Association of Thrombectomy With Functional Outcome for Patients With Ischemic Stroke Who Presented in the Extended Time Window With Extensive Signs of Infarction

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Abstract

**IMPORTANCE** Only limited data are available about a potential benefit associated with endovascular treatment (EVT) for patients with ischemic stroke presenting in the extended time window who also show signs of extensive infarction.

**OBJECTIVE** To assess the association of recanalization after EVT with functional outcomes for patients with ischemic stroke presenting in the extended time window who also show signs of extensive infarction.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective, multicenter cohort study included patients enrolled in the German Stroke Registry–Endovascular Treatment with an Alberta Stroke Program Early CT Score (ASPECTS) of 5 or less who presented between 6 and 24 hours after stroke onset and underwent computed tomography and subsequent EVT between July 1, 2015, and December 31, 2019.

**MAIN OUTCOMES AND MEASURES** The primary end point was a modified Rankin Scale (mRS) score of 3 or less at day 90. The association between recanalization (defined as the occurrence of a modified Thrombolysis in Cerebral Infarction Scale score of 2 or 3) and outcome was assessed using logistic regression and inverse probability weighting analysis.

**INTERVENTION** Endovascular treatment.

**RESULTS** Of 5853 patients, 285 (5%; 146 men [51%]; median age, 73 years [IQR, 62-81 years]) met the inclusion criteria and were analyzed. Of these 285 patients, 79 (27.7%) had an mRS score of 3 or less at day 90. The rate of successful recanalization was 75% (215 of 285) and was independently associated with a higher probability of reaching an mRS score of 3 or less (adjusted odds ratio, 4.39; 95% CI, 1.79-10.72; \( P < .001 \)). In inverse probability weighting analysis, a modified Thrombolysis in Cerebral Infarction Scale score of 2 or 3 was associated with a 19% increase (95% CI, 9%-29%; \( P < .001 \)) in the probability for an mRS score of 3 or more. Multivariable logistic regression analysis suggested a significant treatment benefit associated with vessel recanalization in a time window of up to 17.6 hours and ASPECTS of 3 to 5. The rate of secondary symptomatic intracerebral hemorrhage was 6.3% (18 of 285).

**CONCLUSIONS AND RELEVANCE** In this cohort study reflecting daily clinical practice, vessel recanalization for patients with a low ASPECTS and extended time window was associated with better functional outcomes in a time window up to 17.6 hours and ASPECTS of 3 to 5. The results of

(continued)
Abstract (continued)

This study encourage current randomized clinical trials to enroll patients with a low ASPECTS, even within the extended time window.

Introduction

Previous landmark stroke trials investigating the effect of endovascular treatment (EVT) on patients with large vessel occlusion who presented within 6 to 24 hours from symptom onset led to an expansion of eligibility for EVT and changed the paradigm of stroke care.\(^1\)\(^2\) Patient selection in the DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo)\(^3\) and DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke)\(^4\) trials was based on penumbral imaging, including only patients with a small ischemic core detected by diffusion weighted imaging (DWI) or computed tomography perfusion (CTP). Similarly, CTP and DWI are currently tested as selection tools for patients presenting with extensive baseline strokes (ie, low Alberta Stroke Program Early CT Score [ASPECTS] of 0-5 or core volume >50 mL detected by CTP or DWI). However, a clinical benefit associated with EVT for this patient group is uncertain. The currently ongoing trials for patients with large core infarcts apply a variety of inclusion criteria with regard to imaging details and different definitions of early ischemic changes, including ASPECTS thresholds.\(^5\)\(^6\) In addition, current trials also include patients presenting in the extended time window. The extended time window in the TENSION (Thrombectomy in Stroke With Extended Lesion and Extended Time Window) trial is up to 12 hours from the last time the patient was seen well, and the extended time window in the TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke) trial, SELECT-2 (Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke), and ANGEL-ASPECT (Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core) is up to 24 hours.\(^3\)\(^4\) However, previous observational studies and the meta-analysis of HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) focusing on the early time window with a comparably small number of patients showed conflicting results regarding the association of EVT with functional outcomes.\(^5\)\(^-\)\(^11\) Currently, data on patients with extensive baseline stroke who also presented in the extended time window are sparse.\(^12\) For example, the median time from stroke onset to admission in the recently published RESCUE-Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large Ischemic Core Trial) was 3 hours, with only 30% of patients presenting more than 6 hours after stroke onset.\(^13\)

The purpose of this cohort study was to investigate the association of endovascular recanalization with functional outcomes for patients presenting with an ASPECTS of 5 or less who presented more than 6 hours after stroke onset in a clinical setting. We hypothesized that vessel recanalization would be associated with better functional outcome for patients with an extended time window who also show signs of extensive infarction.

