Interaction of brain imaging features and effects of intensive blood pressure lowering after endovascular treatment for acute ischaemic stroke: the pre-specified secondary analyses of ENCHANTED2/MT trial

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Summary

Background The second Enhanced Control of Hypertension and Thrombectomy Stroke Study (ENCHANTED2/MT) was terminated early when the intensive blood pressure lowering to a systolic level of 120 mm Hg or lower, compared to 140–180 mm Hg, was harmful in patients who received successful endovascular therapy for acute ischaemic stroke due to large-vessel occlusion. We aimed to determine the interaction of key brain imaging features and the effect of treatment on clinical outcomes.

Methods ENCHANTED2/MT was a prospective, randomised, open-label, blinded-endpoint, controlled trial that aimed to assess the effectiveness of different intensities of blood pressure control on the functional independence in patients who had received successful endovascular therapy for acute ischaemic stroke from large-vessel occlusion at 44 hospitals in China between July 20, 2020 and March 7, 2022. In these pre-specified secondary analyses, neuroradiologists reviewed the baseline brain images of participants (computerised tomography [CT], CT with angiography [CTA] and digital subtraction angiography [DSA]) blind to treatment allocation, to determine the degree of cerebral infarction on the Alberta Stroke Program Early CT Score (ASPECTS), collateral status according to modified TAN score, and degree of reperfusion on the expanded Treatment In Cerebral Infarction (eTICI) scale. The primary outcome was functional independence, according to the distribution of scores on the modified Rankin scale (range 0 [no symptoms] to 6 [death]) at 90 days. Multivariable logistic regression analysis was done according to the modified intention-to-treat principle in all participants with available outcome data. ENCHANTED2/MT is registered with ClinicalTrials.gov, NCT04140110.

Findings Of 816 participants in the trial, in whom 407 were assigned to more intensive blood pressure lowering and 409 were assigned to less intensive blood pressure lowering treatment, there were 533, 372, and 757 participants with

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available data for ASPECTS, collateral flow, and eTICI analyses, respectively. Intensive blood pressure lowering was associated with worse functional independence in participants with complete reperfusion (eTICI 3: adjusted odds ratio [aOR] 1.51, 95% CI 1.14–2.02) but not in those with incomplete reperfusion (eTICI 2b/c: aOR 1.29, 95% CI 0.73–2.28), without significant interaction ($p_{interaction}$ = 0.82). There was no significant interaction between blood pressure treatment and ASPECTS (0–5 vs. 6–10: aOR 1.27, 95% CI 0.77–2.11 vs. aOR 1.37, 95% CI 0.91–2.07; $p_{interaction}$ = 0.14) on functional independence. However, more intensive blood pressure lowering treatment was associated with worse functional independence in participants with poor collateral status (aOR 1.99, 95% CI 1.11–3.57) compared to those with good collateral status (aOR 0.87, 95% CI 0.53–1.45), with a moderate level of interaction ($p_{interaction}$ = 0.037).

Interpretation Our study indicates that collateral status may help identify patients at risk from intensive blood pressure lowering treatment to a systolic target of 120 mm Hg or lower, in patients undergoing endovascular therapy for acute ischaemic stroke from large-vessel occlusion.

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Keywords: Randomised trial; Acute ischaemic stroke; Endovascular thrombectomy; Blood pressure; Collateral status

Research in context

Evidence before this study

We searched PubMed (from Jan 1, 1970) and Embase (from Jan 1, 1947) on Dec 10, 2024, for publications with relevant text words in the title or abstract in any language that included "ischaemic stroke", "endovascular treatment", "blood pressure", and "imaging features", without any language restriction. No evidence investigating the interaction between imaging features and blood pressure treatment was reported. In the 4 published randomised controlled trials that included patients with acute ischaemic stroke treated with endovascular thrombectomy for elevated blood pressure, intensive blood pressure control led to either a harmful and neutral effect in two studies, respectively. Explanations for these discrepant findings may relate to differences in the characteristics of patients and intensity of blood pressure lowering. The optimal level of blood pressure control after endovascular treatment for acute ischaemic stroke is uncertain.

Added value of this study

Our study has defined an interaction effect in relation to the status of collateral blood flow but not the imaging features of the volume of cerebral infarction or the degree of reperfusion and the effects of more vs. less intensive blood pressure lowering treatment in participants of the ENCHANTED2/MT clinical trial who achieved successful reperfusion with endovascular thrombectomy for acute ischaemic stroke from large-vessel occlusion. In this secondary analysis, intensive blood pressure lowering treatment was harmful in all subgroups of participants based on point estimates except for those with good collateral blood flow. The result may help to elucidate the harms associated with intensive blood pressure lowering treatment that have been observed in previous trials.

Implications of all the available evidence

These results provide evidence that collateral status evaluated on computerised tomographic angiography may serve as an imaging marker for triaging patients over a role for ancillary intensive blood pressure lowering treatment. The optimal level of systolic blood pressure may be higher for patients with poor collateral status in the setting of acute ischaemic stroke. Further clinical trials are necessary to define the safety and efficacy of blood pressure lowering treatment in relation to the brain imaging characteristics of participants, and particularly in relation to collateral blood flow.

