Stroke

ORIGINAL CONTRIBUTION

Time-Dependent Impact of Mismatch Profiles on Outcomes Following Endovascular Thrombectomy for Large Ischemic Stroke

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BACKGROUND: Endovascular therapy (EVT) has demonstrated efficacy in patients with large core infarctions, yet favorable outcomes remain limited. Although mismatch profiles have long informed EVT decision-making in small-core strokes, their prognostic significance in large-core infarcts remains uncertain and may be affected by time from symptom onset. This study aims to evaluate the relationship between mismatch profiles, time distribution, and EVT efficacy in patients with large ischemic cores.

METHODS: This was a secondary posthoc analysis of the ANGEL-ASPECT trial in patients with large ischemic cores randomized to EVT or medical management. The primary outcome was the modified Rankin Scale score of 0 to 3 at 90 days. Analyses were stratified by mismatch profile (mismatch ratio ≥1.8 and volume ≥15 mL) and onset-to-imaging time (≤6 hours versus >6 hours).

RESULTS: For the primary end point (modified Rankin Scale score, 0–3 at 90 days), no significant treatment-by-time interaction was observed (*P* for interaction=0.412); within time strata, treatment-by-mismatch interaction tests were also nonsignificant (≤6 hours, *P* for interaction=0.166; >6 hours, *P* for interaction=0.301). In the early window (≤6 hours), EVT was associated with higher odds of favorable functional outcome (modified Rankin Scale score, 0–3 at 90 days) in patients with mismatch (48.9% versus 28.4%; odds ratio, 2.41 [95% CI, 1.28–4.55]; *P*=0.006), but not in those without mismatch (23.8% versus 27.3%; odds ratio, 0.83 [95% CI, 0.21–3.29]; *P*=0.795). In the late window (>6 hours), EVT was not associated with a significant improvement in modified Rankin Scale score 0 to 3 in either subgroup.

CONCLUSIONS: Among patients with large infarct cores, the absence of mismatch was more common in the early time window and was associated with diminished benefit from EVT. These results suggest that mismatch evaluation—even in early presenting patients—may help inform treatment selection for patients with large ischemic cores. All interaction tests were nonsignificant; these findings are hypothesis-generating and require prospective, prespecified confirmation.

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Key Words: infarction ■ ischemic stroke ■ perfusion ■ prognosis ■ tomography

Several large multicenter randomized controlled trials have demonstrated that endovascular therapy (EVT) is more effective than medical management (MM) alone in patients with large infarctions.[1–6] These trials collectively indicate that patients with large core infarctions can benefit from EVT. However, only 20% to 30% of these patients achieve functional independence posttreatment, suggesting the need for more precise selection criteria.[1–6]

The mismatch profile, characterized by a small ischemic core and a large penumbra, is a crucial criterion

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Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early Computed Tomography Score
CONSORT	Consolidated Standards of Reporting Trials
EVT	endovascular therapy
HIR	hypoperfusion intensity ratio
ICH	intracranial hemorrhage
IQR	interquartile range
MM	medical management
mRS	modified Rankin Scale
OR	odds ratio
TENSION	Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke With Large Infarct Cores in Non-eligible Patients
TESLA	Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke

for selecting patients with large vessel occlusions for EVT.[7,8] Within the late time window, spanning 6 to 24 hours after symptom onset, EVT has been shown to be beneficial primarily for patients exhibiting a confirmed mismatch between the ischemic core and penumbra, determined through either clinical-radiological or purely radiological criteria.[9,10] However, for patients with large core infarctions, subgroup analyses from the Randomized Controlled Trial to Optimize Patients' Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT-2) trial indicate that EVT might be beneficial across both mismatch and nonmismatch groups, although the number of patients without a mismatch was limited.[11] Interestingly, the SELECT-2 trial also revealed that the proportion of patients with a mismatch profile increases significantly with the time from symptom onset.[11] This raises the question of whether, similar to small core infarctions, the criteria for mismatch profile selection for EVT in patients with large core infarctions should depend on the time from symptom onset. Specifically, for patients in the early or late time window, could the mismatch profile help identify those who would benefit more from EVT? Additionally, how should the criteria for the early or late time window be defined?

Accordingly, we performed a secondary, posthoc analysis of the ANGEL-ASPECT trial to compare outcomes of EVT versus MM in patients with or without a perfusion mismatch within prespecified onset-to-imaging time strata (≤6 hours versus >6 hours), and to test whether mismatch status modified the treatment effect within each time stratum (treatment-by-mismatch interaction); secondarily, we assessed whether onset-to-imaging time modified the treatment effect in the overall cohort (treatment-by-time interaction).

