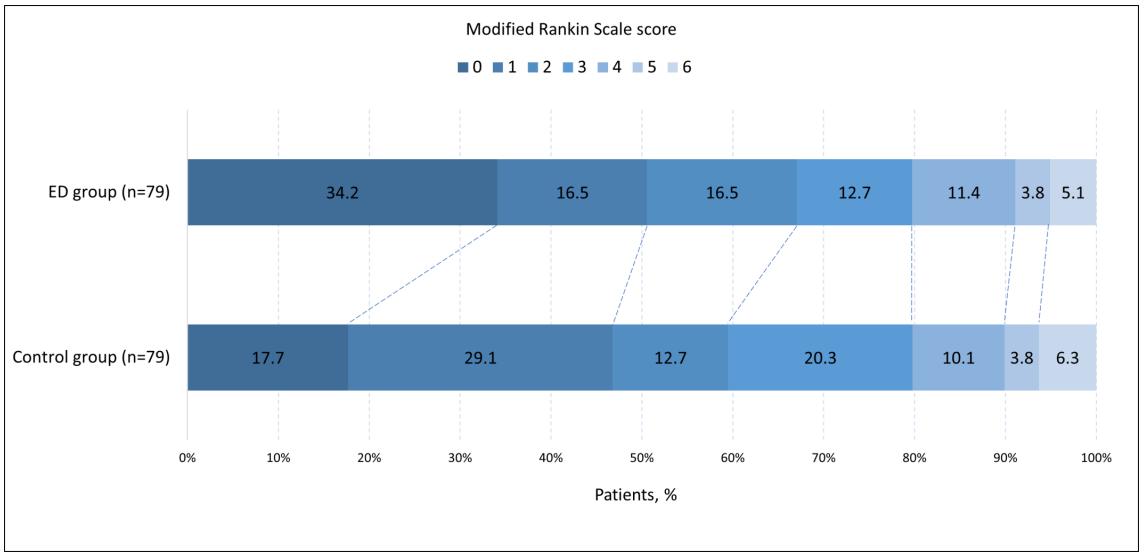
[f] Calculated with Cox regression model.

[g] Defined according to European Cooperative Acute Stroke Study (ECASS).

**Supplementary Table 3. Sensitivity analysis for missing primary outcome in dropout subjects in the Intention to Treatment Set.**

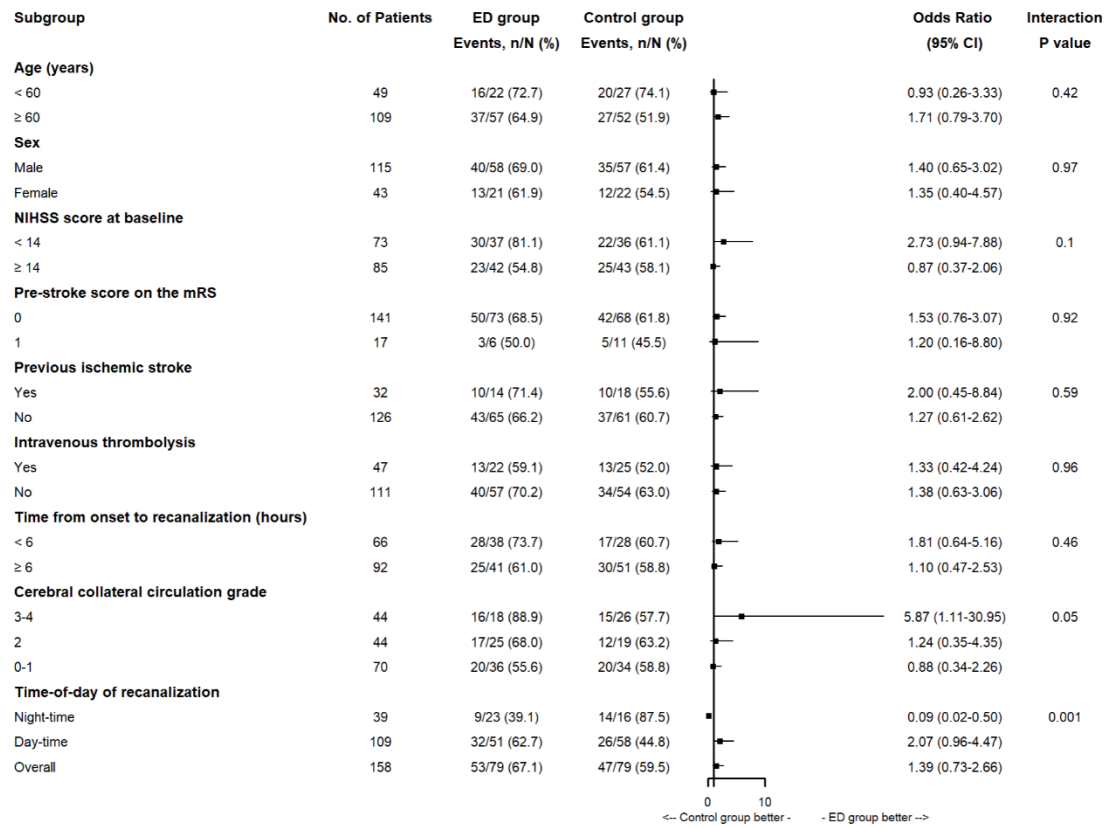
| Methods | Without primary outcome imputation | | | | With primary outcome imputation | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ED group (92) | Control group (94) | Odds ratio (95% CI) | P value | ED group (97) | Control group (103) | Odds ratio (95% CI) | P value | Imputation methods |
| mRS score 0-2 within 90 days, No. (%) | 54/92 (58.7%) | 49/94 (52.1%) | 0.77 (0.43-1.37) | 0.37 | 57/97 (58.8%) | 50/103 (48.5%) | 1.51 (0.86-2.64) | 0.15 | Last observation carried forward |
| | | | | | 54/97 (55.7%) | 49/103 (47.6%) | 0.72 (0.41-1.26) | 0.25 | Worst-case scenario |
| | | | | | 59/97 (60.8%) | 58/103 (56.3%) | 0.83 (0.47-1.46) | 0.52 | Best-case scenario |