Introduction

Despite the success of endovascular thrombectomy for the treatment of patients with acute ischaemic stroke from intracranial large-vessel occlusion, many patients fail to make a good functional independence despite successful reperfusion being achieved.[1] Ancillary control of elevated blood pressure might promote recovery by reducing reperfusion injury and intracerebral haemorrhage.[2,3] Observational studies have been consistent in highlighting the prognostic significance of elevated blood pressure after endovascular thrombectomy.[4,5] However, randomised trials have shown either

harms or a neutral effect of more intensive blood pressure control compared to less intensive blood pressure control in this setting.[6–10] In patients with acute ischaemic stroke from an occlusion of a large-vessel in the anterior circulation, the likelihood of a good functional outcome is dependent upon the volume of infarction, the completeness of recanalisation that is achieved by reperfusion therapy, and the degree of collateral blood flow.[11,12] We investigated these parameters in pre-specified secondary analysis of the second Enhanced Control of Hypertension and Thrombectomy Stroke Study (ENCHANTED2/MT) with the aim of providing information on the effects of intensive blood pressure lowering in relation to the radiological characteristics of cerebral ischaemia after endovascular thrombectomy.

Methods

Study design and participants

ENCHANTED2/MT trial was an investigator-initiated, pragmatic, multicentre prospective, randomised, open-label, blinded-endpoint, parallel-group clinical trial conducted at 45 hospitals in China between July 20, 2020 and March 8, 2022. Details of the study protocol, statistical analysis plan, and primary report of the trial have been published.[6,13] In brief, patients were eligible for participation if they were aged 18 years or older with elevated blood pressure (two or more successive measurements of systolic blood pressure of 140 mm Hg or more over a 10 min period) within 3 h after successful reperfusion being achieved (defined by an expanded Treatment In Cerebral Infarction [eTICI][14] score of 2b or 2c [incomplete reperfusion] or 3 [complete reperfusion]) for acute ischaemic stroke from any large-vessel occlusion. All participants or a representative, provided written informed consent in emergency room. The study protocol was approved by the ethics committee at each participating hospital. The trial is registered at ClinicalTrials.gov (NCT04140110) and the Chinese Clinical Trial Registry (1900027785).

Procedures

After successful reperfusion with endovascular thrombectomy, participants were centrally randomly assigned to a more intensive blood pressure lowering management strategy (target systolic blood pressure 120 mm Hg or lower) or less intensive blood pressure management strategy (target systolic blood pressure in the range 140–180 mm Hg). In both groups of participants, the aim was to achieve the target blood pressure within 1 h of randomisation and for the level to be maintained for 72 h (or until hospital discharge or death, should these events occur earlier). Investigators were requested to upload all the brain scans obtained in participants, including computerised tomography (CT), CT angiography (CTA), and digital subtraction angiography (DSA), according to standardised procedures to a central core laboratory. All these images had to meet certain image acquisition standards and adhere to a minimum set of sequences and parameters, as outlined in the imaging reviewers and imaging protocol provided in the Supplementary Appendix (pp 4 and 82–84).

Investigators uploaded the brain images of participants to the core laboratory in Digital Imaging and Communications in Medicine (DICOM) format and with all personal identifiers replaced with study numbers (pseudo-anonymisation). The images were then checked centrally to ensure the information corresponded to that recorded at the time of randomisation in the clinical database and fulfilled the quality criteria, including for adequate sequences and angiographic viewing angles for each cerebral digital subtraction angiography (DSA) study. After completion of quality checks, the images were uploaded to an electronic archive and allocated to a panel of neuroradiologists via an in-house, web-based, image review system. Reperfusion of a cerebral territory was defined according to expanded Treatment In Cerebral Infarction (eTICI) grading system of grade 2b (50–89%) for 'successful reperfusion', grade 2c (90–99%) for 'extensive reperfusion', and grade 3 (100%) for 'complete or full reperfusion' on DSA.[15] Extent of the collateral circulation was assessed using the modified TAN scale, where collateral filling of 0–50% and 51–100% were graded as 'poor' and 'good', respectively, on the CTA.[16,17] Size of cerebral infarction was assessed using the Alberta Stroke Program Early CT Score (ASPECTS) on baseline non-contrast CT and categorised into two groups, 0–5 and 6–10. All imaging interpretations were performed independently by two board-certified neuroradiologists blinded to clinical outcomes. Interobserver agreement was calculated using Cohen's κ statistics, with κ values of 0.75 for reperfusion, 0.82 for ASPECTS, and 0.78 for collateral circulation, the discrepancies were reviewed by a senior neuroradiologist. Further details of the imaging procedures are outlined in the Appendix (pp 148–151).

