Edaravone dexborneol versus placebo on functional outcomes in patients with acute ischaemic stroke undergoing endovascular thrombectomy (TASTE-2): randomised controlled trial

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ABSTRACT

OBJECTIVE

To assess the efficacy and safety of edaravone dexborneol, a multitarget brain cytoprotectant composed of antioxidant and anti-inflammatory ingredients, in improving functional outcomes among patients with acute ischaemic stroke undergoing endovascular thrombectomy.

DESIGN

Multicentre, double blind, randomised, placebo controlled trial.

SETTING

106 hospitals in China between March 2022 and May 2023.

PARTICIPANTS

1362 patients with clinically diagnosed acute ischaemic stroke within 24 hours of symptom onset, aged 18-80 years, with a National Institutes of Health Stroke Scale (NIHSS) score of 6-25 and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6-10, confirmed large vessel occlusion in the anterior circulation, and planned endovascular thrombectomy.

INTERVENTIONS

Patients were randomly allocated in a 1:1 ratio to receive edaravone dexborneol 37.5 mg (edaravone, 30 mg; (+)–dexborneol, 7.5 mg; 690 patients) or placebo (672 patients) before endovascular thrombectomy and continued the regimen twice daily for a consecutive period of 10-14 days.

MAIN OUTCOME MEASURES

Functional independence at 90 days, defined as a modified Rankin Scale score (range 0 (no symptoms) to 6 (death)) of 0-2, and serious adverse events.

RESULTS

One patient from each group was lost to follow-up at 90 days. Of the 1360 patients included in the intention-to-treat analysis, 379 (55.0%) of 689 patients in the edaravone dexborneol group and 333 (49.6%) of 671 patients in the placebo group achieved functional independence on day 90 (risk ratio 1.11, 95% confidence interval (CI) 1.00 to 1.23; P=0.05; risk difference 5.4%, 95% CI 0.1% to 10.7%). Patients with mismatch at admission (defined as NIHSS score ≥10 and ASPECTS ≥9 or NIHSS score ≥20 and ≥7) were more likely to achieve functional independence in the subgroup analysis (55.5% (178/321) versus 42.9% (134/312); risk ratio 1.29, 1.10 to 1.52; risk difference 13.0%, 5.6% to 20.3%; P for interaction=0.003). The rates of serious adverse events were similar in the two groups (27.2% (188/690) versus 25.7% (173/672); risk ratio 1.06, 0.89 to 1.26; risk difference 1.5%, −3.2% to 6.2%: P=0.53).

CONCLUSIONS

Among patients with acute ischaemic stroke within 24 hours of symptom onset who underwent endovascular thrombectomy, those treated with edaravone dexborneol, compared with placebo, were more likely to achieve functional independence at 90 days without increased safety concerns. This effect seemed to be primarily driven by the subgroup with mismatch present at admission, suggesting that dedicated trials in this population may be warranted.

TRIAL REGISTRATION

ClinicalTrials.gov NCT05249920.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Edaravone dexborneol is a novel multitarget brain cytoprotectant that shows efficacy in both animal models of reperfusion and patients with acute ischaemic stroke without reperfusion therapy

Evidence that administration of edaravone dexborneol before endovascular thrombectomy improves functional outcomes in patients with acute ischaemic stroke is lacking

WHAT THIS STUDY ADDS

Edaravone dexborneol was associated with a trend of improved functional independence at 90 days in patients with acute ischaemic stroke who underwent endovascular thrombectomy

This was particularly apparent in patients with clinical imaging mismatch present at admission

These findings indicate that edaravone dexborneol might potentially serve as an adjunctive therapy alongside reperfusion treatment

Introduction

Acute ischaemic stroke, particularly when characterised by occlusions in proximal intracranial large vessels, is a predominant contributor to morbidity and mortality on an international scale.[1] On the basis of solid evidence from pivotal clinical trials, stroke guidelines has adopted endovascular thrombectomy for treating acute ischaemic stroke in patients with

large vessel occlusion.[2] Although approximately 70-90% of patients with acute large vessel occlusion treated with endovascular thrombectomy achieved successful revascularisation, only an estimated 50% of them achieved favourable outcomes.[3-5] This discrepancy may be partly attributed to the intricate cascade of biochemical reactions, known as ischaemic cascade reactions, initiated by focal cerebral ischaemia. As recommended by the Stroke Treatment Academic Industry Round table, brain cytoprotectants might have the capability of reducing ischaemic brain injury by antagonising detrimental molecular events, especially when combined with reperfusion therapy in this new era of acute ischaemic stroke treatment.[6-8] However, translating basic research into effective stroke treatments has been a challenge in the development of cytoprotective agents.

Edaravone dexborneol, a compound consisting of edaravone and (+)–borneol in a four-to-one ratio, has been investigated in animal models and identified as an innovative multitarget brain cytoprotective agent owing to its synergistic antioxidant and anti-inflammatory effects in preclinical studies.[9] It has been shown to exert cytoprotective effects by suppressing NLRP3 inflammasome induced microglial proptosis in ischaemic stroke reperfusion models, as well as by inhibiting ferroptosis through the activation of the Nrf-2/HO-1/GPX4 axis to protect against reperfusion induced damage to the blood-brain barrier.[10-12] In the TASTE trial, a phase 3 clinical study, treatment with edaravone dexborneol (37.5 mg twice daily) showed superior efficacy and a favourable safety profile compared with edaravone alone in improving functional outcomes in patients with acute ischaemic stroke who did not receive reperfusion therapy.[13] Nevertheless, whether edaravone dexborneol confers additional cytoprotective benefits in patients undergoing reperfusion therapy—a population that may derive the greatest potential benefit from cytoprotective agents—remains uncertain. Therefore, the aim of the TASTE-2 trial was to evaluate the efficacy and safety of edaravone dexborneol in enhancing functional outcome for patients with acute ischaemic stroke undergoing endovascular thrombectomy owing to large vessel occlusion.

Methods

Study design

The TASTE-2 trial was an investigator initiated, multicentre, double blind, randomised, placebo controlled trial conducted at 106 centres in mainland China. The trial was approved by a central institutional review board and endorsed by the ethics committee of each research site; written informed consent was obtained from the patients or their legal representatives before the drugs were used. The trial's rationale and design have been previously described in the protocol.[14] The trial was registered before the first patient was enrolled and monitored by an independent data and safety monitoring board (members are listed in appendix S1).