Data are No. (%). Abbreviation: ED, edaravone dexborneol; CI, confidence interval; mRS, modified Rankin Scale;




**Supplementary Figure 1 Distribution of Modified Rankin Scale Scores at 90 Days in the Per-Protocol Analysis.**

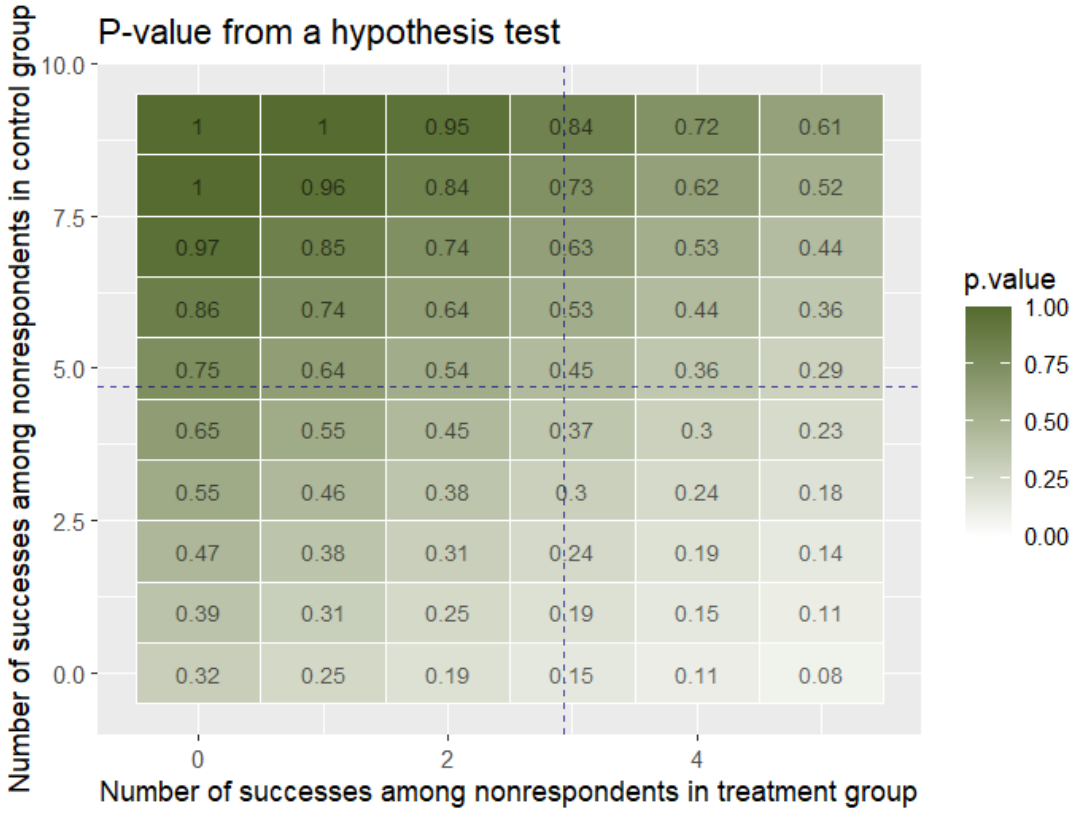
Shown are scores on the modified Rankin scale for the patients in the two treatment groups who had data for the primary outcome. Scores range from 0 to 6 (0 = no symptoms, 1 = symptoms without clinically significant disability,2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death). The odds ratio was 0.66 (95% CI, 0.38-1.14), and the P value was 0.14; the adjusted odds ratio was 0.70 (95% CI, 0.75 (0.40-1.24), and the adjusted P value was 0.22. Percentages may not total 100 because of rounding.




**Supplementary Figure 2 Primary Outcome by Prespecified Subgroups in the Per-Protocol Analysis.**

The primary outcome was a modified Rankin Scale score of 0–2 at 90 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent the 95% CI. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. For the NIHSS score, subgroups were dichotomized according to the median value.

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.




**Supplementary Figure 3 Tipping point analysis in the modified Intention to Treatment Set.**

Heatmap of tipping point analysis in the Intention to Treatment Set.