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ORIGINAL RESEARCH

Study Criteria Applied to Real Life—A Multicenter Analysis of Stroke Patients Undergoing Endovascular Treatment in Clinical Practice

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BACKGROUND: Randomized controlled clinical trials (RCT) have demonstrated the efficacy of endovascular treatment in anterior circulation large vessel occlusions. However, outcome of patients treated in daily practice differs from the results of the clinical trials. We hypothesize that this is attributable to the study criteria and that application of the criteria on patients undergoing endovascular therapy in daily routine would improve their outcome.

METHODS AND RESULTS: Data from a multicenter prospective registry of GSR-ET (German Stroke Registry – Endovascular Treatment) was used. Inclusion criteria and selectivity of SWIFT-PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial), MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands trial), ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times trial), DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo trial) and DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke trial) trials were analyzed. Baseline characteristics, procedural and outcome data of patients from GSR-ET before and after selection were compared with the results of the RCTs. Furthermore, outcome of patients who underwent endovascular treatment despite not fulfilling the RCT criteria was analyzed. A total of 2611 patients were included (median age, 75 years; 49.6% women; median National Institute of Health Stroke Scale, 16). A minority of patients met all inclusion criteria, ranging from 3% (DEFUSE-3 criteria) to 35% (MR CLEAN criteria). Of the patients fulfilling the MR CLEAN criteria, 41% of patients had a good clinical outcome, compared with 34% of patients that did not fulfill MR CLEAN criteria.

CONCLUSIONS: The RCTs represent a selected population with higher rates of good clinical outcome compared with daily practice. The good outcomes of RCTs can be reproduced in clinical routine in patients who fulfill the RCT inclusion criteria. Furthermore, patients who did not meet the criteria of the RCT still had substantial rates of good clinical outcome.

Key Words: endovascular stroke treatment ■ randomized controlled clinical trials ■ real life stroke outcome ■ stroke

See Editorial by Rosenbaum-Halevi.

Randomized controlled clinical trials (RCT) have demonstrated the positive effect of endovascular treatment (EVT) in patients with anterior circulation large vessel occlusion (LVO).[1–5] In most of these trials, strict inclusion and exclusion criteria were applied. Based on these results EVT has become

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CLINICAL PERSPECTIVE

What Is New?

- Only a small subset of stroke patients treated in "real life", daily practice fulfill the inclusion criteria of the large endovascular thrombectomy trials.
- Clinical and procedural outcomes of stroke patients in daily practice were comparable with those of the patients in the endovascular thrombectomy trials after application of the study criteria.
- Even if the patients did not meet the criteria of the endovascular thrombectomy trials, stroke patients still showed high rates of good clinical outcome.

What Are the Clinical Implications?

- The randomized clinical stroke trials represent a carefully selected population with higher rates of good clinical outcome compared with patients treated in "real life" — a fact that should be kept in mind when interpreting and analyzing the procedural and clinical outcome of patients in daily routine.
- The results of this study further suggest that it seems ethical to treat patients outside of the randomized clinical stroke trials qualification criteria.

Nonstandard Abbreviations and Acronyms

EVT	endovascular treatment
GSR-ET	German Stroke Registry – Endovascular Treatment
LVO	large vessel occlusions

the standard of care for patients suffering from LVO. However, current guidelines allow treating patients outside of these criteria to a certain extent. Studies investigating the outcome of stroke patients undergoing EVT for LVO in clinical practice show clinical and procedural outcomes which differ from the one published in the RCT.[6–9]

To our knowledge, this study is the first multicentric study analyzing the extent the criteria of the RCT can be applied and the results expected in stroke patients undergoing endovascular treatment for LVO in daily practice. Furthermore, this work investigates the outcome of real-life patients who underwent endovascular treatment despite not meeting all of the RCT criteria.

To do so, we applied the inclusion and exclusion criteria of the RCT and examined their gross selectiveness as well as patient characteristics, clinical and interventional outcome parameters of stroke patients undergoing EVT in daily routine before and after application of the criteria.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients

A total of 2611 patients enrolled in the GSR-ET were screened for inclusion.[6,7] The GSR-ET is an ongoing, open-label, prospective, multicenter registry of consecutively collected EVT patients, with 25 participating stroke centers in Germany. The inclusion criteria of the SWIFT-PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial), MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands trial), ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times trial), DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo trial), and DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke trial) trials were applied to patients without prior selection (Figure 1A).