Participants

Each centre participating in this study was required to have demonstrated experience in endovascular thrombectomy, having done a minimum of 50 thrombectomy procedures in the previous year to verify its technical proficiency and consistency. All centres are listed in appendix S2. We considered patients meeting the following criteria to be eligible for participation in this trial: age between 18 and 80 years; a diagnosis of acute ischaemic stroke; a National Institutes of Health Stroke Scale (NIHSS; range 0-42, with lager values indicating severe neurological dysfunction) score between 6 and 25; an Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range 0-10, with lower values indicating larger volume of infarction) of 6-10; an anterior large vessel occlusion at intracranial internal carotid artery; a T shaped bifurcation or the first segment of middle cerebral artery (M1); and an endovascular thrombectomy planned within 24 hours after symptom onset. An imaging evaluation of mismatch was done to meet the criteria of DEFUSE-3 (an infarct core <70 mL, a mismatch volume >15 mL, and a mismatch ratio >1.8)[15] or DAWN (an NIHSS score ≥10 with an infarct core volume <31 cm^3 or an NIHSS score ≥20 with an infarct core volume ≤51 cm^3)[16] for those patients who were within six to 24 hours of symptom onset. We used iStroke software (version 3.13) to calculate the infarct core volume, mismatch volume, and mismatch ratio.[17 18] Previous or concomitant intravenous thrombolysis with alteplase was not prohibited if indicated.

Key exclusion criteria were intracranial haemorrhagic diseases; allergy to edaravone, (+)–dexborneol, or auxiliary materials; high systolic blood pressure (≥180 mm Hg) or diastolic blood pressure (≥110 mm Hg) after antihypertensive treatment; elevated serum alanine aminotransferase or aspartate transaminase more than three times above the upper limit of normal; chronic kidney disease or current serum creatinine exceeding 1.5 times the upper limit of normal or estimated glomerular filtration rate <60 mL/min; and receipt of an intravenous thrombolytic drug other than alteplase before endovascular thrombectomy. Details of the inclusion and exclusion criteria are shown in appendix S3.

Randomisation and masking

The randomisation sequence numbers were generated centrally by using random permuted, fixed size blocks methods with SAS 9.4 software. Given that the proportion of crucial factors (sex at birth (male versus female), status of bridging (with versus without alteplase) before endovascular thrombectomy, type of devices (stent retriever versus aspiration device), and onset to puncture time (≤6 hours versus >6 hours)) was not extremely low in a real world registry,[4] we did not incorporate stratification into the randomisation process. Edaravone dexborneol and placebo were prepared as colourless solutions in vials that were visually identical. Each unique sequence number was uniformly labelled on all the drug packages for one

participant and served as the identifier of the drug in the smallest packaging unit without containing group information, so that all trial investigators and participants were fully masked to treatment allocation. All packaged drugs were mailed to each site in randomisation sequence order, and all enrolled patients were randomised with a one-to-one ratio of edaravone dexborneol or placebo within 24 hours after symptom onset. Complete blinding of participants and site investigators, as well as strict allocation concealment, was maintained throughout the entire study.

Procedures

Patients allocated to the intervention group were given intravenous edaravone dexborneol injection 37.5 mg, comprising 30 mg of edaravone and 7.5 mg of (+)–dexborneol, twice a day over a consecutive period of 10-14 days lasting for 30 minutes each time, whereas patients allocated to the control group were given an intravenous placebo injection in the same manner. The placebo comprised all excipient ingredients, including sodium metabisulfite, propylene glycol as a solvent, and hydrochloric acid and/or sodium hydroxide for pH adjustment (with the pH maintained within the range of 3.0-5.0), but excluded the active components edaravone and (+)–dexborneol. The first dose injection of edaravone dexborneol or placebo was given before the treatment of endovascular thrombectomy and no later than the puncture of the femoral artery.

For this trial, endovascular thrombectomy was administered as a fundamental intervention for all randomised patients, and the reperfusion status of the occluded large vessels was evaluated using the extended Thrombolysis in the Cerebral Infarction (eTICI) scale (a seven point scale, with higher scores indicating greater reperfusion). Successful reperfusion was defined as an eTICI score of 2B50 or greater, indicating at least 50-66% reperfusion.[19] Other care at each site was expected to adhere to national guidelines for stroke unit treatment, stroke rehabilitation, and stroke prevention, including intravenous thrombolysis (if eligible), antiplatelet therapy or anticoagulation, statins, and blood pressure and glucose management, as well as other supportive treatments. However, other drugs considered to be cytoprotective were prohibited throughout the entire study process. The modified Rankin Scale and serious adverse events were assessed at 14 days (or at discharge if earlier) and at 90 days through in-person follow-up conducted by local certified medical researchers who were blinded to the treatment allocation.

The clinical assessments were conducted at baseline, on the day of and 24 (±12) hours after randomisation, at 14 days (or at discharge if earlier), and at 90 (±7) days by certified investigators. Modified Rankin Scale scores for assessing global disability, NIHSS scores for neurological deficit, adverse events/serious adverse events for safety, and drug usage for medication adherence were collected. For patients within six hours of symptom onset, baseline radiological assessment was done using computed tomography or diffusion weighted imaging combined with at least one category of angiography (computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography) to certify the location of large vessel occlusion in the anterior circulation. For patients within six to 16 hours of symptom onset, the baseline screening imaging should contain a set of computed tomography, computed tomography angiography, and computed tomography perfusion or a set of diffusion weighted imaging, apparent diffusion coefficient, magnetic resonance angiography, and magnetic resonance perfusion to meet the DEFUSE-3 criteria,[15] or should contain a set of computed tomography, computed tomography angiography, and computed tomography perfusion or a set of diffusion weighted imaging, apparent diffusion coefficient, and magnetic resonance angiography to meet the DAWN criteria.[20] Additionally, for patients within 16-24 hours of symptom onset, the baseline screening imaging should contain a set of computed tomography, computed tomography angiography, and computed tomography perfusion or a set of diffusion weighted imaging, apparent diffusion coefficient, and magnetic resonance angiography to meet the DAWN criteria.[20] Imaging criteria would be reviewed and certified by two experienced 24 hour on-call neurologists if needed. Imaging follow-up was done at 24 (±12) hours after randomisation by using computed tomography or magnetic resonance imaging to detect haemorrhagic transformation, and at any other time if deterioration in neurological symptoms occurred. All DICOM format images were collected by site investigators and transferred to the imaging core laboratory in the National Clinical Research Center of Neurological Diseases in Beijing Tiantan Hospital, Capital Medical University. The 90 (±7) day follow-up was done via in-person interviews by certified investigators at each site, with online video interviews being arranged for patients unable to attend face-to-face sessions.

