Stroke

CLINICAL AND POPULATION SCIENCES

# Good Clinical Outcome Decreases With Number of Retrieval Attempts in Stroke Thrombectomy

## Beyond the First-Pass Effect

Fabian Flottmann, MD; Caspar Brekenfeld, MD; Gabriel Broocks, MD; Hannes Leischner, MD, PhD; Rosalie McDonough, MD; Tobias D. Faizy, MD; Milani Deb-Chatterji, MD; Anna Alegiani, MD; Götz Thomalla, MD; Anastasios Mpotsaris, MD; Christian H. Nolte, MD; Jens Fiehler, MD; Máté E. Maros, MD, MSc; for the GSR investigators*

**BACKGROUND AND PURPOSE:** Endovascular therapy is the standard of care in the treatment of acute ischemic stroke due to large-vessel occlusion. Often, more than one retrieval attempt is needed to achieve reperfusion. We aimed to quantify the influence of endovascular therapy on clinical outcome depending on the number of retrievals needed for successful reperfusion in a large multi-center cohort.

**METHODS:** For this observational cohort study, 2611 patients from the prospective German Stroke Registry included between June 2015 and April 2018 were analyzed. Patients who received endovascular therapy for acute anterior circulation stroke with known admission National Institutes of Health Stroke Scale score and Alberta Stroke Program Early CT Score, final Thrombolysis in Cerebral Infarction score, and number of retrievals were included. Successful reperfusion was defined as a Thrombolysis in Cerebral Infarction score of 2b or 3. The primary outcome was defined as functional independence (modified Rankin Scale score of 0–2) at day 90. Multivariate mixed-effects models were used to adjust for cluster effects of the participating centers and confounders.

**RESULTS:** The inclusion criteria were met by 1225 patients. The odds of good clinical outcome decreased with every retrieval attempt required for successful reperfusion: the first retrieval had the highest odds of good clinical outcome (adjusted odds ratio, 6.45 [95% CI, 4.0–10.4]), followed by the second attempt (adjusted odds ratio, 4.56 [95% CI, 2.7–7.7]), and finally the third (adjusted odds ratio, 3.16 [95% CI, 1.8–5.6]).

**CONCLUSIONS:** Successful reperfusion within the first 3 retrieval attempts is associated with improved clinical outcome compared with patients without reperfusion. We conclude that at least 3 retrieval attempts should be performed in endovascular therapy of anterior circulation strokes.

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**Key Words:** cerebral infarction ■ ischemic stroke ■ reperfusion ■ standard of care ■ thrombectomy

Endovascular therapy (EVT) has been established as the standard of care in large-vessel occlusion stroke,[1] and successful reperfusion is the most important modifiable predictor of good clinical outcome.[2] Often, more than one retrieval attempt is needed to achieve successful reperfusion. In cases of persistent occlusion, it is currently unknown how many retrieval attempts should be performed before terminating the procedure.

Correspondence to: Fabian Flottmann, MD, Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Haus Ost 22 (O 22), Martinistr. 52, 20246 Hamburg, Germany. Email f.flottmann@uke.de

*A list of all GSR Investigators is given in the Appendix.

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For Sources of Funding and Disclosures, see page 489.

## Nonstandard Abbreviation and Acronyms

| | |
|---|---|
| **ASPECTS** | Alberta Stroke Progrm Early CT score |
| **EVT** | endovascular therapy |
| **IQR** | interquartile range |
| **mRS** | modified Rankin Scale |
| **mRS90** | mRS score at 90 days |
| **NIHSS** | National Institutes of Health Stroke Scale |
| **OR** | odds ratio |
| **TICI** | Thrombolysis in Cerebral Infarction |

Studies have reported that clinical outcomes are most favorable in patients achieving a Thrombolysis in Cerebral Infarction (TICI) score of 3 after the first retrieval attempt.[3,4] With multiple retrieval attempts, improved rates of successful reperfusion could be obtained, however, the effect on clinical outcome is not fully understood, with conflicting results in the literature.[5,6] In some studies, multiple retrieval attempts were reported to be negatively associated with good clinical outcome.[7,8] In contrast, a recent study suggested that the number of retrievals required for successful reperfusion is not predictive of good clinical outcome.[9] Most of the cited studies are single-center analyses, and their results are based on the dichotomization of retrieval number. Thus, the relative effect of each subsequent retrieval on clinical outcome is unknown.

The aim of the present study was to provide a detailed analysis describing the effect of the number of retrievals on functional outcome. We hypothesize that, in cases of successful reperfusion, the odds ratio (OR) of a good outcome decreases with increasing number of retrieval attempts.

# METHODS

## Data Availability

Anonymized study data are available from the corresponding author upon reasonable request.

## Patient Selection

Two thousand six hundred eleven patients enrolled in the German Stroke Registry—Endovascular Treatment (GSR-ET 07/2015-04/2018) were screened for inclusion. The German Stroke Registry—Endovascular Treatment is an ongoing, open-label, prospective, multi-center registry of consecutively collected EVT patients, with 25 participating sites in Germany.[10]

The inclusion criteria for the present study were (1) acute ischemic stroke due to large-vessel occlusion in patients >18 years, (2) decision to perform EVT, (3) large-vessel occlusion in the anterior circulation confirmed on digital subtraction angiography and with documented location of occlusion (4) available data on the Alberta Stroke Program Early CT Score (ASPECTS) on admission imaging, admission National Institutes of Health Stroke Scale (NIHSS) score, number of retrieval attempts, final TICI following angiography, and modified Rankin Scale (mRS) score at 90 days (mRS90). Exclusion criteria were occlusions of the extracranial internal carotid artery or internal carotid artery proximal to the carotid-T, as well as concomitant stenting of the extracranial internal carotid artery.