METHODS

Data Availability

Deidentified individual participant data, protocol, and analysis code are available from the corresponding author on reasonable request and subject to steering-committee approval and data-use agreements; no public repository is available at present.

Study Population and Design

This study is a secondary, posthoc analysis of data from the preexisting randomized clinical trial ANGEL-ASPECT, evaluating treatment-subgroup interactions defined by mismatch status and onset-to-imaging time (≤6 hours versus >6 hours).[3] The parent trial assessed the efficacy and safety of EVT versus MM in patients with acute ischemic stroke and large infarct cores in the anterior circulation. Eligibility followed the ANGEL-ASPECT trial criteria: adults aged 18 years to 80 years with intracranial internal carotid artery or M1 segment of middle cerebral artery occlusion within 24 hours, National Institutes of Health Stroke Scale score 6 to 30, prestroke modified Rankin Scale (mRS) score of 0 to 1, and imaging-defined large core per protocol (Alberta Stroke Program Early CT Score, 3–5≤24 hours; or Alberta Stroke Program Early CT Score, 0–2≤24 hours with core 70–100 mL; or Alberta Stroke Program Early CT Score >5 at 6–24 hours with core 70–100 mL).[3] In the main ANGEL-ASPECT report, EVT was associated with a shift toward better 90-day mRS outcomes compared with MM. The mismatch and time subgroups analyzed here were not part of the primary efficacy summary.[3,12] Written informed consent was obtained from all participants or their legally authorized representatives. Ethical approval was granted by the institutional review boards of all participating centers. We followed the CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines.

Imaging Acquisition and Analysis

All participants underwent a baseline neuroimaging protocol, which included noncontrast CT, CT or MR angiography, and CT perfusion or MR diffusion-perfusion imaging. CT perfusion imaging was processed with RAPID (iSchemaView, version 5.0.4) to estimate the ischemic core (relative cerebral blood flow <30%) and critically hypoperfused tissue (Tmax >6 s). On MRI, the ischemic core size was determined using an apparent diffusion coefficient threshold of $<620\times10^{-6}$ mm²/s on diffusion-weighted imaging. Two mismatch definitions were applied: (1) mismatch ratio (the ratio of critically hypoperfused tissue to ischemic core) ≥1.8 and mismatch volume (the difference between these regions) ≥15 mL,[9] and (2) mismatch ratio ≥1.2 and mismatch volume ≥10 mL.[8] Time from symptom onset to imaging, defined as the interval from last-known well to completion of baseline multimodal imaging (CT perfusion or MRI), was recorded for each patient and used to classify patients into 2 groups: ≤6 hours and >6 hours.

Study Outcomes

The primary outcome was a 90-day mRS score of 0 to 3. Secondary end points included the 90-day mRS distribution, 90-day mRS score of 0 to 2, and target-vessel recanalization. Target-vessel recanalization was assessed on follow-up CTA/MRA at 36 hours and defined as modified arterial occlusive lesion grade 2 to 3 (grade 0=no change; grade 1=debulking without recanalization; grade 2=partial/complete recanalization with distal thrombus/occlusion; grade 3=complete recanalization without distal thrombus).[3,13] Safety end points included symptomatic intracranial hemorrhage (ICH)—defined as an National Institutes of Health Stroke Scale score increase of 4 or more in the presence of ICH on follow-up imaging—any ICH, and 90-day mortality. Ninety-day outcomes were assessed using a standardized mRS interview by trained site personnel who were masked to treatment assignment whenever feasible. Follow-up assessments were conducted in the clinic when feasible and otherwise by telephone; proxy interviews were obtained when patients could not be contacted directly. Telephone interviews were audio-recorded for quality control. All participating sites completed prespecified training and certification before enrollment.

Statistical Analysis

Continuous variables were compared using *t* tests or Wilcoxon rank-sum tests, as appropriate. Categorical variables were analyzed using the χ^2 test, Fisher exact test, or the Cochran-Armitage trend test. Baseline characteristics were compared across subgroups defined by mismatch status (mismatch ratio ≥1.8 and mismatch volume ≥15 mL) and by onset-to-imaging time (≤6 hours versus >6 hours). To evaluate the associations between treatment assignment and outcomes, we fit unadjusted binary logistic regression models to estimate odds ratios (ORs) with 95% CIs for 90-day functional outcome (mRS score, 0–3), target-vessel recanalization, and hemorrhagic events. For the ordinal mRS (0–6), we used unadjusted proportional-odds ordinal logistic models. Effect modification was assessed using 2-way interaction terms (treatment-by-time in the full cohort and treatment-by-mismatch with each time stratum). For the primary end point, we additionally fit an exploratory single unadjusted logistic model that included treatment assignment, mismatch status, time stratum, all 2-way interactions, and the 3-way interaction (treatment×mismatch×time). Wald tests provided p for interaction values (df=1). All tests were 2-sided (α=0.05), and *P* for interaction <0.05 was considered statistically significant. Analyses were unadjusted and not corrected for multiplicity. Data analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 456 patients were enrolled in the ANGEL-ASPECT randomized trial. After excluding 1 patient who withdrew consent and 29 with incomplete mismatch data, 426 patients were included in the final analysis. Using CT perfusion/MRI core volume, 346 patients (81.2%) showed a mismatch, defined by a mismatch ratio ≥1.8 and mismatch volume ≥15 mL (Figure 1). Meanwhile, 395 patients (92.7%) exhibited a mismatch profile based on a mismatch ratio ≥1.2 and mismatch volume ≥10 mL.

