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Does the Benefit of Thrombectomy in Large Strokes Depend on Perfusion–Diffusion Mismatch? A Large Stroke Therapy Evaluation Trial *Post Hoc* Analysis

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Background and Purpose Whether perfusion–diffusion mismatch modifies treatment effect of mechanical thrombectomy (MT) for large strokes is poorly known. To address this question, we conducted a *post hoc* secondary analysis of the Large Stroke Therapy Evaluation (LASTE) randomized controlled trial (RCT).

Methods The LASTE RCT compared MT plus best medical treatment (BMT) to BMT alone in patients with large infarct (Alberta Stroke Program Early CT Score 0–5) in the 0–7-hour time-window. This secondary analysis was restricted to patients with available baseline MR perfusion-weighted imaging. We investigated the potential heterogeneity of MT treatment according to the presence of perfusion–diffusion mismatch, defined as a mismatch ratio ≥ 1.2 , calculated as the time-to-maximum >6 seconds cerebral volume divided by ischemic core volume. The primary outcome was better functional outcome (favorable shift in the distribution of modified Rankin Scale [mRS] at 90 days, analyzed using generalized odds ratio [GenOR]).

Results A total of 102/324 patients were included, among whom 55 (54%) had a perfusion–diffusion mismatch. No significant treatment effect heterogeneity by diffusion–perfusion mismatch was observed for the primary outcome (GenOR for better functional outcome: 1.70 [95% confidence interval, CI, 0.95 to 3.05] and 1.04 [95% CI, 0.57 to 1.87] in patients with and without mismatch, respectively; ratio of GenORs: 1.63 [95% CI, 0.71 to 3.74]; P for heterogeneity=0.24) or for the secondary efficacy and safety outcomes.

Conclusions Our study found no evidence of heterogeneity of treatment effect with respect to benefit or safety in patients with unrestricted infarct size at baseline treated with MT by presence of perfusion–diffusion mismatch. An individual participant–data meta-analysis of RCT is needed for definitive conclusions.

Keywords Thrombectomy; Brain infarction; Stroke; Perfusion imaging; Clinical trial

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Introduction

Five recent randomized controlled trials (RCTs) demonstrated the efficacy and safety of mechanical thrombectomy (MT) in patients with baseline large acute stroke due to large vessel occlusion (LVO)^{1–5} in the anterior circulation, while a sixth RCT indicated a potential benefit.⁶ Imaging eligibility criteria and qualifying modalities differed among these trials, with large ischemic cores defined using CT or diffusion-weighted imaging (DWI), mostly based on an Alberta Stroke Program Early CT Score (ASPECTS) of 3 to 5.^{1–6} The Large Stroke Therapy Evaluation (LASTE) trial was the only RCT including patients with ASPECTS between 0 and 5, and it suggested a comparable benefit of MT in both ASPECTS ranges 0–2 and 3–5.⁵

Nevertheless, mechanisms underlying the benefit of MT in large stroke remain largely unknown and it is currently uncertain if some selection tools could help identifying the patients who will benefit from MT or not.⁷ Salvage of penumbral brain tissue may represent one potential mechanism. One key issue in the field,^{7,8} that remains controversial, is whether a mismatch between the infarct size and the hypoperfusion lesion on perfusion

imaging modifies the MT treatment effect in patients with large infarcts, and whether MT is not detrimental in patients without a mismatch.

Several non-randomized studies have explored the impact of the perfusion–diffusion mismatch in predicting MT treatment effect, with conflicting results.^{9–12} In some studies, MT was associated with a higher probability of favorable outcome as mismatch ratio increased,^{9,10} and MT led to better outcome in patients with, but not in those without, a mismatch ratio ≥ 1.2 .¹⁰ Conversely, in another study, recanalization after MT also improved outcomes in patients without mismatch, with similar rates of functional independence between patients with and without perfusion–diffusion mismatch.¹¹

The recent Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2) and Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core (ANGEL-ASPECT) RCTs contributed further to this debate.^{13,14} The SELECT2 trial suggested that there was no significant difference in MT treatment effect between patients with and without mismatch profiles.¹⁴ In contrast, the ANGEL-ASPECT trial found MT

to be more effective than BMT in patients with mismatch profiles, and showed no treatment benefit in those without a mismatch profile.¹³ However, both trials are limited by a very limited number of patients without mismatch, considering a ≥ 1.2 mismatch ratio cut-off.⁷ This led the American Heart Association to conclude that the generalizability of the RCT results requires further exploration for the subgroup of patients without mismatch.¹⁵

The objective of this *post hoc* analysis of the LASTE trial was to explore the potential heterogeneity in the treatment effect of MT (compared with BMT) according to perfusion-diffusion mismatch in patients with available baseline perfusion imaging.

Methods

Population

The present study was a *post hoc* analysis of the LASTE trial (NCT03811769). The LASTE trial was a multicenter, prospective, open-label, randomized, controlled trial with blinded outcome evaluation, conducted at 24 hospitals in France and 6 hospitals in Spain from April 2019 through March 2023, which compared MT plus best medical treatment (BMT) versus BMT alone in patients with large infarcts.^{5,16} Details of the inclusion and exclusion criteria in the LASTE trial have been previously reported.¹⁶ The trial followed the Consolidated Standards of Reporting Trials guidelines for RCT. The trial protocol was approved by the institutional review board at each participating trial site, and enrolled patients or their surrogates provided written informed consent.⁵ A data sharing statement provided by the LASTE authors is available in the main publication.⁵

Patients were eligible for inclusion in the LASTE trial if they were older than 18 years; had an ASPECTS value of 0 to 5 on CT or MRI (except for patients aged over 80, for whom a baseline ASPECTS value of 4 or 5 was required); had an anterior LVO (intracranial internal carotid artery or M1 segment of the middle cerebral artery); had a prestroke mRS score of 0 or 1; had a National Institutes of Health Stroke Scale (NIHSS) score of at least 6; and could undergo randomization within 6.5 hours after last known well (when symptoms onset was unknown, patients could be included if they presented within 24 hours of last known well and if they did not show a positive corresponding lesion on the fluid attenuation inversion recovery sequence). Choice of baseline imaging was left to the team-in-charge, and magnetic resonance imaging (MRI) was the imaging method used for selection in 84% of the patients,⁵ being the preferred first-line imaging modality in France. Realization of an initial perfusion imaging was optional and was not a selection criterion. The trial was sponsored by the Montpellier University Hospital through an

unrestricted grant from an industry consortium that was not involved in the design or implementation of the trial. OLEA Medical® (La Ciotat, France) provided financial support for the repatriation and storage of radiological data, but was not involved in the design or implementation of this *post hoc* analysis.