Outcomes

The primary outcome of functional independence, defined by a shift in the range of scores on the modified Rankin scale between groups at 90 days, and all the secondary outcomes have been reported elsewhere.[6] These outcomes were ascertained and adjudicated as described in the protocol and primary report of the trial. Good and poor functional independence were defined as mRS 0–2 and 3–6 at 90 days, respectively. Secondary outcomes included dichotomous analysis of scores on the mRS at 90 days (3–6 [disability or death] vs. 0–2, and 3–5 [major disability] vs. 0–2 [independent function] in survivors), death or neurological deterioration at Day 7 according to shift to a higher NIHSS score, serious adverse events, and symptomatic intracranial haemorrhage.

Statistical analysis

These analyses was pre-specified in the study protocol and statistical analysis plan to identify any heterogeneity in the effects of more intensive blood pressure according to key brain imaging parameters (Appendix pp 46, 141–142, and 182).[18] The treatment effects of more-vs. less-intensive blood pressure lowering treatment on outcomes were determined in ordinal logistic regression models. The analysis for each subgroup was performed by adding the variable as well as its interaction with the intervention as fixed effects to the model. In the main model, the inputs were treatment allocation as a fixed effect, site as a random effect, and time from onset to reperfusion and baseline score on the National Institutes of Health stroke scale (NIHSS) as fixed covariates. Proportional odds regression models were used to determine the treatment effects on the full distribution of scores of the modified Rankin scale across the subgroups of eTICI, ASPECTS and mTAN scores; the proportional odds assumption was fulfilled in all models. The association of ASPECTS score (0–5 vs. 6–10), eTICI (2b/c vs. 3), and collateral status (good vs. poor) with functional independence, death, and symptomatic intracerebral haemorrhage were estimated in logistic regression models with adjustment for the following covariates: time from onset to reperfusion (<6 h vs. ≥6 h), age, sex, ethnicity (H an vs. other), baseline systolic blood pressure, baseline NIHSS score, medical history (stroke, coronary artery disease, diabetes mellitus, atrial fibrillation, hypercholesterolaemia, estimated premorbid level of function according to scores 0 or 1 on the modified Rankin scale, and use of warfarin, aspirin, or other antiplatelet agent) and in-hospital management over the first 7 days (mean systolic blood pressure within 24 h and 72 h). Sensitivity analyses were performed to assess the robustness of the primary findings, including variations in statistical models and handling of missing data through multiple imputation techniques. Data are reported as odds ratio (OR) and 95% confidence intervals (CI). A two-sided p value of <0.05 is considered statistically significant. All analyses were performed with SAS, version 9.3 (SAS Institute Inc).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 816 participants in the trial, 407 were assigned to more intensive blood pressure lowering treatment and 409 to less intensive blood pressure lowering treatment (Fig. 1). Overall, 757 (92.8%), 372 (45.6%), and 533 (65.3%) participants had imaging data suitable for analysis of reperfusion on DSA (eTICI 2b/c vs. 3), collateral status on CTA (good vs. poor), and ASPECTS on NCCT (0–5 vs. 6–10). Further details of the

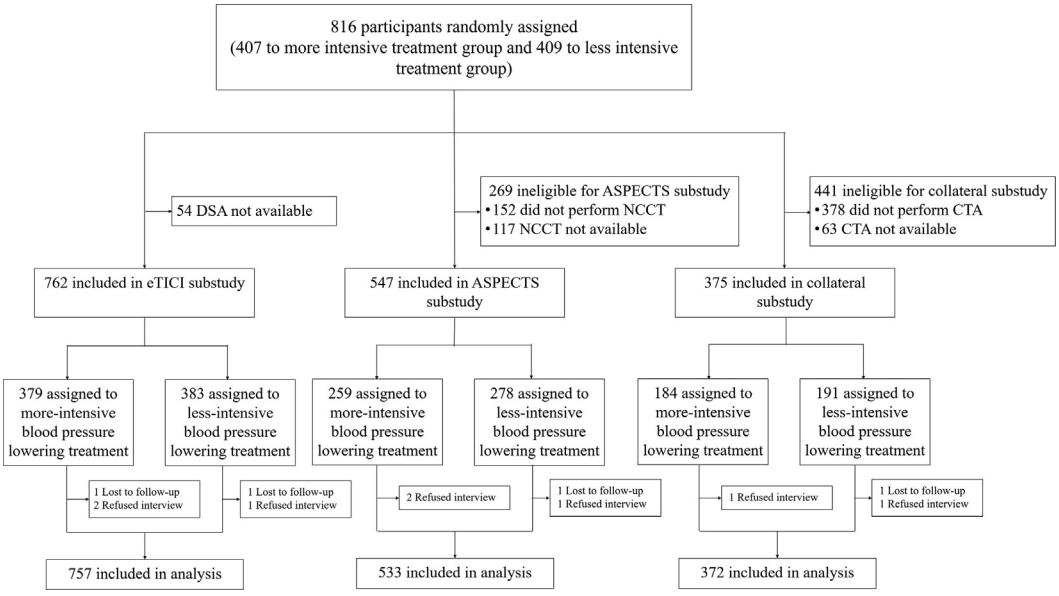

Fig. 1: **Flow of patients**. ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; DSA, digital subtraction angiography; NCCT, non-contrast computed tomography.