Mismatch Profile Distribution Over Time

Although the Cochran-Armitage trend test did not demonstrate a significant monotonic trend across population-quartile strata of onset-to-imaging time (*P*=0.201), the proportion meeting the mismatch ratio ≥1.8 and mismatch volume ≥15 mL definition differed across these strata (χ^2 test, *P*=0.005; Table S1). The proportion was lowest in the <4 hours group (70.9%) and highest in the 4 to 6 hours group (88.0%). The proportion meeting the alternative definition (ratio ≥1.2 and volume ≥10 mL) did not differ significantly across population quartiles over time.

Baseline Imaging Characteristics by Mismatch and Time Window

Patients were categorized as with or without a mismatch, defined as a mismatch ratio ≥1.8 and mismatch volume ≥15 mL, and further stratified by the onset-to-imaging time (≤6 hours versus >6 hours). In the early time window (≤6 hours), ischemic core volumes were smaller in the with mismatch group than in the without mismatch group (median, 63 mL [interquartile range, 30–83] versus 80 mL [51–134]; *P*<0.001). A similar trend was seen in the late time window (>6 hours), with the mismatch group showing smaller ischemic core volumes (median, 48 mL [18–68] versus 82 mL [73–114]; *P*<0.001). Baseline Alberta Stroke Program Early CT Scores were significantly different in the late window (*P*=0.001), with lower scores more common in the group without mismatch (Table 1). In addition, the hypoperfusion intensity ratio (HIR), a perfusion parameter reflecting the severity of hypoperfusion, was significantly lower in the mismatch group in both early and late windows (early: median, 0.57 [interquartile range, 0.44–0.67] versus 0.76 [0.60–0.82], *P*<0.001 and late: 0.54 [0.38–0.63] versus 0.66 [0.56–0.71], *P*<0.001; Table 1).

Effectiveness of EVT in the Early Window by Mismatch Profile

Patients with a mismatch in the early time window (≤6 hours) experienced substantial benefits from EVT. Specifically, EVT was associated with higher odds of mRS score of 0 to 3 at 90 days compared with MM (48.9% versus 28.4%; OR, 2.41 [95% CI, 1.28–4.55]; *P*=0.006; Table 2; Figure 2). Additionally, the EVT group demonstrated a markedly higher recanalization rate at 36 hours compared with MM (90.0% versus 36.9%; OR, 15.38 [95% CI, 6.33–37.34]; *P*<0.001). In contrast, among patients without a mismatch in the early time window,

