Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-endpoint, randomised controlled trial

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Summary

Background The optimum systolic blood pressure after endovascular thrombectomy for acute ischaemic stroke is uncertain. We aimed to compare the safety and efficacy of blood pressure lowering treatment according to more intensive versus less intensive treatment targets in patients with elevated blood pressure after reperfusion with endovascular treatment.

Methods We conducted an open-label, blinded-endpoint, randomised controlled trial at 44 tertiary-level hospitals in China. Eligible patients (aged ≥18 years) had persistently elevated systolic blood pressure (≥140 mm Hg for >10 min) following successful reperfusion with endovascular thrombectomy for acute ischaemic stroke from any intracranial large-vessel occlusion. Patients were randomly assigned (1:1, by a central, web-based program with a minimisation algorithm) to more intensive treatment (systolic blood pressure target <120 mm Hg) or less intensive treatment (target 140–180 mm Hg) to be achieved within 1 h and sustained for 72 h. The primary efficacy outcome was functional recovery, assessed according to the distribution in scores on the modified Rankin scale (range 0 [no symptoms] to 6 [death]) at 90 days. Analyses were done according to the modified intention-to-treat principle. Efficacy analyses were performed with proportional odds logistic regression with adjustment for treatment allocation as a fixed effect, site as a random effect, and baseline prognostic factors, and included all randomly assigned patients who provided consent and had available data for the primary outcome. The safety analysis included all randomly assigned patients. The treatment effects were expressed as odds ratios (ORs). This trial is registered at ClinicalTrials.gov, NCT04140110, and the Chinese Clinical Trial Registry, 1900027785; recruitment has stopped at all participating centres.

Findings Between July 20, 2020, and March 7, 2022, 821 patients were randomly assigned. The trial was stopped after review of the outcome data on June 22, 2022, due to persistent efficacy and safety concerns. 407 participants were assigned to the more intensive treatment group and 409 to the less intensive treatment group, of whom 404 patients in the more intensive treatment group and 406 patients in the less intensive treatment group had primary outcome data available. The likelihood of poor functional outcome was greater in the more intensive treatment group than the less intensive treatment group (common OR 1·37 [95% CI 1·07–1·76]). Compared with the less intensive treatment group, the more intensive treatment group had more early neurological deterioration (common OR 1·53 [95% 1·18–1·97]) and major disability at 90 days (OR 2·07 [95% CI 1·47–2·93]) but there were no significant differences in symptomatic intracerebral haemorrhage. There were no significant differences in serious adverse events or mortality between groups.

Interpretation Intensive control of systolic blood pressure to lower than 120 mm Hg should be avoided to prevent compromising the functional recovery of patients who have received endovascular thrombectomy for acute ischaemic stroke due to intracranial large-vessel occlusion.

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Research in context

Evidence before this study

We searched PubMed (from Jan 1, 1970) and Embase (from Jan 1, 1947) on Aug 31, 2022, for publications with relevant text words in the title or abstract in any language that included "ischaemic stroke", "endovascular therapy" or "endovascular treatment" or "thrombectomy", "blood pressure", or "blood pressure lowering". Studies were eligible for inclusion if they assessed the effect of blood pressure lowering treatment on clinical outcome. We identified one completed randomised controlled trial (BP-TARGET), which did not show superior efficacy of a more intensive versus less intensive blood pressure lowering strategy on the risk of radiographic intraparenchymal haemorrhage after successful endovascular therapy. However, this randomised trial was small and used a short-term surrogate endpoint as the primary outcome rather than longer term functional status. We also searched the registered trials on ClinicalTrials.gov and identified five ongoing trials, including ENCHANTED2, BEST-II, OPTIMA-BP, CRISIS I, and HOPE, all of which are assessing the effects of intensive blood pressure lowering with different systolic targets on functional outcome at 90 days, and one pilot trial (DETECT) designed for feasibility. A 2022 meta-analysis of individual patient data, which included seven published studies, showed that increasing mean systolic blood pressure after endovascular thrombectomy is associated with a lower odds of functional improvement. Five retrospective observational studies were included in a 2020 meta-analysis, in which a reduction in systolic blood pressure was inversely associated with worse outcomes after successful reperfusion by thrombectomy, while a narrative review provided additional information that less blood pressure variability after successful thrombectomy was associated with favourable outcomes. As a result of limitations in study design and methodologies, neither the completed randomised trial nor the previous meta-analyses provide sufficient evidence on which to recommend a policy regarding the optimum target for blood pressure lowering after successful endovascular therapy.

Added value of this study

ENCHANTED2/MT is the largest randomised controlled trial of intensive blood pressure lowering after endovascular therapy for acute ischaemic stroke from intracranial large-vessel occlusion to date. The primary result was that more intensive blood pressure lowering to a systolic target of less than 120 mm Hg was associated with worse functional outcomes (measured on the modified Rankin scale) at 90 days when compared with a less intensive systolic target of 140–180 mm Hg, and this adverse effect manifested as neurological deterioration within 7 days of commencing treatment. There was insufficient evidence to show heterogeneity on the primary outcome across predefined patient subgroups. The incidence of symptomatic intracranial haemorrhage, mortality, and serious adverse events did not significantly differ between the randomised groups.

Implications of all the available evidence

Overall, these results indicate that a more intensive blood pressure management strategy to achieve a systolic blood pressure target of less than 120 mm Hg after successful endovascular thrombectomy should be avoided in clinical practice. Combined with the results of the BP-TARGET and ENCHANTED trials, which assessed the effects of intensive blood pressure lowering after thrombolysis treatment in individuals receiving endovascular treatment and in a broad range of patients, respectively, with acute ischaemic stroke, the results suggest that the benefit of blood pressure lowering in reducing the risk of reperfusion-related intracranial haemorrhage might not extend beyond a certain systolic blood pressure target of less than 140 mm Hg. Although the findings of ENCHANTED2/MT showed that more intensive blood pressure lowering is harmful, the most appropriate level of blood pressure control for optimum outcomes after endovascular thrombectomy for acute ischaemic stroke was not defined. Further randomised trials to resolve this area of clinical uncertainty are warranted.