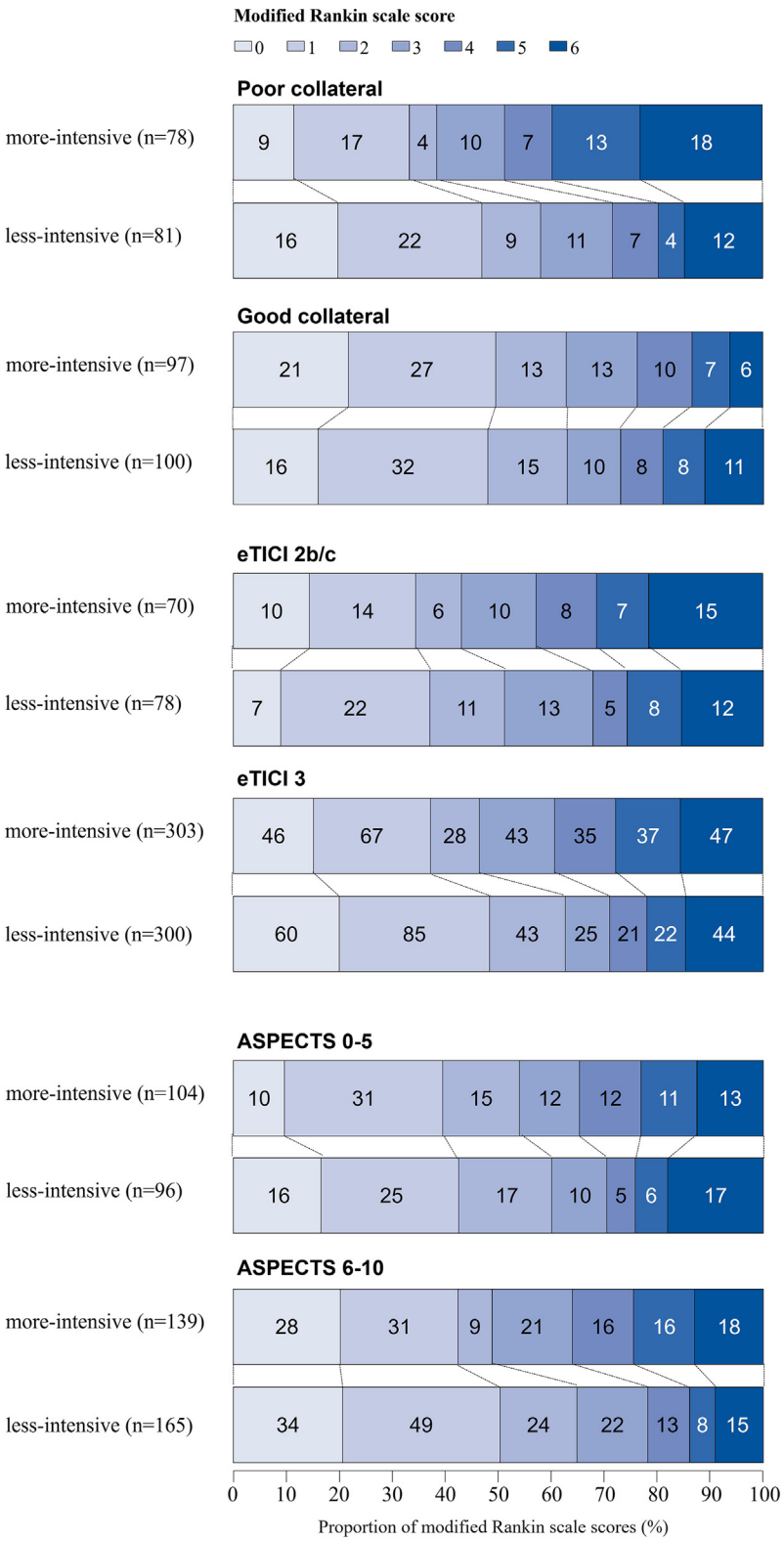

Fig. 2: **The effect of intensive blood pressure lowering treatment on functional outcome after endovascular therapy for acute ischaemic stroke by the degree of collateral blood flow, reperfusion of the occluded vessel, and size of cerebral infarction**. ASPECTS, Alberta Stroke Program Early CT Score; eTICI, expanded Treatment In Cerebral Infarction.

characteristics of participants according to the availability of these particular brain images are provided in the Appendix (pp 102–108) (Fig. 2).

There are no significant differences in most of the characteristics of participants allocated to the more-intensive group and less-intensive group (Table 1, Appendix pp 109 and 122). Participants who achieved eTICI 2b/c had a higher diastolic blood pressure and larger volume of visible cerebral infarction compared to those with eTICI 3 at baseline. Nevertheless, the overall time from the onset of symptoms to the time of initiating endovascular therapy and the time from reperfusion to randomisation were comparable (Table 1). In participants with data on collateral blood flow, there was lower diastolic blood pressure, higher NIHSS scores, shorter time from the onset of symptoms to the diagnostic brain scan, higher use of intravenous thrombolysis, and larger volumes of ischaemic core, perfusion lesion, and mismatch in those with a poor collateral status compared with those with a good collateral status (Appendix p 109). In participants with ASPECTS data, only small imbalances in diastolic blood pressure at baseline were noted (Appendix p 122).