Statistical Analysis

Baseline characteristics were compared performing Fisher Exact test for categorical variables, Mann–Whitney *U* test (non-normally distributed data) and the unpaired Student *t*-test (normally distributed data) for continuous variables. Statistical analyses were performed using SPSS Version 22. Study protocols and procedures were conducted in compliance with the Declaration of Helsinki and in accordance to ethical guidelines. A $P<0.05$ was considered statistically significant.

RESULTS

Trial Criteria Applied to Patients of the GSR-ET Registry

Following selection, it was found that only 35% (MR CLEAN), 14% (ESCAPE), 9% (SWIFT-PRIME), 4% (DAWN), and 3% (DEFUSE-3) of all patients of the GSR-ET could have been included in the respective trials (Figure 1A and 1B). Because the patients of the GSR-ET were treated before the publication of the DAWN and DEFUSE-3 trials, and in accordance with guidelines with more stringent time windows, only few

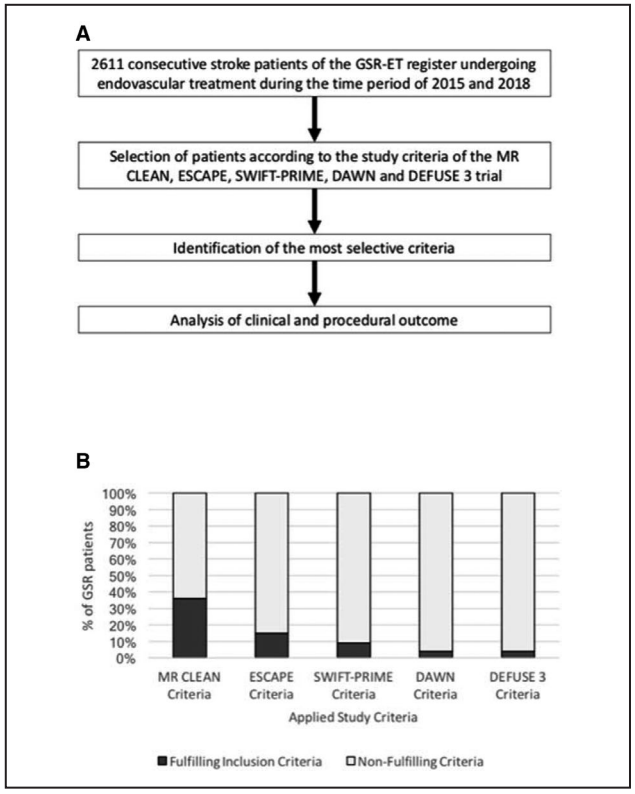

Figure 1. Workflow of the study (**A**). Percentage of patients of the GSR-ET (German Stroke Registry – Endovascular Treatment) fulfilling the inclusion criteria of SWIFT-PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial), MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands trial), ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times trial), DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo trial), and DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke trial) (**B**).

patients met the criteria and were therefore excluded from statistical analysis.

Clinical Factors That Deferred From the Trial Criteria and Their Influence on the Clinical and Procedural Outcomes

An analysis of the clinical characteristics of the patients of the GSR-ET showed differences in a multitude of aspects compared with the trial populations of the RCT (Table 1). With regard to clinical characteristics, the patients of the GSR-ET were older than the patients of the RCT with a median age of 75 years (interquartile range, 64–82 years). In terms of their medical history, the patients of the GSR-ET had a lower percentage of individuals with a modified Rankin Scale of 0 or 1 (81%) compared with the MR CLEAN (90%) or the SWIFT-PRIME trial (98%). As for the occluded vessel, we observed several differences, eg, a lower percentage of patients suffering from an occlusion of the proximal segment (M1) of the middle cerebral artery (54% versus 66% in the MR CLEAN or 77% in the SWIFT-PRIME study). Additionally, the GSR-ET trial population includes patients with an occlusion of the anterior cerebral artery (3%) and in 5% of the cases an occlusion in the posterior circulation.