For the current *post hoc* study, patients included in the LASTE trial were considered for inclusion when they underwent a baseline conventional perfusion-weighted magnetic resonance imaging (PWI-MRI) using gadolinium (patients with arterial spin labeling were not included as no time-to-maximum [Tmax] maps can be processed with this sequence). Patients who withdrew consent or showed non-interpretable PWI due to motion artifacts or gadolinium injection issues were excluded.

Definition of mismatch

On baseline perfusion data, critically hypoperfused tissue was defined as the volume of brain tissue with a Tmax greater than 6 seconds,^{17,18} obtained using the OLEA Sphere® post-processing 3D software (OLEA Medical), with manual correction performed by a trained vascular neurologist (ATS) when necessary.

The initial ischemic core volume was measured by the core lab using manual definition of region-of-interest delineation of the ischemic lesion on each axial imaging slice of the DWI sequence. Volumetric calculation of all axial region-of-interest areas was performed including exact slice thickness, accounting for any gaps. We used the ischemic core volumes provided by core lab rather than those provided by the automated software for two main reasons: first, all of the DWI images could not be processed by the Olea Sphere® software; second, OLEA Sphere® software does not generate continuity between voxels during the segmentation, potentially leading to an underestimation of the ischemic core volume,¹⁹ particularly in large ischemic strokes.

The mismatch ratio was defined as the Tmax >6 seconds cerebral volume divided by the ischemic core volume. Patients were categorized based on perfusion-diffusion mismatch, using a mismatch ratio threshold of ≥ 1.2 , based on existing literature.^{10,13,14} Patients with a mismatch ratio <1.2 were categorized as having an absence of mismatch profile (i.e., "no-mismatch" group). Of note, all of the patients from the "mismatch group" included in this analysis, i.e., with a mismatch ratio ≥ 1.2 , also had a mismatch volume ≥ 10 mL as per the Extending the Time for Thrombolysis in Emergency Neurological Deficits criteria.¹⁸

Study outcomes

The primary outcome was better functional outcome, defined as a favorable shift in the distribution of the modified Rankin Scale (mRS) score at 90 days after randomization, combining scores of 5 and 6.²⁰ Secondary outcomes included the mRS score at

180 days after randomization, mRS score of 0 to 2 (favorable outcome) and of 0 to 3 (independent ambulation) at 90 days and 180 days, and early neurological improvement (defined as a decrease in the NIHSS score of ≥ 8 points from baseline at either 7 days or the time of hospital discharge).

The safety outcome included early neurologic worsening (defined as an increase in the NIHSS score of ≥ 10 points from baseline at day 7), any intracranial hemorrhage on 24-hour control imaging,²¹ and 90-day mortality.⁵

Statistical analysis

Quantitative variables were expressed as median (interquartile range) and categorical variables were expressed as frequencies and percentages. To assess for potential selection bias, baseline characteristics were described in patients included or not in this secondary analysis. Among included patients, baseline characteristics were described first according to the allocated LASTE trial arm and then according to mismatch subgroups. Imbalance in baseline characteristics between groups was assessed by calculating the standardized difference; an absolute standardized difference $>20\%$ was considered to be a meaningful difference.²² We investigated the potential role of mismatch (mismatch ratio ≥ 1.2) on MT treatment effect on clinical outcomes by estimating the treatment effect sizes in mismatch subgroups and the corresponding ratio of effect sizes (presence/absence of mismatch), with their 95% confidence intervals (CIs). Treatment effect size for shift in mRS (after pooling together mRS 5 and 6) at 90 days (primary outcome) and at 180 days was assessed using the generalized odds ratio (GenOR) by splitting ties equally between groups. Treatment effect size in secondary binary outcomes was assessed by calculating the relative risks by adding a pseudo count value (0.5) in all cells of 2×2 tables to account the small sample size and the presence of zero count. We also investigated the potential impact of mismatch ratio treated as continuous variable on MT treatment effect on primary outcome and the key secondary outcome (independent ambulation at 3 months). Distribution of mRS at 3 months was plotted according to mismatch ratio and treatment group, and we calculated Spearman's rank correlation coefficient between mismatch ratio and mRS in each treatment group separately. For independent ambulation, heterogeneity was investigated using a logistic regression model by including treatment group, mismatch ratio, and the corresponding interaction term. Predicted independent ambulation probability according to mismatch ratio and treatment group are plotted with their 95% CIs. We restricted to perform a formal heterogeneity test only for primary outcome using a Z-score statistics comparing the two mismatch-specific GenORs or the two Spearman's rank correlation coefficients (after applying a