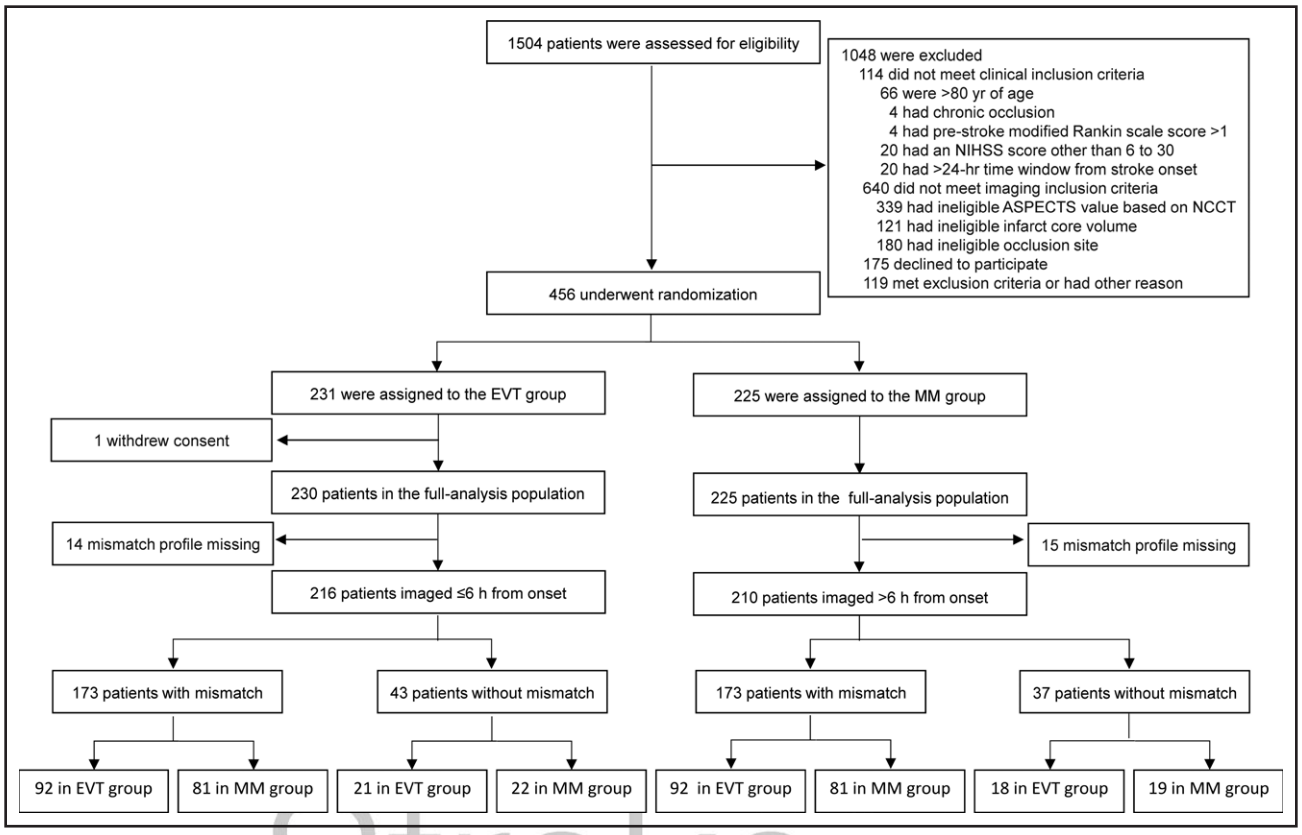

Figure 1. Flow diagram of the study participants.
ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; EVT, endovascular therapy; MM, medical management; and NIHSS, National Institutes of Health Stroke Scale.

the 90-day mRS score of 0 to 3 was similar between the EVT and MM groups (23.8% versus 27.3%; OR, 0.83 [95% CI, 0.21–3.29]; *P*=0.795; Table 2; Figure 2). Although the EVT group showed a higher recanalization rate (80.0%) compared with MM (46.7%), this difference did not reach statistical significance (*P*=0.066).

Outcomes of EVT in Late Window by Mismatch Profile

In the late time window (>6 hours), the benefits of EVT were less evident. Among patients with mismatch, mRS score of 0 to 3 at 90 days was comparable between the EVT group (47.8%) and the medical-management group (42.0%; OR, 1.27 [95% CI, 0.69–2.31]; *P*=0.441; Table 2; Figure 2). In patients without a mismatch, EVT conferred no significant advantage in terms of functional outcomes (Table 2; Figure 2).

Interaction Analyses

For the primary end point (mRS score, 0–3 at 90 days), there was no evidence of effect modification by onset-to-imaging time (treatment-by-time p for interaction=0.412; Table S2). Within each time window, treatment-by-mismatch interaction tests for the primary end point were also non-significant (≤6 hours, *P* for interaction=0.166; >6 hours, *P* for interaction=0.301; Table 2). In the same unadjusted model that contained all main effects and 2-way terms, the exploratory 3-way interaction (treatment×mismatch×time) for the primary end point was not statistically significant (*P*=0.163). For secondary efficacy and safety end points, interaction tests were likewise nonsignificant (Table 2).

Sensitivity Analyses Excluding Wake-Up Stroke Patients

Sensitivity analyses excluding 140 patients with wake-up stroke showed results consistent with the primary findings in both time windows. Among patients with mismatch, EVT was associated with a numerically higher rate of favorable functional outcomes, but this difference was not statistically significant; no evidence of benefit was observed in those without mismatch (Table S3).