Introduction

Endovascular thrombectomy, with or without intravenous thrombolysis, is an established treatment for patients with acute ischaemic stroke due to intracranial large-vessel occlusion in the brain,[1] widely transforming the organisation of stroke services.[2] By eliminating the site of obstruction or clot in an artery through the endovascular insertion of a stent retriever, aspiration, or combination of such devices (ie, recanalisation), blood flow can be effectively restored (ie, reperfusion) to an ischaemic area in the brain, the so-called penumbral tissue. However, many patients have poor functional recovery despite the achievement of a good radiological result, and the risks of symptomatic intracranial haemorrhage and other forms of reperfusion injury remain high;[3,4] therefore, there is much interest in the use of adjuvant approaches to protect or sustain penumbral tissue from reperfusion injury after endovascular thrombectomy.[5] Blood pressure might represent a modifiable factor to prevent reperfusion injury, since it is often elevated, readily modifiable, and observational studies have clearly shown it has prognostic significance in acute ischaemic stroke with endovascular treatment.[6–12] Complex relationships are likely to exist between blood pressure, efficiency of collateral cerebral blood flow, degree of reperfusion, size of the ischaemic penumbra, and clinical outcomes in acute ischaemic stroke.[13] Thus, in the absence of randomised evidence, clinical guidelines[14,15] have continued to recommend a conservative level of blood pressure control (systolic pressure of <180 mm Hg and diastolic pressure of 105 mm Hg) before and after endovascular thrombectomy, consistent with levels recommended for patients eligible

for intravenous thrombolysis after acute ischaemic stroke. However, increasing confidence in the use of endovascular thrombectomy, a desire to reduce the risks of ischaemia-reperfusion injury, and influential data on the association between blood pressure at the time of presentation and subsequent clinical outcomes,[7] has shifted opinion towards more intensive control of systolic blood pressure in research[16] and practice.[17] For example, a survey across 58 institutions in the USA showed a wide variation in the systolic blood pressure targets used by clinicians according to the success of endovascular thrombectomy: for the minority of patients who had poor reperfusion after endovascular thrombectomy, most clinicians aim for a systolic blood pressure of 180 mm Hg or lower, whereas for patients with good reperfusion, 5%, 36%, 21%, and 28% of clinicians adhered to systolic blood pressure targets of less than 120, 120–139, 140–159, and 180 mm Hg or lower, respectively, in the 24 h after thrombectomy.[17] Previous meta-analyses of observational studies provide further support for the adverse effects of increasing systolic blood pressure after endovascular thrombectomy, with mean, maximum, and fluctuating levels, all being associated with a greater likelihood of symptomatic intracerebral haemorrhage and death, and lower odds of achieving functional independence.[8,12]

The international Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED),[18] done in a broad range of patients treated with thrombolysis for acute ischaemic stroke before the uptake of endovascular thrombectomy, showed that achieving a lower systolic blood pressure target (<140 mm Hg) compared with that recommended in guidelines (<180 mm Hg) was safe and significantly reduced the risk of major intracerebral haemorrhage. However, this approach to intensive treatment had no effect on functional outcome, according to scores on the modified Rankin scale at 90 days. The 2021 BP-TARGET study[19] showed that more intensive systolic blood pressure control over 24 h (mean achieved in 24 h, 128 mm Hg) versus standard systolic blood pressure control (mean achieved in 24 h, 138 mm Hg) was similarly safe but did not improve outcome specifically in 324 patients after endovascular thrombectomy for acute ischaemic stroke from large-vessel occlusion of the anterior circulation. One explanation for the neutral effects on functional recovery in these trials was the modest difference in the achieved blood pressure between the randomised groups. Therefore, in this study (Enhanced Control of Hypertension and Thrombectomy Stroke Study [ENCHANTED2/MT]) we aimed to assess the safety and efficacy of more intensive blood pressure management compared with less intensive treatment after successful reperfusion following endovascular thrombectomy.

Methods

Study design and participants

ENCHANTED2/MT was an investigator-initiated, pragmatic, multicentre, open-label, blinded-endpoint randomised controlled phase 3 trial, done at 44 tertiary-level hospitals in China, with the intention of extending to other countries on the basis of funding availability. We purposefully designed our study to ensure a beneficial effect on functional outcome could be detected from a reduction in the likelihood of major intracranial haemorrhage and other forms of reperfusion injury. A more intensive treatment target (<120 mm Hg) was identified as optimal in a large multicentre observational study,[9] and, when compared with a more conservative flexible range (140–180 mm Hg), would allow a large separation in blood pressure to be achieved between randomised groups. The protocol and statistical analysis plan have been published elsewhere,[19,20] and are available in the appendix (pp 57, 130).

Adults (aged ≥18 years) were eligible if they had elevated blood pressure (≥2 successive measurements of systolic blood pressure ≥140 mm Hg for >10 min) within 3 h of successful reperfusion (defined by an expanded Treatment In Cerebral Infarction [eTICI] score of 2b or 2c [incomplete reperfusion] or 3 [complete reperfusion])[21] for acute ischaemic stroke from any large vessel occlusion. The treating investigator had to be uncertain about the balance of benefits and risks of the different approaches to blood pressure lowering after reperfusion. Although systolic blood pressure might have been temporarily low, either before or during endovascular thrombectomy (eg, if general anaesthesia was used), persistent elevated blood pressure after the procedure was mandatory for inclusion.

Key exclusion criteria included that a patient was unlikely to benefit from therapy (eg, advanced dementia or high likelihood of death within 24 h post-endovascular thrombectomy), as judged by the responsible treating clinician; had another medical illness that would interfere with outcome assessments and follow-up (eg, known significant pre-stroke disability, with estimated scores of 3–5 on the modified Rankin scale, advanced cancer or dialysis for renal failure); had a definite indication or contraindication to either more intensive or less intensive blood pressure management; had a specific contraindication to any of the antihypertensive drugs to be used; had aortic isthmus stenosis or arteriovenous shunt; was lactating; or was participating in another trial that might have interfered with the outcome assessments. Full details of the inclusion and exclusion criteria are provided in the appendix (pp 15–16, 72–73).

The study was approved by the ethics committee of each participating clinical centre and appropriate regulatory agencies. All participants, or their approved surrogate for patients who were too unwell, provided written informed consent.

Randomisation and masking

After confirmation of eligibility, patients were randomly assigned (1:1) via a central web-based program with a minimisation algorithm to balance the stratification factors of site, time from onset of symptoms to

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See **Online** for appendix

reperfusion being achieved (<6 *vs* ≥6 h), and level of neurological impairment on the National Institutes of Health Stroke Scale (NIHSS) at the time of hospital admission (<17 *vs* ≥17 points; range 0–42, with higher scores indicating greater severity). Follow-up evaluations were done at 90 days, either by telephone or in person, by trained certified medical staff masked to treatment allocation. Central adjudication of safety outcomes including death, symptomatic intracranial haemorrhage, and recurrent stroke was done by expert clinicians unaware of treatment assignment.

