Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial

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Summary

Background **Intravenous thrombolysis with alteplase alone cannot reperfuse most large-artery strokes. We aimed to determine whether mechanical thrombectomy in addition to intravenous thrombolysis improves clinical outcome in patients with acute ischaemic stroke.**

Methods **THRACE is a randomised controlled trial done in 26 centres in France. Patients aged 18–80 years with acute ischaemic stroke and proximal cerebral artery occlusion were randomly assigned to receive either intravenous thrombolysis alone (IVT group) or intravenous thrombolysis plus mechanical thrombectomy (IVTMT group). Intravenous thrombolysis (alteplase 0·9 mg/kg [maximum 90 mg], with an initial bolus of 10% of the total dose followed by infusion of the remaining dose over 60 min) had to be started within 4 h and thrombectomy within 5 h of symptom onset. Occlusions had to be confirmed by CT or magnetic resonance angiography. Randomisation was done centrally with a computer-generated sequential minimisation method and was stratified by centre. The primary outcome was the proportion of patients achieving functional independence at 3 months, defined by a score of 0–2 on the modified Rankin scale, assessed in the modified intention-to-treat population (ie, patients lost to follow-up and those with missing data were excluded). Safety outcomes were analysed in the per-protocol population (ie, all patients who did not follow the protocol of their randomisation group precisely were excluded from the analysis). THRACE is registered with ClinicalTrials.gov, NCT01062698.**

Findings **Between June 1, 2010, and Feb 22, 2015, 414 patients were randomly assigned to the IVT group (n=208) or the IVTMT group (n=204). Four patients (two in each group) lost to follow-up and six (four in the IVT group and two in the IVTMT group) with missing data were excluded. 85 (42%) of 202 patients in the IVT group and 106 (53%) of 200 patients in the IVTMT group achieved functional independence at 3 months (odds ratio 1·55, 95% CI 1·05–2·30; p=0·028). The two groups had no significant differences in mortality at 3 months (24 [12%] deaths of 202 patients *vs* 27 [13%] of 206; p=0·70) or symptomatic intracranial haemorrhage at 24 h (four [2%] of 185 *vs* three [2%] of 192; p=0·71). Common adverse events related to thrombectomy were vasospasm (33 [23%] patients) and embolisation in a new territory (nine [6%]).**

Interpretation **Mechanical thrombectomy combined with standard intravenous thrombolysis improves functional independence in patients with acute cerebral ischaemia, with no evidence of increased mortality. Bridging therapy should be considered for patients with large-vessel occlusions of the anterior circulation.**

Funding **French Ministry for Health.**

Introduction

Intravenous administration of alteplase, a tissue plasminogen activator, within 4·5 h of stroke onset improves the chance of a good outcome, and early treatment is associated with proportionally larger benefits.[1–4] However, revascularisation rates are reduced in occlusions of large proximal vessels, and the prognosis for patients with these occlusions remains poor.[5,6] Endovascular treatments increase the chance of successful and rapid recanalisation. Therefore, the use of intravenous alteplase with mechanical thrombectomy should, in theory, combine their respective advantages: quick administration and improved recanalisation.

Several randomised clinical trials have assessed this combined approach. The results of initial trials[7–9] did not show a benefit of this approach, which might be explained by the fact that imaging was not used for diagnosis and localisation of occlusion for some patients and by the low rate of reperfusion. Moreover, these studies did not use the most recent devices (eg, stent retrievers Solitaire and Trevo) that have greatly improved the speed and efficacy of recanalisation. The results of subsequent randomised trials[10–15] have consistently shown that, in patients who receive standard care, mechanical thrombectomy significantly improves revascularisation and functional independence at 3 months with no increase in mortality. Some of these trials selected patients who were most likely to benefit from a combined approach by using imaging characteristics such as ischaemia-associated abnormalities in the Alberta Stroke Program Early CT

Research in context

Evidence before this study

We searched PubMed with the terms "stroke + thrombectomy" for articles published in English before Dec 31, 2015. Our search returned numerous single-centre or multicentre studies or registry studies in which endovascular treatment improved recanalisation, and eight randomised clinical trials that investigated the effect of endovascular treatment on functional outcomes. The results of the three trials published in 2013 were negative, whereas those of the five trials published in 2015 showed that, in patients receiving standard care, complementary mechanical thrombectomy led to an increased proportion of patients achieving functional independence at 3 months with no increase in mortality.

Added value of this study

The THRACE trial also assessed functional outcomes after treatment with intravenous alteplase for thrombolysis plus mechanical thrombectomy versus intravenous thrombolysis alone in patients with acute cerebral ischaemia. To our knowledge, it is the largest study to show that mechanical thrombectomy is better than standard care alone. Although our results are consistent with those of other recent studies, the THRACE trial is unique because of its wide patient selection, with no imaging-based criteria beyond the requirement for large-vessel occlusion, and its rapid randomisation (<20 min after intravenous thrombolysis initiation), so that fast responders to intravenous alteplase were not excluded. Thus, results of the THRACE trial showed a benefit in functional outcome for the combined approach in a broad population of patients similar to that encountered in routine clinical practice.