Overall, there was no significant heterogeneity in the effect of intensive blood pressure lowering treatment according to baseline ASPECTS and eTICI score (Table 2, appendix pp 117, 125–127). There was no significant interaction of blood pressure lowering treatment and eTICI (adjusted $p_{interaction}$ = 0.62) or ASPECTS (adjusted $p_{interaction}$ = 0.82). In participants with eTICI grade 3, intensive blood pressure lowering treatment was associated with worse functional outcome (OR 1.51, 95% CI 1.14–2.02; p = 0.0047). However, there was no significant effect of intensive blood pressure lowering treatment in those with eTICI grade 2b/c (OR 1.29, 95% CI 0.73–2.28; p = 0.39), or according to either low (OR 1.27, 95% CI 0.77–2.11; p = 0.35) and high (OR 1.37, 95% CI 0.91–2.07; p = 0.14) ASPECTS. These results were consistent across sensitivity analyses and pre-specified subgroups of characteristics of participants, as shown in Fig. 3 and the Appendix (pp 128–129).

Variable	eTICI 2b/c (n = 150)	eTICI 3 (n = 607)	p value
Mean age, y	65.7 (12.0)	67.6 (12.0)	0.093
Sex			0.054
Male	103/150 (68.7)	365/607 (60.1)	
Female	47/150 (31.3)	242/607 (39.9)	
Mean systolic blood pressure, mm Hg	158.7 (23.2)	158.3 (24.3)	0.87
Mean diastolic blood pressure, mm Hg	90.2 (15.3)	89.1 (15.0)	0.50
Pre-stroke modified Rankin scale score			
0	127/150 (84.7)	504/607 (83.0)	0.70
1	16/150 (10.7)	79/607 (13.0)	
2	7/150 (4.7)	24/607 (4.0)	
Median NIHSS score (severity of neurological deficit)[a]	16 (11–20)	15 (10–20)	0.82
Median GCS score (level of consciousness)[b]	12 (8.0, 15.0)	12.0 (9.0, 15.0)	0.90
Median time from symptom onset to diagnostic brain imaging, h	4.3 (2.3, 7.0)	4.3 (2.0, 8.4)	0.45
Median time from groin puncture to reperfusion, h	1.1 (0.7, 1.7)	1.0 (0.6, 1.5)	0.079
Median time from procedure completion to randomisation, h	1.3 (0.7, 2.2)	1.4 (0.7, 2.0)	0.27
Use of intravenous thrombolysis	51/150 (34.0)	177/607 (29.2)	0.25
Use of general anaesthesia	70/150 (46.7)	246/607 (40.5)	0.17
Mean systolic blood pressure after procedure, mm Hg	158.0 (14.5)	159.7 (14.5)	0.22
Mean diastolic blood pressure after procedure, mm Hg	90.9 (13.4)	88.3 (13.3)	0.032
Brain imaging features			
Visible early ischaemic changes	53/144 (36.8)	224/584 (38.4)	0.73
Visible cerebral infarction lesion	51/144 (35.4)	154/584 (26.4)	0.031
Visible cerebral infarction with mass effect	2/144 (1.4)	19/584 (3.3)	0.23
Side			0.10
Left	79/126 (62.7)	261/478 (54.6)	
Right	47/126 (37.3)	217/478 (45.4)	
CT perfusion abnormalities[c]			
Median volume of ischaemic core, mL[d]	14.0 (0.0, 30.0)	7.0 (0.0, 27.0)	0.055
Median volume of perfusion lesion, mL[e]	110.0 (56.0, 162.0)	94.0 (50.0, 174.0)	0.66
Median volume of mismatch, mL[f]	87.5 (44.0, 138.0)	83.0 (43.0, 147.0)	0.21
Site of occlusion			
A1	2/138 (1.4)	3/519 (0.6)	0.74

(Table 1 continues on next page)

Variable	eTICI 2b/c (n = 150)	eTICI 3 (n = 607)	p value
(Continued from previous page)			
A2	2/138 (1.4)	7/519 (1.3)	
A3	1/138 (0.7)	1/519 (0.2)	
ICA	40/138 (29.0)	134/519 (25.8)	
M1	62/138 (44.9)	255/519 (49.1)	
M2	23/138 (16.7)	87/519 (16.8)	
M3	0/138 (0.0)	3/519 (0.6)	
P1	3/138 (2.2)	4/519 (0.8)	
PCOM	0/138 (0.0)	2/519 (0.4)	
VA	5/138 (3.6)	21/519 (4.0)	
Others	0/138 (0.0)	2/519 (0.4)	
Site of occlusion in anterior circulation	130/138 (94.2)	490/519 (94.4)	0.92
Cause of large-vessel occlusion[g]			0.99
Intracranial atherosclerosis	71/150 (47.3)	289/607 (47.6)	
Extracranial atherosclerosis	6/150 (4.0)	21/607 (3.5)	
Cardioembolism from atrial fibrillation	43/150 (28.7)	176/607 (29.0)	
Cardioembolism from other source	8/150 (5.3)	40/607 (6.6)	
Dissection	4/150 (2.7)	9/607 (1.5)	
Uncertain	18/150 (12.0)	72/607 (11.9)	