Methods

Study Cohort and Patients

All patients included in this cohort study were enrolled in the German Stroke Registry–Endovascular Treatment (GSR-ET; ClinicalTrials.gov identifier: NCT03356392) and treated between July 1, 2015, and December 31, 2019. The GSR-ET is an ongoing, open-label, prospective, multicenter registry of 25 stroke centers in Germany collecting data on consecutive patients undergoing EVT.\(^14\)\(^35\) As the leading committee, the ethics committee of the Ludwig-Maximilians University (Munich, Germany)
approved the GSR-ET. In addition, local ethics committees of the participating hospitals gave approval as well. This retrospective multicenter analysis only used fully anonymized data. Patient identification is hence not possible, and therefore informed consent was waived after ethics committee review. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

The a priori-defined inclusion criteria for this study were as follows: (1) CT-based diagnosis and treatment decision-making after direct admission to the tertiary care center providing EVT, (2) ischemic stroke due to anterior circulation large vessel occlusion, (3) ASPECTS of 5 or less assessed on nonenhanced CT scans, and (4) time from symptom onset of 6 to 24 hours (if this parameter was unavailable, the time metric of time last known well of 6 to 24 hours was used instead). All patients underwent EVT, and the association of vessel recanalization with functional outcomes at 90 days and early neurologic improvement (ENI) was investigated. The primary end point was favorable clinical outcome, defined as a modified Rankin Scale (mRS) score of 3 or less at 90 days. Secondary outcomes were functional independence at 90 days, defined as an mRS score of 2 or less, and ENI, defined as a binary score based on a decrease in the National Institutes of Health Stroke Scale (NIHSS) of 8 points or more or reaching a NIHSS score of 0 or 1 at 24 hours. In the GSR-ET, routine CT imaging 24 hours after mechanical thrombectomy was used to detect intracranial hemorrhage according to the ECASS II (European Cooperative Acute Stroke Study [part II]) definition irrespective of the presence of new clinical symptoms.15 Symptomatic intracerebral hemorrhage was defined as parenchymal hemorrhage type 2 detected on the 22- to 36-hour posttreatment imaging scan, combined with neurologic deterioration of 4 points or more on the NIHSS from baseline or from the lowest NIHSS value between baseline and 24 hours, or leading to death. Successful recanalization was defined as the occurrence of a modified Thrombolysis in Cerebral Infarction Scale (mTICI) score of 2b or 3.

**Statistical Analysis**

Normal distribution was assessed using Shapiro-Wilk tests. Continuous variables were presented as mean values with 95% CIs or SDs or as median values and IQRs. Patients were assembled and compared based on their final recanalization status. To compare groups with successful and unsuccessful recanalization, the t test (normal distribution) or the Mann-Whitney test (nonnormal distribution) was used to determine differences in the acquired parameters (Table 1). Categorial variables were compared using the χ² test. To assess the association between the independent variables (age, ASPECTS, NIHSS on admission, application of intravenous alteplase, time window, and recanalization status) and the dependent variable (favorable outcome), multivariable logistic regression analyses were performed using stepwise variable selection (Table 2). Correlation analysis was used to test for multicollinearity, and Box-Tidwell tests were used to confirm the linearity of the independent variables and log odds. Likewise, logistic regression models were assessed for end points of functional independence and ENI. Absolute NIHSS changes were assessed using multivariable linear regression analysis with the same aforementioned independent variables. The association of recanalization with death was tested using the same logistic regression model. The average treatment effect of successful recanalization was calculated using inverse probability weighting analysis, with a weighted mean outcome model and a logit treatment model for favorable outcome (mRS score, 0-3), functional independence (mRS score, 0-2), and ENI. Age, NIHSS on admission, alteplase administration (yes or no), and ASPECTS were selected as confounders because they were the available variables with a known association with functional outcome.16 The propensity score overlap was tested to demonstrate that the positivity assumption was not significantly violated (eFigure 1 in Supplement 1). Locally weighted regression plots (locally estimated scatterplot smoothing) for ASPECTS and time window were used to confirm the assumption of linearity (eFigure 2 and eFigure 3 in Supplement 1). A subanalysis was performed to assess the average treatment effect of vessel recanalization for patients in the 12- to 24-hour time window. A subanalysis compared outcomes with the untreated control cohort of the HERMES meta-analysis7
All P values were from 2-sided tests, and results were deemed statistically significant at $P < .05$. Analyses were performed using Stata/MP, version 17.0 (StataCorp LLC) and R, version 4.1 (R Project for Statistical Computing).