Procedures

Participants were randomly assigned to a more intensive blood pressure lowering management strategy (target systolic blood pressure <120 mm Hg) or less intensive blood pressure management strategy (target systolic blood pressure 140–180 mm Hg). For both groups, the aim was to achieve the target blood pressure within 1 h of random assignment and to maintain this target for 72 h (or until hospital discharge or death, should these events occur earlier). Blood pressure measurements were frequently recorded on automated devices applied to the non-hemiparetic arm according to standard guideline-recommended procedures,[14] with measurements taken every 15 min in the first hour, hourly between 1 and 6 h, every 6 h between 6 and 24 h, and then twice daily for 6 days (or until hospital discharge or death, if earlier), and uploaded to the research database. Intravenous blood pressure lowering protocols guided the titration of locally available drugs through repeated bolus or infusions to achieve blood pressure goals. A systolic blood pressure of lower than 100 mm Hg was the threshold for cessation of treatment and use of intravenous fluids and inotropes as indicated. All patients were managed in a neurointensive care unit or similar monitoring facility, and were treated according to local guidelines.

A detailed assessment schedule is listed in the study protocol (appendix pp 79–84). Briefly, screening logs were entered into the database for all patients with acute ischaemic stroke from large-vessel occlusion identified by brain imaging and who had provided written consent before endovascular thrombectomy; this was to ascertain the key reasons for excluding potentially eligible patients. Demographic and clinical data were collected at the time of presentation to hospital and at randomisation. Follow-up data were collected at 24 h, 7 days (or at discharge, if sooner), and 90 days. All brain imaging (CT, MRI, or angiogram) undertaken at baseline, 24 h, 7 days, and at additional timepoints if clinically indicated, were uploaded to a central server for analysis by trained clinicians who were masked to treatment group. Patients could also be included in two nested, parallel, pilot feasibility trials that were designed to assess different approaches to the timing of initiation of anticoagulation (in patients with a cardioembolic cause of ischaemic stroke) and duration of dual antiplatelet therapy (in patients with a specific indication) for secondary prevention after endovascular thrombectomy. Full details of these procedures are in the appendix (pp 87–95).

Outcomes

The primary outcome was functional recovery, assessed by a shift in the range of scores on the modified Rankin scale between groups at 90 days. The modified Rankin scale is a standard global 7-level measure of disability, in which scores of 0–1 indicate a favourable outcome without or with symptoms but no disability, scores of 2–5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death. Secondary efficacy outcomes were assessed by dichotomous analysis of scores on the modified Rankin scale at 90 days: 3–6 (disability or death) versus 0–2, and 3–5 (major disability) versus 0–2 in survivors. Additional secondary efficacy outcomes were death or neurological deterioration at day 7 according to a shift in NIHSS scores, categorised into seven levels (<5, 5–9, 10–14, 15–19, 20–24, ≥25, and death); symptomatic intracranial haemorrhage primarily according to the Heidelberg Bleeding Classification criteria,[22] and criteria of the National Institutes of Neurological Diseases and Stroke and the Safe Implementation of Thrombolysis in Stroke-Monitoring Study; intracranial haemorrhage of any type in brain imaging within ≤7 days of treatment; and any symptomatic intracerebral haemorrhage after endovascular thrombectomy, within 90 days; duration of hospitalisation; mortality within 90 days; health-related quality of life on the three-level EuroQoL 5-Dimension Self-Report Questionnaire (EQ-5D-3L) at 90 days; and residence. All serious adverse events were recorded through to study completion. The following secondary outcomes will be reported separately: analysis of various brain imaging features (cerebral ischaemia and oedema, collateral blood flow, and the location and degree of vascular stenosis), and health economic data. No data on the secondary outcome of residence were collected, and cannot be reported.

On March 6, 2022, the independent data and safety monitoring board recommended that patient recruitment was suspended due to concerns regarding safety arising from review of primary outcome data that were available for 347 randomly assigned patients. On further review of the outcome data from all participants on June 22, 2022, the board recommended that the trial be stopped early due to persistent concerns over the effect of more intensive blood pressure management on the primary outcome of functional recovery. The steering committee adopted these recommendations on June 24, 2022, and made the decision to stop the trial, to unmask the study personnel and patients, and report the data (details are outlined in the appendix [pp 8–11]).

Statistical analysis

The study was designed with 90% power (α=0·0482) to detect a common odds ratio (OR) of 0·77 for worse functional outcome at 90 days between randomised

groups. This required a sample size of 2257 patients based on the assumption that the distribution in scores on the modified Rankin scale in the less intensive treatment group would be similar to that in the control group reported in a meta-analysis of trials of endovascular thrombectomy,[1] accounting for a 5% loss to follow-up rate and 5% dropout rate. Therefore, if 54% of patients had a poor outcome (modified Rankin scale scores 3–6) in the less intensive group, this would correspond to an absolute decrease of 6·48% in functional outcome in the more intensive treatment group.

Efficacy was analysed in all randomly assigned patients who provided consent and had data available for the primary outcome (ie, those who were known to have died or with modified Rankin scale scores at 90 days). The primary analysis was performed using ordinal logistic regression with treatment allocation as a fixed effect, site as a random effect, and time from the onset of symptoms to reperfusion and baseline NIHSS score as fixed covariates. Additional adjusted analysis was performed by adding the covariates pre-stroke function (estimated modified Rankin scale scores 0–2), age, and sex. Patients who received the allocated treatment and did not have any major protocol violations were included in the per-protocol analysis. There were 11 prespecified subgroups for analysis with tests of interaction between the specific baseline characteristic and the treatment effect on the primary outcome. Considering the negligible amount of missing primary outcome data, only complete case analysis was conducted. Safety was assessed in all randomly assigned patients.

Accounting for the prespecified Haybittle-Peto stopping boundary (3 SDs of the expected treatment effect) with one interim analysis, the significance threshold for the primary outcome was $p<0·049$. For the seven secondary outcomes, the family-wise error rate was controlled with a Holm-Sidak correction[23] to facilitate interpretation of the findings.[24] We did post-hoc analyses to determine differences in the frequency of recurrent ischaemic stroke events between groups. Between-group differences in systolic and diastolic blood pressure from randomisation to day 7 were also assessed in a repeated-measure linear mixed model with adjustments for treatment (a fixed effect), time (a fixed categorical effect), between treatment and time (a fixed interaction), within-patient correlations (a repeated patient effect assuming a compound-symmetry structure), and the minimisation variables that were used at randomisation. These estimates were weighted to reflect the unequal spacing between measurements. We used SAS Enterprise Guide (version 8.2) and R (version 4.0.0 or above) for statistical analysis.