Outcomes

The primary efficacy outcome was the proportion of patients achieving functional independence, characterised by a modified Rankin Scale score of 0-2 at 90 days. The primary safety outcome was the proportion of serious adverse events that occurred throughout the entire study period. The secondary efficacy outcomes encompassed shift analysis of modified Rankin Scale scores, excellent functional outcome characterised by a modified Rankin Scale score of 0-1 at 90 days, change in NIHSS score from baseline to 10-14 days, a decrease in NIHSS score ≥4 from baseline to 10-14 days, and the occurrence of new ischaemic or haemorrhagic stroke within 90 days. We implemented a minor protocol amendment following the enrolment of several patients and included a shift analysis of modified Rankin Scale score as a secondary efficacy outcome without causing any disruption or effect on the trial's executive processes (appendix S16). The secondary safety outcomes included

all cause mortality within 90 days, symptomatic intracranial haemorrhage within 36 hours as defined by the Heidelberg Bleeding Classification,[21] early deterioration in neurological deficit defined as a ≥4 point increase in the NIHSS score from baseline to day 1, and the proportion of adverse events within 90 days (appendix S4). All serious adverse events were evaluated by an independent clinical events committee (appendix S1).

Statistical analysis

According to the findings from the Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischaemic Stroke (ANGEL-ACT) Registry, a large prospective cohort study of Chinese patients with acute ischaemic stroke undergoing endovascular thrombectomy, 45.4% of patients achieved modified Rankin Scale scores of 0-2 at 90 days.[4] In the TASTE trial, the edaravone dexborneol group showed a 13.9% relative increase in neurological improvement compared with the edaravone alone group in patients with acute ischaemic stroke.[13] Therefore, we anticipated an expected 20% relative increase in neurological improvement when comparing edaravone dexborneol with placebo in the TASTE-2 trial, resulting in approximately 54% functional independence at 90 days for the intervention group versus 45% for the control group. On the basis of these assumptions, a total estimated sample size of 1362 patients (with a predicted 5% dropout rate) with an equal distribution of 681 patients per group would yield a statistical power of 90% to detect the superiority of edaravone dexborneol over placebo in improving neurological function at a two sided α significance level of P=0.05. No interim analysis was planned during the process.

We did the primary efficacy evaluation in the modified intention-to-treat population, which included all randomly assigned patients except those lost to follow-up at 90 days. Safety analyses used the safety dataset. We assessed differences in the proportion of modified Rankin Scale score 0-2 at 90 days between study groups with a logistic regression model. We presented the results as risk ratios and risk differences, both with 95% confidence intervals. We did sensitivity analyses for the primary efficacy outcome to assess the robustness of treatment effects. This involved calculating the odds ratio and its 95% confidence interval, doing multiple imputations of modified Rankin Scale score for participants lost to follow-up at 90 days, and adjusting for baseline covariates that might be unbalanced by chance.

We applied similar strategies to those used for analysing the primary outcome to other categorical outcomes. For shift analysis, we used an ordinal logistic regression model to calculate a common odds ratio along with its 95% confidence interval for the ordinal 90 day modified Rankin Scale score. All hypothesis tests adopted a two sided α level of significance set at 0.05 (α=0.05). We also did a per protocol analysis of the primary outcome in the population that completed the assigned treatment without any major violations of the trial protocol or missing data for the primary efficacy endpoints, using similar analytical strategies.

We did a pre-specified subgroup analysis to evaluate the heterogeneity of treatment effects by testing the interaction effect between treatment and subgroup with logistic regression models, with subgroups defined on the basis of the following variables: sex at birth (male or female), age (≤65 or >65), medical history (hypertension, hypercholesterolaemia, diabetes mellitus, stroke, and coronary heart disease status, separately; yes or no), time interval between last known well and randomisation (≤6 hours or >6 hours), NIHSS score range (6-15 or >15), ASPECTS range (8-10 or 6-7), mismatch status (yes or no, with mismatch defined using three models: model 1, defined as NIHSS score >15 and ASPECTS ≥8; model 2, defined as NIHSS score ≥10 and ASPECTS ≥9 or NIHSS score ≥20 and ASPECTS ≥7; and model 3, defined as NIHSS score ≥10 and ASPECTS ≥8 or NIHSS score ≥20 and ASPECTS ≥6), administration of bridging therapy before the endovascular thrombectomy procedure (with or without alteplase), location of large vessel occlusion site (within the intracranial internal carotid artery or M1 segment of middle cerebral artery), and reperfusion status of occluded vessels after the endovascular thrombectomy procedure according to eTICI scale categories (2B-3 *v* 0-2A).

We used SAS version 9.4 for statistical analyses, in accordance with a predefined statistical analysis plan that was provided before the database was unmasked and locked (appendix S16). The trial was monitored by an independent data monitoring committee.

Patient and public involvement

At the time when patient recruitment for the TASTE-2 trial started, no official national guideline on patient involvement had yet been released in China. The relevant guidance, issued by the Center for Drug Evaluation, became available only in November 2022, around eight months after enrolment began.[22] As a result, patients and the public were not engaged in the study's design or implementation process. However, the study protocol and manuscript were thoroughly reviewed and discussed by physicians and neurologists, who will assist in communicating the research outcomes to medical professionals, patients, and the general public.

Results

Participants

Between 18 March 2022 and 17 February 2023, a total of 14 233 patients with acute ischaemic stroke were screened and 1362 of them were enrolled at 106 sites. Of these, 690 were randomised into the edaravone dexborneol group and 672 were randomised into the placebo group. One patient in the edaravone dexborneol group and one in the placebo group were excluded from the primary efficacy outcome analysis because of loss to follow-up at 90 days, leaving 1360 patients in the modified intention-to-treat population. No patient was excluded from the primary safety