Implications of all the available evidence

Mechanical thrombectomy seems to be beneficial and should be considered for a wide range of patients with large-vessel occlusions of the anterior circulation, regardless of age, sex, clinical severity, or intracranial location of the occlusion.

score (ASPECTS) or cerebral perfusion data to distinguish between permanent lesions and hypoperfused but potentially rescuable penumbra.[11–14] The use of imaging criteria might increase the effect of treatment but might also exclude many patients who could benefit from intra-arterial treatment.

The THRACE (THRombectomie des Artères CErebrales) trial was designed in 2009, before the results of the IMS III trial[7] became available, and has a similar protocol.[7] In THRACE, we aimed to compare standard treatment—intravenous thrombolysis alone—with intravenous thrombolysis plus mechanical thrombectomy by use of the newest devices to determine their effect on functional independence at 3 months in patients with moderate-to-severe stroke due to an occlusion of a proximal cerebral artery within 4 h of symptom onset.

Methods

Study design and participants

THRACE was a randomised controlled trial done in 26 centres in France. Patients with acute ischaemic stroke were eligible for inclusion if they were aged 18–80 years; had a US National Institutes of Health Stroke Scale (NIHSS) score of 10–25; had an occlusion of the intracranial internal carotid artery, the M1 segment of the middle cerebral artery, or the superior third of the basilar artery confirmed by CT or magnetic resonance angiography; could be administered intravenous thrombolysis within 4 h of symptom onset; and if thrombectomy could be initiated within 5 h of symptom onset. The time limit for intravenous thrombolysis initiation was initially within 3 h of symptom onset; on May 14, 2011, after enrolment of 80 patients, the trial steering committee decided to extend the time limit for intravenous thrombolysis initiation to 4 h, but the time limit for thrombectomy initiation was not changed. Patients who had cervical internal carotid artery occlusion and subocclusive stenosis were excluded (see the appendix for complete inclusion and exclusion criteria).

See Online for appendix

The study protocol was approved by the CPP (Comité de Protection des Personnes) III Nord Est Ethics Committee and the research boards of the participating centres. All patients or their legal representatives provided written informed consent.

Randomisation and masking

Patients were randomised (1:1) as soon as possible during intravenous thrombolysis to receive intravenous thrombolysis and mechanical thrombectomy (IVTMT group) or intravenous thrombolysis alone (IVT group). Randomisation was done at the coordination centre by a computer analyst who was masked to the investigation centres and to the patients. Randomisation was done with a computer-generated sequence and was stratified by centre, and sequential minimisation with a factor of 85% was used to avoid imbalance in treatment.[16] Participants were enrolled by local investigators and assigned to the trial group according to the random number. Masking of investigators and patients was not feasible because of the nature of the intervention.

Procedures

All patients received intravenous thrombolysis as per standard care—ie, 0·9 mg/kg of alteplase (maximum 90 mg), with an initial bolus of 10% of the total dose, and then infusion of the remaining dose over 60 min, irrespective of group assignment. Initially, patients allocated to the IVTMT group were to be clinically assessed after the completion of intravenous thrombolysis but before angiography. From Oct 12, 2012,

onwards, to reduce time to reperfusion, the trial steering committee recommended clinical assessment before the end of thrombolysis.

For the IVTMT group, if patients had clinically significant improvement, defined as a decrease in the NIHSS score of at least 4 points, angiography and thrombectomy were cancelled, because it was deemed unethical to do an endovascular procedure when the patient had improved. Otherwise, angiography was done and followed by thrombectomy if the modified Thrombolysis in Cerebral Infarction (mTICI) grade was less than 2. The mTICI scale scores perfusion from 0 (no perfusion) to 3 (complete antegrade perfusion of the downstream territory).

For thrombectomies, the interventional neuroradiologists had to choose a device from the trial's regularly updated list of devices that had been granted the European Conformity mark and approved by the ethics committee and the French National Agency For Medicines And Health Products Safety. Furthermore, practitioners had to show proof of performance of at least five interventions with a given system before using it in the trial. A complementary intra-arterial injection of a maximum of 0·3 mg/kg of alteplase at the end of thrombectomy was authorised only in cases of persistent distal occlusions. Use of conscious sedation or general anaesthesia was left to the judgment of the interventional neuroradiologist.

Baseline examinations included the determination of ASPECTS[17,18] and the localisation of the arterial occlusion by CT or magnetic resonance angiography. At day 1 and discharge (before day 7) or day 7, ASPECTS, haemorrhagic transformation, or other signs of intracranial bleeding were assessed. CT and MRI images were reviewed by an independent committee of four experienced neuroradiologists who were masked to randomisation group and patient clinical outcome. Three other experienced independent interventional neuroradiologists who were masked to patient clinical outcome and other imaging data reviewed the angiograms before and after thrombectomy and provided a consensus evaluation. Cerebral perfusion was assessed with the mTICI scale.[19] Clinical assessments were done by vascular neurologists who were not masked to the treatment to which the patients had been allocated.