Table 1. Patients’ Baseline, Procedural, and Outcome Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Favorable outcome (mRS score of 0-3) (n = 79)</th>
<th>Poor outcome (mRS score of 4-6) (n = 206)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>67 (54-75)</td>
<td>75 (66-83)</td>
<td>&lt;.001</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>31 (39)</td>
<td>108 (52)</td>
<td>.05</td>
</tr>
<tr>
<td>Male</td>
<td>48 (61)</td>
<td>98 (48)</td>
<td>.05</td>
</tr>
<tr>
<td>Time window, h</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>9.6 (8.2-12.7)</td>
<td>11.7 (8.8-15.3)</td>
<td>.045</td>
</tr>
<tr>
<td>6-11</td>
<td>60 (76)</td>
<td>122 (59)</td>
<td></td>
</tr>
<tr>
<td>12-24</td>
<td>19 (24)</td>
<td>84 (41)</td>
<td></td>
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<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5 (4-5)</td>
<td>4 (3-5)</td>
<td>.08</td>
</tr>
<tr>
<td>≤2</td>
<td>5 (6)</td>
<td>19 (9)</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>74 (94)</td>
<td>187 (91)</td>
<td></td>
</tr>
<tr>
<td>NIHSS score on admission, median (IQR)</td>
<td>14 (9-18)</td>
<td>17 (15-20)</td>
<td>&lt;.001</td>
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<tr>
<td>Treatment and follow-up</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intravenous alteplase administration</td>
<td>29 (37)</td>
<td>66 (32)</td>
<td>.45</td>
</tr>
<tr>
<td>Successful recanalization (mTICI score of 2b or 3)</td>
<td>69 (87)</td>
<td>146 (71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NIHSS score, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 24 h</td>
<td>8 (5-15)</td>
<td>20 (15-26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At discharge</td>
<td>5 (3-10)</td>
<td>16 (12-23)</td>
<td>&lt;.001</td>
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<tr>
<td>mRS score, median (IQR)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>At discharge</td>
<td>3 (2-4)</td>
<td>5 (5-6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At day 90</td>
<td>2 (1-3)</td>
<td>6 (5-6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 2. Multivariable Logistic Regression Analyses for Functional Outcome at Day 90

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Multivariable logistic regression analysis</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS score of 0-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTICI score of 2b or 3</td>
<td>4.30 (1.63-11.34)</td>
<td>2.13</td>
<td>.003</td>
</tr>
<tr>
<td>Age</td>
<td>0.94 (0.91-0.96)</td>
<td>0.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>0.89 (0.84-0.94)</td>
<td>0.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>1.20 (0.85-1.71)</td>
<td>0.22</td>
<td>.30</td>
</tr>
<tr>
<td>Intravenous alteplase</td>
<td>1.02 (0.49-2.11)</td>
<td>0.38</td>
<td>.97</td>
</tr>
<tr>
<td>Time window, min</td>
<td>0.999 (0.998-1.000)</td>
<td>0.001</td>
<td>.049</td>
</tr>
<tr>
<td>mRS score of 0-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTICI score of 2b or 3</td>
<td>7.24 (2.01-26.09)</td>
<td>4.74</td>
<td>.002</td>
</tr>
<tr>
<td>Age</td>
<td>0.93 (0.89-0.96)</td>
<td>0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>0.81 (0.75-0.88)</td>
<td>0.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>1.08 (0.71-1.65)</td>
<td>0.23</td>
<td>.72</td>
</tr>
<tr>
<td>Intravenous alteplase</td>
<td>0.60 (0.25-1.44)</td>
<td>0.27</td>
<td>.25</td>
</tr>
<tr>
<td>Time window, min</td>
<td>0.998 (0.997-0.999)</td>
<td>0.001</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; mTICI, modified Thrombolysis In Cerebral Infarction Scale; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.
Results