Safety Outcomes Across Mismatch Profiles and Time Windows

The incidence of symptomatic ICH was comparable between the EVT and MM groups across all time

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Table 1. Baseline Characteristics

Characteristics	Time from onset to image ≤6 Hours			Time from onset to image >6 Hours		
	With mismatch (n=173)	Without mismatch (n=43)	*P* value	With mismatch (n=173)	Without mismatch (n=37)	*P* value
Age, mean (SD), y	66.8 (8.5)	67.5 (9.4)	0.645	65.1 (10.8)	66.1 (10.7)	0.611
Male, n (%)	103 (59.5)	19 (44.2)	0.069	110 (63.6)	24 (64.9)	0.883
Medical history, n (%)						
Hypertension	104 (60.1)	27 (62.8)	0.748	103 (59.5)	20 (54.1)	0.539
Dyslipidemia	7 (4.1)	5 (11.6)	0.052	13 (7.5)	1 (2.7)	0.287
Diabetes	29 (16.8)	11 (25.6)	0.183	30 (17.3)	6 (16.2)	0.869
Current smoking	45 (26.0)	14 (32.6)	0.389	57 (33.0)	17 (46.0)	0.133
Cardiovascular disease	36 (20.8)	11 (25.6)	0.497	28 (16.2)	3 (8.1)	0.209
Prior ischemic stroke	25 (14.5)	7 (16.3)	0.763	30 (17.3)	4 (10.8)	0.328
Atrial fibrillation	42 (24.3)	12 (27.9)	0.623	37 (21.4)	5 (13.5)	0.277
Heart failure	19 (11.0)	9 (20.9)	0.082	9 (5.2)	0	0.156
Wake-up stroke, n (%)	28 (16.2)	5 (11.6)	0.457	89 (51.5)	18 (48.7)	0.757
Systolic blood pressure, median (IQR)	149 (130–168)	145 (128–169)	0.706	150 (133–165)	154 (135–165)	0.667
Diastolic blood pressure, median (IQR)	84 (73–96)	85 (72–93)	0.874	85 (76–95)	88 (80–97)	0.260
Baseline mRS, n (%)			0.210			0.160
0	154 (89.0)	41 (95.4)		156 (90.2)	36 (97.3)	
1	19 (11.0)	2 (4.7)		17 (9.8)	1 (2.7)	
Baseline NIHSS, median (IQR)	16 (13–20)	19 (14–22)	0.109	15 (12–18)	18 (14–20)	0.044
ASPECTS, n (%)			0.383			0.001
0–2	28 (16.2)	3 (7.0)		17 (9.8)	13 (35.1)	
3	79 (45.7)	21 (48.8)		75 (43.4)	12 (32.4)	
4	39 (22.5)	13 (30.2)		46 (26.6)	6 (16.2)	
5	27 (15.6)	6 (14.0)		35 (20.2)	6 (16.2)	
Occlusion site, n (%)			0.465			0.537
ICA	64 (37.0)	14 (32.6)		62 (35.8)	12 (32.4)	
M1	108 (62.4)	28 (65.1)		110 (63.6)	24 (64.9)	
M2	1 (0.6)	1 (2.3)		1 (0.6)	1 (2.7)	
Ischemic core volume, median (IQR), mL	63 (30–83)	80 (51–134)	<0.001	48 (18–68)	82 (73–114)	<0.001
Intravenous thrombolysis, n (%)	70 (40.5)	19 (44.2)	0.657	32 (18.5)	6 (16.2)	0.744
Time from stroke onset to randomization, median (IQR), min	312 (234–372)	235 (197–316)	0.002	739 (570–948)	795 (595–939)	0.630
HIR, median (IQR)	0.57 (0.44–0.67)	0.76 (0.60–0.82)	<0.001	0.54 (0.38–0.63)	0.66 (0.56–0.71)	<0.001

ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular therapy; HIR, hypoperfusion intensity ratio; ICA, internal carotid artery; IQR, interquartile range; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

windows and mismatch categories. However, the rate of any ICH was higher in the EVT group compared with MM in both early and late time windows (Table 2).

DISCUSSION

This study underscores that, among patients with large infarct cores receiving EVT in the early time window, the absence of mismatch was more frequent and was associated with an attenuated treatment effect. Temporal analysis indicates that the EVT benefit appeared more evident in patients with mismatch profiles imaged within ≤6 hours. These findings highlight the pivotal role of imaging-based profiling and timely assessment in refining treatment strategies. Given the modest subgroup sizes and the posthoc, unadjusted nature of these analyses, these findings should be viewed as hypothesis-generating and warrant confirmation in prospective, prespecified studies.