Study protocols and procedures were conducted in compliance with the Declaration of Helsinki and in accordance to ethical guidelines (the leading ethics committee of the Ludwig-Maximilians University Munich approved the German Stroke Registry—Endovascular Treatment and the study obtained additional approval from the local ethics committees of the participating hospitals).

## Data Acquisition and Management

Data acquisition was performed according to the protocol of the German Stroke Registry—Endovascular Treatment, as previously described.[10,11] In summary, all data were collected by the local neurointerventionalists and neurologists, and the collected data underwent standardized quality checks to control for consistency, plausibility, and completeness.

ASPECTS was determined on preintervention nonenhanced computer tomography scans or diffusion-weighted imaging (in the case of magnetic resonance imaging). The TICI score was assessed on the final angiographic series by the attending interventionalist. Successful reperfusion was defined as a final TICI score of 2b or 3. The total number of retrievals performed was documented following intervention by the neurointerventionalist and included both aspiration attempts, as well as retrievals with stent retriever devices. Good clinical outcome was defined as mRS90 of ≤2.

## Statistical Analysis

All analyses were performed with the R statistics program (v.3.5.2, R Core Team 2018, Vienna Austria; RStudio IDE v. 1.1.463, Boston, MA).[12] Normally distributed variables are displayed as mean and SD. Non-normally distributed data are displayed as median and interquartile range (IQR). Categorical variables are reported as proportions.

The number of retrieval attempts needed to achieve successful reperfusion was included in the multivariable analysis. Patients requiring >6 retrieval attempts were combined into one category. Patients who did not achieve successful reperfusion at the end of the procedure after any number of attempts were used as the reference group. We performed complete-case analyses using the well-established framework of generalized mixed-effects models with random intercepts to account for the cluster effect of the participating centers while using the binomial link function when modeling the primary outcome, mRS90, binarized at mRS score ≤2 versus mRS score >2.[13,14] The distribution of the random effects was considered to follow a gaussian distribution. To increase comparability with previous studies[15] and the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) meta-analyses,[16] the applied mixed-effect logistic regression model was also adjusted for (fixed effects of) age, baseline stroke severity (NIHSS) score, baseline ASPECTS, and successful

**Table 1. Baseline Clinical Data**

| Variable | |
|---|---|
| Age, y (mean, SD) | 73.0 (13.2) |
| Female sex (%) | 53.1% |
| Hypertension (%) | 74.7% |
| Diabetes (%) | 20.2% |
| Dyslipidemia (%) | 32.4% |
| Atrial fibrillation (%) | 44.5% |
| Initial NIHSS score (median, Q1–Q3) | 15 (10–19) |
| Initial ASPECTS (median, Q1–Q3) | 9 (7–10) |
| Initial occlusion site, % | |
| Left hemisphere | 51.0% |
| Location of vessel occlusion | |
| Carotid-T | 14.3% |
| M1 proximal | 37.1% |
| M1 distal | 22.0% |
| M2 | 21.8% |
| Intravenous tPA, n (%) | 55.7% |
| Onset to admission, min (median, Q1–Q3)* | 116 (55–193) |
| Stroke cause | |
| Cardioembolism | 56.3% |
| Dissection | 0.8% |
| Atherosclerosis | 18.6% |
| Other determined cause | 5.0% |
| Unknown cause | 19.2% |

ASPECTS indicates Alberta Stroke Program Early CT score; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.
*Available for 747/1225 patients.

reperfusion of the *N*-th retrieval attempt. In line with findings of recent meta-analyses, we chose to omit sex and the site of intracranial occlusion.[17,18] Nonetheless, as sensitivity analyses, we investigated the robustness of the base model's estimates by additionally adjusting for sex and time from groin puncture to flow restoration (Table I in the Data Supplement) and site of intracranial occlusion (terminal internal carotid artery, middle cerebral artery [proximal M1, distal M1, M2], and anterior cerebral artery; Table II in the Data Supplement). We furthermore investigated the effect of combining the groups of successful reperfusion achieved after ≥4 retrievals on the predictor estimates of the primary model (Table III in the Data Supplement). Model fits were compared using the likelihood-ratio test,[13,14] as well as the Bayesian- and Akaike-information criteria.[19] To facilitate the clinical application of our results, we additionally calculated average marginal predicted probabilities with 95% CI overall levels of the random effects (all centers). Thus, we can provide the average fixed effect of the number of retrievals required and the corresponding probability of good functional outcome (mRS score ≤2) across the range of baseline model predictors, which should be representative on a populational level for all (participating) German neurointerventional centers. Figures were created using the ggplot2 grammar of graphics. $P<0.05$ were considered significant. Due to the explorative nature of our analyses, *P* values were not adjusted for multiple testing.

# RESULTS

## Baseline Characteristics

We identified 2611 patients in the complete data set, 1225 of which fulfilled the inclusion criteria (patient selection flowchart, Figure I in the Data Supplement). Among these, 53.1% were female, and the mean age was 73.0 (±13.2) years (Table 1). The median NIHSS score on admission was 15 (IQR, 10–19). The median ASPECTS on admission imaging was 9 (minimum: 1, IQR: 7–10, maximum: 10). The median number of retrievals was 2 (minimum: 0, IQR 1–3, maximum: 20).