In an additional step, we set out to identify the most selective parameter of the RCTs (Figure 2); in the MR CLEAN trial, the criterion to start treatment within 6 hours from symptom onset was the most selective, and was fulfilled by 51% of all patients of the GSR-ET. For those that did not fulfill the criterion, the time point of symptom onset was either unknown (43%) or the time from symptom onset to start of treatment exceeded 6 hours (6%). For the SWIFT-PRIME trial, initiation of i.v. lysis within 4.5 hours from symptom onset was amongst the most selective criteria, because of the fact that 45% of all patients of the GSR-ET did not receive i.v. lysis. In contrast, the initiation of endovascular treatment within 60 minutes of baseline non-contrast CT was the most selective criterion of the ESCAPE trial (fulfilled by 47% of all patients of the GSR-ET).

Following application of the inclusion criteria, the patients of the GSR-ET showed an increase of excellent (modified Rankin scale at 90 days of 0–1) and good (modified Rankin Scale at 90 days of 0–2) functional outcome (Table 2). Statistically significant differences were observed if the criteria of the SWIFT-PRIME (excellent clinical outcome in 26% [unselected GSR] versus 42% [selected GSR]; P=0.031) and ESCAPE (excellent clinical outcome 26% [unselected GSR] versus 35% [selected GSR]; P=0.042) trial were applied (Table S1). The same held true for the percentage of Thrombolysis in Cerebral Infarction Scale 2b and 3 recanalizations (Table 2) which, after application of the trial criteria, increased from 83% (all patients of the GSR-ET) to 85% (MR CLEAN), 91% (SWIFT-PRIME) or 88% (ESCAPE) (Table S2).

Clinical and Procedural Outcomes of Patients of the GSR-ET Inside and Outside the Clinical Trials

Furthermore, the clinical outcomes of the patients of the GSR-ET who fulfilled the study criteria of the MR CLEAN, SWIFT-PRIME, and ESCAPE trials were compared with the EVT arm of each of these studies. The percentage of excellent clinical outcome of the patients of the GSR-ET increased, regardless of the applied study criteria. The results were comparable with the published data of the RCT (Figure 3A). The patients of the GSR-ET showed a good clinical outcome in 42% if

Table 1. Clinical Characteristics of Stroke Patients After Selection Using the Inclusion Criteria of the Large Endovascular Treatment Trials

	All patients from GSR-ET (n=2611)	Patients of the DEFUSE 3 trial (n=92)	Patients of the GSR-ET after selection according to the DEFUSE-3 criteria (n=30)	Patients of the DAWN trial (n=107)	Patients of the GSR-ET after selection according to the DAWN criteria (n=57)	Patients of the MR-CLEAN trial (n=233)	Patients of the GSR-ET after selection according to the MR CLEAN criteria (n=910)	Patients of the SWIFT-PRIME trial (n=98)	Patients of the GSR-ET after selection according to the SWIFT-PRIME criteria (n=256)	Patients of the ESCAPE trial (n=165)	Patients of the GSR-ET after selection according to the ESCAPE criteria (n=378)
Characteristics											
Age, y (IQR)	75 (64–82)	70 (59–79)	67 (63–81)	69.4 (±14)	77 (65–83)	65.8 (54.5–76)	75 (64–81)	65	68 (56–75)	71 (60–81)	74 (63–80)
Women, %	50	50	63	61	35	42	47	44	42	52	45
NIHSS, median (IQR)	15 (10–19)	16 (10–20)	15 (13–18)	17 (13–21)	17 (15–20)	17 (14–21)	15 (11–19)	17 (13–19)	15 (11–18)	16 (13–20)	15 (11–19)
ASPECTS, median (IQR)	9 (7–10)	8 (7–9)	9 (7–10)	n.a.	9 (8–10)	9 (7–10)	9 (7–10)	9 (8–10)	9 (8–10)	9 (8–10)	9 (8–10)
Medical history, %											
Hypertension	76	77	70	78	77	42	73	58	61	64	72
Diabetes	21	30	13	24	21	15	20	15	15	20	20
Atrial fibrillation	41	37	50	40	40	28	43	39	29	37	38
Prestroke mRS 0 or 1, %	81	97	93	93	80	90	80	98	100	n.a.	100
Occluded vessel, %											
Internal carotid artery	26	35	16	21	12	33	23	16	20	28	25
Middle cerebral artery (M1)	54	65	25	78	58	66	54	77	80	68	60
Middle cerebral artery (M2)	20	0	0	2	30	8	19	6	0	13	15
Anterior cerebral artery	3	0	0	0	0	0.4	3	n.a.	0	0	0

ASPECTS indicates Alberta Stroke Program Early CT Score; GSR-ET, German Stroke Registry—Endovascular Treatment; IVT, intravenous thrombolysis; IQR, interquartile range; M1, medial cerebral artery M1 segment; M2, middle cerebral artery M2 segment; mRS, modified Rankin Scale; and NIHSS, National Institute of Health Stroke Scale.