Modified Rankin score and NIHSS were assessed at 24 h, discharge or day 7, and 3 months. Barthel index was assessed at 3 months.

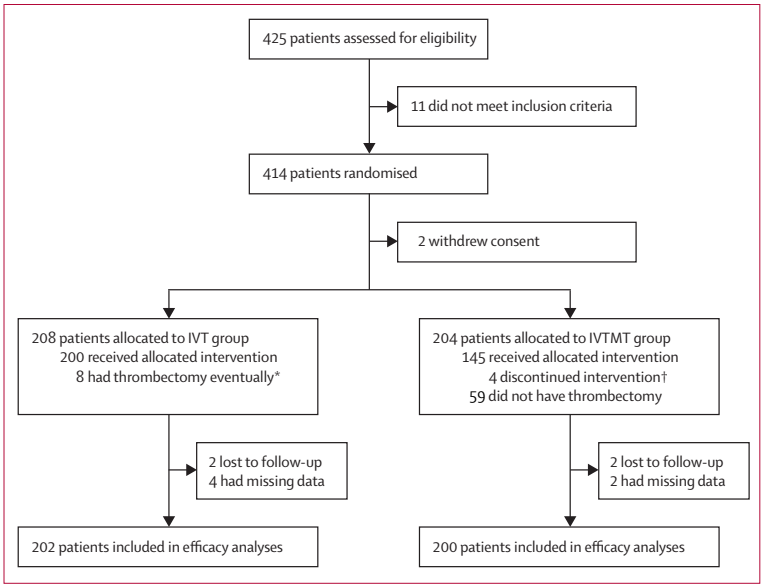

Figure 1: **Trial profile**
IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy. *Because of poor clinical evolution, eight patients had thrombectomy eventually. †Because of problems with the catheterisation.

Outcomes

The primary outcome was the proportion of patients with a score of 0–2 on the modified Rankin scale, indicating functional independence, at 3 months after the intervention.[20] Scores range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability (ie, able to carry out all usual activities, despite some symptoms); 2, slight disability (ie, able to look after one's own affairs without assistance but unable to carry out all previous activities); 3, moderate disability (ie, requires some help but able to walk unassisted); 4, moderately severe disability (ie, unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (ie, requires constant nursing care and attention, bedridden, and incontinent); and 6, death. The primary outcome was assessed at each centre.

Secondary efficacy outcomes included the NIHSS score at 24 h, discharge or day 7, and 3 months; performance in activities of daily living at 3 months, assessed with the Barthel index;[21] and quality of life at 3 months, assessed with the EuroQol EQ-5D questionnaire.[22] We plan to report results of our economic evaluation separately.

An independent data and safety board monitored the the trial. The main safety endpoints were death at 3 months and symptomatic intracranial haemorrhage at 24 h. Symptomatic haemorrhage was defined as visible intracranial bleeding on CT or MRI plus an increase in the NIHSS score of at least 4 points. Secondary safety endpoints were asymptomatic haemorrhage on CT or MRI at 24 h, frequency and severity of extracerebral haemorrhage, arterial and femoral puncture site complications in the IVTMT group, and potentially treatment-induced biological consequences—ie, changes in haemoglobin concentrations, changes in haematocrit, or renal failure.

Statistical analysis

Data management and statistical analyses were done by the INSERM CIC-EC 1433. To show a 15% increase in the proportion of patients with modified Rankin scores of 0–2 in the IVTMT group compared with the IVT group

(ie, 40% *vs* 25%) at 3 months post-intervention, with a power of 90% and a probability of type I error of 5%, 220 patients were needed per group. Assuming a 10% loss to follow-up, our enrolment target was 240 patients in each group.

A planned interim analysis was done after enrolment of 220 patients; the O'Brien-Fleming method was used to minimise type I error. After the release of results from MR CLEAN,[10] a second unplanned interim analysis was done with an adjusted alpha method after 385 patients had been enrolled.

Differences between the IVT and IVTMT groups were assessed with an unadjusted logistic regression. The primary outcome, modified Rankin scores, was also treated as a seven-category variable and analysed with an ordinal logistic regression. In addition to the odds ratios (ORs) generated in the regression models, we calculated relative risks using Poisson regression with robust standard error to avoid overestimation of the risk when the outcome is not rare.[23] Safety outcomes were assessed with χ^2 tests for categorical variables (eg, death and serious adverse events) and Student's *t* test for continuous variables.

In a post-hoc analysis, prognostic factors for the primary outcome—ie, age, blood glucose, NIHSS score, ASPECTS, occlusion location, and Fazekas score[24] at baseline—were calculated with multivariate logistic regression. We also did a prespecified subgroup analysis to determine the effect size of thrombectomy in the primary outcome variable by patient characteristics (sex, age, diabetes, hypertension, hypercholesterolaemia, time to randomisation, occlusion site, and NIHSS score). ORs and associated p values of each interaction term were estimated from separate logistic regression models across the prespecified subgroups and ASPECTS. Analyses of primary outcome were done in the modified intention-to-treat population (ie, patients lost to follow-up and those with missing data were excluded) and in the per-protocol population (ie, all patients who did not follow the protocol of their randomisation group precisely were excluded from the analysis). The safety endpoints were analysed in the per-protocol population. Statistical analyses were done with SAS/STAT (version 9.3).