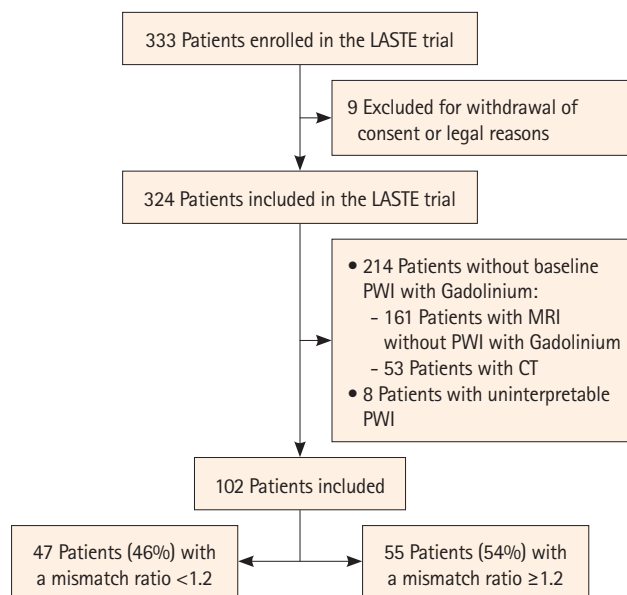


Figure 1. Flowchart of patient selection. LASTE, Large Stroke Therapy Evaluation; PWI, perfusion-weighted imaging; MRI, magnetic resonance imaging; CT, computed tomography.

Fisher z-transformation). The credibility of treatment effect heterogeneity by perfusion-diffusion mismatch was assessed with the Instrument for assessing the Credibility of Effect Modification Analyses. Because there was no plan for the adjustment of multiple comparisons following the limited sample size, the CIs should not be used to infer statistically significant differences.²³ Data were analyzed with SAS software version 9.4 (SAS Institute, Cary, NC, USA) and by using Gen-odds R package version 4.1.2 (<https://CRAN.R-project.org/package=genodds>).

Results

Among the 333 patients enrolled in the LASTE trial, nine were excluded due to consent withdrawal or legal reasons. Of 324 patients considered for inclusion in this *post hoc* analysis, 222 were excluded (baseline MRI without PWI with Gadolinium: $n=161$; baseline CT-scan: $n=53$; uninterpretable baseline PWI: $n=8$) (Figure 1). The baseline characteristics of included and non-included patients in the present study are reported in Supplementary Table 1.

In total, 102 patients were included in this *post hoc* analysis, of whom 56 patients were randomized to the MT+BMT arm and 46 to the BMT arm. Table 1 shows the baseline characteristics according to the allocated arm. A mismatch ratio ≥ 1.2 was identified in 55 patients (54%), including 27 (48.2%) in the MT arm and 28 (60.9%) in the control arm. Most baseline characteristics were similar for patients with and without mismatch, except for the initial infarct volume which was higher in patients

Table 1. Baseline characteristics of included patients according to Large Stroke Therapy Evaluation allocated arm

Characteristics	BMT+MT (n=56)	BMT (n=46)	Standardized difference (%)
Demographic			
Age (yr)	73 (60 to 78)	74 (65 to 78)	-4.8
Male sex	27 (48.2)	26 (56.5)	-16.7
Medical history			
Hypertension	37 (66.1)	25 (54.3)	24.1
Hypercholesterolemia	18 (32.1)	17 (37.0)	-10.1
Diabetes	11 (19.6)	8 (17.4)	5.8
Current smokers	13 (23.2)	9 (19.6)	24.2
Coronary artery disease	13 (23.2)	7 (15.2)	20.4
Previous stroke or TIA	11 (19.6)	3 (6.5)	39.7
Previous atrial fibrillation	8 (14.3)	9 (19.6)	-14.1
Previous antithrombotic medications	31 (55.4)	19 (41.3)	28.4
Antiplatelets	23 (41.1)	12 (26.1)	32.1
Anticoagulants	13 (23.2)	7 (15.2)	20.4
Current stroke event			
Directly admitted to thrombectomy center	32 (57.1)	24 (52.2)	10.0
Pre-stroke mRS			
0	39 (69.6)	36 (78.3)	28.4
1	15 (26.8)	10 (21.7)	
>1	2 (3.6)	0 (0)	
Admission SBP (mm Hg)	140 (122 to 160)	156 (136 to 170)	-40.5
Admission glucose (g/L)	1.3 (1.1 to 1.5) [n=55]	1.3 (1.2 to 1.5) [n=45]	-20.1
NIHSS at randomization	21 (18 to 25)	21 (18 to 25)	-6.7
Infarct volume (mL)	134 (108 to 183)	131 (104 to 171)	9.1
ASPECTS values			
0-2	33 (58.9)	26 (56.5)	-4.9
3-6	23 (41.1)	20 (43.5)	
Occlusion site			
ICA	26 (46.4)	22 (47.8)	2.8
M1	30 (53.6)	24 (52.2)	
Mismatch ratio <1.2	29 (51.8)	18 (39.1)	-25.6
Intravenous thrombolysis	12 (21.4)	11 (23.9)	-5.9
Stroke etiology			
Large artery atherosclerosis	6 (10.7)	2 (4.3)	32.8
Cardioembolic	25 (44.6)	22 (47.8)	
Other certain cause	3 (5.4)	1 (2.2)	
Unknown	22 (39.3)	21 (45.7)	
Unknown-onset stroke	17 (30.4)	15 (32.6)	4.9
Workflow times (min)			
Last-seen well to randomization	259 (173 to 366)	280 (236 to 345)	-15.0
Last-seen well to qualifying imaging	208 (129 to 315)	241 (167 to 309)	-10.4
Last-seen well to CSC	214 (101 to 310)	235 (171 to 300)	-5.0

Values are n (%) or median (25th to 75th percentiles) [number of available patients].

BMT, best medical treatment; MT, mechanical thrombectomy; TIA, transient ischemic attack; mRS, modified Rankin Scale; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Acute Stroke Prognosis Early CT Score; ICA, internal carotid artery; CSC, Comprehensive Stroke Center.

without mismatch (167 [119 to 210] vs. 122 [82 to 149] (Supplementary Table 2).