Baseline and Procedural Characteristics
Of 6635 patients from the GSR-ET registry, 5853 showed an anterior circulation large vessel occlusion. Of these 5853 patients, 285 (5%; 146 men [51%]; median age, 73 years [IQR, 62-81 years]) met the inclusion criteria (Table 1). The median time window was 11.3 hours (IQR, 8.1-14.4 hours), and the median ASPECTS was 5 (IQR, 4-5). Overall, 24 patients (8%) presented with an ASPECTS of 2 or less, and 261 patients (92%) had an ASPECTS of 3 to 5. The median NIHSS score was 17 (IQR, 13-19), and 95 patients (33%) received intravenous alteplase. Successful vessel recanalization after thrombectomy, defined as an mTICI score of 2b or 3, was achieved for 215 patients (75%).

Functional Outcome and Complications
A favorable outcome (ie, mRS score of ≤3 at day 90) was observed for 79 patients (28%) and occurred more often among patients with successful recanalization than those with unsuccessful recanalization (32% [69 of 215] vs 13% [9 of 70]; P = .004). The rate of functional independence was 20% (57 of 285) and was higher among patients with successful recanalization than those with unsuccessful recanalization (23% [50 of 215] vs 9% [6 of 70]; P = .01). The rates of favorable outcome and functional independence for patients with an mTICI score of 3 were 36% (38 of 106) and 26% (28 of 106), respectively. The rates of favorable outcome and functional independence for elderly patients (>75 years) were 16% (19 of 121) and 11% (13 of 121), respectively. The median NIHSS score at 24 hours for all patients was 17 (IQR, 10-24). For patients with successful recanalization, the median NIHSS score at 24 hours was 16 (IQR, 9-21), which was lower than the median NIHSS score at 24 hours for patients with unsuccessful recanalization (22 [IQR, 15-30]; P < .001). Binary ENI occurred for 77 patients (27%) and was present more often after successful recanalization than after unsuccessful recanalization (27% [21 of 77] vs 14% [11 of 77]; P = .01). For 50 patients (18%), favorable outcomes occurred despite not achieving ENI at 24 hours. The rate of any intracranial hemorrhage was 19% (54 of 285), and the rate of symptomatic intracerebral hemorrhage was 6% (18 of 285). A total of 100 patients (35%) died (mRS score of 6 at day 90).

Multivariable Logistic Regression Analysis
Correlation analyses showed that correlation coefficients among all variables were 0.15 or less, excluding multicollinearity. Box-Tidwell tests confirmed the assumption of linearity of independent variables and log odds. In multivariable logistic regression analysis, successful recanalization (adjusted odds ratio [aOR], 4.39; 95% CI, 1.79-10.72; P < .001), age (aOR, 0.95; 95% CI, 0.92-0.97; P < .001), and NIHSS score (aOR, 0.89; 95% CI, 0.85-0.94; P < .001) were independently associated with a favorable outcome at day 90 (Figure 1). The association with functional independence at 90 days was similar and is shown in Table 2. Successful recanalization was the only parameter independently associated with binary ENI (aOR, 2.49; 95% CI, 1.15-5.37; P = .02) and change in NIHSS score from baseline to 24 hours (aOR, 5.93; 95% CI, 2.96-8.91; P < .001). Figure 2 illustrates the association of baseline ASPECTS and recanalization status with the probability for favorable outcome at day 90, showing that recanalization is significantly associated with a treatment benefit only for patients with an ASPECTS of 3 or more. This association was similar for functional independence and ENI end points.