THRACE is registered with ClinicalTrials.gov, number NCT01062698.

Role of the funding source

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

Results

Between June 1, 2010, and Feb 22, 2015, 425 patients were assessed for eligibility, of whom 414 met the inclusion criteria and were randomised (figure 1). On March 3,

	IVT group (n=208)	IVTMT group (n=204)
Age, years		
Median (IQR)	68 (54–75)	66 (54–74)
≤70	121 (58%)	122 (60%)
>70	87 (42%)	82 (40%)
Sex		
Male	104 (50%)	116 (57%)
Female	104 (50%)	88 (43%)
Comorbidities and risk factors*		
Hypertension	118/208 (57%)	96/200 (47%)
Type 2 diabetes	35/208 (17%)	17/204 (8%)
History of stroke	14/208 (7%)	14/204 (7%)
Hypercholesterolaemia	109/189 (58%)	80/179 (45%)
Current or past tobacco use	79/187 (42%)	85/179 (47%)
Coronary disease	30/198 (15%)	32/195 (16%)
Clinical examination		
Systolic blood pressure, mm Hg	142 (129–160)	140 (127–157)
Blood glucose, g/L	1·2 (1·0–1·4)	1·2 (1·0–1·4)
NIHSS score	17 (13–20)	18 (15–21)
Imaging location*		
Left hemisphere	96/204 (47%)	101/198 (51%)
Right hemisphere	108/204 (53%)	95/198 (48%)
Occlusion site		
ICA	39 (19%)	24 (12%)
M1	164 (79%)	176 (86%)
TB	2 (1%)	2 (1%)
M2†	2 (1%)	0
ASPECTS score‡		
0–4	35 (17%)	22 (11%)
5–7	52 (26%)	80 (41%)
8–10	115 (57%)	94 (48%)
Workflow duration, min		
From onset to imaging	111 (88–145)	112 (86–136)
From onset to intravenous thrombolysis	153 (124–180)	150 (120–178)
From onset to randomisation	170 (138–199)	168 (143–195)
From onset to thrombectomy	NA	250 (210–290§)
From onset to the end of thrombectomy	NA	303 (261–345)

Data are n (%), n/N (%), or median (IQR). IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy. NIHSS=US National Institutes of Health Stroke Scale International. ICA=intracranial internal carotid artery. M1=proximal portion of the middle cerebral artery. TB=upper third of the basilar artery. M2=insular portion of middle cerebral artery. ASPECTS=Alberta Stroke Program Early CT score. NA=not applicable. *Patients with missing data (or unknown comorbidities) were excluded. †M1–M2 junction occlusions included as M1 occlusions but classified as M2 by the core laboratory. ‡Retrospectively determined by four independent reviewers; after excluding patients with poor-quality images and incomplete exams, 202 patients were included in the IVT group and 196 patients were included in the IVTMT group. §In the protocol, thrombectomies were to be started within 300 min; 20 patients were treated beyond that time limit but retained in the analysis.

Table 1: **Baseline characteristics**

2015, the trial steering committee decided to terminate the trial early, after 414 patients were randomised, because the second unplanned interim analysis showed superiority of intravenous thrombolysis plus mechanical thrombectomy over intravenous thrombolysis alone. Two patients withdrew consent after randomisation. Of the remaining 412 patients, 208 were randomised to the IVT group and 204 to the IVTMT group. Eight (4%) patients assigned to the IVT group eventually had thrombectomy, and 59 (29%) patients assigned to the IVTMT group did not have thrombectomy because of significant clinical improvement (35 patients), partial or complete recanalisation (18 patients), or violation of exclusion criteria (six patients; history of surgery that made catheterisation impossible or presence of a cervical carotid artery occlusion). Four patients (two in each group) were lost to follow-up and six (four in the IVT group and two in the IVTMT group) had missing data and were excluded from efficacy analyses. These ten patients did not have substantial differences in baseline clinical and imaging data compared with the 402 patients included in the primary analysis (appendix p 4).

	IVT group	IVTMT group	Odds ratio (95% CI)	p value
Modified Rankin score of 0–2 at 3 months*	85/202 (42%)	106/200 (53%)	1·55 (1·05–2·30)	0·028
NIHSS score at 24 h†				
n	192	187	..	..
Median (IQR)	12 (6–19)	9 (4–18)	..	0·04
NIHSS score at discharge or 7 days†				
n	172	168	..	..
Median (IQR)	8 (2–16)	4 (1–14)	..	0·001
NIHSS score at 3 months†				
n	167	158	..	..
Median (IQR)	4 (0–10)	2 (0–8)	..	0·01
Barthel index at 3 months†				
n	161	152	..	..
Mean (SD)	73·0 (32·2)	80·4 (30·5)	..	..
Barthel index 95–100	79 (49%)	92 (61%)	1·59 (1·02–2·49)	0·04
EQ-5D at 3 months†				
n	130	130	..	..
Mean (SD)	0·515 (0·39)	0·533 (0·40)	..	..
Median (IQR)	0·616 (0·3–0·8)	0·642 (0·3–0·8)	..	0·38
Deaths at 3 months‡	27/206 (13%)	24/202 (12%)	0·81 (0·53–1·24)	0·70
Symptomatic haemorrhages at 24 h†	3/192 (2%)	4/185 (2%)	1·39 (0·31–6·31)	0·71