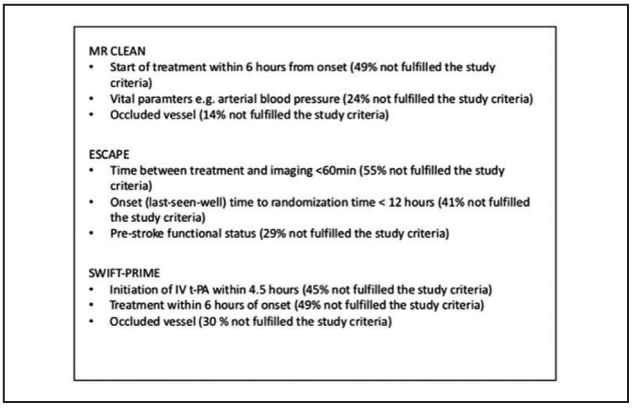

Figure 2. Most selective inclusion criteria of the MR CLEAN, ESCAPE, and SWIFT-PRIME trials.
ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times trial; Intravenous t-PA, intravenous thrombolysis; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands trial; and SWIFT-PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial.

selected according to the MR CLEAN criteria (33% in the EVT study arm of the MR CLEAN trial), 56% if the SWIFT-PRIME criteria were applied (60% in the EVT study arm of the SWIFT-PRIME trial), and 46% if the patients of the GSR-ET were selected according to the criteria of the ESCAPE trial (53% in the EVT study arm of the ESCAPE trial). No statistical significance could be demonstrated.

In a next step, we investigated the outcome of patients of the GSR-ET who did not meet the inclusion criteria of the MR CLEAN study (n=1701). We observed a decrease in good clinical outcome from 41% to 34% (Figure 3B) which was still comparable with the results published by the investigators of the MR CLEAN trial (33%, Figure 3A).

DISCUSSION

In this study, <35% of the patients who were treated in clinical routine would have met the inclusion criteria of the recent large RCTs.[6,7] Following selection according to the trial criteria, the clinical and procedural outcome parameters of the patients of the GSR-ET improved significantly. We observed that the clinical and procedural outcomes of the patients from the GSR-ET were comparable with those of the RCT after selection and that patients who did not meet the criteria of the RCT still had high rates of good clinical outcome.[1–3] To the best of our knowledge, our study is the first multicentric study to investigate how and to which extent the results of the large EVT trials can be applied to stroke patients treated on a daily basis in the clinical routine. We show that only a relatively small subset of the patients fulfilled the inclusion criteria of the large EVT trials, a fact that should be kept in mind when interpreting the outcome parameters of patients who are treated during daily practice.

Interestingly, amongst the MR CLEAN, SWIFT-PRIME, and ESCAPE studies, the degree of patient selection varies greatly.[1–5,10,11] We demonstrated that, for our cohort, the MR CLEAN trial is the least selective, with 35% of our patients fulfilling the criteria. This result could likely be explained by several deferring factors. For example, the MR CLEAN trial has the fewest, least stringent criteria amongst the RCT.[1] This is in stark contrast to the SWIFT-PRIME and ESCAPE trials, which have not only more, but also more narrowly defined inclusion criteria, leading to a highly selective patient study population and, subsequently, a higher rate of good and excellent outcomes.[2,3] Indeed, <10% of the patients from the GSR-ET fulfilled the criteria of the ESCAPE and SWIFT-PRIME study. Amongst the factors that most frequently diverged from the trial criteria and guideline recommendations were patient characteristics and time metrics. One factor are preexisting disabling deficits (modified Rankin Scale >1) which can be found in 19% of the patients of the GSR-ET, compared with much lower rates in the RCT (10% in the MR CLEAN or 2% in the SWIFT-PRIME trial).[1,3,6,7,9] Other factors are the median patient age (75 years) which is higher in the GSR-ET group than in the RCT trials (eg, age 66 years in the MR CLEAN or 65 years in the SWIFT-PRIME study) as well as a high proportion (28%) of patients with an unknown time of symptom onset and the fact that the GSR-ET registry contains patients with a low ASPECT score.[6,7] These factors are known predictors to influence the clinical outcome of stroke patients and are integral parts of international guidelines for the treatment of stroke patients,[12–14] thereby providing an explanation for the inferior clinical outcome of unselected stroke patients treated in real life when compared with the results of the RCT.