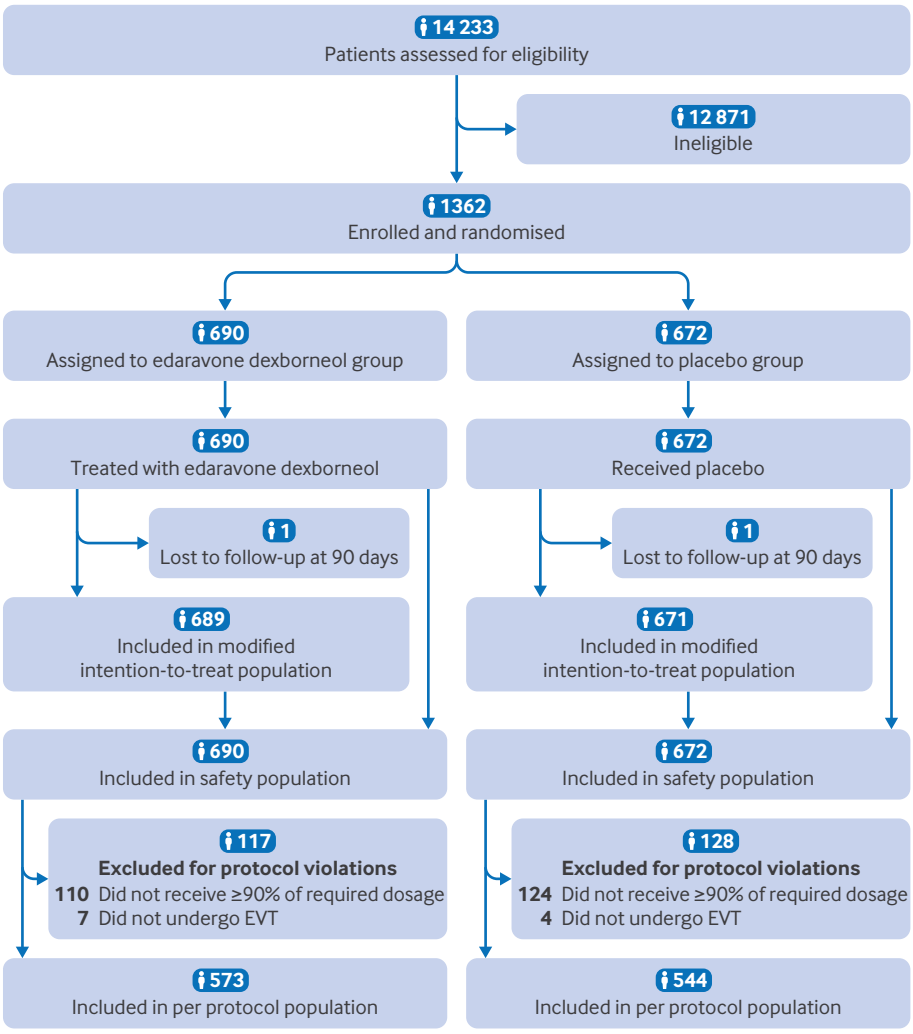


Fig 1 | Trial profile. EVT=endovascular thrombectomy

outcome analysis. After exclusion of 245 patients for protocol violations (117 in the edaravone dexborneol group and 128 in the placebo group), a total of 1117 patients were included into the per protocol analysis (fig 1).

Baseline demographics, medical and medication history, clinical characteristics, and time parameters were comparable between the groups (table 1). Of all patients, 64.0% were male, the median age was 67.0 (interquartile range 58.0-73.0) years, the median NIHSS score was 15 (12.0-19.0), and the median ASPECTS was 9.0 (7.0-10.0). The frequency of intravenous tissue plasminogen activator before endovascular thrombectomy in the placebo group was 4.4% lower than in the edaravone dexborneol group. The median time from symptom onset to first dose of drugs was 274.5 (189.0-358.0) minutes in the edaravone dexborneol group and 283.0 (194.0-365.0) minutes in the placebo group (table 1).

Primary and secondary outcomes

In the modified intention-to-treat population, 379 (55.0%) of 689 patients in the edaravone dexborneol group and 333 (49.6%) of 671 patients in the placebo group achieved the primary efficacy outcome (modified Rankin Scale score of 0-2 at 90 days; risk ratio 1.11, 95% confidence interval (CI) 1.00 to 1.23; risk difference 5.4%, 95% CI 0.1% to 10.7%; P=0.05) (fig 2 and table 2). The number needed to treat was 19. In the sensitivity analysis, multiple imputation for missing data for the primary efficacy outcome yielded results consistent with the main analysis (risk ratio 1.11, 1.01 to 1.21; risk difference 5.5%, 0.2% to 10.8%; P=0.04) (appendix S6), and odds ratio analysis conducted for the primary efficacy outcome showed a similar result (odds ratio 1.24, 95% CI 1.00 to 1.54; P=0.05) (appendix S7). Furthermore, we observed a similar finding after adjusting for some potentially favourable factors for the intervention group, including occlusion site, medical history of hypertension and diabetes, pre-treatment with alteplase before endovascular thrombectomy, and time interval from symptom onset to first drug administration (adjusted risk ratio 1.13, 95% CI 1.02 to 1.24; adjusted risk difference 6.1%, 0.8% to 11.3%; P=0.02) (appendix S8). In the per protocol analysis, 351 (61.3%) of 573 patients in the

Table 1 | Baseline characteristics of intention-to-treat population. Values are numbers (percentages) unless stated otherwise

Characteristics	Edaravone dexborneol (n=690)	Placebo (n=672)
Demographics		
Sex at birth:		
Male	435 (63.0)	436 (64.9)
Female	255 (37.0)	236 (35.1)
Ethnicity:		
Han	677 (98.1)	657 (97.8)
Others	13 (1.9)	15 (2.2)
Median (IQR) age, years	67.0 (57.0-73.0)	67.0 (58.0-73.0)
≤65 years	305 (44.2)	303 (45.1)
>65 years	385 (55.8)	369 (54.9)
Median (IQR) body mass index	24.0 (22.0-26.0)	24.0 (22.0-26.0)
Medical history*		
Stroke	144 (20.9)	136 (20.2)
Hypertension	398 (57.7)	355 (52.8)
Diabetes	130 (18.8)	98 (14.6)
Dyslipidaemia	32 (4.6)	28 (4.2)
Coronary heart diseases	134 (19.4)	114 (17.0)
Atrial fibrillation	174 (25.2)	171 (25.4)
Peripheral arterial disease	8 (1.2)	6 (0.9)
Medication history		
Antiplatelet therapy	54 (7.8)	49 (7.3)
Lipid lowering agents	55 (8.0)	37 (5.5)
Blood pressure lowering agents	297 (43.0)	250 (37.2)
Hypoglycaemic agents	107 (15.5)	76 (11.3)
Clinical characteristics		
Median (IQR) NIHSS score at admission†	15.0 (12.0-19.0)	15.0 (11.0-19.0)
6-14	362 (52.5)	342 (50.9)
≥15	328 (47.5)	330 (49.1)
Median (IQR) ASPECTS at admission‡	9.0 (8.0-10.0)	9.0 (7.0-10.0)
6-7	170 (24.7)	177 (26.3)
8-10	519 (75.3)	495 (73.7)
Occlusion site:		
ICA occlusion	225 (32.6)	208 (31.0)
MCA occlusion	398 (57.7)	409 (60.9)
M1 segment occlusion	364 (52.8)	359 (53.4)
M2 segment occlusion	34 (4.9)	50 (7.4)
Other	67 (9.7)	55 (8.2)
Alteplase before EVT	268 (38.8)	231 (34.4)
Time parameters—median (IQR), min		
Symptom onset to door	150 (83-270)	169 (80-272)
Symptom onset to randomisation	261 (180-345)	273 (179-352)
Symptom onset to first dose of drug	274.5 (189.0-358.0)	283.0 (194.0-365.0)
Door to groin puncture§	112.0 (77.0-163.5)	112.5 (77.0-157.0)
Groin puncture to revascularisation ¶	60.0 (40.0-95.0)	60.0 (38.0-94.0)
First dose of drug to revascularisation**	70.0 (46.0-115.0)	77.0 (45.0-115.0)
eTICI score after EVT††		
0-2A	35 (5.1)	27 (4.0)
2B-3	648 (94.9)	641 (96.0)