The distribution of the mRS score at 90 days and at 180 days is presented in Figure 2. Regarding the primary outcome (favorable shift in the distribution of 90-days mRS), no significant treatment effect heterogeneity by perfusion-diffusion mismatch was observed (GenOR for better functional outcome: 1.70 [95% CI, 0.95 to 3.05] and 1.04 [95% CI, 0.57 to 1.87] in patients with and without mismatch, respectively; ratio of GenORs: 1.63 [95% CI, 0.71 to 3.74]; *P* for heterogeneity=0.24). We found similar results at 180 days (GenOR: 1.64 [95% CI, 0.71 to 3.79]). In addition, when mismatch ratio was analysed as continuous variable, there was no evidence of interaction between mismatch ratio and treatment group on mRS distribution (Supplementary Figure 1). No correlation was found in BMT group ($\rho=0.03$; 95% CI, -0.26 to 0.32) and a weak negative correlation was found in BMT+MT group ($\rho=-0.18$; 95% CI, -0.43 to 0.09), with a non-significant heterogeneity test (*P*=0.14).

Regarding secondary efficacy outcomes, there was no evidence of heterogeneity in MT treatment effect according to mismatch profile (Figure 3). MT was associated with a higher nominal rate of independent ambulation (mRS 0–3) at 90 days in both patients with mismatch (MT: 38.5% vs. BMT: 17.9%; RR: 2.05 [95% CI, 0.84 to 4.99]) and without mismatch (MT: 20.7% vs. BMT: 0%; RR: 8.23 [95% CI, 0.49 to 137.92]) (ratio of RRs: 0.25 [95% CI, 0.01 to 4.79]). As shown in Supplementary Figure 2, the difference in independent ambulation probability between MT and BMT group remained constant across the mismatch ratio values. MT was also associated with a higher nominal rate results in both patients with and without mismatch for favorable outcome (mRS 0–2) at 90 and 180 days, independent ambulation at 180

days and early neurological improvement. There was also no evidence of heterogeneity in MT-related treatment effect regarding safety outcomes (early neurologic worsening, all-types of intracranial hemorrhage on 24-hour control imaging, and 90-days or 180-days mortality) (Figure 3).

Discussion

In this sub-analysis of the LASTE trial, 102 patients with LVO of the anterior circulation, large ischemic core (ASPECT 0–5) within 7 hours, and baseline PWI-MRI were included, of whom half had a perfusion-diffusion mismatch (defined as a mismatch ratio ≥ 1.2). Our study does not suggest that presence or absence of a diffusion-perfusion mismatch influences the benefit or safety of MT in patients with unrestricted infarct size at baseline. On the primary outcome (better functional outcome, defined by a favorable shift in the distribution of 90-day mRS), there was no clear treatment effect heterogeneity based on the presence or absence of mismatch (ratio of GenOR: 1.63 [95% CI, 0.71 to 3.74], *P* for heterogeneity test=0.24). Results were similar at 180 days and for the other secondary efficacy outcomes, with no evidence of heterogeneity in MT treatment effect according to mismatch profile. Regarding safety, no concerning signal was observed in the no-mismatch group: there was no significant difference in hemorrhagic risk or early neurological worsening between treatment arms, regardless of the mismatch profile. However, we cannot entirely rule out a potential increase in mortality in patients without a mismatch.

The few data in the literature addressing the impact of perfusion-diffusion mismatch on the outcomes of patients after MT in large cores are contradictory, both in non-randomized stud-

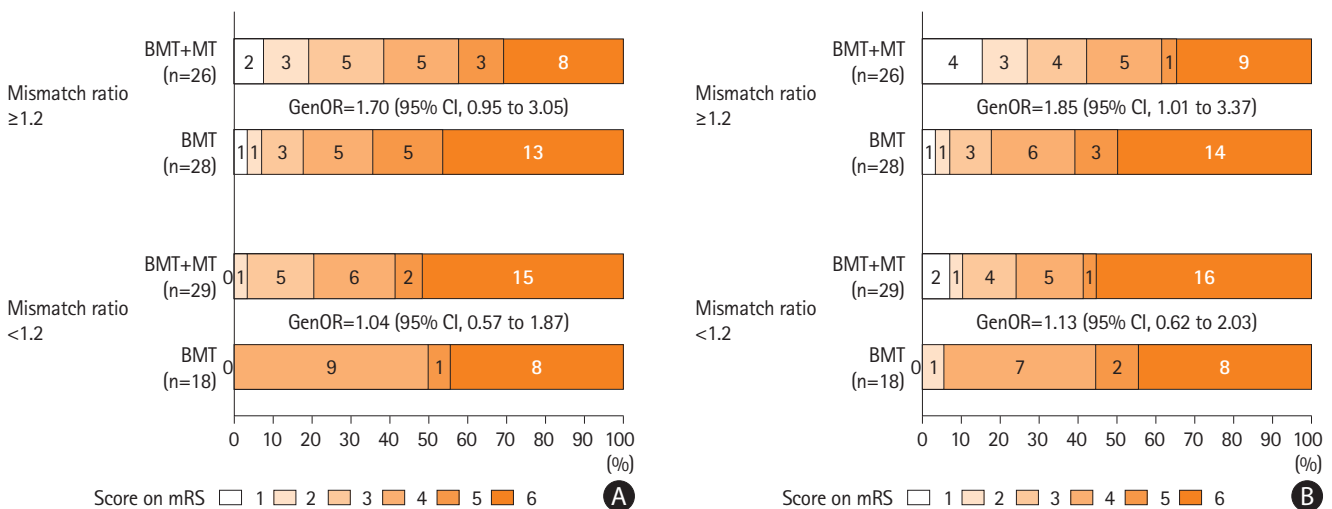


Figure 2. mRS at 90 days (A) and 180 days (B) according to treatment groups and pre-treatment mismatch ratio (<1.2 vs. ≥ 1.2). GenOR indicates generalized odds ratio for thrombectomy versus control calculated after pooled mRS 5 and 6 together (A: at 90 days, B: at 180 days). BMT, best medical treatment (control); MT, mechanical thrombectomy; GenOR, generalized odds ratio; CI, confidence interval; mRS, modified Rankin Scale.