The importance of the above mentioned time metrics for the daily practice becomes even more obvious, when looking at the large percentage of patients from the GSR-ET who did not meet the inclusion criteria of RCT because of the fact that the time of symptom onset could not be determined or was too long (Figure 2A). This important aspect was addressed by the DAWN and DEFUSE-3 trials which changed the stroke treatment guidelines with regard to the time metrics, since these RCT demonstrated that thrombectomy can improve the outcome of stroke patients beyond 6 hours since symptom onset if multimodal imaging was used for patients selection.[10,11] Therefore it appears that there are other factors besides time for which we have to adjust for when making treatment decisions for stroke patients in daily practice, which is currently being investigated in ongoing studies.

In addition, there are several other aspects that should be considered when interpreting the outcomes of patients of the GSR-ET after selection according to the

Table 2. Outcome Parameters of Patients of the GSR-ET After Selection Using the Inclusion Criteria of the Large Endovascular Treatment Trials

	All Patients from GSR-ET (n=2611)	Patients of the DEFUSE 3 trial (n=92)	Patients of the GSR-ET after selection according to the DEFUSE-3 criteria (n=30)	Patients of the DAWN trial (n=107)	Patients of the GSR-ET after selection according to the DAWN criteria (n=57)	Patients of the MR-CLEAN trial (n=233)	Patients of the GSR-ET after selection according to the MR CLEAN criteria (n=910)	Patients of the SWIFT-PRIME trial (n=98)	Patients of the GSR-ET after selection according to the SWIFT-PRIME criteria (n=256)	Patients of the ESCAPE trial (n=165)	Patients of the GSR-ET after selection according to the ESCAPE criteria (n=378)
Interventional outcome											
mTICI grade (2b+3), %	83	76	90	84	89	59	85	88	91	72	88
Functional outcome after 90 d											
Excellent outcome (mRS 0–1), %	26	9	13	30	12	12	31	43	42	36	35
Good outcome (mRS 0–2), %	37	41	25	49	22	33	42	60	56	53	46
Death (mRS 6), %	29	13	25	27	26	21	26	9	13	10	20

DAWN indicates DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo trial; DEFUSE, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke trial; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times trial; GSR-ET, German Stroke Registry – Endovascular Treatment; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands trial; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; SWIFT-PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial; and TICI, Thrombolysis in Cerebral Infarction Scale.

RCT trial criteria. Amongst others this includes the year of patient admission. Treatment of the patients of the GSR-ET took place between 2015 and 2018, a period in which EVT of stroke patients was already the standard of care for patients with LVO at the participating study centers. In contrast, at the time of the RCTs, endovascular treatment of stroke patients was a novel approach. Thus, the observed differences in clinical and procedural outcome could be partially attributable to the level of experience of the interventionalists.

The RCTs were conducted in large, highly specialized stroke departments whereas the real-world data show the results from a heterogeneous group of stroke centers, ranging from hospitals with <50 cases to hospitals with several hundred cases a year. Because of this heterogeneity, one could expect inferior clinical and procedural outcome in real-life patients since several studies have shown the association of annual hospital volume and the outcome of stroke patients, and higher mortality has been described in real world data.[7,15,16] However, the results of our study showed that applying the inclusion criteria of the RCT on real-world data made the real-world data comparable with the results of the RCT (Figure 3). This held true not only for clinical outcome but also for procedural parameters. Hence, our data suggest that the procedural quality of MT in real-life is comparable with that in RCT.

Intriguingly the results of our study suggest that it seems ethical to treat patients outside of the trial qualification criteria, since when looking at the outcome of patients of the GSR-ET who did not fulfill all of the trial criteria, their clinical outcome was not inferior to the MR CLEAN results,[1] even if these patients had a relatively poor prognosis in the natural course (eg, because of their significantly higher age). Good clinical outcome has been previously reported in patients treated outside top-tier evidence.[17–19] Hence, overly selective treatment criteria could lead to the exclusion of patients that benefit from EVT.[15] Therefore, we need further trials to identify factors beyond the established inclusion and exclusion criteria of the RCTs or recommendations of international guidelines to identify stroke patients who benefit from endovascular stroke treatment.