In the graphical plot analysis of recanalization status according to time window (Figure 3), we identified time cutoffs for favorable and independent functional outcome. Accordingly, the 95% CIs of the determined marginal mean values overlapped after 13.8 hours for favorable functional outcome and 17.6 hours for independent functional outcome, indicating a loss of treatment benefits. Furthermore, recanalization (aOR, 0.30; 95% CI, 0.14-0.61; P = .001), age (aOR, 1.07; 95% CI, 1.05-1.10; P < .001), NIHSS score on admission (aOR, 1.06; 95% CI, 1.01-1.11; P = .01), and administration of alteplase (aOR, 0.52; 95% CI, 0.27-0.99; P = .046) were independently associated with death (mRS score of 6 at day 90).
Inverse Probability Weighting Analysis

The average treatment effect of recanalization was calculated using inverse probability weighting analyses with favorable outcome (mRS score of 0-3), functional independence (mRS score of 0-2), and ENI as dependent variables, adjusted for age, NIHSS score on admission, alteplase administration (yes or no), and ASPECTS. The propensity score overlap was tested to demonstrate that the positivity assumption was not significantly violated. No significant probability mass was seen near 0 and 1, and the 2 estimated densities had most of their respective masses in regions in which they overlap. Thus, there was no evidence that the overlap assumption was violated (eFigure 1 in Supplement 1). The estimated average treatment effect of successful recanalization (ie, mTICI score of 2b or 3) increased 19% (95% CI, 9%-29%; P < .001) in the likelihood of a favorable outcome, 16% (95% CI, 8%-24%; P < .001) in the likelihood of functional independence, and 14% (95% CI, 3%-25%; P = .01) in the likelihood of binary ENI. The association of successful recanalization with outcome was confirmed among the subgroup of patients with a 12- to 24-hour time window, evidencing an estimated average treatment effect of 24% (95% CI, 23%-26%; P < .001) for a favorable outcome and 18% (95% CI, 17%-20%; P < .001) for functional independence. There was, however, no significant association of recanalization with ENI for patients with a 12- to 24-hour time window (3%; 95% CI, −16% to 22%; P = .75).

Figure 1. Association of Baseline Alberta Stroke Program Early CT Score (ASPECTS) and Recanalization With Favorable Outcome

The graph illustrates the association of recanalization with favorable outcomes (modified Rankin Scale [mRS] score of 0-3) according to the baseline ASPECTS. Error bars indicate 95% CIs, which overlap for ASPECTS of 0 to 2.

Figure 2. Association of Time and Recanalization With Estimated Favorable Outcome

The association of recanalization with outcomes is illustrated according to the existing time window. Error bars indicate 95% CIs, which overlap for a time window greater than 1056 minutes. mRS indicates modified Rankin Scale.
Discussion

This retrospective multicenter cohort study investigating the association of endovascular recanalization with functional outcomes in the setting of CT-based treatment selection for patients with ischemic stroke presenting with low ASPECTS and an extended time window revealed several findings. First, the rate of favorable outcomes after successful endovascular recanalization among this patient cohort was similar to previously reported outcomes among patients with low ASPECTS in the early time window, suggesting that patients with large core infarcts may benefit even in the extended time window. Second, successful recanalization was significantly associated with better outcomes for patients with ASPECTS of 3 to 5 and a time window of up to 13.8 hours (mRS score of 0-2) or 17.6 hours (mRS score of 0-3), supporting the exclusion of patients with very low ASPECTS of 2 or less or patients presenting in a very late time window, as reflected by some inclusion criteria of ongoing trials (eg, the TENSION trial). Third, successful recanalization was the only factor independently associated with ENI in the extended time window with extensive signs of infarction.