This trial is registered with ClinicalTrials.gov, NCT04140110, and the Chinese Clinical Trial Registry, 1900027785, and recruitment has stopped at all participating centres.

Role of the funding source

The sponsors and funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 20, 2020, and March 7, 2022, 821 patients were randomly assigned. One patient was immediately withdrawn by the investigator for not meeting the inclusion criteria, and four patients withdrew their consent immediately after randomisation. 404 patients in the more intensive blood pressure lowering group and 406 patients in the less intensive blood pressure lowering group had data available on the primary outcome and were included in efficacy analysis; figure 1; appendix pp 28, 39). Nine patients in the more intensive group and eight patients in the less intensive group had protocol violations, including one patient assigned to the less intensive treatment who was actively managed according to the more intensive treatment protocol, and two patients were lost to follow-up (appendix pp 29, 39). 119 patients in the more intensive treatment group and 138 patients in the less intensive treatment group were additionally randomly assigned to the substudies (appendix p 54).

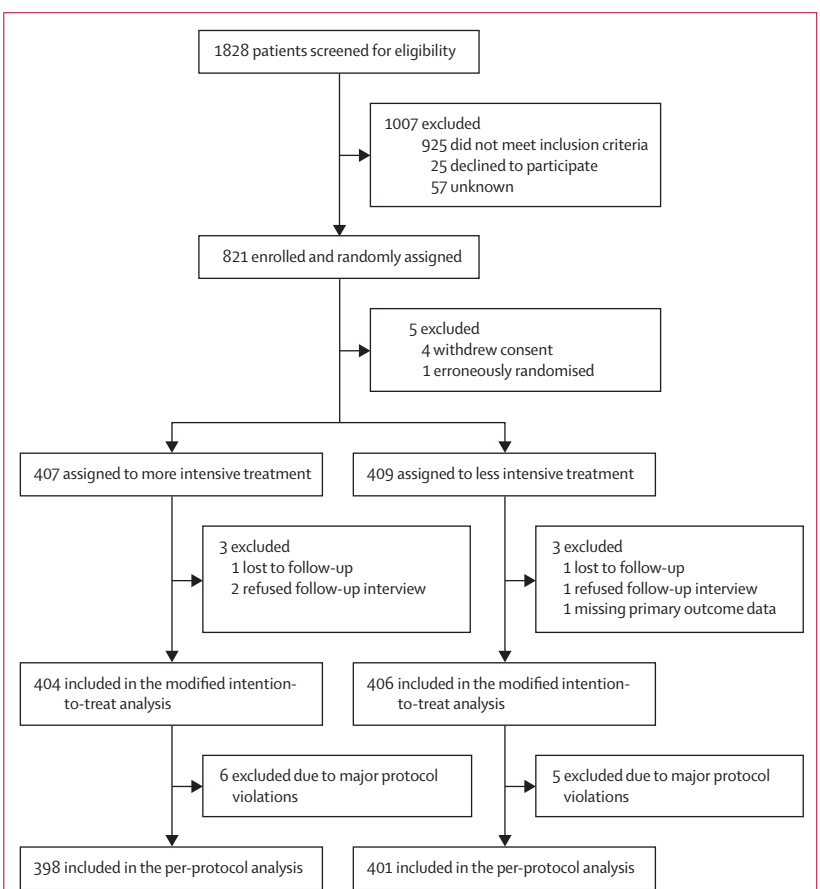

Figure 1: **Trial profile**

	More intensive treatment group (n=407)	Less intensive treatment group (n=409)
Mean age, years	68 (12)	67 (12)
Sex		
Female	158 (39%)	152 (37%)
Male	249 (61%)	257 (63%)
Ethnicity		
Chinese	407 (100%)	409 (100%)
Other	0	0
Medical history		
Hypertension	267 (66%)	261 (64%)
Previous stroke	107 (26%)	139 (34%)
Coronary artery disease	51 (13%)	59 (14%)
Valvular heart disease	16 (4%)	17 (4%)
Other heart disease	19 (5%)	16 (4%)
Atrial fibrillation	84 (21%)	98 (24%)
Diabetes	81 (20%)	82 (20%)
Hypercholesterolaemia	14 (3%)	13 (3%)
Modified Rankin scale score of 1–2 before stroke onset*	71 (18%)	781 (19%)
Medications		
Antihypertensive drugs	176 (43%)	179 (44%)
Statin or other lipid-lowering drug	30 (7%)	30 (7%)
Aspirin or other antiplatelet drug	34 (8%)	39 (10%)
Anticoagulation drug	20 (5%)	20 (5%)
Mean systolic blood pressure, mm Hg	158·1 (25)	158·7 (23)
Mean diastolic blood pressure, mm Hg	89·4 (16)	89·5 (15)
Median NIHSS score (severity of neurological deficit)†	15 (10–20)	15 (10–20)
Median GCS score (level of consciousness)‡	12 (9–15)	12 (8–15)
Median time from symptom onset to diagnostic brain imaging, h	4·6 (2·1–8·9)	4·0 (2·1–7·2)
Brain imaging features§		
Signs of cerebral ischaemia on CT scan	149/391 (38%)	145/394 (37%)
Signs of cerebral infarction on MRI	44/66 (67%)	54/67 (81%)
CT perfusion abnormalities¶		
Median volume of ischaemic core, mL‖	8 (0–27)	7 (0–28)
Median volume of perfusion lesion, mL**	107 (55–171)	96 (49–173)
Median volume of mismatch, mL††	83 (46–146)	84 (42–144)
Cause of large-vessel occlusion‡‡		
Intracranial atherosclerosis	177 (44%)	214 (53%)
Extracranial atherosclerosis	20 (5%)	10 (3%)
Cardioembolism from atrial fibrillation	118 (29%)	114 (28%)
Cardioembolism from other source	27 (7%)	23 (6%)
Dissection	7 (2%)	6 (2%)
Uncertain	58 (14%)	41 (10%)
Site of occlusion in anterior circulation§§	264 (81%)	269 (85%)
Median time from groin puncture to recanalisation, h	0·9 (0·7–1·5)	1·0 (0·7–1·6)
Use of intravenous alteplase	132 (32%)	115 (28%)
Use of general anaesthesia	173 (43%)	172/408 (42%)
eTICI score at the end of the procedure (level of reperfusion)¶¶		
2b	37 (9%)	43 (11%)
2c	28 (7%)	26 (6%)
3	342 (84%)	340 (83%)
Median time from procedure completion to randomisation, h	1·4 (0·6–2·0)	1·4 (0·7–2·1)