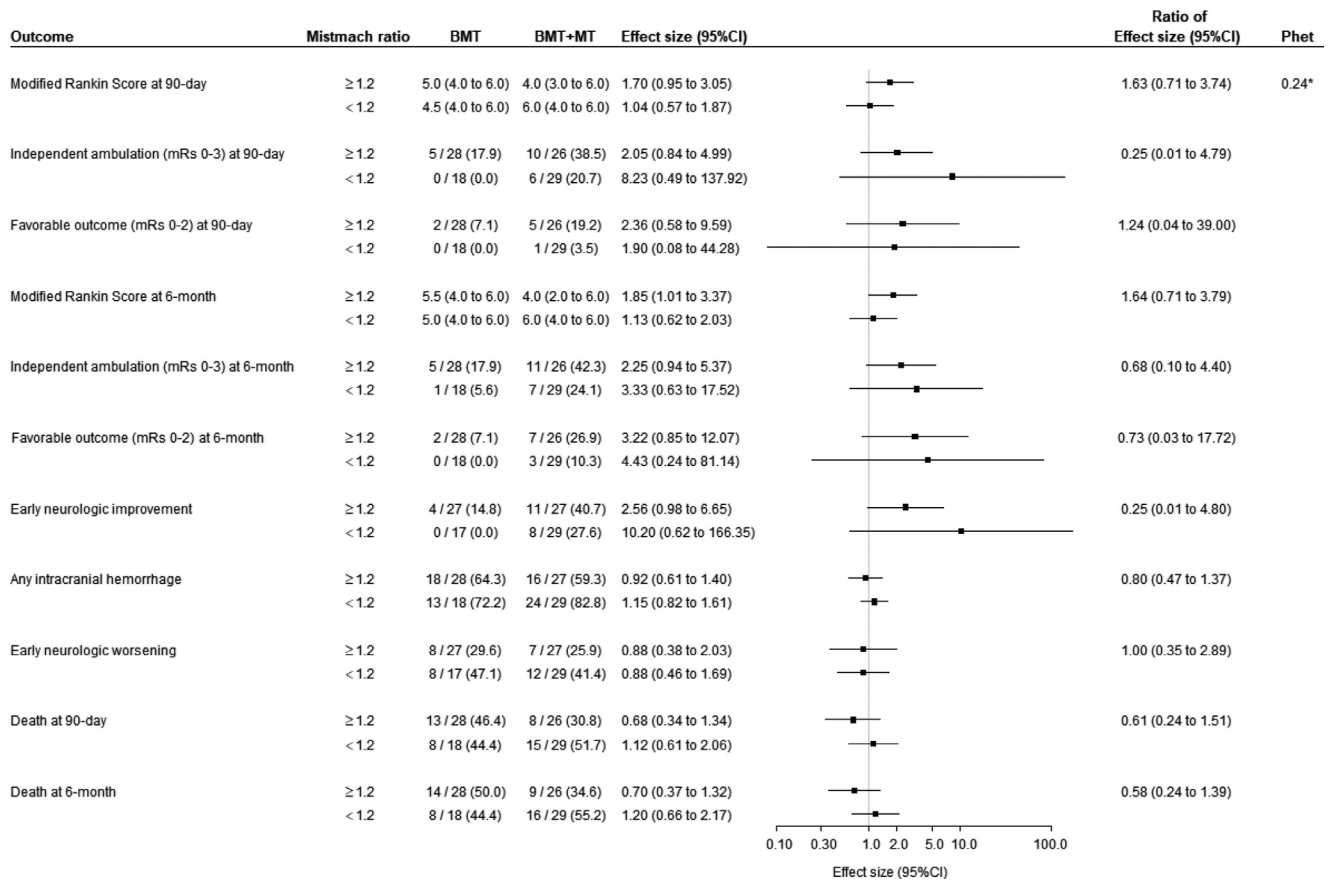


Figure 3. Effect sizes for thrombectomy versus control on primary and secondary outcomes according to mismatch ratio (<1.2 vs. ≥1.2). Values are no. (%) or median (25th to 75th percentiles) unless otherwise as indicated. Independent ambulation is defined as mRS score of 0 to 3 and favorable outcome as mRS score of 0 to 2. Early neurological improvement is defined as a decrease in the NIHSS score of ≥8 points from baseline at either 7 days or the time of hospital discharge. Early neurologic worsening is defined as an increase in the NIHSS score of ≥10 points from baseline at day 7. Effect sizes were generalized odds ratio for modified mRS treated as ordinal outcome (after pooled mRS 5 and 6 together) or relative risk for binary outcomes (after applying a pseudo count value of 0.5 for all cells of 2*2 tables). Ratio of effect sizes for presence versus absence of mismatch were reported with their 95% CIs calculated using the Z-score statistics. *P* het indicates *P*-value for heterogeneity calculated using Z-score statistics calculated for primary outcome only. BMT, best medical treatment; MT, mechanical thrombectomy; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

ies and RCT.^{6,9-11,13,14,24,25} Three RCT on large core reported the impact of mismatch (SELECT2, ANGEL-ASPECT, and Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke [TESLA]).^{6,13,14} SELECT2 and ANGEL-ASPECTS defined mismatch as a mismatch ratio ≥1.2 and a mismatch volume ≥10 mL.^{13,14} There was no significant difference in MT treatment effect between patients with and without mismatch in SELECT-2,¹⁴ while MT was found to be more effective than BMT only in the patients with mismatch in ANGEL-ASPECT.¹³ A meta-analysis of these trials reported no MT benefit for patients without mismatch.²⁶ However, the number of patients without mismatch in these 2 trials was very limited, representing only about 30 patients in each trial⁷ (>90% of patients had a mismatch). In the TESLA trial, which did not meet the primary endpoint on the utility-weighted mRS (uw-mRS), the authors used more stringent criteria (mismatch ratio >1.5, mismatch volume >50 mL, and core volume of 70–120 mL for age ≤70 years or 70–100 mL for age