Data are n/N (%), unless indicated otherwise. IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy. NIHSS=US National Institutes of Health Stroke Scale International. *Primary outcome. †Patients with missing data, those lost to follow-up, or those who did not respond to EQ-5D were not included in the analysis. ‡Two patients in each group were lost to follow-up.

Table 2: **Treatment effects**

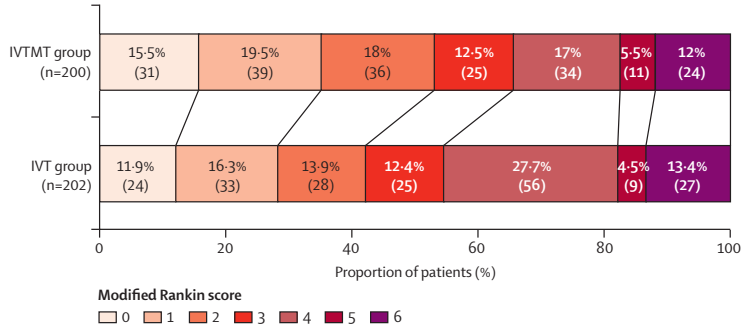

Figure 2: **Functional independence (modified Rankin score) at 3 months**
Data are proportion of patients (n). IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy.

The baseline characteristics of the 412 patients did not differ between groups, although the IVT group had higher proportions of patients with diabetes, hypertension, and hypercholesterolaemia (table 1). Initial radiological assessments were done with MRI in 153 (74%) of 208 patients in the IVT group and 148 (73%) of 204 patients in the IVTMT group. The median time from stroke onset to imaging was similar for patients who had CT (109 min, IQR 86–136) and those who had MRI (111 min, 88–138).

The two groups did not differ in terms of the delay between symptom onset and initiation of intravenous thrombolysis (table 1), bolus and infusion doses of alteplase, and infusion duration (appendix p 5). The median time from thrombolysis initiation to randomisation was 18 min (IQR 6–32), and the median time from stroke onset to thrombolysis was similar in patients who had CT (153 min, 123–180) and those who had MRI (150 min, 122–178). Thrombolysis was eventually followed by thrombectomy in 141 (69%) of the 204 patients in the IVTMT group (thrombectomy was not done in four patients because of problems with the catheterisation). Stent retriever systems were used as the first system in 116 (83%) patients and aspiration systems in 23 (16%) cases; the system used for thrombectomy was not known for two patients. In 19 (13%) patients, a second system was used. A mean dose of 8·8 mg (SD 6·4) of complementary alteplase was administered intra-arterially at the end of the intervention in 15 (11%) of 141 patients. These technical aspects of thrombectomy did not affect the primary outcome criterion (appendix p 12)

For patients who had thrombectomy, general anaesthesia with intubation was used in 69 (49%) patients and local anaesthesia or conscious sedation in 74 (52%) patients; this information was not available for two patients (reason not known). The median delay from symptom onset to the beginning of thrombectomy did not differ significantly between patients who had general anaesthesia with intubation (243 min, IQR 205–284) and those who did not (252 min, 217–292; p=0·192). Median thrombectomy duration was slightly shorter in those who had general anaesthesia (45 min, IQR 28–70) than in those who had local anaesthesia or conscious sedation (56 min, 24–86; p=0·547).

The median delay between symptom onset and thrombectomy was 250 min (IQR 210–290) in the IVTMT group. Thrombectomies were started before the end of intravenous alteplase infusion in 22 (16%) of 141 patients, in the hour following the end of infusion in 81 (57%) patients, or more than 1 h after the end of infusion in 38 (27%) patients.

The primary outcome was assessed in 402 patients. At 3 months, 106 (53%) of 200 patients in the IVTMT group and 85 (42%) of 202 in the IVT group had functional independence (ie, modified Rankin score 0–2; OR 1·55, 95% CI 1·05–2·30; p=0·028; table 2). Nine patients needed to be treated with alteplase plus thrombectomy to prevent one functional dependency or death at 3 months. Considering the modified Rankin score at 3 months as an ordinal variable in a regression model, we did not find any difference between the IVTMT and IVT groups (OR 1·39, 95% CI 0·99–1·97; p=0·05; figure 2).

The median NIHSS score at discharge or day 7 was 4 points lower in the IVTMT group than in the IVT group (table 2). Compared with the IVT group, patients in the IVTMT group had a higher mean score on the Barthel index, and a higher proportion of patients in the IVTMT group had a Barthel score of 95–100 at 3 months (table 2). By contrast, no significant differences were seen in responses to the EQ-5D questionnaire between the two groups at 3 months (table 2).