Such results align with evidence from randomized controlled trials, including the SELECT-2 trial and the TENSION trial (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke With Large Infarct Cores in Non-eligible Patients), which investigated the efficacy of EVT in patients with substantial infarct cores.[2,4] In contrast, the TESLA trial (Thrombectomy for

Table 2. Analyses of Outcomes Based on Mismatch Profiles and Time from Onset to Imaging (≤6 Hours Versus >6 Hours)

Outcome	With mismatch		OR (95% CI)	*P* value	Without mismatch		OR (95% CI)	*P* value	*P* for interaction
Time ≤6 h (n=216)	EVT, n=92	MM, n=81			EVT, n=21	MM, n=22			
mRS score 0–3 at 90 d, n (%)	45 (48.9)	23 (28.4)	2.41 (1.28–4.55)	0.006	5 (23.8)	6 (27.3)	0.83 (0.21–3.29)	0.795	0.166
mRS at 90 d, median (IQR)*	4 (2–5.5)	4 (3–5)	0.60 (0.36–1.03)	0.063	5 (4–6)	5 (3–6)	1.08 (0.37–3.20)	0.887	0.329
mRS score 0–2 at 90 d, n (%)	31 (33.7)	9 (11.1)	4.07 (1.80–9.20)	<0.001	3 (14.3)	3 (13.6)	1.06 (0.19–5.93)	0.951	0.168
Target-vessel recanalization at 36 h, n (%)†	72 (90.0)	24 (36.9)	15.38 (6.33–37.34)	<0.001	12 (80.0)	7 (46.7)	4.57 (0.90–23.14)	0.066	0.198
sICH within 48 h, n (%)	4 (4.4)	5 (6.2)	0.69 (0.18–2.67)	0.591	2 (9.5)	0 (0.0)	NA	NA	NA
Any ICH within 48 h, n (%)	45 (48.9)	20 (24.7)	2.92 (1.53–5.59)	0.001	10 (47.6)	4 (18.2)	4.09 (1.03–16.28)	0.046	0.665
Death within 90 d, n (%)	23 (25.0)	14 (17.3)	1.60 (0.76–3.36)	0.219	9 (42.9)	9 (40.9)	1.08 (0.32–3.64)	0.897	0.594
Time >6 h (n=210)	EVT, n=92	MM, n=81			EVT, n=18	MM, n=19			
mRS score 0–3 at 90 d, n (%)	44 (47.8)	34 (42.0)	1.27 (0.69–2.31)	0.441	9 (50.0)	5 (26.3)	2.80 (0.71–11.10)	0.143	0.301
mRS at 90 d, median (IQR)*	4 (2–4.5)	4 (3–5)	0.64 (0.37–1.08)	0.096	3.5 (3–4)	4 (3–5)	0.43 (0.13–1.41)	0.164	0.821
mRS score 0–2 at 90 d, n (%)	31 (33.7)	10 (12.4)	3.61 (1.64–7.96)	0.002	1 (5.6)	1 (5.3)	1.06 (0.06–18.30)	0.969	0.417
Target-vessel recanalization at 36 h, n (%)†	68 (85.0)	28 (40.0)	8.50 (3.90–18.50)	<0.001	11 (73.3)	4 (23.5)	8.94 (1.80–44.34)	0.007	0.955
sICH within 48 h, n (%)	6 (6.5)	1 (1.2)	5.58 (0.66–47.38)	0.115	2 (11.1)	0 (0.0)	NA	NA	NA
Any ICH within 48 h, n (%)	49 (53.3)	13 (16.1)	5.96 (2.90–12.26)	<0.001	6 (33.3)	0 (0.0)	NA	NA	NA
Death within 90 d, n (%)	14 (15.2)	12 (14.8)	1.03 (0.45–2.38)	0.941	3 (16.7)	3 (15.8)	1.07 (0.19–6.13)	0.942	0.973

P for interaction values are from Wald tests of the treatment×mismatch product term (df=1, 2-sided α=0.05) in unadjusted regression models. Binary end points (including 90-day mRS score, 0–3) used unadjusted binary logistic regression; the ordinal mRS score (0–6) used an unadjusted proportional-odds ordinal logistic model. cOR indicates common odds ratio; EVT, endovascular therapy; ICH, intracranial hemorrhage; IQR, interquartile range; MM, medical management; mRS, modified Rankin Scale; OR, odds ratio; and sICH, symptomatic intracranial hemorrhage.

*For the row 90-day mRS, median (IQR), the medians (IQR) are descriptive only; the reported OR and *P* for interaction correspond to the cOR from the proportional-odds model for the full mRS distribution.

†Recanalization was assessed on follow-up CTA/MRA at 36 h and defined as a modified arterial occlusive lesion grade of 2 or 3. Missing follow-up imaging for recanalization: ≤6 h, 12 (EVT) and 16 (MM) with mismatch, 6 (EVT) and 7 (MM) without mismatch; >6 h, 12 (EVT) and 11 (MM) with mismatch, 3 (EVT) and 2 (MM) without mismatch.