ASPECTS=Alberta Stroke Program Early CT Score; eTICI=extended Thrombolysis in Cerebral Infarction; EVT=endovascular therapy; ICA=internal carotid artery; IQR=interquartile range; MCA=middle cerebral artery; NIHSS=National Institutes of Health Stroke Scale.
*Based on self-report.
†Scores on NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits.
‡Scores on ASPECTS range from 0 to 10, with lower scores indicating more severe ischaemic core lesion; 1 patient in edaravone dexborneol group with missing data of ASPECT score at admission.
§Data were analysed for 1349 patients; 11 who patients did not undergo endovascular therapy and 2 patients who had missing data on puncture time were excluded from this analysis.
¶Data were analysed for 1287 patients; 11 patients who did not receive EVT, 62 patients who did not reach revascularisation, and 2 patients who had missing data on puncture time were excluded from this analysis.
**Data were analysed for 1289 patients; 11 patients who not receive EVT and 62 patients who did not reach revascularisation were excluded from this analysis.
††Data were analysed for 1349 patients; 11 patients who did not undergo endovascular therapy were excluded from this analysis.

edaravone dexborneol group and 302 (55.5%) of 544 in the placebo group achieved a modified Rankin Scale score of 0-2 at 90 days (risk ratio 1.12, 95% CI 1.00 to 1.25; risk difference 5.7%, 0.0% to 11.5%; P=0.05) (appendix S10).

For secondary efficacy outcomes, statistical analyses did not indicate a significant association between the intervention and the ordinal modified Rankin Scale score at 90 days (P=0.38). For excellent functional outcome, 277 (40.2%) of 689 patients in

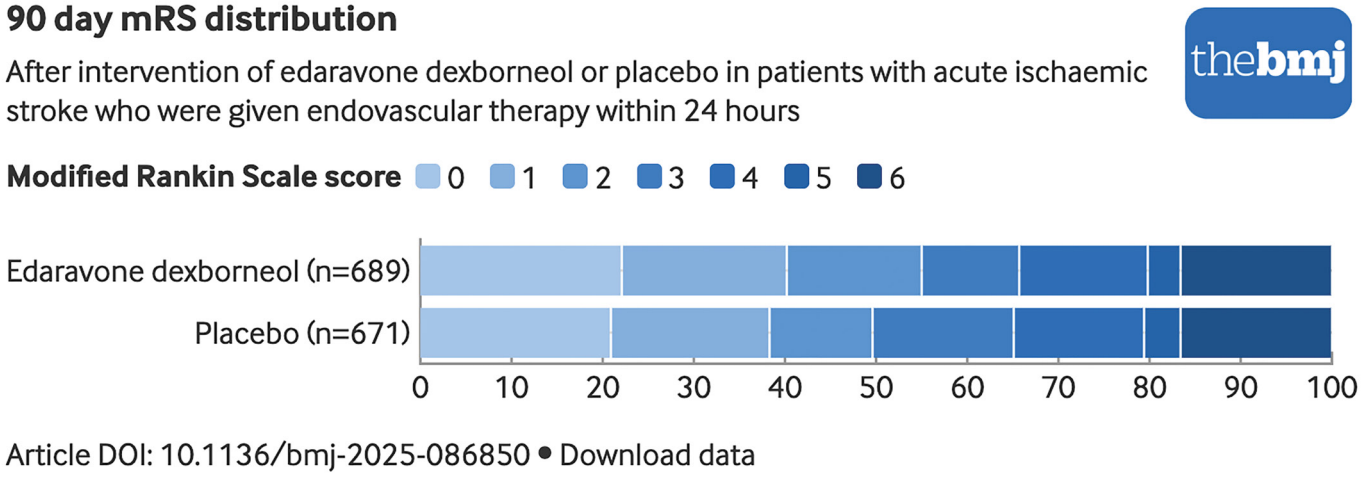


Fig 2 | Modified Rankin Scale score at 90 days. Scores on modified Rankin Scale are shown for patients in edaravone dexborneol group (n=689) and placebo group (n=671). Scores range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability (requiring some help but able to walk unassisted); 4, moderately severe disability (unable to attend body needs and unable to walk); 5, severe disability (requiring constant nursing care and attention); and 6, death. Treatment with edaravone dexborneol was likely to achieve functional independence (score of 0- 2 on modified Rankin Scale) at 90 days, with risk ratio of 1.11 (95% confidence interval 1.00 to 1.23) and risk difference of 5.4% (0.1% to 10.7%) (P=0.05). An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/26783154/

the edaravone dexborneol group and 257 (38.3%) of 671 in the placebo group achieved a modified Rankin Scale score of 0-1 at 90 days (risk ratio 1.05, 95% CI 0.92 to 1.20; risk difference 1.9%, −3.3% to 7.1%; P=0.47). Furthermore, treatment with edaravone dexborneol was not associated with improvement in the predefined secondary outcomes, which included recurrence of stroke, changes in NIHSS score at 10-14 days from baseline, and the proportion of patients with a reduction of ≥4 in NIHSS score by day 10 from baseline (table 2). We noted similar results in the per protocol analysis (appendix S10).

Predefined subgroup analysis suggested that heterogeneity of treatment effects occurred mainly in patients with ASPECTS 8-10 on admission and with a presence of mismatch defined as NIHSS ≥10 and ASPECTS ≥9 or NIHSS ≥20 and ASPECTS ≥7. Edaravone dexborneol was associated with a 13.0% absolute increase in functional independence (risk ratio 1.29, 95% CI 1.10 to 1.52; risk difference 13.0%, 5.6% to 20.3%), compared with no significant difference in the non-mismatch subgroup (P for interaction=0.003) (fig 3 and fig 4).

Safety outcomes

Serious adverse events occurred in 188 (27.2%) of 690 patients in the edaravone dexborneol group and 173 (25.7%) of 672 in the placebo group (risk ratio 1.06, 95% CI 0.89 to 1.26; risk difference 1.5%, −3.2% to 6.2%; P=0.53). We found no significant differences in secondary safety outcomes between the groups (table 2). All serious adverse events and adverse events that occurred during the trial are listed by categories in appendix S12 and S13.

Discussion

In patients with acute ischaemic stroke who underwent endovascular thrombectomy within 24 hours of symptom onset, edaravone dexborneol was associated with possibly improved functional independence at 90 days, compared with placebo, without increased safety events. This effect was predominantly observed in the subgroup of patients who presented with a mismatch profile.