The primary outcome mRS90 showed an almost uniform distribution across scores 0 to 5 (minimum–maximum: 8.3%–14.9%) while a score of 6 accounted for 28.3%. Hence, generalized mixed-effects models using binomial regression frameworks were used on binarized mRS scores (poor outcome: mRS score >2, 62.5% versus favorable outcome: mRS score ≤2, 37.5%).

**Table 2. Patient Characteristics and Outcome by Number of Retrieval Attempts and Reperfusion Status**

| Final retrieval/aspiration attempt, number of patients | No attempt performed (n=38) | First attempt (n=536) | | Second attempt (n=281) | |
|---|---|---|---|---|---|
| TICI score at end of procedure | 0–2a | 2b/3* | 0–2a | 2b/3* | 0–2a |
| No. of patients | 38 (100%) | 502/1225 (41.0%) | 34/1225 (2.8%) | 235/648 (36.2%) | 46/648 (7.1%) |
| Age, y (mean, SD) | 77.4 (12.3) | 73.3 (13.0) | 74.5 (13.6) | 73.0 (13.6) | 72.2 (14.8) |
| Female sex (%) | 57.9% | 51.7% | 55.9% | 56.1% | 50.0% |
| Admission NIHSS score† (median, Q1–Q3) | 14.5 (8–20) | 15 (10–18) | 15 (8–18) | 15 (9–19) | 14.5 (12–18) |
| ASPECTS on admission imaging (median, Q1–Q3) | 8 (7–9) | 9 (7–10) | 8 (6–9) | 9 (7.5–10) | 8.5 (6–10) |
| Time from groin puncture to final TICI score, min (median, Q1–Q3)† | 58 (34–82) | 28 (20–44) | 40 (31–66) | 37 (28–55) | 48 (31–64) |
| Good clinical outcome (mRS score at 90 days ≤2, %) | 23.7% | 49.4% | 32.4% | 42.1% | 19.6% |

(*Continued*)

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Seventeen centers contributed patients who fulfilled all inclusion criteria and the number of patients showed a highly skewed distribution. The top 4 recruiting centers (each of which treated >10% of the total collective) generated ≈55% of the study cohort. Another 7 centers, each providing 2% to 10% of the cases, accounted for ≈37%. The remaining 6 (contributing <2% of the collective each) provided ≈8% of the total. Similarly, the inclusion of cluster effects resulted in a strong trend towards improved model fit ($\chi^2$=3.27, $P_{LRT}$=0.071) compared with the base model without the random term for participating centers.

## Patient Characteristics by Number of Retrieval Attempts

In 536/1225 (43.8%) patients, only one retrieval attempt was performed (Table 2). The mean age was 73.5 years, the median NIHSS score was 15, and the median ASPECTS was 9. Of these patients, 257 (48%) had a good clinical outcome. In 76 patients, >5 retrievals were performed. These patients were younger (mean age 70 years), and their median NIHSS score was slightly higher at 16, while their median ASPECTS was slightly lower at 8. Of these, 11.8% had a good clinical outcome. In 38 patients, no retrieval attempt was performed due to technical or procedural difficulties, with final TICI scores of 0 to 2a. Of these, 23.7% had a good clinical outcome.

## Cumulative Analysis of Reperfusion and Good Clinical Outcome by Number of Retrievals

Successful reperfusion after one retrieval attempt was achieved in 502/1225 patients (41.0%), increasing to 83.4% after considering the total number of attempts (Figure 1A). While 4 or more passes resulted in higher rates of successful reperfusion, no substantial improvement in clinical outcome was observed (Figure 1B). In general, the greater the number of attempts, the worse the mRS90, with the exception of cases in which 5 retrieval attempts were required (Figure 1C).

## Primary Multivariate Analyses

The primary mixed-effects logistic regression model (Table 3) showed a model fit Akaike information criterion=1247, which was significantly ($P_{LRT}$ <0.001) better than any combination or subset of the included predictors. The random effects intercept for centers showed a variance of 0.048 and SD=0.22 on the logit scale. The inclusion of center-based cluster effects showed a trend towards ($P$=0.12) improved model fit compared with fitting the same model using ordinary logistic regression with no clustering.

The model revealed highly significant negative associations between older age and higher baseline NIHSS score and mRS90 ≤2. A positive association was observed for ASPECTS of 8 to 9 and 10 ($P$=0.011 and 0.013, respectively). Success after the first, second, and third retrievals showed a highly significant positive association with mRS score ≤2 at 90 days. The effect sizes gradually decreased from success after the first to the fourth retrieval with OR of 6.45 to 1.70, respectively (Table 3). Interestingly, successful reperfusion after the fifth retrieval attempt was significantly associated with a larger positive effect (OR, 2.90 [95% CI, 1.11–7.59]). The estimated effect on outcome then reverted to negative in cases requiring 6 or more retrievals, without statistical significance (OR, 0.82 [95% CI, 0.32–2.14]). The primary model-based estimates of averaged marginal probabilities of good clinical outcome (mRS score ≤2) across all centers with respect to number of retrievals required for successful reperfusion adjusted for age, baseline NIHSS score, and ASPECTS are depicted in Figure 1D.