Data are or n/N (%). mean (SD), or median (IQR). NIHSS, National Institutes of Health stroke scale; GCS, Glasgow coma scale; eTICIm expanded Treatment In Cerebral Infarction. [a]Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. [b]Scores on the GCS range from 15 (normal) to 3 (deep coma). [c]Volumes assessed with use of RAPID automated software (iSchemaView, Menlo Park, CA, USA). [d]Data available for 209 patients in the more intensive group and 208 patients in the less intensive group. [e]Data available for 205 patients in the more intensive group and 208 patients in the less intensive group. [f]Data available for 202 patients in the more intensive group and 203 patients in the less intensive group. [g]The cause of stroke was assessed according to the medical history, clinical features, and results on digital subtraction angiography.

Table 1: **Baseline characteristics of participants according to the degree of reperfusion after endovascular thrombectomy, according to the expanded Treatment In Cerebral Infarction (eTICI) grading system.**

There was a significant interaction of the effect of blood pressure lowering treatment on functional outcome according to collateral status (adjusted $p_{interaction} = 0.037$) (Table 2, Appendix pp 126–127). In those with poor collateral status, intensive blood pressure lowering treatment was associated with worse functional independence (OR 1.99, 95% CI 1.11–3.57; p = 0.021) compared to those with good collateral status (OR 0.87, 95% CI 0.53–1.45; p = 0.60). Furthermore, there was no interaction between the brain image parameters and the effect of treatment on symptomatic intracranial haemorrhage, mortality, or serious adverse events (Appendix pp 117, 125–127).

Discussion

In this secondary analysis of ENCHANTED2/MT trial, the adverse effect of intensive blood pressure lowering treatment to a systolic target of 120 mm Hg or lower was

	OR	Univariate p value	p interaction	OR	Multivariable p value	p interaction
Reperfusion[a]			0.49			0.62
eTICI 2b/c	1.22 (0.70–2.14)	0.49		1.29 (0.73–2.28)	0.39	
eTICI 3	1.53 (1.15–2.03)	0.0036		1.51 (1.14–2.02)	0.0047	
Infarct core[b]			0.47			0.82
ASPECTS 0–5	1.19 (0.7–1.94)	0.48		1.27 (0.77–2.11)	0.35	
ASPECTS 6–10	1.51 (1.01–2.26)	0.046		1.37 (0.91–2.07)	0.14	
Collateral status[c]			0.012			0.037
Poor	2.19 (1.24–3.86)	0.0068		1.99 (1.11, 3.57)	0.021	
Good	0.84 (0.51–1.36)	0.48		0.87 (0.53–1.45)	0.60	

ASPECTS, Alberta Stroke Program Early CT Score; eTICI, expanded Treatment in Cerebral Infarct; NCCT, non-contrast computed tomography; OR, odds ratio. [a]Reperfusion degree is assessed with eTICI score on DSA, with eTICI 2b/c equivalent to 50–99% reperfusion of the cerebral territory and eTICI 3 equivalent to 100% reperfusion. [b]Infarct core is assessed with ASPECTS score on baseline NCCT, with ASPECTS 0–5 indicating large core and 6–10 indicating small core. [c]Collateral status is assessed with modified Tan score on baseline CTA, with good collateral indicating 51–100% and poor collateral indicating 0–50% collateral filling, respectively.

Table 2: **Likelihood of poor functional outcome by degree of reperfusion, cerebral infarction and collateral blood flow.**