(Table 1 continues on next page)

Baseline demographic, clinical, and reperfusion treatment characteristics were well balanced between treatment groups (table 1; appendix pp 30–31). The most common device used for endovascular thrombectomy was a stent retriever (609 [78%] of 777 patients) in which the most common occlusion was at the M1 segment of the middle cerebral artery (310 [48%] of 643 patients). Ancillary use of intravenous heparin was used in 543 (56%) of 815 patients and the highly selective, short-acting, non-peptide glycoprotein IIb/IIIa platelet receptor antagonist, tirofiban, was used in 369 (45%) patients (appendix p 31). The mean age was 67 years (SD 12) and 310 (38%) of 816 patients were female. The site of occlusion was in the anterior circulation in 533 (83%) of 653 patients, the median baseline NIHSS score was 15 (IQR 10–20), and 247 (30%) of 816 patients had received intravenous alteplase before endovascular thrombectomy. Investigators reported complete reperfusion (eTICI score 3) after endovascular thrombectomy in 682 (84%) of 816 participants at a median of 7·3 h (IQR 4·6–10·9) from symptom onset. The median time from reperfusion to randomisation was 1·4 h (0·7–2·0), when the mean systolic blood pressure was 160 mm Hg (SD 15).

In the more intensive group, the proportion of patients administered any intravenous blood pressure lowering drug during the first 24 h was significantly higher than in the less intensive group (379 [93%] of 407 patients *vs* 241 [59%] of 409 patients; p<0·0001; appendix pp 32–33). The most common intravenous drugs used were urapidil (439 [76%] of 577 patients), nicardipine (99 [17%]), nimodipine (87 [15%]), nitroglycerine (50 [9%]), and frusemide (45 [8%]; appendix pp 32–33). A significantly higher proportion of patients in the more intensive group received blood pressure lowering therapy between days 2 and 7 than did patients in the less intensive treatment group (371 [92%] of 405 patients *vs* 267 [66%] of 404 patients; p<0·0001; appendix pp 34–35). Mean systolic blood pressure was 125 mm Hg (SD 18) at 1 h and 121 mm Hg (13) at 24 h in the more intensive group, and 143 mm Hg (18) at 1 h and 139 mm Hg (18) at 24 h in the less intensive group (adjusted mean difference over 24 h was –18 mm Hg [95% CI –19 to –17; p<0·0001; figure 2; appendix pp 36–37). 187 (46%) of 407 patients in the more intensive treatment group and 51 (12%) of 409 patients in the less intensive treatment group had systolic blood pressure readings lower than 100 mm Hg in the first 24 h after randomisation. With the exception of a greater proportion of patients in the more intensive treatment group requiring assisted feeding and dialysis than in the less intensive treatment group, no significant differences were observed in other aspects of clinical management in the 7 days after thrombectomy (appendix p 38).

Data on the primary outcome of death or disability were not available for three patients in each of the more intensive and the less intensive groups (two patients were alive but did not have modified Rankin scale assessment

and one patient was lost to follow-up; figure 1; appendix p 39). Patients in the more intensive group had worse scores on the modified Rankin scale than those in the less intensive group (common OR 1·37 [95% CI 1·07–1·76]; table 2, figure 3). The unfavourable shift in modified Rankin scale scores in the more intensive group was consistent in adjusted sensitivity analysis (table 2; appendix pp 40–41). There was no significant heterogeneity in the treatment effect on the primary outcome across all prespecified subgroups (appendix p 55).

The incidence of death or neurological deterioration at 7 days was higher in the more intensive treatment group than the less intensive treatment group (common OR 1·53 [95% CI 1·18–1·97]), and a between-group difference emerged at 24 h (appendix p 56). Overall, the incidence of death or disability (modified Rankin scale scores 3–6) at 90 days was higher among patients in the more intensive treatment group than the less intensive treatment group (212 [53%] of 404 patients *vs* 159 [39%] of 406 patients; OR 1·85 [95% CI 1·36–2·51]; p=0·0001). Among those who survived, more patients in the more intensive treatment group had major disability (modified Rankin scale scores 3–5) at 90 days than did patients in the less intensive treatment group (146 [43%] of 138 patients *vs* 98 [28%] of 345; OR 2·07 [1·47–2·93]; p<0·0001; table 2). Patient-reported physical subcategories of health-related quality of life were significantly worse in the more intensive group than the less intensive group, but no significant between-group differences were identified in the other outcomes, including symptomatic intracranial haemorrhage (23 [6%] of 407 patients in the more intensive treatment group *vs* 25 [6%] of 409 patients in the less intensive treatment group) and all-cause mortality (66 [16%] of 406 *vs* 61 [15%] of 408; table 2; appendix pp 40–41, 45). Results were consistent in the per-protocol analysis and after controlling the family-wise error for multiple testing (appendix pp 42–44, 46–47). Causes of death are provided in the appendix (pp 48–49). Exploratory analysis showed no significant interaction between the substudies and the effect of blood pressure lowering treatment on the primary and secondary clinical outcomes.

Overall, no significant difference was identified between the more intensive and less intensive groups with regard to serious adverse events (114 [28%] of 407 patients *vs* 111 [27%] of 409 patients; table 2; appendix pp 50–52). In post-hoc analysis, no significant differences were identified in the number of adjudicated recurrent ischaemic stroke events (25 [6%] of 407 patients *vs* 20 [5%] of 409 patients) at 90 days. No episodes of severe hypotension were reported as a serious adverse event. A complete list of serious adverse events is provided in the appendix (pp 50–52).