**Table 2. Continued**

| Third attempt (n=171) | | Fourth attempt (n=77) | | Fifth attempt (n=46) | | ≥6 attempts (n=76) | |
|---|---|---|---|---|---|---|---|
| 2b/3* | 0–2a | 2b/3* | 0–2a | 2b/3* | 0–2a | 2b/3* | 0–2a |
| 148/367 (40.3%) | 23/367 (6.2%) | 58/196 (29.6%) | 19/196 (9.7%) | 35/119 (29.4%) | 11/119 (9.2%) | 44/76 (57.8%) | 32/76 (42.1%) |
| 73.5 (12.6) | 74.0 (10.2) | 72.5 (13.5) | 69.3 (12.3) | 71.6 (14.6) | 65.1 (17.2) | 69.6 (13.2) | 70.6 (12.4) |
| 50.0% | 69% | 53.4% | 52.6% | 60% | 45.5% | 45.4% | 56.3% |
| 15 (11–19) | 16 (10–19) | 17 (15–20) | 15 (9–18) | 17 (14–19) | 21 (17–22) | 15 (12–17) | 16 (14.5–19.5) |
| 9 (7–10) | 9 (7–10) | 8.5 (8–9) | 8 (6.5–9) | 8 (7–10) | 7 (6–8) | 8 (7–9.25) | 8 (6–9) |
| 51 (30–75) | 85 (71–98) | 56.5 (35–85) | 68 (52–74) | 60 (53–88) | 125 (118–179) | 93 (64–117) | 80 (61–122.5) |
| 33.1% | 4% | 22.4% | 10.5% | 31.4% | 9.1% | 18.2% | 3% |

ASPECTS indicate Alberta Stroke Program Early CT score; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TICI, Thrombolysis in Cerebral Infarction.

*Included in multivariable analysis.

†Available for 1090/1225 patients.

## Secondary Analyses Including Time From Groin Puncture to Flow Restoration

Time from groin puncture to flow restoration was available in 88.1% (1090/1225) of patients. It showed a skewed distribution with a median time from groin puncture to flow restoration of 38.0 minutes (IQR, 25–61). The subset of patients with available time from groin puncture to flow restoration achieved successful reperfusion in 91% of the cases. Figure 2 depicts the influence of number of retrievals on clinical outcome, stratified by time from groin puncture to flow restoration. The secondary mixed-effects model was additionally adjusted for time from groin puncture to flow restoration and sex, as well as predictors of the base model (Table 3). Detailed estimates of this secondary model are available in (Table I in the Data Supplement). The effect sizes remained robust for age, NIHSS score, and ASPECTS 8 to 10. Likewise, the positive association between success after the first (OR, 4.56 [95% CI, 2.47–8.44]), second (OR, 3.30 [95% CI, 1.72–6.35]), and third (OR, 2.14 [95% CI, 1.07–4.28]) retrieval and good outcome were significant, although effect sizes were slightly reduced. Furthermore, although not statistically significant, the estimated coefficients of the effects of the fourth and fifth retrievals ($p_{4th}$=0.55, $p_{5th}$=0.18) remained positive, whereas 6 or more retrievals resulted in a negative effect size (OR, 0.59 [95% CI, 0.21–1.64]).

As a sensitivity analysis, the model was further expanded and adjusted for treatment with intravenous thrombolysis and site of intracranial occlusion (Table II in the Data Supplement). The significant association with good outcome (including both the effect sizes and their directions) remained fairly constant for age, NIHSS score, and success at the first, second, and third retrieval attempts, while treatment with intravenous thrombolysis and ASPECTS 8 to 9 and 10 narrowly escaped the 0.05 significance threshold. None of the considered occlusion sites showed a significant association. This was primarily done for comparability to the model applied in the HERMES meta-analysis.

Results of the sensitivity analysis refitting the primary model by combining the heterogenous subgroups of success at >4 retrieval attempts remained highly consistent