>70 years), resulting in 63% of patients with mismatch.⁶ A subgroup analysis of this neutral trial found no significant benefit of MT on uw-mRS in both mismatch and no-mismatch patients, with an unexpectedly trend towards MT benefit in the no-mismatch group.⁶

Our population differs from those of these other trials. Above all, using the ≥1.2 mismatch ratio cut-off criteria, our study included a significantly higher proportion of no-mismatch patients (46%), comparable to rates reported in observational studies.^{7,10,25} This discrepancy with other RCTs may stem from several factors. First, due to the absence of an upper limit on infarct size, LASTE included patients with larger baseline infarcts (58% of the patients in this study had an ASPECTS 0–2 on MRI),⁵ resulting in substantially higher baseline volumes (median 132 mL in this *post hoc* analysis) compared to the other trials (60 mL in ANGEL-ASPECT and 74 mL in SELECT2^{13,14}). Second, this *post hoc* study exclusively included patients with baseline PWI-MRI. In

contrast, ANGEL-ASPECT and SELECT2 trials relied predominantly on computed-tomography perfusion (93% and 95% patients, respectively^{13,14}), which can underestimate initial infarct volume,²⁷ possibly leading to a lower proportion of patients with mismatch. Third, clinicians in SELECT2 and ANGEL-ASPECT may have preferentially enrolled patients with a mismatch, as suggested by the authors,^{13,14} while the spirit of LASTE was to include patients with unrestricted infarct size, without mandatory perfusion imaging, and irrespective of the results of perfusion imaging if it was performed.¹⁶ Hence, the high rate of no-mismatch in our study suggests that perfusion data did not influence patient inclusion in LASTE. Finally, our methodology for calculating mismatch differed. We used core volumes provided by the core lab instead of software-generated values as in SELECT2 and ANGEL-ASPECT (RAPID AI® software). This decision was made to ensure consistent data availability, as some DWI images could not be processed with OLEA Sphere®. Moreover, OLEA Sphere software does not generate continuity between voxels during the segmentation, potentially leading to an underestimation of the core volume.¹⁹ Further validation of our study findings using perfusion core estimates from other software platforms may help extend the study's generalizability.

Consistent with previous studies,^{13,14,28} patients without mismatch had a lower absolute proportion of favorable outcome (mRS 0–2) and independent ambulation (mRS 0–3) at 90 and 180 days compared to those with mismatch in our study, regardless of the treatment arm. This may partly be explained by the larger initial core volume in patients without mismatch. However, the absence of treatment effect heterogeneity, and the higher proportion of patients achieving independent ambulation in the MT group among patients without mismatch suggest that MT may confer benefits beyond penumbral salvage, such as edema prevention and reduction of final true infarct volume within the initial heterogeneous core.²⁹ Indeed, similar to findings in animal models, the concept of gradient injury within the infarct core has been described in humans by numerous authors,^{30–32} and a reduction of tissue loss undetectable on MRI could represent a potential beneficial effect of MT in large core patients. Moreover, infarct volume estimation on initial imaging, even with DWI-MRI, remains highly debated. Notably, reversible diffusion abnormalities have been reported in up to a quarter of patients.³³ Of note, our study focused solely on the impact of the presence or absence of a mismatch, whereas other characteristics, such as its localization, may also play a role. Hence, emerging evidence from observational studies suggests that the functional relevance of the salvaged tissue, rather than its sheer volume, may influence the benefit of MT in large core strokes.^{12,34}

Our study has several limitations.

First, the sample size was small (one-third of the patients enrolled in LASTE) because perfusion imaging was optional in LASTE, and was unavailable in some recruiting centers. In addition, the LASTE trial was not originally designed to detect an effect modification by perfusion–diffusion mismatch. Hence, it is important to acknowledge that the ability to detect a meaningful interaction effect in this *post hoc* analysis is inherently limited. Therefore, even though we did not find a significant interaction between mismatch and MT effect (P for heterogeneity=0.24), we have lacked statistical power to formally exclude heterogeneity in the treatment effect, as indicated by the wide CIs of the effect size ratios. However, our study includes the largest reported population of RCT patients without mismatch (defined by a <1.2 mismatch ratio cut-off), providing a unique contribution to the ongoing debate on mismatch as a treatment effect modifier in MT for large core stroke.^{13,14} Further pooled analyses with larger individual patient datasets will be needed to confirm our findings.

Second, some baseline characteristics were not well-balanced between included and non-included patients (i.e., patients who either did not MR-perfusion imaging [$n=206$] or had technically inadequate perfusion sequences [$n=8$]), as admission mode (mothership vs. drip-and-ship), intravenous thrombolysis (IVT) use, and time from last-seen-well to qualifying imaging (Supplementary Table 1). However, key prognostic factors in acute ischemic stroke, including age, sex, NIHSS at randomization, baseline infarct volumes, and ASPECTS values, were comparable between groups. Part of these discrepancies may be due to the predominance of patients with available perfusion data coming from mothership pathways, as perfusion imaging was rarely performed in PSCs, and repeat imaging upon Comprehensive Stroke Center arrival was not mandatory in LASTE.¹⁶ This selective inclusion may nonetheless have introduced a risk of selection bias and limited the external validity of our findings. Caution is thus warranted when generalizing our results to other stroke populations not routinely evaluated with advanced imaging.