Emergent Salvage of Large Anterior Circulation Ischemic Stroke) did not demonstrate a significant clinical benefit of EVT in its primary analysis. However, TESLA provided important insights into patient selection based on noncontrast CT imaging alone.[5] Our analysis builds on these findings by highlighting the interaction between mismatch profiles and imaging timing. While SELECT-2 reported that mismatch status did not significantly influence EVT outcomes—showing clinical improvements with EVT irrespective of mismatch criteria (defined by a mismatch ratio ≥1.8 and a mismatch volume ≥15 mL)—our data suggest that mismatch status is more prognostic during the early time window.[2,11] This observation emphasizes the importance of identifying salvageable tissue early to maximize EVT efficacy, reinforcing the necessity of imaging-based evaluation for optimal patient selection and improved outcomes. Moreover, our findings complement studies on small core infarctions by emphasizing the relationship between mismatch status and EVT success in the early stages of stroke.[14–17] Evidence suggests that patients with unfavorable mismatch profiles treated with EVT early after symptom onset are significantly more likely to experience poor functional outcomes and an elevated risk of symptomatic ICH.[14]

Variability in collateral blood flow plays a central role in the progression of ischemia, resulting in substantial differences in the extent of salvageable penumbra during the acute phase of ischemic stroke.[18] Approximately 20% of patients reportedly undergo complete infarction within the initial hours of stroke onset, reflecting the rapid ischemic progression in individuals with compromised collateral circulation.[19] This phenomenon likely explains the frequent absence of substantial penumbra in the early time window, particularly in patients with large infarct cores.[20] The efficacy of EVT in patients with mismatch can be attributed to the preservation of salvageable tissue and prevention of infarct expansion. These patients often demonstrate more favorable baseline perfusion metrics, including robust collateral flow and slower infarct progression, which enhance the effectiveness of reperfusion therapies. In contrast, the lack of mismatch in large core infarctions during the early phase of stroke may indicate exhausted collaterals and irreversible ischemic injury, thereby reducing the potential benefits of

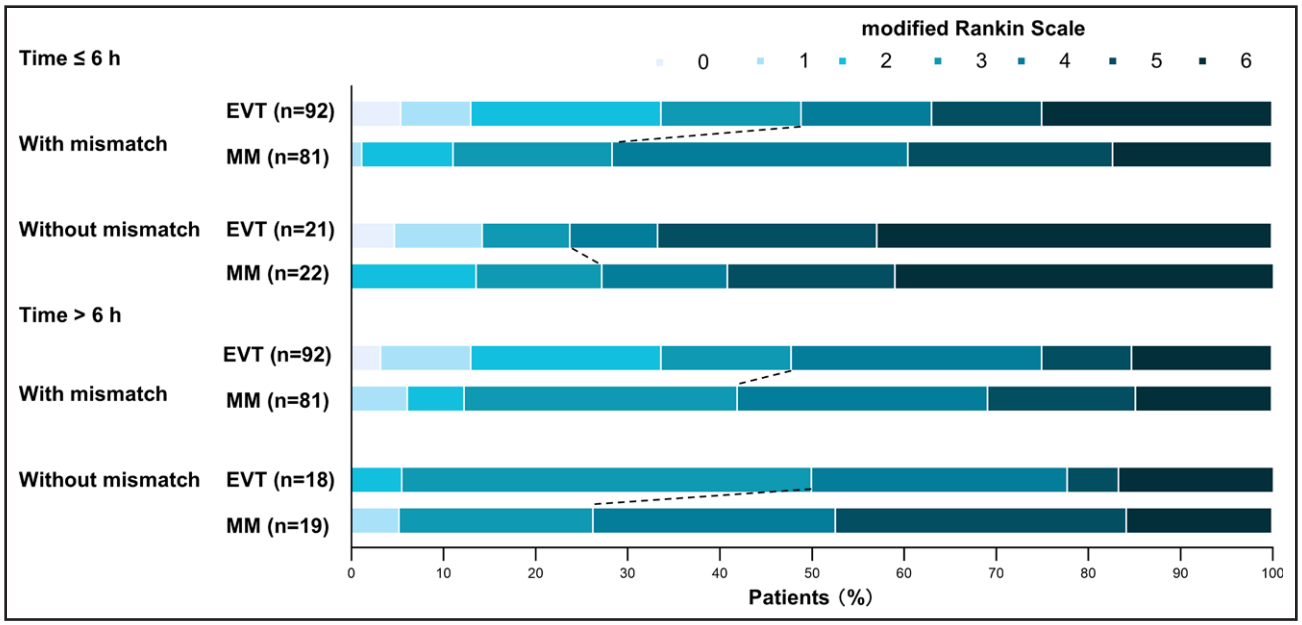

Figure 2. Distribution of modified Rankin Scale score at 90-day follow-up in the study population.
EVT indicates endovascular therapy; and MM, medical management.