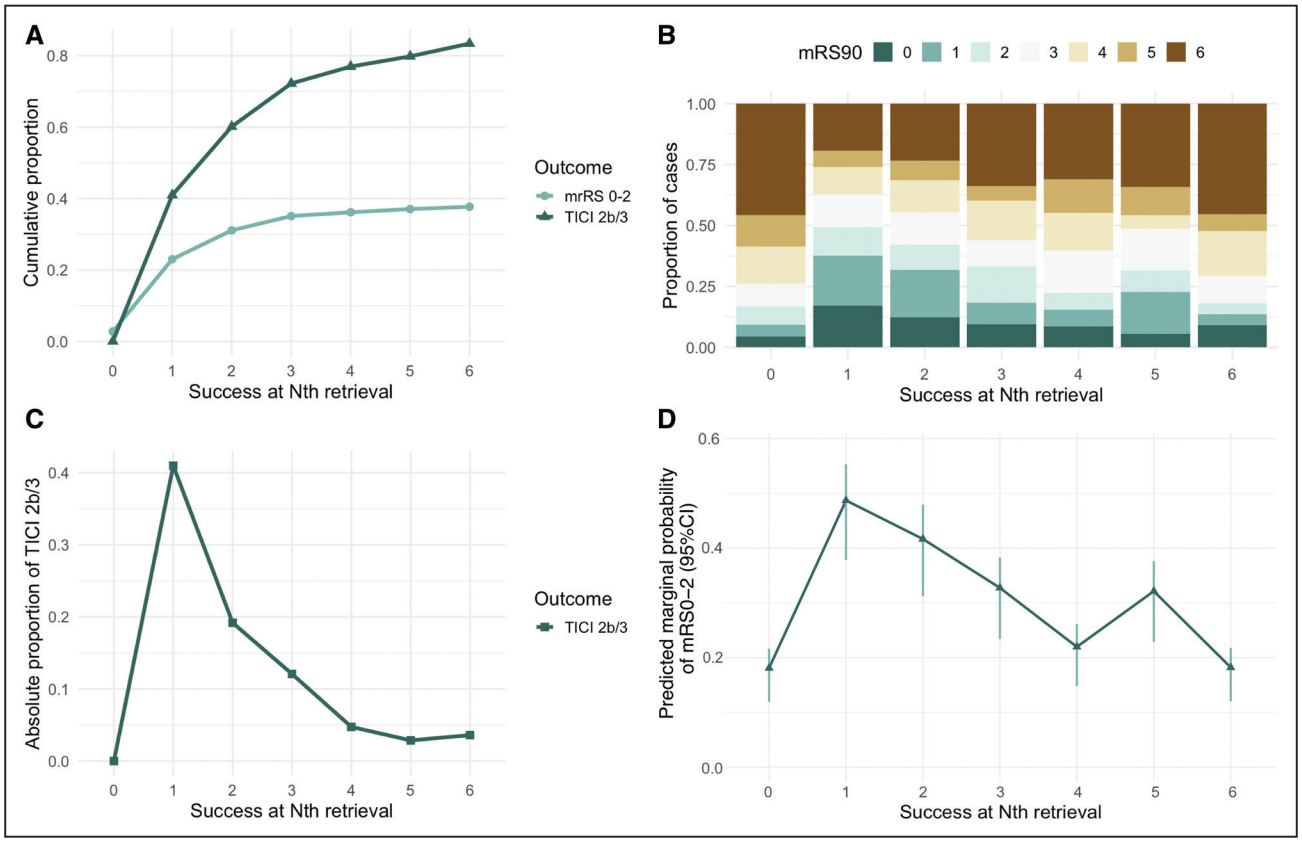


**Figure 1. Association of the number of retrieval attempts with good clinical outcome (modified Rankin Scale score at 90 d [mRS90] ≤2) and successful reperfusion (Thrombolysis in Cerebral Infarction [TICI] score of 2b/3).**
**A**, Cumulative proportion of good clinical outcome and successful reperfusion by the number of retrieval attempts needed to achieve successful reperfusion. **B**, Contribution of each successful retrieval attempt to the absolute proportion of patients with successful reperfusion (TICI score of 2b/3). **C**, Relative proportion of mRS90 by number of retrieval attempts needed to achieve successful reperfusion. **D**, Primary mixed-effects model-based estimates of averaged marginal probabilities of good clinical outcome (mRS score ≤2) with 95% CI across all participating centers with respect to number of retrievals required for successful reperfusion, adjusted for age, baseline National Institutes of Health Stroke Scale score, and Alberta Stroke Program Early CT score. 0 denotes no successful reperfusion achieved (TICI score of 0–2a); 6, aggregation of ≥6 attempts.

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**Table 3. Summary Table of Predictor Estimates by the Primary Multivariate Mixed-Effects Logistic Regression Model With Cluster Effects for Centers**

| Predictor variable | OR (95% CI)* |
|---|---|
| Age† | 0.94 (0.93–0.95) |
| NIHSS score† | 0.88 (0.85–0.90) |
| ASPECTS 0–5 | Reference level |
| ASPECTS 6–7 | 0.99 (0.53–1.84) |
| ASPECTS 8–9 | 2.10 (1.19–3.72) |
| ASPECTS 10 | 2.12 (1.17–3.82) |
| No Success (TICI 0–2a) | Reference level |
| Success at first retrieval | 6.45 (4.00–10.39) |
| Success at second retrieval | 4.56 (2.69–7.73) |
| Success at third retrieval | 3.16 (1.77–5.64) |
| Success at fourth retrieval | 1.70 (0.74–3.92) |
| Success at fifth retrieval | 2.90 (1.11–7.59) |
| Success at sixth retrieval | 0.82 (0.32–2.14) |
| (Intercept) | 66.0 (22.7–192.3) |

Coefficients and standard errors are reported on the logit scale. ASPECTS indicates Alberta Stroke Program Early CT score; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and TICI, Thrombolysis in Cerebral Infarction.

*Please note that CIs are not necessarily symmetrical for mixed-effects models.

†Age and NIHSS score were treated as continuous variables; ASPECTS and success at N-th retrieval were treated as factors.

with the above results and are available in Table III in the Data Supplement.

## DISCUSSION

In this large multi-center cohort of patients with EVT for anterior circulation stroke, multivariate outcome analyses were performed to investigate the association between number of EVT retrieval attempts and clinical outcome. The main finding of our in-depth analyses is that, after adjusting for well-known confounders (age, NIHSS score, and ASPECTS), successful reperfusion achieved during the first, second, and third retrieval attempt was significantly associated with improved clinical outcome compared with patients without successful reperfusion. These positive effects persisted after adjusting for procedural time from groin puncture to flow restoration, as well as for intravenous thrombolysis or site of occlusion.[16] However, the effect size gradually decreased with increasing number of attempts.