Furthermore, our study raises the question of the external validity of the large RCT. Based on the results of the RCT, EVT has become the cornerstone of ischemic stroke management but unfortunately it remains unclear to which extend the results of the trials can be reasonably applied to stroke patients with LVO in routine practice. In real life, RCTs cannot be expected to produce results that are directly relevant to all patients and all settings, but they should be designed and reported in a way that allows clinicians to judge to whom they can reasonably be applied. Unfortunately, the applicability varies amongst the RCT for patients with LVO, mostly because of differences in the selection of the patients, setting of

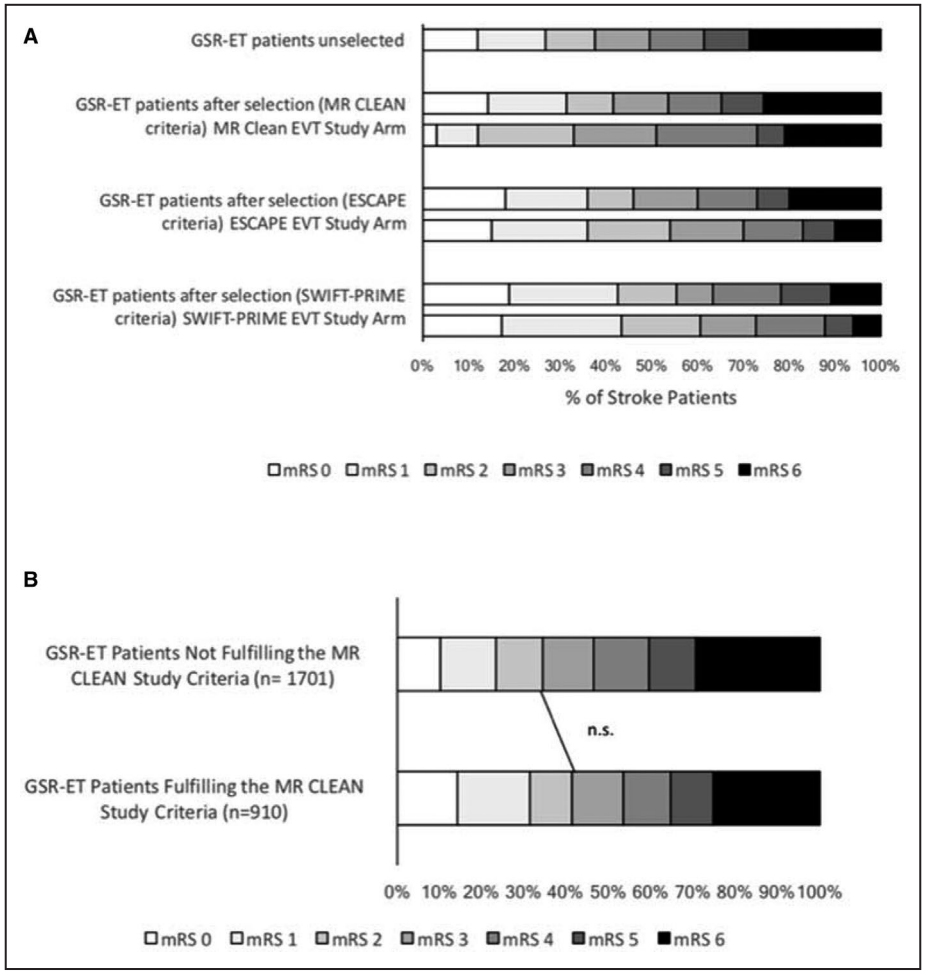

Figure 3. Outcome (modified Rankin Scale at 90 days) of patients who fulfill the inclusion criteria of the randomized controlled clinical trial compared with the endovascular treatment study arm of each trial (A).
Outcome (mRS 90 days) of patients from GSR-ET who do not fulfill all inclusion criteria of the MR CLEAN trial (**B**). EVT indicates endovascular treatment; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; GSR-ET, German Stroke Registry – Endovascular Treatment; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale; and SWIFT-PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment.

the trials as well differences between the trial protocol and routine practice.[20,21] This leaves the clinician with uncertainty which patient to treat and which not, if they do not completely fulfill the study criteria of the RCT.

Our study has several limitations. Our registry included patients treated by EVT based on individual treatment decisions by the interventionalists. This may lead to a selection bias towards patients in whom EVT was deemed to likely be successful. As this was not an RCT, we cannot judge efficacy of EVT. However, recanalization rates and clinical outcome of selected patients of the GSR-ET were comparable or even better than those of the treatment arm of the MR CLEAN trial and therefore a treatment effect is highly probable.