Comparison with other studies

In contrast to previous studies, such as the TASTE trial (Treatment of Acute Ischaemic Stroke with Edaravone Dexborneol)[13] and the TASTE-SL trial (Treatment of Acute Ischaemic Stroke with Sublingual Edaravone Dexborneol),[23] which enrolled patients either beyond the reperfusion window or without endovascular thrombectomy, our study specifically focused on the reperfusion population. The TASTE trial was designed to investigate the effects of edaravone dexborneol versus edaravone on 90 day functional outcome in patients with acute ischaemic stroke and included 1165 patients who did not receive reperfusion therapy within 48 hours of symptom onset. Although a more favourable functional outcome was reported (67.18% *v* 58.97%; odds ratio 1.42, 95% CI 1.12 to 1.81; P=0.004), the generalisability of these results to contemporary reperfusion practice remains limited. Similarly, the TASTE-SL trial showed a benefit of sublingual edaravone dexborneol compared with placebo in patients with acute ischaemic stroke within 48 hours of onset; however, the enrolled population also consisted of patients within this extended time window and excluded those receiving endovascular

Table 2 | Efficacy and safety outcomes at 90 days. Values are numbers (percentages) unless stated otherwise

	Edaravone dexborneol (n=690)	Placebo (n=672)	Risk ratio (95% CI)	Risk difference (95% CI)	P value
Primary efficacy outcome					
mRS score of 0-2 at 90 days*	379/689 (55.0)	333/671 (49.6)	1.11 (1.00 to 1.23)	5.4 (0.1 to 10.7)	0.05
Secondary efficacy outcomes					
Median (IQR) ordinal mRS score at 90 days*	2 (1-4)	3 (1-4)	-	-	0.38
0	152/689 (22.1)	140/671 (20.9)			
1	125/689 (18.1)	117/671 (17.4)			
2	102/689 (14.8)	76/671 (11.3)			
3	74/689 (10.7)	104/671 (15.5)			
4	97/689 (14.1)	96/671 (14.3)			
5	25/689 (3.6)	27/671 (4.0)			
6	114/689 (16.5)	111/671 (16.5)			
mRS score of 0-1 at 90 days*	277/689 (40.2)	257/671 (38.3)	1.05 (0.92 to 1.20)	1.9 (−3.3 to 7.1)	0.47
Recurrence of stroke	10/686 (1.5)	8/667 (1.2)	1.22 (0.48 to 3.06)	0.3 (−0.1 to 1.5)	0.68
Mean (SD) changes in NIHSS score at 10-14 days from baseline†	−7.1 (7.7)	−7.0 (8.3)	−0.1 (−1.0 to 0.8)‡	–	0.81
NIHSS score reduced ≥4 at day 10 from baseline†	479/655 (73.1)	478/639 (74.8)	0.98 (0.92 to 1.04)	−1.7 (−6.5 to 3.1)	0.49
Primary safety outcome					
Serious adverse events	188/690 (27.2)	173/672 (25.7)	1.06 (0.89 to 1.26)	1.5 (−3.2 to 6.2)	0.53
Secondary safety outcomes					
All cause mortality within 90 days	114/690 (16.5)	111/672 (16.5)	1.00 (0.79 to 1.27)	0.0 (−3.9 to 3.9)	>0.99
Symptomatic intracranial haemorrhage within 36 h‡	36/683 (5.3)	43/658 (6.5)	0.81 (0.52 to 1.24)	−1.3 (−3.8 to 1.3)	0.33
Early neurological deterioration	73/680 (10.7)	82/663 (12.4)	0.87 (0.65 to 1.17)	−1.6 (−5.1 to 1.8)	0.35
Adverse events	354/690 (33.0)	332/672 (49.4)	1.04 (0.93 to 1.15)	1.9 (−3.4 to 7.2)	0.48

CI=confidence interval; IQR=interquartile range; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale.
*mRS scores range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.
†NIHSS scores range from 0 to 42, with higher scores indicating greater stroke severity. Mean difference derived from linear regression was reported for changes in NIHSS score at 10 to 14 days from baseline.
‡Symptomatic intracranial haemorrhage was defined by Heidelberg Bleeding Classification.

treatment. These differences in treatment context and timing restrict the applicability of their findings to current standards of care in the reperfusion era.

Building on these findings, the population enrolled in the TASTE-2 study comprised patients who received endovascular treatment within 24 hours of symptom onset, aligning with the Stroke Treatment Academic Industry Round table principles for cytoprotective agents.[8 24] The baseline median NIHSS score for patients in this trial was 15 (interquartile range 11-19), markedly higher than the baseline median NIHSS scores of 6 (5-8) observed in the TASTE trial and 7 (7-8) in the TASTE-SL trial. This indicates that the TASTE-2 trial population primarily consisted of patients with moderate to severe strokes. Given the more severe condition of the enrolled patients, as evidenced by the proportion of modified Rankin Scale score 4-6 at 90 days exceeding one third in both groups, this may contribute to the less pronounced statistical difference in the primary outcome compared with the TASTE and TASTE-SL trials, despite a comparable sample size. This might reflect potentially limited efficacy of edaravone dexborneol as a cytoprotective agent to achieve clinically meaningful reversal in cases of severe stroke.

In this trial, edaravone dexborneol was associated with a 5.4% absolute increase in functional independence compared with placebo, reaching borderline significance. Actually, econometric studies have indicated that effects as low as 2% of the patients moving from modified Rankin Scale score 5 to 2 would save significant costs,[25] and even such small benefits, when averaged over a large number of cases, will in total accrue to a large positive impact on public health.[26] The Stroke Treatment Academic Industry Round table has suggested that for cytoprotective therapies, absolute effect sizes of 2-8% (dichotomous) would be acceptable.[27] Although the primary efficacy outcome reached only borderline statistical significance, this magnitude of difference may still represent a clinically meaningful benefit, particularly in the predefined mismatch subgroup, where a 13.0% (95% CI 5.6% to 20.3%) absolute increase was observed. These findings suggest that patients with favourable clinical imaging profiles may derive greater benefit, consistent with the concept of targeted cytoprotection in the context of endovascular therapy. The study population and beneficial trends observed in this trial align with those reported in a recent phase 2 trial conducted by Chen and colleagues.[28]

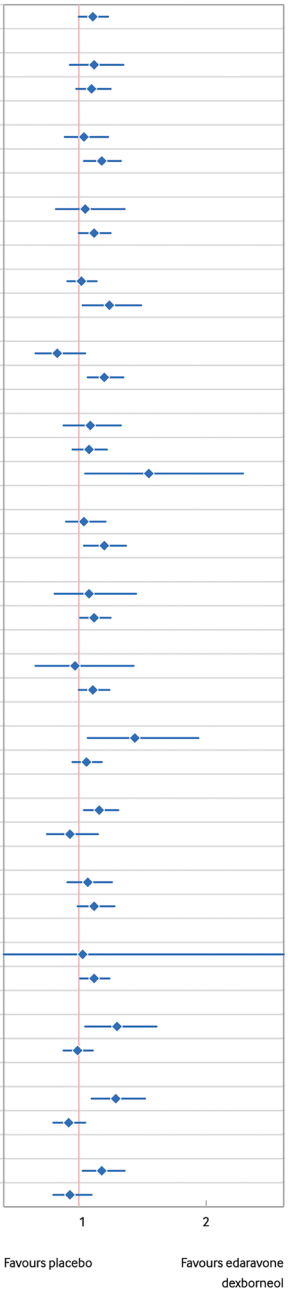
In subgroup analyses, we observed significant treatment interactions for both baseline ASPECTS (8-10 *v* 6-7) and the presence of clinical imaging mismatch (defined as NIHSS score ≥10 and ASPECTS ≥9 or NIHSS score ≥20 and ASPECTS ≥7), supporting the potential benefit of edaravone dexborneol in patients with salvageable penumbral tissue. This suggests that the drug may exert a "penumbra freezing" effect by mitigating ischaemia-reperfusion injury and secondary inflammation when administered before and after endovascular therapy.[6 29] Such a mechanism aligns with the concept of cytoprotection as an adjunct