Third, slight differences were observed between patients with and without mismatch (Supplementary Table 2), regarding IVT rates and onset-to-randomization times. However, these differences are unlikely to have influenced the absence of interaction observed between mismatch status and the therapeutic effect of EVT, because these variables were overall well balanced between the EVT and BMT groups (Table 1).

Fourth, our decision to include only patients with MRI-based perfusion imaging excluded those with CT perfusion, potentially limiting the generalizability of our findings, given that CT is the predominant imaging modality for acute stroke treatment worldwide. However, only a small subset of LASTE patients had CT5,

and restricting inclusion to patients with PWI-MRI ensured sample homogeneity while leveraging MRI's superior accuracy in mismatch estimation.

Fifth, manual segmentation of the acute ischemic core volumes may have led to an overestimation of the initial infarct size and, consequently, the number of patients classified as no-mismatch.⁷ However, there is currently no gold standard for estimating initial core volume between manual segmentation and perfusion software, and some studies comparing multiple software tools have shown significant variability in core volume estimations.¹⁹

Conclusions

In this *post hoc* analysis of the LASTE trial, which included patients with large-core infarcts in the early time window, half of the patients had a perfusion-diffusion mismatch defined as a mismatch ratio of ≥ 1.2 on baseline MRI. We found no significant heterogeneity in the treatment effect based on perfusion-diffusion mismatch for either efficacy or safety outcomes, with no concerning trends in the no-mismatch group. These findings do not support withholding MT in patients without a perfusion-diffusion mismatch.

Given the limited number of no-mismatch patients across RCT assessing MT in large core strokes, an individual patient data meta-analysis is however needed to draw more definitive conclusions. Additionally, standardizing ischemic core and mismatch volume measurements across software platforms, as well as mismatch definition, is essential to enhance generalizability. Such efforts will help clarify the potential role of mismatch characterization in selecting patients with large-core stroke for MT.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2025.01200>.

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Conflicts of interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication

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Supplementary Table 1. Baseline characteristics of included and non-included patients (i.e., with vs. without usable MR-perfusion imaging)

Characteristics	Not included (n=222)	Included (n=102)	Standardized differences (%)
Allocated LASTE trial arm			
BMT	119/222 (53.6)	46/102 (45.1)	17.1
BMT+MT	103/222 (46.4)	56/102 (54.9)	
Demographics			
Age (yr)	74 (66 to 81)	73 (62 to 78)	-20.6
Male sex	117/222 (52.7)	53/102 (52.0)	-1.5
Medical history			
Hypertension	153/222 (68.9)	62/102 (60.8)	-17.1
Hypercholesterolemia	86/222 (38.7)	35/102 (34.3)	-9.2
Diabete	51/222 (23.0)	19/102 (18.6)	-10.7
Current smokers	32/221 (14.5)	22/102 (21.6)	18.6
Coronary artery disease	37/222 (16.7)	20/102 (19.6)	7.6
Previous stroke or TIA	42/222 (18.9)	14/102 (13.7)	-14.1
Previous atrial fibrillation	59/222 (26.6)	17/102 (16.7)	-24.3
Previous antithrombotic medications	103/222 (46.4)	50/102 (49.0)	5.2
Antiplatelets	70/222 (31.5)	35/102 (34.3)	5.9
Anticoagulants	41/222 (18.5)	20/102 (19.6)	2.9
Current stroke event			
Directly admitted to thrombectomy center	85/222 (38.3)	56/102 (54.9)	33.8
Pre stroke mRS			
0	184/222 (82.9)	75/102 (73.5)	22.5
1	36/222 (16.2)	25/102 (24.5)	
>1	2/102 (2.0)	2/102 (2.0)	
Admission SBP (mm Hg)	147 (130 to 166)	149 (130 to 167)	-0.8
Admission glucose (g/L)	1.3 (1.2 to 1.6) [n=217]	1.3 (1.1 to 1.5) [n=100]	-13.3
NIHSS at randomization	20 (18 to 24)	21 (18 to 25)	20.7
Infarct volume (mL)	135 (106 to 187)	132 (104 to 172)	-4.3
ASPECTS values			
0-2	122/222 (55.0)	59/102 (57.8)	-5.8
3-6	100/222 (45.0)	43/102 (42.2)	
Occlusion site			
ICA	95/222 (42.8)	48/102 (47.1)	25.5
M1	119/222 (53.6)	54/102 (52.9)	
Others	8/222 (3.6)	0/102 (0.0)	
Intravenous thrombolysis	90/222 (40.5)	23/102 (22.5)	-39.5
Stroke etiology			
Large artery atherosclerosis	14/222 (6.3)	8/102 (7.8)	11.6
Cardioembolic	112/222 (50.5)	47/102 (46.1)	
Other certain cause	11/222 (5.0)	4/102 (3.9)	
Unknown	85/222 (38.3)	43/102 (42.2)	
Unknown-onset stroke	63/222 (28.4)	32/102 (31.4)	-6.6
Workflow times (min)			
Last-seen well to randomization	268 (205 to 338)	273 (199 to 356)	6.5
Last-seen well to qualifying imaging	153 (107 to 263)	222 (148 to 309)	46.1
Last-seen well to CSC	249 (148 to 306) [n=216]	230 (135 to 300)	-5.5

Values are number/total number (%) or median (25th to 75th percentiles) [number of available patients].