In an unplanned analysis of the IVTMT group, 95 (69%) of 138 patients had good reperfusion (defined by an mTICI grade of 2b or 3; appendix p 11).

No significant differences in 3 month mortality were seen between the IVT group and the IVTMT group (table 2). Similarly, no significant differences were seen in the proportion of patients with symptomatic or asymptomatic haemorrhages at 24 h (table 2; table 3). Thrombectomy-associated complications occurred in nine (6%) of 145 patients—the treated artery was affected in six patients and the puncture site was affected in three patients. On post-treatment angiography, nine (6%) of the 141 patients who had thrombectomy in the IVTMT group had an embolus in a new location (table 3). However, at 3 months, no significant differences were seen in the proportion of patients with adverse events (65 [31%] of 208 patients in the IVT group *vs* 55 [27%] of 204 patients in the IVTMT group; p=0·33; table 3).

Prognostic factors for acute stroke (NIHSS score, age, occlusion location, ASPECTS, blood glucose, and Fazekas score) showed high predictive value for clinical outcome. No effects were found for diabetes, hypertension, or hypercholesterolaemia—comorbidities that were more frequent in the IVT group (appendix p 8).

The subgroup analyses did not show any significant thrombectomy effect modification of NIHSS score, sex, age, occlusion location, ASPECTS, diabetes, hypertension, hypercholesterolaemia, and time to randomisation (figure 3). 57 patients had poor baseline ASPECTS (0–4), 56 on diffusion-weighted MRI and one on CT. At 3 months, 17 (30%) patients (nine [26%] of 35 in the IVT group and eight [36%] of 22 in the IVTMT group) had modified Rankin scores of 0–2. After excluding patients with missing data, 51 (76%) of 67 patients in the general anaesthesia group and 43 (62%) of 69 who had local anaesthesia or conscious sedation achieved post-thrombectomy revascularisation (p=0·059). The proportion of patients with modified Rankin scores of 0–2 at 3 months did not differ significantly between the two groups (35 [52%] of 67 *vs* 36 [49%] of 74; p=0·670).

336 patients (195 in the IVT group and 141 in the IVTMT group) were included in the per-protocol analysis. 83 (43%) patients in the IVT group and 70 (50%) in the IVTMT group had modified Rankin scores of 0–2 at 3 months (OR 1·33, 95% CI 0·86–2·06; p=0·198). Mortality at 3 months did not differ between the groups (26 [13%] of 195 *vs* 15 [11%] of 141; p=0·46).

	IVT group (n=208)	IVTMT group (n=204)	p value
Intracranial haemorrhage at 24 h*			
Haemorrhagic infarction and parenchymal haematoma			0·53
Haemorrhagic infarction type 1	24/201 (12%)	21/195 (10%)	..
Haemorrhagic infarction type 2	23/201 (11%)	27/195 (13%)	..
Parenchymal haematoma type 1	11/201 (5%)	13/195 (6%)	..
Parenchymal haematoma type 2	8/201 (4%)	14/195 (7%)	..
Other bleeding			0·16
Subarachnoid haemorrhage	2/201 (1%)	8/195 (4%)	..
Intraventricular haemorrhage	5/201 (2%)	8/195 (4%)	..
Remote haemorrhage	6/201 (3%)	3/195 (2%)	..
Procedure-related complications†			
Embolisation in a new territory	NA	9 (6%)	NA
Arterial perforation	NA	1 (1%)	NA
Dissection	NA	5 (3%)	NA
Vasospasm (any)	NA	33 (23%)	NA
Groin haematoma	NA	3 (2%)	NA
Biology			
Haemoglobin, g/100 mL			<0·0001
Mean (SD)	13·5 (1·7)	12·8 (1·6)	..
Median (IQR)	13·5 (12·5–14·6)	12·8 (11·9–13·9)	..
Renal failure	13 (6%)	21 (10%)	0·12

Data are n (%) or n/N (%), unless indicated otherwise. IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy. NA=not applicable. *Patients with missing data were excluded from analysis. †Only 145 patients in the IVTMT group received thrombectomy.