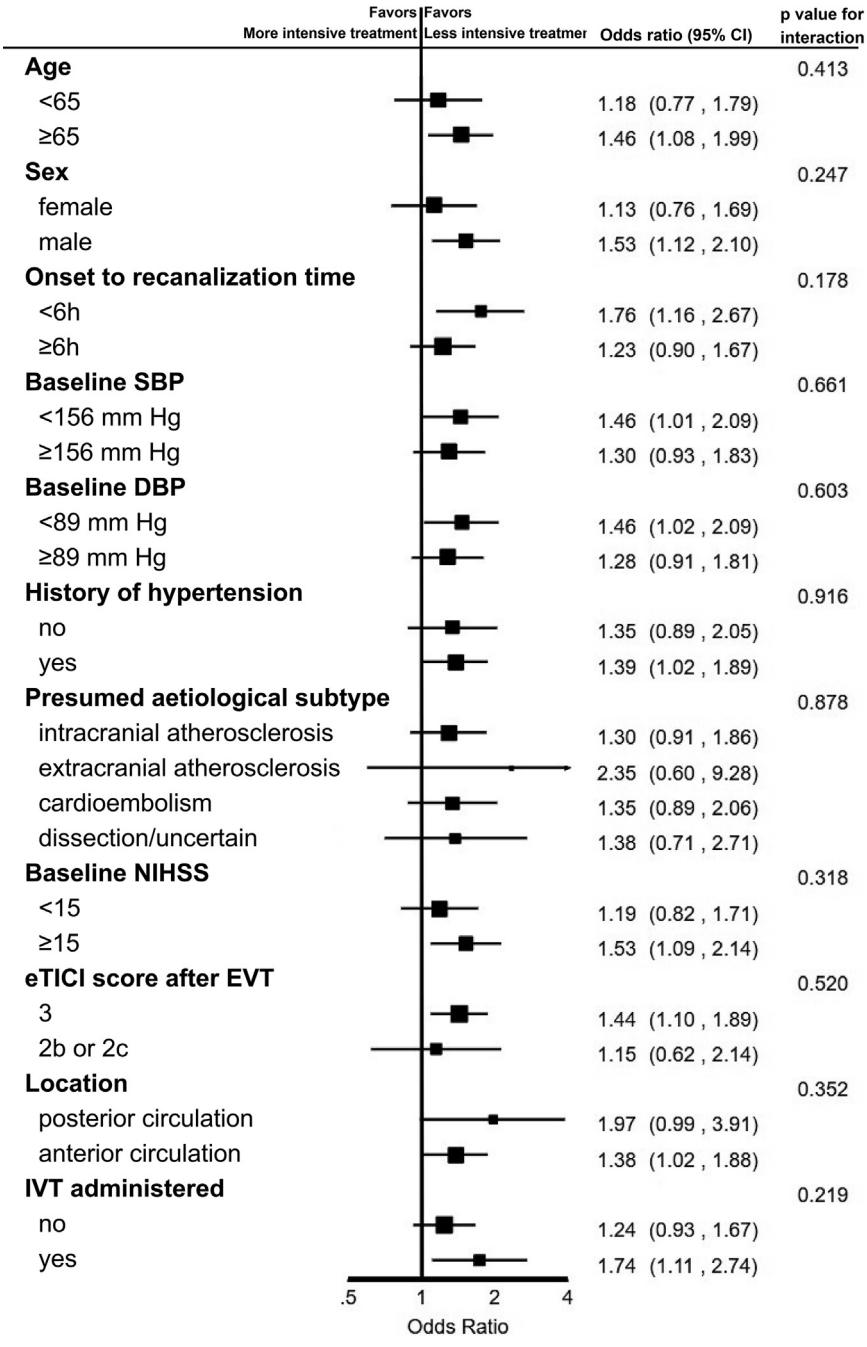

Fig. 3: **Likelihood of favorable functional independence in eTICI substudy**. BP, blood pressure; eTICI, expanded Treatment In Cerebral Infarction; EVT, endovascular thrombectomy; IV, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale.

strongly influenced by the degree of collateral blood flow but not in relation to the other brain imaging parameters of size of cerebral infarction or degree of reperfusion after endovascular therapy for acute ischaemic stroke from large-vessel occlusion ($P_{interaction}$ = 0.037). There were no interaction of the brain imaging parameters and the effect of treatment on symptomatic intracranial haemorrhage, mortality, or serious adverse events. These results may help explain the neutral or harmful effects of intensive blood pressure treatment after endovascular therapy in participants of other randomised controlled trials.

Favourable imaging features of good collateral, high ASPECTS, and high eTICI score are strongly correlated

with functional independence after acute ischaemic stroke, and are used for patient selection and prognosticating the effect of reperfusion therapy.[16,19] While historical controversy existed regarding reperfusion therapy in patients with low ASPECTS, recent randomized controlled trials have demonstrated improved functional outcomes with reperfusion therapy compared to medical management in carefully selected patients with large ischemic cores.[20–22] This evidence supports expanded application of reperfusion therapy in this population when advanced imaging confirms favourable tissue viability profiles. Despite the positive relationship between functional outcomes and imaging features, their role in therapeutic decision making for blood pressure treatment remains poorly established. In our study, a moderate interaction was found between the degree of blood pressure lowering and degree of collateral blood flow rather than ASPECTS or eTICI score, which may be less sensitive to the dynamic aspects of infarct progression and the microcirculation. Conversely, collateral blood flow is directly related to the hemodynamics of salvageable brain tissue. Collateral vessel recruitment is critical for the maintenance of brain tissue and exhibits a heightened sensitivity to fluctuation of systemic blood pressure,[23,24] rendering it more amenable to intensive and sustained blood pressure lowering treatment.