This is the first multi-center register study investigating the relationship between number of retrieval attempts and good clinical outcome, adjusting both for confounders, and for cluster effects possibly caused by multi-center data acquisition. Adjusting for the cluster effect of treating centers by using random effects terms has a fundamental conceptual difference and advantage compared with using ordinary multivariate logistic regression to evaluate multi-centric registry data,[6] because, by doing so, we do not assume that the treatment effect within each center is deterministically equal, but rather that it is drawn from a common distribution centered on the overall effect across centers.[16] Furthermore, we expect that good clinical outcome and number of retrievals required for reperfusion are correlated within the centers. To emphasize this concept, for the first time, we also provided model estimates of averaged marginal probabilities of good clinical outcome (mRS90 ≤ 2) across all centers with respect to number of retrievals required for successful reperfusion adjusted for age, baseline NIHSS score, and ASPECTS (Figure 1D), which should be representative of the entire underlying population (ie, participating German centers). These probability estimates can be directly interpreted in the clinical decision-making process, unlike estimates on the odds ratio scale.[20]

Improved clinical outcome after successful reperfusion with one retrieval has been previously reported as the first-pass effect, but the cohort used for comparison was heterogenous (TICI 0–3).[3] In their study, Nikoubashman et al[4] addressed this issue and were able to confirm a true first-pass effect when comparing TICI 3 reperfusion after one device pass versus multiple passes in a matched cohort of patients. Following their argumentation, we compared outcomes in patients with successful reperfusion, stratified by number of retrievals, as a means to look beyond the (true) first-pass effect. We found that the odds for good clinical outcome decreased within the first 3 retrievals leading to reperfusion, even after adjusting for the time from groin puncture to flow restoration. It is of note that the investigated patient collective (n=1225) is large in comparison to the pooled patient data of 5 trials included in the EVT treatment path of the HERMES meta-analysis (n=645), further supporting the robustness of our estimates. Our rate of good clinical outcome (37.7%) was comparable to the HERMES analysis (46%)[16]; the difference is most likely explained by the stricter inclusion criteria of randomized controlled trials.

The rate of successful reperfusion after the first retrieval attempt was 41%, decreasing to ≈30% with subsequent attempts, as has been previously published.[5,8] It is perhaps intuitive that, although the first attempt is the most important, subsequent attempts are still effective to achieve reperfusion. Nevertheless, as shown in Figure 1A, although >3 device passes improves the rate of reperfusion, the rate of good clinical outcome does not increase, which has been previously reported.[5,6]

Bai et al[6] investigated the effect of mechanical thrombectomy in a similarly multi-centric (n=21) registry study including 698 patients from Chinese centers. They used ordinary multivariate logistic regression without incorporating cluster (ie, center) effects. The number of passes were dichotomized at ≤3 versus >3. The proportion of >3 passes required (65/472; 13.8%) was comparatively low and was almost identical to our cohort (137/1022;