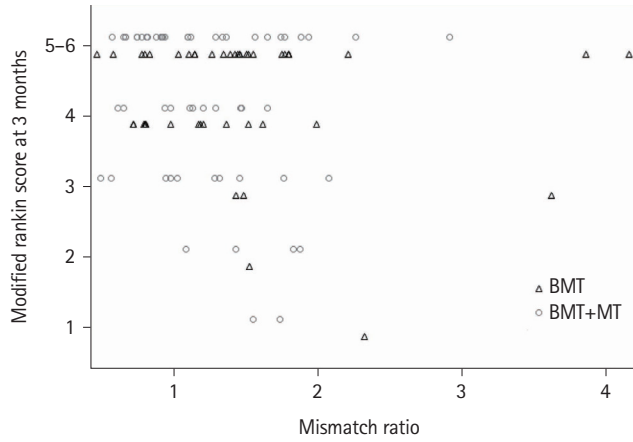
LASTE, Large Stroke Therapy Evaluation; BMT, best medical treatment; MT, mechanical thrombectomy; TIA, transient ischemic attack; mRS, modified Rankin Scale; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Acute Stroke Prognosis Early CT Score; ICA, internal carotid artery; CSC, Comprehensive Stroke Center.

Supplementary Table 2. Baseline characteristics of included patients according to the mismatch ratio

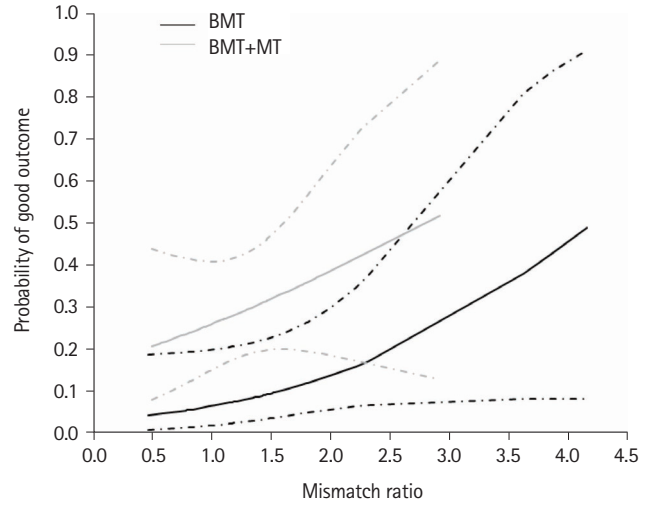
Characteristics	Mismatch ratio <1.2 (n=47)	Mismatch ratio ≥1.2 (n=55)	Standardized differences (%)
Allocated LASTE trial arm			
BMT	18 (38.3)	28 (50.9)	-25.6
BMT+MT	29 (61.7)	27 (49.1)	
Demographics			
Age (yr)	73 (60 to 77)	74 (65 to 79)	22.7
Male sex	22 (46.8)	31 (56.4)	19.2
Medical history			
Hypertension	27 (57.4)	35 (63.6)	12.7
Hypercholesterolemia	16 (34.0)	19 (34.5)	1.1
Diabetes	11 (23.4)	8 (14.5)	-22.7
Current smokers	11 (23.4)	11 (20.0)	9.8
Coronary artery disease	6 (12.8)	14 (25.5)	32.7
Previous stroke or TIA	8 (17.0)	6 (10.9)	-17.7
Previous atrial fibrillation	8 (17.0)	9 (16.4)	-1.8
Previous antithrombotic medications	24 (51.1)	26 (47.3)	-7.6
Antiplatelets	14 (29.8)	21 (38.2)	17.8
Anticoagulants	12 (25.5)	8 (14.5)	-27.7
Current stroke event			
Directly admitted to thrombectomy center	22 (46.8)	34 (61.8)	30.5
Pre-stroke mRS			
0	30 (63.8)	45 (81.8)	46.2
1	15 (31.9)	10 (18.2)	
>1	2 (4.3)	0 (0.0)	
Admission SBP (mm Hg)	145 (121 to 162)	153 (134 to 168)	16.4
Admission glucose (g/L)	1.4 (1.1 to 1.6) [n=46]	1.3 (1.1 to 1.5) [n=54]	-30.0
NIHSS at randomization	21 (18 to 24)	22 (19 to 25)	18.1
Infarct volume (mL)	167 (119 to 210)	122 (82 to 149)	-78.1
ASPECTS values	2 (1 to 3)	2 (2 to 3)	12.0
0–2	28 (59.6)	31 (56.4)	6.5
3–6	19 (40.4)	24 (43.6)	
Occlusion site			
ICA	18 (38.3)	30 (54.5)	33.0
M1	29 (61.7)	25 (45.5)	
Intravenous thrombolysis	8 (17.0)	15 (27.3)	24.9
Stroke etiology			
Large artery atherosclerosis	1 (2.1)	7 (12.7)	48.4
Cardioembolic	21 (44.7)	26 (47.3)	
Other certain cause	3 (6.4)	1 (1.8)	
Unknown	22 (46.8)	21 (38.2)	
Unknown-onset stroke	11/47 (23.4)	21 (38.2)	-32.4
Workflow times (min)			
Last-seen well to randomization	288 (215 to 343)	249 (191 to 377)	-4.6
Last-seen well to qualifying imaging	245 (170 to 309)	210 (148 to 322)	-10.9
Last-seen well to CSC	244 (161 to 307)	209 (113 to 300)	-9.7

Values are no. (%) or median (25th to 75th percentiles) [number of available patients].

LASTE, Large Stroke Therapy Evaluation; BMT, best medical treatment; MT, mechanical thrombectomy; TIA, transient ischemic attack; mRS, modified Rankin Scale; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Acute Stroke Prognosis Early CT Score; ICA, internal carotid artery; CSC, Comprehensive Stroke Center.



Supplementary Figure 1. Distribution of primary outcome (modified Rankin score at 3 months after pooled modified Rankin Scale 5 and 6 together) according to mismatch ratio and treatment arm. BMT, best medical treatment; MT, mechanical thrombectomy.



Supplementary Figure 2. Good outcomes at 3 months predicted by mismatch ratio according to treatment arm. Predicted values with their 95% confidence intervals (plotted using dashed lines) are estimated from logistic regression model including treatment group, mismatch ratio (treated as a continuous variable), and the corresponding interaction term (product term). BMT, best medical treatment; MT, mechanical thrombectomy.