Previously, several landmark stroke trials evidenced a benefit associated with endovascular recanalization for patients with intracranial large vessel occlusion in the anterior circulation. Nonetheless, most of these trials limited the indication for thrombectomy to patients with better prognostic factors, such as shorter time interval from symptom onset and lower extent of early ischemic changes. More recently, the effectiveness of thrombectomy has been observed among patients presenting up to 24 hours after symptom onset or last time seen well. However, these studies used only perfusion imaging for patients with a small ischemic core infarct while excluding patients with larger core infarcts or low ASPECTS. In the HERMES meta-analysis, a nonsignificant trend toward a treatment benefit associated with thrombectomy for patients with low ASPECTS was observed. This association could be biased by a low number of patients who were mainly selected based on magnetic resonance imaging (MRI), acknowledging that CT imaging represents the most frequently applied modality for the detection and treatment of large vessel occlusion stroke. Recently, Almallouhi et al investigated the association of recanalization with outcomes for patients with an extended time and lesion window and observed a potential treatment benefit with regard to 90-day outcomes. This study included only 90 patients with an extended time window and low ASPECTS and generally excluded patients with an ASPECTS less than 2. Still, the question remains whether thrombectomy may be beneficial for patients with an extended time and lesion window.

Several randomized clinical trials are currently investigating the effect of thrombectomy in this patient group by applying different inclusion criteria, particularly regarding the time window or the extent of early ischemic changes, and by including patients up to 24 hours after stroke onset and with different lower ASPECTS thresholds. Recently, the RESCUE-Japan LIMIT observed a significant
treatment benefit associated with thrombectomy among patients with an ASPECTS of 3 to 5. To our knowledge, this was the first trial showing a benefit associated with thrombectomy for patients with a large, early infarction; however, some limitations should be considered. First, the trial comprised a highly selected patient cohort including only 100 patients per treatment group, selected from 45 centers over 2 years that mainly used MRI as the baseline imaging modality (85% MRI). The comparability of CT-based and MRI-based ASPECTSs has limitations, and patients with a low ASPECTS as rated by DWI often show higher ASPECTSs when rated by CT depending on how the rating is performed. Second, 70% of the treated patients presented 6 hours or less from stroke onset, which precludes patients with an extended time and lesion window. Patients presenting 6 to 24 hours after stroke onset and with a low ASPECTS were included only in the absence of a corresponding lesion detected by fluid-attenuated inversion recovery, which may be seen as a comparably rare constellation and underlines the strict patient selection. Third, observations among an Asian population are not necessarily transferable to non-Asian populations considering the significantly different results in the Asian vs non-Asian direct mechanical thrombectomy studies. Fourth, the substantial treatment effect that was also similar for patients included in the HERMES meta-analysis (ie, 19%), despite inclusion of only 100 patients, may have resulted from rigorous patient selection, also noting that the TENSION trial estimated an enrollment of 665 patients to show a treatment effect. Fifth, the use of MRI as the primary imaging modality might be problematic for patients with a low ASPECTS and severe clinical deficits considering the lower patient compliance required for MRI, which therefore might constitute a further selection bias (ie, patients with less severe deficits who may undergo MRI and an overestimation of ASPECTSs rated by CT). In summary, these results still emphasize a need for further studies analyzing the association of mechanical thrombectomy with outcomes among patients with a low ASPECTS in daily clinical practice, in particular using CT-guided decision-making considering its better availability, applicability, and speed.

We observed that recanalization was the only parameter independently associated with ENI, a well-investigated early surrogate of final functional outcome. Inverse probability weighting analysis revealed that, in the time window of 12 to 24 hours, successful recanalization was associated with good outcomes but not with ENI at day 90. Still, 18% of the patients without ENI showed favorable outcomes at day 90. In contrast, only 11% of patients in a previous cohort showed good outcomes despite lack of ENI. Although it is generally known that a significant proportion of patients with stroke experience delayed recovery, the “stunned brain” phenomenon (ie, good final functional outcome despite lack of early clinical improvement) has mainly been associated with smaller baseline and posttreatment lesion volumes and has not yet been described for patients with extensive baseline stroke. Furthermore, studies on good functional outcome despite lack of early clinical improvement after ischemic stroke are mainly from the prethrombectomy era, often including patients without substantial vessel reperfusion or unknown substantial vessel reperfusion. The occurrence of delayed recovery even in the extended time and lesion window may serve as an argument in favor of EVT, highlighting the potential of future adjuvant treatment strategies in this treatment scenario (eg, the administration of nerinetide, a recently tested neuroprotectant). Considering that nerinetide showed a significant treatment effect on functional outcome only among patients who did not receive intravenous alteplase, the use of nerinetide may be particularly applicable in an extended time and lesion window constellation, where alteplase is often contraindicated. Furthermore, drugs, such as nerinetide, could be combined with other anti-edematous drugs, such as glyburide, that may also support the reduction of ischemic edema formation and better outcomes for patients with extensive strokes.