Table 3: **Safety outcomes and adverse events**

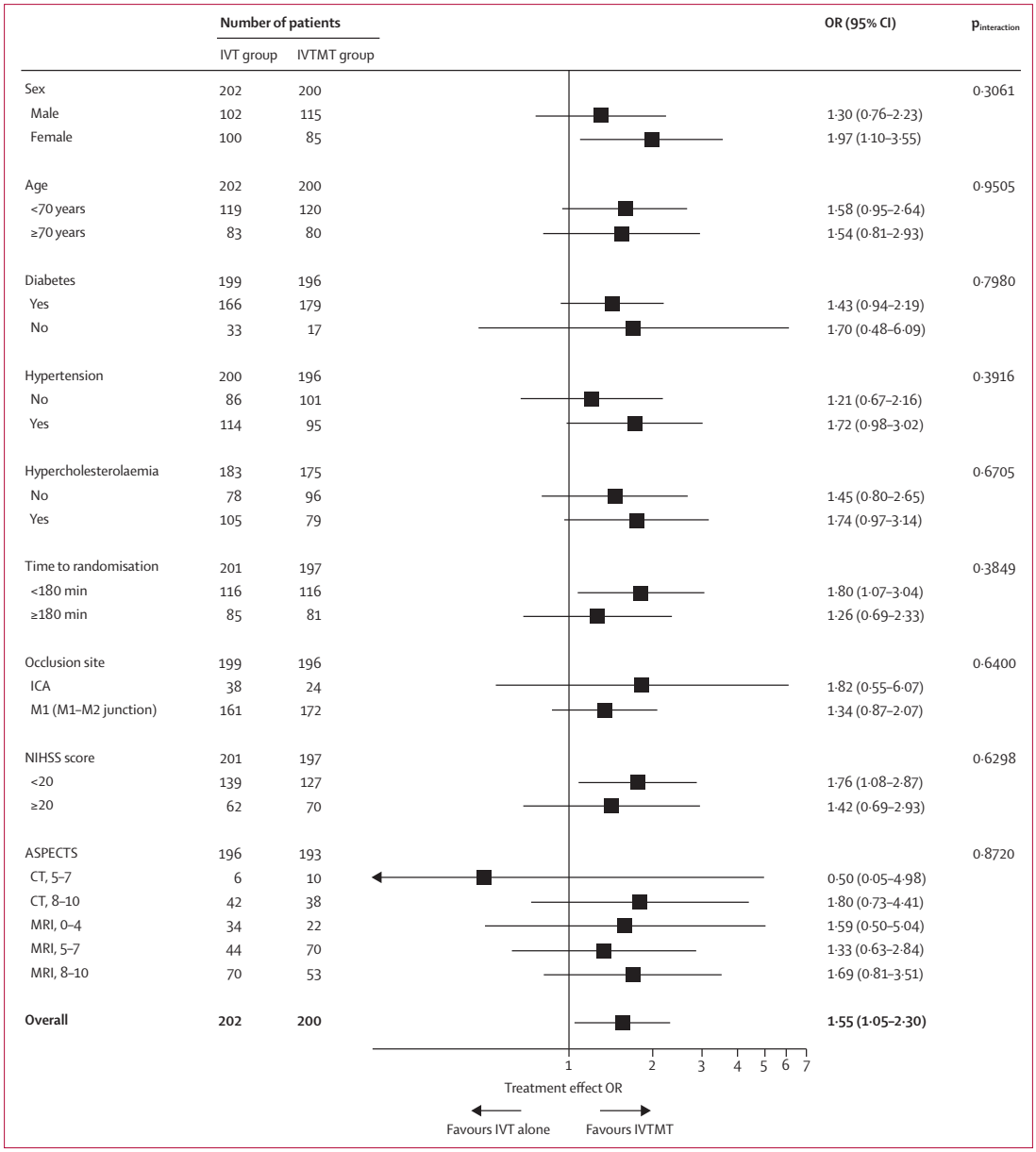

Figure 3: **Treatment effects of thrombectomy on modified Rankin score at 3 months, by patient characteristics**
Relative risk estimates from Poisson regression are shown in appendix p 8. The number of patients is different in the subgroups because some had missing data. ASPECTS=Alberta Stroke Program Early CT score. ICA=intracranial internal carotid artery. IVT=intravenous thrombolysis. IVTMT=intravenous thrombolysis plus mechanical thrombectomy. M1=proximal portion of the middle cerebral artery. M2=insular portion of middle cerebral artery. NIHSS=US National Institutes of Health Stroke Scale International. OR=odds ratio.

A modified Rankin score of 0–2 was achieved in 35 (59%) of the 59 patients in the IVTMT group who did not have thrombectomy for any reason and in 28 (80%) of the 35 patients who did not have thrombectomy because of significant clinical improvement before angiography. Median improvement in NIHSS score immediately before angiography in these 35 patients was 8 points (IQR 6–12).

Discussion

Our results confirm those of other recent studies showing that mechanical thrombectomy improves

functional independence in patients after acute ischaemic stroke caused by proximal intracranial arterial occlusion. However, our trial differs notably from those earlier studies, particularly with respect to patient selection criteria and delays to randomisation.

The design of the THRACE trial most closely resembles that of IMS III[7] in that both studies compared bridging therapy with intravenous thrombolysis alone. Furthermore, all patients in these two trials were given standard intravenous thrombolysis and randomised quickly. However, important distinctions between the two trials also exist. In particular, all of our patients had CT or magnetic resonance angiography at enrolment to confirm and localise the arterial occlusion, and all of our thrombectomies were done with the newest stent retriever or aspiration devices. These distinctions might explain the differences in outcomes between the two trials.

Although cerebral and vascular imaging was done for all patients before their inclusion in the trial, these imaging data were not used to select patients on the basis of the size of their ischaemic zone as determined by ASPECTS or on cerebral perfusion. In our trial, 17 (30%) of 57 patients who had poor baseline ASPECTS (0–4) had good clinical outcomes at 3 months. Although this proportion is lower than that of patients with better baseline ASPECTS (≥5), it is nonetheless not negligible and should invite careful reflection for the inclusion of these patients in future studies.