Reperfusion therapy is the mainstay of the treatment of acute ischaemic stroke. Yet, futile reperfusion of the cerebral microcirculation, including distal fragmentation of the clot, constriction of pericytes, activation of neutrophils in capillaries, and collapse of distal arterioles, may all influence the effect of the endovascular treatment on the evolving ischaemic brain in relation to the status of collateral blood flow.[25] Observational studies have shown that patients with good collateral status have a better response to intravenous alteplase and endovascular treatment, slower progression of cerebral ischaemia, and better neurological outcomes. Binder et al. used two photon microscopy and laser speckle cortical imaging to show that mice with poor leptomeningeal collateral, distal arterial segments collapse, and deleterious hyperaemia cause haemorrhage and death after reperfusion.[25] The extent of leptomeningeal collateral also affects the haemodynamics of post-reperfusion blood flow. Most studies have focused on correlating collateral status with functional outcomes, but the interaction between collateral status and blood pressure lowering treatment has been poorly characterised. Impaired reperfusion of the microcirculation despite complete reperfusion could have also contribute to poor clinical outcome. Further analyses from completed trials[6–9] and possibly new trials are needed to better estimate the effect of intensive blood pressure lowering in patients with poor collateral status.

The cerebral microcirculation plays a pivotal role in delivering oxygen to the cells and maintains cerebral perfusion. Recent perfusion imaging studies performed in patients with large vessel occlusion at the end of successful endovascular treatment show high frequencies of areas of hypoperfusion in patients with normal angiograms, indicating the limitation of conventional perfusion imaging in evaluation of the microcirculation.[26] In the Chemical Optimization of Cerebral Embolectomy (CHOICE) trial, the use of adjunct intra-arterial alteplase compared with placebo following thrombectomy resulted in a greater likelihood of excellent neurological outcome at 90 days in patients with large vessel occlusion acute ischaemic stroke and successful reperfusion.[27] The result suggests that the improved functional outcomes may be explained by an amelioration in the microcirculatory reperfusion. This may further explain why more intensive treatment resulted in worse functional outcomes.

We have outlined the main strengths and limitations of our trial elsewhere.[6] For these analyses, all the angiographic images were adjudicated by experienced and trained neuroradiologists masked to the treatment allocation using validated rating scales, which reduced the likelihood of reporting bias. Participating sites were required to perform brain imaging on participants according to a standardised protocol, and a high level of DSA images (92.8%, 757/816) were able to be read centrally. However, we acknowledge that these analyses were performed on study population of relatively small sample size and there were some minor baseline imbalances in the characteristics of participants in the randomized groups that could have contributed some degree of confounding. Despite our best efforts, only 65.3% of NCCT and 45.6% of CTA were available for analyses. A significant proportion of participants had missing collateral status data, and those with missing data differed in baseline characteristics, which may have introduced selection bias. The interaction between collateral status and treatment effect should be interpreted cautiously given the exploratory nature of subgroup analyses and potential for type I error. Although these analyses were planned, we did pre-specify a particular sample size such that these results could related to chance associations overall and through multiple testing. Additionally, our study population was predominantly of Chinese, which may limit the generalizability of our findings to other ethnic groups.

In summary, this analysis of ENCHANTED2/MT indicates an interaction between the effect of intensive blood pressure lowering and the degree of collateral blood flow in patients who received successful endovascular therapy for acute ischaemic stroke due to large-vessel occlusion. Our findings suggest that intensive blood pressure lowering is harmful after endovascular thrombectomy, and this harmful effect is more pronounced in patients with poor collateral circulation on baseline CTA. Further data are needed to better estimate the effect of intensive blood pressure treatment in patients with poor collateral on CTA or DSA.

Contributors

The trial was designed by XZ, JL, PY, Lili S and CSA. All authors contributed to data collection. Data were verified by Yongxin Z, Yongwei Z, HS, LZ, PX, PZ, WH, FS, BT, WC, HH, LZ, CX, TL, YG, YZ, QZ, YG, DD, RZ, Qiang Li, QH, YX, XC, Lingli S, and QL provided comments on the study design and were responsible for data collection and quality control procedures. LB wrote the statistical analysis plan with input from CSA and Lily S. XR and QL performed the statistical analysis. XZ wrote the first draft with input from PY, Yongwei Z, Lily S and CSA. All authors contributed to manuscript writing and critical reviewing of the manuscript and had full access to all the study data. All authors had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Individual, deidentified participant data used in these analyses will be shared on request from any qualified investigator following approval of a protocol and signed data access agreement via both the trial steering committee and the Research Office of The George Institute for Global Health, Australia.

Declaration of interests

CSA reports funding from the National Health and Medical Research Council (NHMRC) of Australia, Medical Research Foundation (MRF) of the UK and AstraZeneca. He also reports being President-elect of the World Stroke Organisation, Editor-in-Chief of Cerebrovascular Diseases and the Chairperson of the Data and Safety Monitoring Board of several investigator-initiated randomized controlled trials. JL and PY reports funding from the Shanghai Hospital Development Center, China Stroke Prevention, Shanghai Changhai Hospital, Science and Technology Commission of Shanghai Municipality, Takeda China, Hasten Biopharmaceutic, Genesis Medtech, and Penumbra.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103197.

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