90 day primary outcome by pre-specified subgroups

Relative risks after intervention of edaravone dexborneol versus placebo in patients with acute ischaemic stroke who underwent endovascular therapy within 24 hours of symptom onset

Interaction between treatment and subgroups

Outcome	Relative risk (95% CI)	P for interaction
Overall	1.11 (1.00 to 1.23)	
Sex		0.93
Female	1.12 (0.93 to 1.35)	
Male	1.10 (0.98 to 1.25)	
Age		0.053
>65	1.04 (0.89 to 1.23)	
≤65	1.18 (1.04 to 1.33)	
Previous stroke		0.47
Yes	1.05 (0.82 to 1.36)	
No	1.12 (1.00 to 1.25)	
NIHSS score at admission		0.34
6-15	1.02 (0.91 to 1.14)	
>15	1.24 (1.03 to 1.49)	
ASPECT at admission		0.002
6-7	0.83 (0.66 to 1.05)	
8-10	1.20 (1.07 to 1.35)	
Occlusion site		0.82
ICAS occlusion	1.09 (0.88 to 1.33)	
MCA occlusion	1.08 (0.95 to 1.22)	
Other	1.55 (1.05 to 2.29)	
Previous hypertension		0.09
Yes	1.04 (0.90 to 1.21)	
No	1.20 (1.04 to 1.37)	
Previous diabetes		0.63
Yes	1.08 (0.81 to 1.45)	
No	1.12 (1.01 to 1.25)	
Previous hypercholesterolaemia		0.63
Yes	0.97 (0.66 to 1.43)	
No	1.11 (1.00 to 1.24)	
Coronary heart disease		0.1
Yes	1.44 (1.07 to 1.94)	
No	1.06 (0.95 to 1.18)	
Time from symptom onset		0.08
< 6 hours	1.16 (1.04 to 1.31)	
≥6 hours	0.93 (0.75 to 1.15)	
Bridging therapy		0.77
Yes	1.07 (0.91 to 1.26)	
No	1.12 (0.99 to 1.28)	
eTICI score		0.63
0-2A	1.03 (0.41 to 2.61)	
2B-3	1.12 (1.01 to 1.24)	
Mismatch 1		0.06
Yes	1.30 (1.05 to 1.61)	
No	0.99 (0.88 to 1.11)	
Mismatch 2		0.003
Yes	1.29 (1.10 to 1.52)	
No	0.92 (0.80 to 1.05)	
Mismatch 3		0.06
Yes	1.18 (1.03 to 1.36)	
No	0.93 (0.80 to 1.10)	



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ASPECTS=Alberta Stroke Program Early CT Score; CI=confidence interval; ICA=internal carotid artery; MCA=middle cerebral artery; NIHSS=National Institutes of Health Stroke Scale. Mismatch 1 defined as NIHSS score >15 and ASPECTS score ≥8; mismatch 2 defined as NIHSS score ≥10 and ASPECTS score ≥9 or NIHSS score ≥20 and ASPECTS score ≥7; mismatch 3 defined as NIHSS score ≥10 and ASPECTS score ≥8 or the NIHSS score ≥20 and ASPECTS score ≥6

Fig 3 | Primary outcome by pre-specified subgroups (relative risks). Significantly greater likelihood of achieving functional independence with edaravone dexborneol, compared with placebo, was observed in predefined subgroups of ASPECTs and mismatch (defined as NIHSS score ≥10 and ASPECTS ≥9 or NIHSS score ≥20 and ASPECTS ≥7), with P for interaction <0.05. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/26783332/

to reperfusion. However, as these insights arise from subgroup analyses, they remain exploratory and warrant validation in future prospective studies.

Notably, none of the secondary outcomes, including ordinal analysis of the modified Rankin Scale score and the proportion of patients achieving a modified Rankin Scale score of 0-1, showed statistically significant differences. Consequently, the primary outcome of this trial should be interpreted with caution. We propose several factors that might explain the neutral results observed for the secondary outcomes, particularly for the modified Rankin Scale score 0-1 endpoint. Firstly, the trial enrolled patients with moderate to severe stroke, in whom near complete recovery (modified Rankin Scale score 0-1) following edaravone dexborneol treatment is inherently difficult to achieve. Secondly, the modified Rankin Scale is a broad categorical scale with subjective assessment components, leading to potential inter-rater variability.[30] In particular, discrimination between modified Rankin Scale scores of 1 and 2 is often subtle, and in cases of uncertainty assessors may tend to favour a "worse outcome" preference, potentially reducing the observed proportion of patients classified as modified Rankin Scale score 1. Finally, although the possibility that the primary outcome occurred by chance cannot be entirely excluded, exploratory subgroup analysis of the modified Rankin Scale score 0-1 outcome showed a significant treatment-by-subgroup interaction in patients with baseline mismatch (risk difference 7.5%, 95% CI 0.5% to 14.5%; P for interaction=0.04; see appendix S14). This finding aligns with the subgroup analysis of the primary outcome and lends support to the overall conclusions of the trial.