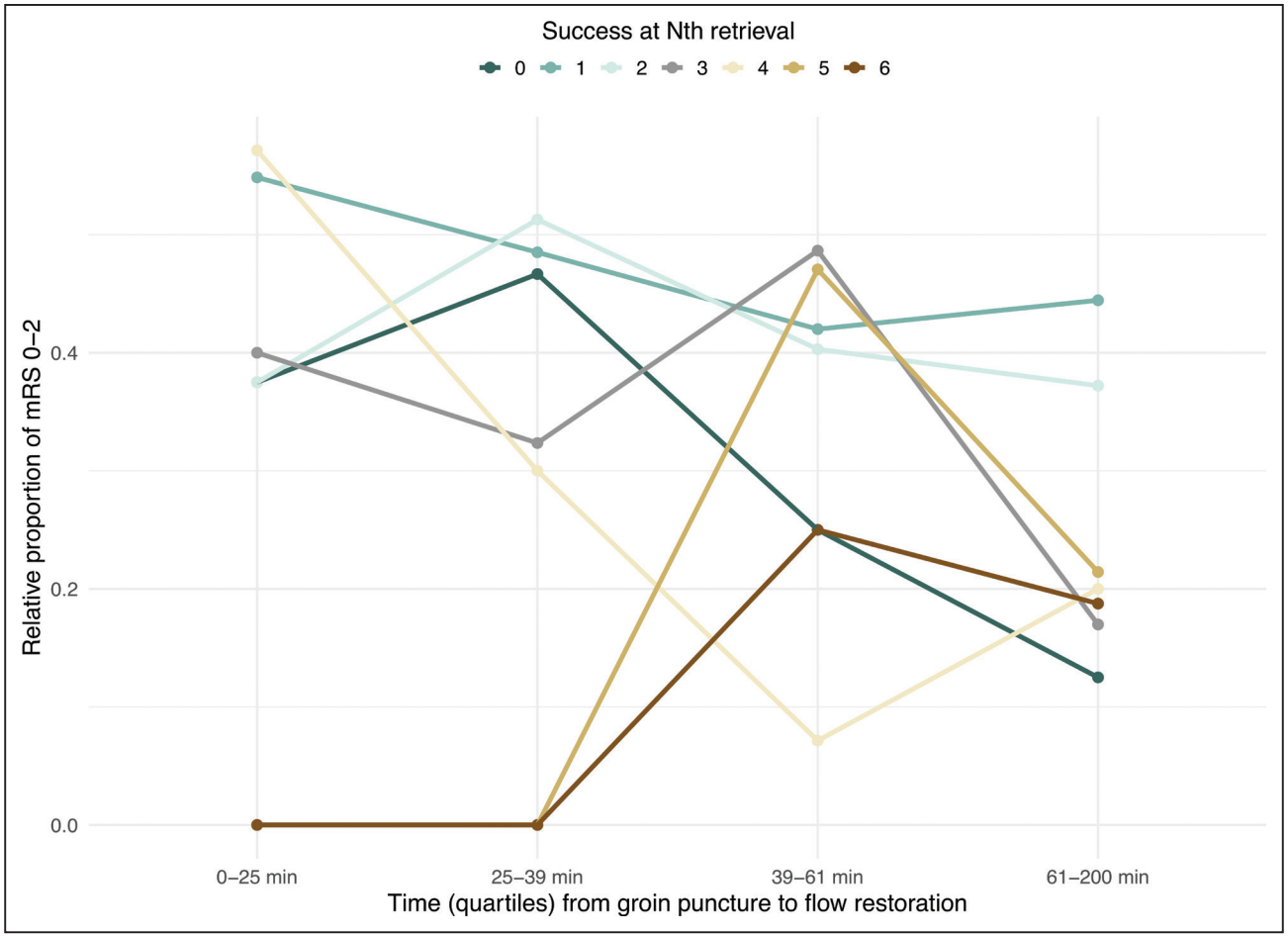


**Figure 2. Relative proportion of good clinical outcome (modified Rankin Scale [mRS] score at 90 0-2) by successful retrieval, stratified by quartiles of time from groin puncture to final Thrombolysis in Cerebral Infarction (TICI) score.**
Even after adjusting for time from groin puncture to final TICI score, up to 3 retrieval attempts were significantly associated with good clinical outcome in secondary multivariate analyses. 0 denotes no successful reperfusion achieved (TICI score of 0–2a); 6, aggregation of ≥6 attempts.

13.4%). Bai et al found poorer clinical outcomes after >3 device passes, which is also confirmed by our results.

A recent study by Bourcier et al[15] investigated the effect of ≤3 versus >3 passes on adverse events, particularly with regard to symptomatic intracranial hemorrhage in acute anterior ischemic stroke. They employed a similar statistical framework of mixed-effects model to our study, albeit in a considerably smaller cohort of 281 patients, and reported a tendency towards negative clinical outcome when >3 device passes with stent retrievers were needed to achieve reperfusion.

In contrast, Tonetti et al reported that the number of passes is not an independent predictor of good clinical outcome. They compared patients with successful reperfusion after >3 passes to patients without reperfusion. However, the comparison group of patients without reperfusion was very small (n=20). Furthermore, none of the patients without reperfusion had a good clinical outcome (compared with 16.7% in our study).

One could argue that the number of retrieval attempts is a surrogate for the procedure time. However, as shown in Figure 2, ≥4 retrievals were generally associated with lower rates of good clinical outcome, independent of the time from groin puncture to flow restoration. The secondary analysis, corrected for this time frame, revealed 2 findings: first, the procedure time was not a significant predictor of clinical outcome. This might be due to the fact that the time from groin puncture to flow restoration is only a small portion of the total vessel occlusion time. Second, the odds of good clinical outcome by number of retrievals changed only marginally, with the first 3 retrievals still being significantly superior compared with no reperfusion at all.

In our study cohort, success during the first 3 and fifth attempts had a significant positive association with good outcome (when not correcting for time from groin puncture to flow restoration). The positive association observed for the fifth retrieval might be explained by a random subsample of cases with a higher proportion of better collaterals. However, this effect diminished in the expanded models, which also included time from groin puncture to flow restoration and sex (Table I in the Data Supplement), along with intravenous thrombolysis and site of intracranial occlusion (Table II in the Data

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Supplement). Interestingly, the odds ratio estimator for ≥6 retrievals remained negative, albeit not significantly so. However, it potentially suggests that successful retrievals after >5 attempts could result in a worse clinical outcome when compared with no retrieval attempt at all. Further studies are warranted to investigate this hypothesis. A possible cause for the negative effects of multiple retrieval attempts could be vessel damage induced by the stent retriever and aspiration devices.[21]

Further studies should consider different locations of occlusion (eg, posterior circulation strokes), investigate the influence of different procedural techniques (aspiration or stent-retriever first), and try to identify patients who benefit (or are possibly harmed) from reperfusion after multiple attempts.

The present study includes data from 17 different stroke centers. We adjusted our results for the most important confounders (age, NIHSS score, ASPECTS). However, other known predictors of stroke severity could not be considered (eg, time from symptom onset, collateral status, EVT technique). Dichotomizing patients into successful reperfusion (TICI score of 2b/3) and unsuccessful reperfusion (TICI score of 0–2a) leads to information loss, as TICI 2a represents a heterogenous group of patients and clinical outcome can differ substantially between TICI 2b and 3.[22,23] We did not elaborate on reasons for failure of reperfusion and resulting termination of procedure.[24] We could not differentiate the underlying cause for multiple retrieval attempts, especially between intracranial atherosclerosis, persistent occlusions, and reocclusions,[25,26] and no distinction was possible between sudden and step-wise recanalization.[27] Some variables had missing data, which led to the exclusion of patients and, therefore, a possible selection bias, although the average rate of missing data for the primary multivariate analysis was considerably low with 9.7% (Figure I and Table IV in the Data Supplement). Furthermore, the determination of ASPECTS on admission, final TICI score, as well as the documentation of the number of retrievals, was done by the treating interventionalist and is subject to interrater variability.[28]

## SUMMARY

Our analyses provide detailed insights about the association between clinical outcome and the number of attempts leading to successful reperfusion in a large multi-centric register study. In EVT for anterior circulation strokes, at least 3 retrieval attempts should be performed in cases of persistent occlusion; in up to 5 attempts, a beneficial association with good clinical outcome is expected.