	More intensive treatment group (n=407)	Less intensive treatment group (n=409)
(Continued from previous page)		
Median time from the onset of symptoms to randomisation, h	9·3 (6·4–13·6)	8·6 (6·2–12·2)
Mean systolic blood pressure after procedure, mm Hg	159 (15)	160 (14)
Mean diastolic blood pressure after procedure, mm Hg	88 (13)	90 (13)

Data are mean (SD), n (%), median (IQR), or n/N (%). NIHSS=National Institutes of Health Stroke Scale. GCS=Glasgow coma scale. eTICI=expanded Treatment In Cerebral Infarction. *Scores on the modified Rankin scale of functional recovery range from 0 (no symptoms) to 6 (death); a score of ≤2 indicates functional independence; modified Rankin scale score before stroke onset was assessed by the treating physician by use of information obtained from patients (if possible) or their family members; only patients with a modified Rankin scale score of 0–2 were included in the trial. †Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ‡Scores on the GCS range from 15 (normal) to 3 (deep coma). §Investigators reported the results of brain imaging among randomly assigned patients using scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ¶Volumes assessed with use of RAPID automated software (iSchemaView, Menlo Park, CA, USA). ||Data available for 233 patients in the more intensive group and 232 patients in the less intensive group. **Data available for 229 patients in the more intensive group and 232 patients in the less intensive group. ††Data available for 225 patients in the more intensive group and 226 patients in the less intensive group. ‡‡The cause of stroke was assessed according to the medical history, clinical features, and results on digital subtraction angiography. §§Data available for 325 patients in the more intensive group and 318 in the less intensive group. ¶¶Reperfusion was defined as the first visualisation of successful reperfusion, as indicated by an eTICI score of 2b, 2c, or 3 (on a scale from 0 [no reperfusion] to 3 [complete reperfusion]).

Table 1: **Patient characteristics at baseline and after endovascular thrombectomy treatment**

Discussion

In this pragmatic multicentre clinical trial, which was stopped early, more intensive blood pressure lowering to a systolic treatment target of less than 120 mm Hg, compared with a less intensive approach (140–180 mm Hg), led to worse functional outcome for patients with successful reperfusion after endovascular thrombectomy for acute ischaemic stroke from large-vessel occlusion. The adverse effect was primarily on worsening disability at 90 days, with significantly greater neurological deterioration observed in the more intensive group within 7 days. No differences in symptomatic intracranial haemorrhage, mortality, or serious adverse events were identified between groups.

We specifically designed our study to achieve both an optimum intensive treatment target and a large difference in systolic blood pressure between randomised groups, since these targets have been challenging to achieve in previous trials of current guidelines that recommend control of blood pressure to less than 180 mm Hg, without specifying any treatment target.[14,15] We chose a more intensive treatment target that had previously been identified as optimum for functional recovery with a reduced risk of symptomatic intracerebral haemorrhage in patients who had achieved reperfusion after acute ischaemic stroke in two retrospective multicentre observational studies,[9,10] which was further confirmed in registry studies[25] and systematic reviews.[8,12] Our protocol was also reviewed by neurologists and neurointerventionalists in China and other high-income countries who we engaged with during the planning of the trial, many of whom indicated that they were already adopting a systolic target of less than 140 mm Hg, and some less than 120 mm Hg, in routine practice. These clinicians recognised their approaches were based primarily on observational studies,[7–12] and considered our protocol

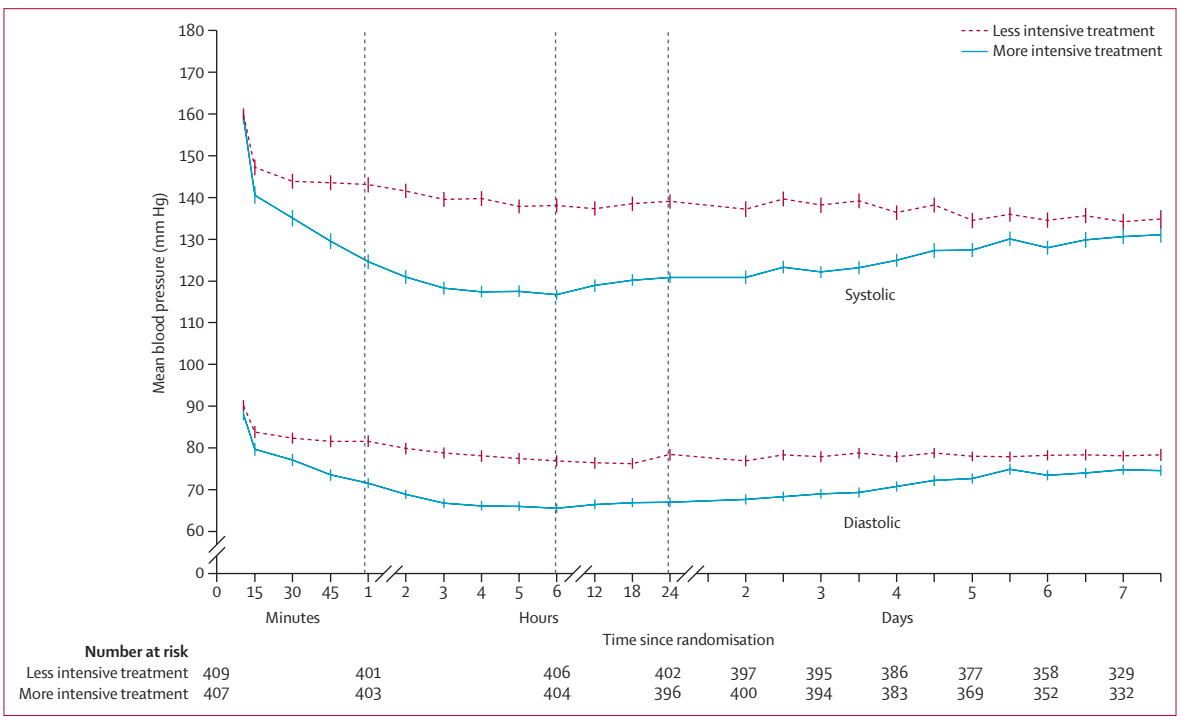

Figure 2: **Mean systolic and diastolic blood pressure from randomisation to day 7**
Blood pressure values are shown for the more intensive and less intensive treatment groups based on recordings at 15-min intervals for the first hour after randomisation (time 0), hourly from 1 h to 6 h, 6-hourly until 24 h, and twice daily until day 7. The mean between-group difference in systolic blood pressure over 24 h was –17·9 mm Hg (95% CI –19·3 to –16·5; p<0·0001) and mean between-group difference in diastolic blood pressure over 24 h was –10·0 mm Hg (–11·1 to –8·8; p<0·0001).

was an acceptable approach to help resolve uncertainty and develop policy.

Although comparisons between studies are complicated by differences in criteria and methods for selecting patients, and in the approaches taken to assess outcomes, the prognosis of patients in the low intensity treatment group in this study was better, in terms of NIHSS and modified Rankin scale scores on follow-up, than in other recent trials of endovascular thrombectomy for acute ischaemic stroke in China.[26–28] By contrast with the results of ENCHANTED,[18] no differences were identified in the rates of symptomatic intracranial haemorrhage between randomised groups. These findings suggest that the less intensive treatment group derived some benefit from blood pressure lowering, and that the optimum target for systolic blood pressure after mechanical thrombectomy might be within the range of 120–140 mm Hg. Conversely, the findings could indicate that elevated blood pressure is a normal reaction to a dynamic relationship between the severity of acute ischaemia, reperfusion, and cerebral autoregulation, which was adversely influenced by intensive treatment. Other explanations as to why our results differed from observational studies include heterogeneity in effects across different antihypertensive drugs,[29] workflow time delays and reporting errors in the assessment of reperfusion, excessive hypotensive events and restriction of mobilisation of patients in the more intensive group, and confounding from periprocedural hypotensive events and use of drugs that increase blood pressure within target ranges, for which data were not collected.