Overall, 33% of patients in this cohort study received intravenous alteplase despite presenting in an extended time and lesion window. The administration of intravenous alteplase in the extended time window may be guided using CTP as investigated by the EXTENT study. Regarding the degree of ischemic changes detected on baseline imaging, current guidelines state that the application of alteplase is recommended “in the setting of early ischemic changes on CT of mild to moderate extent.” However, alteplase is not recommended for patients with extensive regions of clear
hypoattenuation. Thus, it remains uncertain how to visually distinguish the extent of early hypoattenuation in the absence of objectifiable thresholds considering the low interrater reliability of early ischemic changes. Accordingly, it is expected that decision-making regarding intravenous alteplase in daily clinical practice for patients with extensive stroke may significantly vary between practitioners and that future randomized clinical trials are necessary to investigate the effect of alteplase on patients with an extended time and lesion window.

Limitations
This study has some limitations. The main limitation is based on the absence of randomization as well as the limited sample size and missing imaging data for further quantitative analysis. The comparably high proportion of patients with favorable outcomes despite the extended time window and extended lesion window might be partially caused by selection bias (eg, by including patients exhibiting more favorable imaging profiles [ie, better collaterals or lower CTP-derived core volumes with larger penumbra]). Hence, this study cannot be used to draw valid conclusions for decision-making for stroke patients with an extended time window and extended lesion window.

Conclusions
In daily clinical practice, endovascular recanalization after CT-based treatment selection in the extended time and lesion window was significantly associated with improved outcomes among patients with an ASPECTS of 3 to 5 and up to 17.6 hours after stroke onset. The results of this cohort study should be encouraging to currently ongoing randomized clinical trials investigating treatments for patients in the extended time window who also show signs of extensive infarction, especially trials that only provide thrombectomy as treatment for patients with an ASPECTS below 3 or presenting in very late time windows.
Administrative, technical, or material support: Broocks, Hanning, Faizy, Flottmann, Kniep, Deb-Chatterji.

Supervision: Broocks, Hanning, Brekenfeld, Thomalla, Kemmling, Fiehler.

Conflict of Interest Disclosures: Drs Broocks and Meyer reported receiving compensation as a speaker from Balt and personal fees from Eppdata GmbH outside the submitted work. Drs Flottmann and Kniep reported receiving personal fees from Eppdata GmbH outside the submitted work. Dr Deb-Chatterji reported receiving grants from Werner Otto Stiftung outside the submitted work. Dr Thomalla reported receiving personal fees from Acandis, Alexion, Amin, Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Daiichi Sankyo, Portola, and Stryker outside the submitted work. Dr Fiehler reported receiving personal fees from Cerenovus, Medtronic, Phenox, and Penumbra outside the submitted work. No other disclosures were reported.

Group Information: The German Stroke Registry–Endovascular Treatment (GSR-ET) Study Group Collaborators are listed in Supplement 2.

Additional Information: The data that support the findings of this study are available on reasonable request after approval of the ethics committee and all participating centers.

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**SUPPLEMENT 1.**

-eAppendix. Subanalysis - Untreated Subjects in the Literature

-eTable. Comparative Analysis

-eFigure 1. Overlap Plot to Demonstrate Positivity Assumption After Inverse-Probability Weighting

-eFigure 2. LOESS Plot to Illustrate Linearity Assumption Between ASPECTS and Outcome
eFigure 3. LOESS Plot to Illustrate Linearity Assumption Between Time (Log) From Onset to Imaging and Outcome

SUPPLEMENT 2.
Nonauthor Collaborators. The German Stroke Registry-Endovascular Treatment (GSR-ET) Study Group
Collaborators

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Thrombectomy for Patients With Ischemic Stroke With Extended Time and Lesion Window


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