## ARTICLE INFORMATION

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### Affiliations

Department of Diagnostic and Interventional Neuroradiology (F.F., C.B., G.B., H.L., R.M., T.D.F., J.F.) and Department of Neurology (M.D.-C., A.A., G.T.), University Medical Center Hamburg-Eppendorf, Germany. University Clinic for Neuroradiology, Otto-von-Guericke-University Magdeburg, Germany (A.M.). Department of Neurology (C.H.N.) and Center for Stroke Research Berlin (C.H.N.), Charité-Universitätsmedizin Berlin, Germany. Department of Neuroradiology (M.E.M.) and Department of Biomedical Informatics at the Center for Preventive Medicine and Digital Health (M.E.M.), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

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Drs Flottmann, Brekenfeld, Fiehler, and Maros conceptualized the study. Drs Flottmann and McDonough performed data analyses. Drs Flottmann, McDonough, Fiehler, Brekenfeld, and Maros wrote the article. Dr Maros performed mixed-effects modeling, generated predicted probabilities, and created figures. Drs Flottmann, Maros, Broocks, Faizy, and Leischner performed data preparation. Drs Leischner, Deb-Chatterji, Alegiani, Thomalla, and members of the German Stroke Registry composed the cohort. Drs Mpotsaris and Nolte critically revised the article. Drs Fiehler, Brekenfeld, and Thomalla supervised the clinical aspects of the study. Drs Fiehler, Brekenfeld, and Maros supervised the work. All authors critically reviewed the article and approved the final version.

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### Supplemental Materials

Figure I
Tables I–IV

## APPENDIX

### German Stroke Registry—Steering Committee

Site Investigators: Tobias Boeckh-Behrens, MD, Klinikum r.d.Isar, Munich, Germany; Silke Wunderlich, MD, Klinikum r.d.Isar, Munich, Germany; Martin Wiesmann, MD, Uniklinik RWTH Aachen, Germany; Ulrike Ernemann, MD, Tübingen University Hospital, Germany; Till-Karsten Hauser, MD, Tübingen University Hospital, Germany; Eberhard Siebert, MD, Charité—Campus Benjamin Franklin und Campus Charité Mitte, Berlin, Germany; Sarah Zweynert, MD, Charité—Campus Virchow Klinikum, Berlin, Germany; Georg Bohner, MD, Charité—Campus Virchow Klinikum, Berlin, Germany; Alexander Ludolph, MD, Sana Klinikum Offenbach, Germany; Karl-Heinz Henn, MD, Sana Klinikum Offenbach, Germany; Waltraud Pfeilschifter, MD, Uniklinik Frankfurt/ Main, Germany; Marlis Wagner, MD, Uniklinik Frankfurt/Main, Germany; Joachim Röther, MD, Asklepios Klinik Altona, Hamburg, Germany; Bernd Eckert, MD, Asklepios Klinik Altona, Hamburg, Germany; Jörg Berrouschot, MD, Klinikum Altenburger Land, Altenburg, Germany; Albrecht Bormann, MD, Klinikum Altenburger Land, Altenburg, Germany; Christian Gerloff, MD, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Elke Hattingen, MD, University Hospital Bonn, Germany; Gabor Petzold, MD, University Hospital Bonn, Germany; Sven Thonke, MD, Klinikum Hanau, Germany; Christopher Bangard, MD, Klinikum Hanau, Germany; Christoffer Kraemer, MD, Klinikum Lüneburg, Germany; Martin Dichgans, MD, Ludwig Maximilian University of Munich, Germany; Frank Wollenwebe, MD, Ludwig Maximilian University of Munich, Germany; Lars Kellert, MD, Ludwig Maxi-

milian University of Munich, Germany; Franziska Dorn, MD, Ludwig Maximilian University of Munich, Germany; Moriz Herzberg, MD, Ludwig Maximilian University of Munich, Germany; Marios Psychogios, MD, Georg-August-Universität Göttingen, Germany; Jan Liman, MD, Georg-August-Universität Göttingen, Germany; Martina Petersen, MD, Klinikum Osnabrück, Germany; Florian Stögbauer, MD, Klinikum Osnabrück, Germany; Peter Kraft, MD, University Hospital Würzburg, Germany; Mirko Pham, MD, University Hospital Würzburg, Germany; Michael Braun, MD, Bezirkskrankenhaus Günzburg, Germany; Gerhard F. Hamann, MD, Bezirkskrankenhaus Günzburg, Germany; Andreas Kastrup, MD, Klinikum Bremen Mitte, Germany; Christian Roth, MD, Klinikum Bremen Mitte, Germany; Klaus Gröschel, MD, University Medical Center Mainz, Germany; Timo Uphaus, MD, University Medical Center Mainz, Germany; Volker Limmroth, MD, Kliniken Köln, Germany.

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