Serious clinical events from vessel reocclusion, paranchymal haemorrhage, and cerebral oedema, are more readily detected by routine clinical assessments, brain imaging, and cerebral angiography than insidious reperfusion injury to the cerebral microcirculation. Increasing use of endovascular thrombectomy has renewed concerns over ischaemia-reperfusion injury due to the rapid restoration of blood flow that is achieved.[30,31] The large mismatch of perfusion deficit evident in our study participants before endovascular thrombectomy indicates that they were particularly susceptible to more intensive and sustained blood pressure lowering treatment, but otherwise we could not identify any heterogeneity in the treatment effect across several patient characteristics. Further analysis of the perfusion imaging data obtained in our study might better define the extent of clinically relevant distal ischaemia, which has been shown to be common and responsive to intra-arterial thrombolysis after successful thrombectomy with a normal angiogram.[32]

Key strengths of our trial were the efforts used to minimise the risk of reporting biases in an open-label design by implementing several validated procedures. These procedures included the concealment of treatment

allocation with a minimisation algorithm to ensure prognostic variables were balanced between randomised groups. Objectively defined and masked central adjudication of intracranial haemorrhage was used, and there was masked evaluation of clinical outcomes using established criteria. Although the trial was stopped early, this was based on conservative criteria, so the likelihood of the findings being due to chance is remote. However,

	More intensive treatment (n=407)	Less intensive treatment (n=409)	Odds ratio (95% CI)	p value
Primary outcome				
Ordinal analysis of category scores on the mRS†	..	..	1·37 (1·07 to 1·76)‡	0·01
0 (no symptoms at all)	62/404 (15%)	72/406 (185)	..	..
1 (no significant disability despite symptoms)	91/404 (23%)	116/406 (28%)	..	..
2 (slight disability)	39/404 (10%)	59/406 (15%)	..	..
3 (moderate disability requiring some help)	55/404 (14%)	38/406 (9%)	..	..
4 (moderate-severe disability requiring assistance with daily living)	45/404 (11%)	28/406 (7%)	..	..
5 (severe disability, bed-bound, and incontinent)	46/404 (11)	32/406 (8)	..	..
6 (death)	66/404 (16)	61/406 (15)	..	..
Secondary outcomes				
Ordinal analysis of category scores for neurological impairment or death at day 7	..	..	1·53 (1·18 to 1·97)§	0·001
<5	129/406 (32%)	184/408 (455)	..	..
5–9	82/406 (20%)	61/408 (15%)	..	..
10–14	70/406 (17%)	55/408 (14%)	..	..
15–19	35/406 (9%)	34/408 (8%)	..	..
20–24	13/406 (3%)	15/408 (4%)	..	..
≥25	39/406 (10%)	29/408 (7%)	..	..
Death	38/406 (9%)	30/408 (7%)	..	..
Death or disability at 90 days (mRS score 3–6)	212/404 (53%)	159/406 (39%)	1·85 (1·36 to 2·51)	<0·0001
Major disability among survivors at 90 days (mRS score 3–5)	146/338 (43%)	98/345 (28%)	2·07 (1·47 to 2·93)	<0·0001
Death at 90 days	66/406 (16%)	61/408 (15%)	1·14 (0·76 to 1·70)	0·53
Symptomatic intracranial haemorrhage¶	23/407 (6%)	25/409 (6%)	0·93 (0·51 to 1·68)	0·80
Health-related quality of life (EQ-5D-3L)‖				
Mobility	..	..	1·60 (1·18 to 2·16)	0·003
No problems	172/342 (50%)	214/347 (62%)	..	..
Some problems	96/342 (28%)	80/347 (23%)	..	..
Confined to bed	74/342 (22%)	53/347 (15%)	..	..
Self-care	..	..	1·68 (1·24 to 2·27)	<0·0001
No problems	162/342 (47%)	206/347 (59%)	..	..
Some problems	75/342 (22%)	68/347 (20%)	..	..
Unable to wash or dress	105/342 (31%)	73/347 (21%)	..	..
Usual activities	..	..	1·78 (1·32 to 2·41)	<0·0001
No problems	154/342 (45%)	204/347 (59%)	..	..
Some problems	106/342 (31%)	84/347 (24%)	..	..
Unable to perform usual activities	82/342 (24%)	59/347 (17%)	..	..
Pain or discomfort	..	..	1·20 (0·86 to 1·69)	0·28
No problems	234/342 (68%)	252/345 (73%)	..	...
Some problems	96/342 (28%)	78/345 (23%)	..	..
Extreme pain or discomfort	12/342 (4%)	15/345 (4%)	..	..
Anxiety or depression	..	..	1·13 (0·79 to 1·60)	0·51
No problems	244/342 (71%)	258/345 (75%)	..	..
Some problems	87/342 (25%)	74/345 (21%)	..	..
Extremely anxious or depressed	11/342 (3%)	13/345 (4%)	..	..
Mean overall health utility EQ-5D-3L score (SD; n)	72·2 (22·6; n=342)	76·8 (21·7; n=346)	–4·49 (–1·42 to –7·55)	0·004
Median duration of hospitalisation (IQR), days	12 (7–24)	11 (7–21)	0·91 (0·78 to 1·07)	0·25

(Table 2 continues on next page)