Additionally, the median age, baseline NIHSS score, baseline ASPECTS, and distribution of arterial occlusion sites at admission closely aligned with those reported in the HERMES and AURORA studies,[3 5] indicating that the study participants were representative of the general population undergoing endovascular thrombectomy. However, the proportion of eTICI score achieving 2B-3 following thrombectomy was approximately 95%, markedly higher than the 71-81% reported in the HERMES and AURORA studies.[3 5] This discrepancy may be attributed to the selection criteria for participating centres. The primary objective of this study was to evaluate the efficacy of edaravone dexborneol in patients undergoing reperfusion therapy, with endovascular thrombectomy serving as the cornerstone of treatment. To ensure consistency and minimise variability in treatment outcomes, we selected only those centres that did more than 50 endovascular thrombectomy procedures annually. These kinds of centres possessed well established techniques and substantial experience in endovascular procedures and accounted for approximately 39% of all endovascular thrombectomy centres in China in 2021 (data from internal investigation). Furthermore, the proportion of male participants in this trial was 64.0%, aligning with data from a real world nationwide endovascular thrombectomy registry and several

90 day primary outcome by pre-specified subgroups

Risk differences after intervention of edaravone dexborneol versus placebo in patients with acute ischaemic stroke who underwent endovascular therapy within 24 hours of symptom onset

Interaction between treatment and subgroups

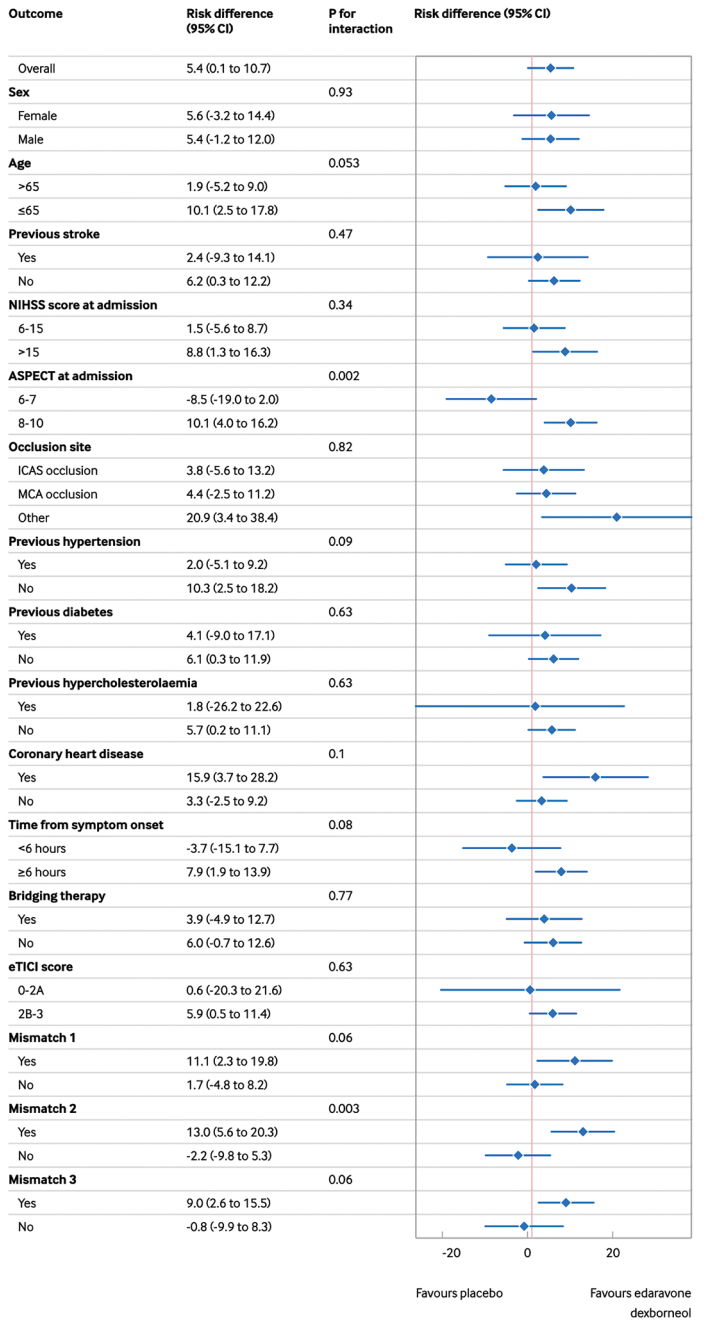

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Fig 4 Primary outcome by pre-specified subgroups (risk differences). Significantly greater likelihood of achieving functional independence with edaravone dexborneol, compared with placebo, was observed in predefined subgroups of ASPECTs and mismatch (defined as NIHSS score ≥10 and ASPECTS ≥9 or NIHSS score ≥20 and ASPECTS ≥7), with P for interaction <0.05. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/26824711/

recent randomised controlled trials of reperfusion therapy in China.[4 31 32]

Strengths and limitations of study

The strengths of this study lie in its adherence to Stroke Treatment Academic Industry Round table recommendations and its specific focus on the endovascular thrombectomy population. The study drugs were administered before endovascular thrombectomy and continued for 10-14 days, encompassing nearly an entire phase of ischaemia-reperfusion injury. Despite the potent efficacy of endovascular thrombectomy in early management of acute ischaemic stroke, the impact of edaravone dexborneol remained evident. Additionally, edaravone dexborneol showed compatibility with alteplase, making it a potential adjunct to both endovascular thrombectomy and intravenous thrombolysis.

This trial had several limitations. Firstly, the effect of edaravone dexborneol compared with placebo was initially overestimated in the endovascular thrombectomy population; the anticipated 20% relative increase in neurological improvement actually amounted to about 11%. This discrepancy ultimately resulted in findings that were marginally significant, probably owing to an insufficient sample size. Secondly, the study population represented only 9.6% of all screened patients, raising concerns about potential selection bias in the clinical trial population; however, most excluded patients were ineligible for endovascular thrombectomy rather than having problems related to the study drug. Thirdly, our study primarily included patients with anterior circulation strokes, and these findings may not be applicable to patients undergoing thrombectomy in the posterior circulation. Fourthly, this trial was conducted exclusively among Chinese patients; therefore, it is important that these findings are validated across diverse ethnic populations. Fifthly, a much higher proportion of eTICI scores reaching 2B-3 (approximately 95%) might indicate centre selection bias, as only specialised centres (doing ≥50 endovascular thrombectomy procedures annually) were included. Although this ensured procedural consistency and minimised variability in thrombectomy performance, it may limit the generalisability of the findings to less experienced settings. Finally, owing to convergence issues, the random centre effect was not included in the analysis; the number of patients included from each centre is listed in appendix S5.

Conclusions

Edaravone dexborneol was well tolerated and associated with a trend of improved functional independence at 90 days in patients with acute ischaemic stroke who underwent endovascular thrombectomy. This treatment effect seemed to be driven by the performance of edaravone dexborneol in the subgroup of patients presenting with a mismatch profile at admission. Further validation through dedicated randomised controlled trials is warranted.

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Ethical approval: The study was approved by the ethics committee at Beijing Tiantan Hospital (No KY2021-177-01) and each participating site. Written informed consent was obtained from the patients or their legal representatives before the study drugs were used

Data sharing: The code used to analyse the data in the paper can be found in appendix S15. The data underlying the findings in this paper are openly and publicly available and can be found at https://www.ncmi.cn//phda/dataDetails.do?id=CSTR:17970.11.A004X.202509.2.V1.0. If you encounter problems when accessing the data, please contact the corresponding author.

Transparency statement: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The public media and clinical sites will report the findings of TASTE-2 and provide the text link to audiences and patients.

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Web appendix: Supplementary appendices