EVT. These findings highlight the importance of developing individualized treatment strategies based on imaging features and the physiological condition of the affected brain tissue.

Interestingly, in the >6 hours mismatch group, 42% of patients receiving MM achieved a 90-day mRS score of 0 to 3, a relatively favorable outcome. This may be attributed to more favorable baseline characteristics, such as smaller infarct cores or more robust collateral flow. Moreover, effective collateral circulation may preserve tissue viability beyond 6 hours, permitting spontaneous recovery without the need for reperfusion therapy. Prior studies have shown that robust collaterals are associated with delayed infarct progression and endogenous reperfusion.[15] These findings raise the possibility that a subset of patients with mismatch beyond 6 hours and favorable baseline profiles may derive meaningful benefit from MM. However, this interpretation should be approached with caution, as it is based on a limited sample size and nonrandomized comparisons. Importantly, the potential efficacy of EVT in this population cannot be excluded. Although in the late window (>6 hours), among patients without mismatch, EVT was associated with a numerically higher rate of favorable outcome compared with MM (50.0% versus 26.3%), although this difference did not reach statistical significance. This trend suggests that some patients without a clear perfusion mismatch may still benefit from EVT in extended time windows, potentially due to successful recanalization. Subgroup analyses from SELECT-2 revealed consistent EVT efficacy regardless of mismatch presence, supporting a more flexible approach to EVT eligibility.[11] Current evidence does not support excluding patients from EVT solely based on the absence of perfusion mismatch, particularly when other clinical and radiological indicators are favorable.[21] Further investigations are needed to refine imaging and clinical criteria for EVT candidacy in late-window stroke.

In addition, we found that the HIR, a perfusion-derived marker of collateral status, was significantly lower in mismatch patients than in nonmismatch patients, regardless of time window. HIR is defined as the proportion of severely hypoperfused tissue (Tmax >10 s) relative to the total hypoperfused region (Tmax >6 s). Lower HIR values reflect better collateral perfusion, slower infarct growth, and improved clinical outcomes.[22–24] Previous studies have validated HIR as a surrogate of infarct progression and EVT benefit, supporting its potential role in refining patient selection beyond traditional mismatch criteria.[22–24] Future studies are warranted to investigate whether incorporating HIR into clinical decision-making algorithms can further improve patient selection and outcomes.

Several limitations of this study should be noted. First, most patients enrolled in the ANGEL-ASPECT trial exhibited mismatch features. Although the absence of a mismatch was not an exclusion criterion, it is plausible that investigators were less inclined to randomize patients lacking mismatch characteristics, potentially introducing selection bias and affecting the representativeness of the cohort. Second, subgroup analyses stratified by mismatch status and time window involved relatively small sample sizes, which may have reduced the statistical power to detect significant effects, particularly in patients without mismatch profiles. This limitation raises the risk of type II errors and highlights

the need for future studies with larger, more balanced cohorts to validate these findings. Third, the study population was predominantly composed of individuals of Chinese ethnicity. Although the multicenter, randomized design enhances the study's reliability, the results may not be directly generalizable to other ethnic or regional populations. Validation in more diverse cohorts is necessary to establish broader applicability. Fourth, collateral circulation, an important factor influencing the relationship between mismatch and clinical outcomes, was not included in the present analysis. In this trial, collateral status was assessed using the ASITN/SIR grading system based on DSA; however, such data were largely unavailable in the medical treatment group, precluding further analyses. Future studies with systematic collateral assessment across both treatment arms are warranted. Finally, the interaction analyses were underpowered and should be interpreted as exploratory. All tests for interaction were non-significant—both for the treatment-by-time comparison in the overall cohort and for treatment-by-mismatch within each time window (Table 2; Table S3). Given the posthoc nature of these subgroup analyses, the limited sample size in the without-mismatch strata, and the absence of multiplicity adjustment, apparent subgroup patterns should be viewed cautiously; the subgroup literature is well known to yield false-positive signals when analyses are not prespecified or adequately powered. Our subgroup findings are, therefore, hypothesis-generating and warrant confirmation in larger, prospectively planned data sets.

CONCLUSIONS

In this secondary, posthoc analysis of ANGEL-ASPECT, absence of perfusion mismatch was more frequent within ≤6 hours and was associated with a less apparent benefit of EVT. These exploratory findings warrant prospective, prespecified confirmation to define how mismatch profiles and imaging timing should inform EVT selection in large-core stroke.

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Disclosures

None.

Supplemental Material

Table S1–S3

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