	More intensive treatment (n=407)	Less intensive treatment (n=409)	Odds ratio (95% CI)	p value†
(Continued from previous page)				
Safety				
Serious adverse events during follow-up**				
Events reported, n††	130	135	..	..
Any patient with at least one serious adverse event	114 (28%)	111 (27%)	1·06 (0·77 to 1·48)	0·71
Recurrent ischaemic stroke‡‡	25 (6%)	20 (5%)	1·32 (0·71 to 2·45)	0·38

mRS=modified Rankin scale. EQ-5D-3L=three-level EuroQoL Group 5-Dimension Self-Report Questionnaire. NIHSS=National Institutes of Health Stroke Scale. *Values adjusted for treatment allocation as a fixed effect, site as a random effect, and time from the onset of symptoms to recanalisation and baseline NIHSS score as fixed covariates. †The mRS evaluates global disability; scores range from 0 (no symptoms) to 6 (death); a score of 2–5 indicates some degree of disability. ‡Estimated from an ordinal logistic regression model and indicates the common odds of worse functional outcome for the more intensive group compared with the less intensive group. §Estimated from an ordinal logistic regression model and indicates the odds of worse neurological deterioration measured on the NIHSS or death for the more intensive group compared with the less intensive group; scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ¶Symptomatic intracranial haemorrhage was defined as a haematoma occupying ≥30% of the infarcted tissue with obvious mass effect, as judged by an adverse-event committee as per Heidelberg criteria.[15] ||The EQ-5D-3L covers five domains of health-related quality of life: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression; each domain has three graded levels of response: no problems, moderate problems, or extreme problems; scores from these levels are combined to provide an overall health utility score that was calculated with population norms from the UK. **Any serious adverse event defined by standard criteria includes any events that might or might not be considered related to the treatment that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in medical or surgical intervention to prevent permanent impairment to body structure or function. ††Refers to the number of reported serious adverse events; a patient could have more than one event . ‡‡Adjudicated by an adverse-event committee unaware of treatment allocation according to the definition of an ischaemic event with a different symptom profile, ischaemic location on the imaging report, recanalisation on angiography, or after a stable time period, from the index ischaemic stroke event.

Table 2: **Primary and secondary efficacy and safety outcomes at 90 days***

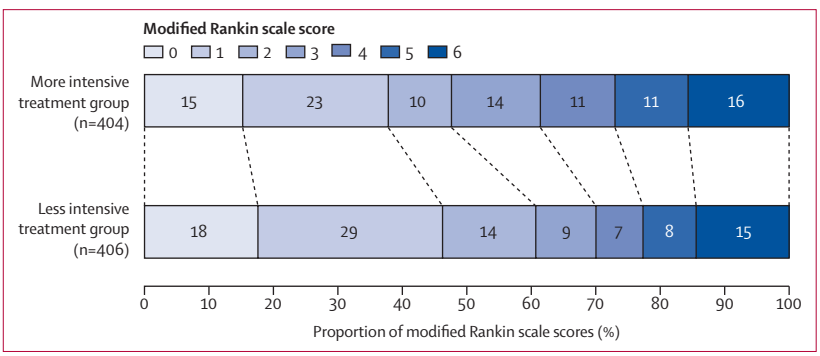

Figure 3: **Distribution of modified Rankin scale scores at 90 days by treatment group**
Raw distribution of scores is shown. Scores on the modified Rankin scale range from 0 to 6: 0=no symptoms, 1=symptoms without clinically significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death.

we acknowledge the potential for residual confounding from incomplete adjustment of some baseline variables that were imbalanced between groups at the time of randomisation, and that little data were collected on the pattern of stenosis before and after the endovascular procedure. Moreover, due to small numbers, insufficient evidence was derived of the treatment effect across subgroups and some secondary endpoints. There might be concerns regarding the generalisability of the findings, since the study was only done in China, where intracranial atherosclerosis and cerebral small vessel disease are common due to a high prevalence of hypertension. There are also differences in the use of ancillary approaches, such as potent antithrombotic agents, between China and other high-income countries. Despite longer workflow times and lower use of intravenous thrombolysis, outcomes from endovascular treatment for acute ischaemic stroke seem to be comparable between China and other high-income countries.[33] We acknowledge that our pragmatic approach with broad inclusion criteria and use of a variety of antihypertensive drugs in the context of usual standard of care, and where predominately risk-based monitoring was used during close-out of the study due to COVID-19 quarantine restrictions in China, might have led to differences in patient management compared with other health-care settings and compromised data quality, respectively.

In conclusion, in patients with acute ischaemic stroke who had raised blood pressure after successful reperfusion with endovascular thrombectomy, more intensive blood pressure lowering to a systolic target of less than 120 mm Hg resulted in worse functional outcome than less intensive systolic blood pressure control (140–180 mm Hg). The early increase in neurological deterioration supports the hypothesis that more intensive treatment compromised perfusion of the cerebral microcirculation. The optimum systolic blood pressure after endovascular thrombectomy for patients with acute ischaemic stroke is yet to be defined.

Contributors
PY, LS, Yongwei Zhang, JLi, and CSA designed the study, with input from XC, XW, MWP, KB, BC, TGR, MG, DDi, YR, CM, LW, and Yongjun Wang. XZ, XC, YL, LS, and YW provided quality control oversight. Qiang Li[1] and XR did statistical analyses and reports. LB wrote the statistical analysis plan with input from CSA and LS. HS, Lei Zhang, ZL, PX, Yongxin Zhang, PZ, WH, FS, Yihan Zhou, BT, WC, HH , Liyong Zhang, CX, TL, YP, XY, SC, CW, SW, CY, MW, HS, GN, SL, WL, YC, YS, MC, Yu Zhou, QZ, DDa, RZ, Qiang Li[2], QH, YX, BD, TW, and Jianping Lu provided comments on the study design and were responsible for data collection and quality control procedures. CSA wrote the first draft of the manuscript. The first authors and

corresponding authors had full access to verify all the study data, and had final responsibility for the decision to submit the paper for publication. All authors commented on drafts of the manuscript and approved the final manuscript for submission.

Declaration of interests

PY reports funding from Shanghai Changhai Hospital and honoraria for lectures from Stryker, Medtronic, Microvention, and Cerenovus. LS reports grants and speaker fees from Takeda China. CM reports grants from the Dutch Heart Foundation, the European Commission, Stryker, and Healthcare Evaluation Netherlands. MG reports grants from NoNo, Medtronic, and Cerenovus; and consulting fees from Medtronic, Microvention, Stryker, and Mentice; and is the inventor and receives royalties for a novel imaging system for the diagnosis of acute ischaemic stroke (GE Healthcare systems licensing agreement; patents US9324143 and US 9486176) and a device for accessing intracranial vessels (Microvention licensing agreement; US 10,456,552). Jianmin Liu reports grants from the China Stroke Prevention Project and the Science and Technology Commission of Shanghai Municipality. CSA reports grants from the National Health and Medical Research Council (NHMRC) and Medical Research Futures Fund (MRFF) of Australia, the UK Medical Research Council, Penumbra, and Takeda China; and is a board member for the World Stroke Organisation and the Editor-in-Chief of *Cerebrovascular Disease*. All other authors declare no competing interests.

Data sharing

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.

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