In our trial, the median delay from intravenous thrombolysis to randomisation was less than 20 min. Hence, patients were enrolled before the effect of thrombolysis was known. In other recent trials,[10,12–14] longer delays ranging from 47 min to 121 min were reported, allowing fast responders to intravenous thrombolysis to be excluded from the trial. The short randomisation delay in our trial and the conditions in which thrombolysis was done contributed to the high rate (42%) of functional independence at 3 months in the IVT group. This rate is similar to that reported in the control group of IMS III, in which the delay from intravenous thrombolysis to randomisation was less than 40 min, and shorter than that of the control groups of other randomised studies.[10,12–14]

Furthermore, the short delay between intravenous thrombolysis and randomisation contributed to the large proportion (59 [29%] of 204) of patients in the IVTMT group who did not have thrombectomy. This proportion is higher than that of the MR CLEAN trial (17 [7%] of 233),[10] in which the median delay between thrombolysis initiation and randomisation was more than 100 min. In our opinion, our strategy better reflects routine clinical practice, where the recommendation is not to delay thrombectomy in populations eligible for a bridging strategy.

In the IVTMT group, 53% of patients had a good clinical outcome at 3 months, a proportion that is within the range of those reported in recent randomised studies and close to those of the pooled analysis.[25] Furthermore, the frequencies of complications or adverse events were similar in the two groups, and the frequencies of asymptomatic and symptomatic haemorrhage were low and similar to those of the pooled analysis.[25]

The absolute difference in functional independence at 3 months (11%) between the two groups in our study is low compared with other studies.[10–14] The time from randomisation to groin puncture was considerably higher (82 min) than that in other trials. This long time had a negative effect only in the IVTMT group and might explain, at least partly, the reduced difference in functional independence between the groups.

The rate of mTICI grade 2b–3 reperfusion at procedure completion (69%) is within the range of rates reported in recent randomised studies (58–88%).[10–14] During our 4 year trial, we integrated new, better-performing systems as they became available and we improved our thrombectomy techniques, thereby increasing efficacy. This dynamic might explain why our recanalisation rate, established over 4 years, is lower than those reported in recent studies or registries.[11,13]

Our trial has several limitations. The modified Rankin score was estimated by vascular neurologists who were not masked to the treatment to which the patients had been allocated. Protocol changes occurred during the course of the study. For example, the window for initiation of intravenous thrombolysis was initially limited to 3 h but, after enrolment of 80 patients, we decided to extend the time limit to 4 h, while maintaining a time limit of 5 h for thrombectomy initiation. Also, up to Oct 12, 2012, patients had to receive the full dose of alteplase and then be reassessed before proceeding to angiography. This rule was then changed to allow earlier intervention. Finally, the trial was originally designed to include patients with occlusions of the superior third of the basilar artery. However, only two patients were available for inclusion, since occlusions in that location are normally treated with an endovascular approach in France. Thus, the findings of the trial apply only to patients with anterior circulation strokes.

In conclusion, results from the THRACE trial showed that, in patients presenting with moderate-to-severe stroke caused by occlusion of a large artery of the anterior circulation and who are not selected on the basis of imaging-based criteria, an approach combining mechanical thrombectomy with standard intravenous thrombolysis provides a significantly higher rate of functional independence at 3 months with no evidence of increased mortality than intravenous thrombolysis alone. Bridging therapy seems to be beneficial and should be considered for patients with large-vessel occlusions of the anterior circulation, irrespective of their age, sex, clinical severity, or intracranial location of the occlusion.

Contributors

SBr conceived the study, obtained funding, and was the principal investigator. SBr, XD, and FG designed the study and managed the THRACE trial with help from JLM and TM. SBr, JLM, FG, TM, and

XD drafted the report. CO programmed and coordinated imaging assessment. MS is the study statistician who prepared the analysis for this report. FG advised on statistical aspects. FG and MS take responsibility for the integrity of the data and the accuracy of the data analysis. AB and XL were members of the trial steering committee. NA, MB, RB, FC, HR, SR, SS, MT, ALD, and ON analysed the data. SBa, FB, YB, JB, MBi, THC, JC, CC, CD, OD, AFa, AFe, LG, SG, BG, EH, BL, MM, JPN, MO, AP-P, MP, LP, FR, TR, GS, IS, JS, CS, LS, FT, and SV collected the data. All authors commented on the draft and approved the final version.

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Declaration of interests

SBr reports grants from the French Ministry of Health during the conduct of the study, and personal fees from General Electric Medical Systems and non-financial support from Microvention Europe outside the submitted work. AB reports personal fees from Microvention outside the submitted work. FC reports personal fees from Codman Neurovascular and Medtronic outside the submitted work. LP reports personal fees from Microvention, Medtronic, Neuravi, Penumbra, and Sequent outside the submitted work. FT reports grants from Stryker and Medtronic outside the submitted work. All other authors declare no competing interests.

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