In conclusion, the majority of stroke patients treated by EVT in clinical practice do not meet the stringent criteria of the large EVT guideline defining RCT, despite this observation, patients who did not meet the criteria of the RCT still had considerable rates of good clinical outcome.

APPENDIX

GSR-ET Collaborators

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Disclosures

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Supplementary Material

Tables S1–S2

REFERENCES

1. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Dippel DWJ. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. DOI: 10.1056/NEJMoa1411587.
2. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. DOI: 10.1056/NEJMoa1414792.
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. DOI: 10.1056/NEJMoa1414905.
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. DOI: 10.1056/NEJMoa1503780.
5. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. DOI: 10.1056/NEJMoa1415061.
6. Alegiani AC, Dorn F, Herzberg M, Wollenweber FA, Kellert L, Siebert E, Nolte CH, von Rennenberg R, Hattingen E, Petzold GC, et al. Systematic evaluation of stroke thrombectomy in clinical practice: the German Stroke Registry Endovascular Treatment. *Int J Stroke*. 2019;14:372–380. DOI: 10.1177/1747493018806199.
7. Wollenweber FA, Tiedt S, Alegiani A, Alber B, Bangard C, Berrouschot J, Bode FJ, Boeckh-Behrens T, Bohner G, Bormann A, et al. Functional outcome following stroke thrombectomy in clinical practice. *Stroke*. 2019;50:2500–2506. DOI: 10.1161/STROKEAHA.119.026005.
8. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, Schellinger PD, Toni D, de Vries J, White P, et al. European Stroke Organisation (ESO)- European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg*. 2019;11:535–538. DOI: 10.1136/neurintsurg-2018-014568.
9. Deb-Chatterji M, Pinnschmidt H, Flottmann F, Leischner H, Alegiani A, Brekenfeld C, Fiehler J, Gerloff C, Thomalla G. Stroke patients treated by thrombectomy in real life differ from cohorts of the clinical trials: a prospective observational study. *BMC Neurol*. 2020;20:81. DOI: 10.1186/s12883-020-01653-z.
10. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718. DOI: 10.1056/NEJMoa1713973.
11. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Jovin TG. Thrombectomy 6 to 24

hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21. DOI: 10.1056/NEJMoa1706442.
12. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five andomized trials. *Lancet*. 2016;387:1723–1731. DOI: 10.1016/S0140-6736(16)00163-X.
13. van Horn N, Kniep H, Leischner H, McDonough R, Deb-Chatterji M, Broocks G, Thomalla G, Brekenfeld C, Fiehler J, Hanning U, et al. Predictors of poor clinical outcome despite complete reperfusion in acute ischemic stroke patients. *J Neurointerv Surg*. 2021;13:14–18. DOI: 10.1136/neurintsurg-2020-015889.
14. Bhogal P, Andersson T, Maus V, Mpotsaris A, Yeo L. Mechanical thrombectomy—a brief review of a revolutionary new treatment for thromboembolic stroke. *Clin Neuroradiol*. 2018;28:313–326. DOI: 10.1007/s00062-018-0692-2.
15. Saposnik G, Baibergenova A, O'Donnell M, Hill MD, Kapral MK, Hachinski V; On behalf of the Stroke Outcome Research Canada (SORCan) Working Group. Hospital volume and stroke outcome: does it matter? *Neurology*. 2007;69:1142–1151. DOI: 10.1212/01.wnl.0000268485.93349.58.
16. Shim D-H, Kim Y, Roh J, Kang J, Park K-P, Cha J-K, Baik SK, Kim Y. Hospital volume threshold associated with higher survival after endovascular recanalization therapy for acute ischemic stroke. *J Stroke*. 2020;22:141–149. DOI: 10.5853/jos.2019.00955.
17. Goyal N, Tsivgoulis G, Frei D, Turk A, Baxter B, Froehler MT, Mocco J, Vachhani J, Hoit D, Elijovich L, et al. A Multicenter study of the safety and effectiveness of mechanical thrombectomy for patients with acute ischemic stroke not meeting top-tier evidence criteria. *J Neurointerv Surg*. 2018;10:10–16. DOI: 10.1136/neurintsurg-2016-012905.
18. Bhole R, Goyal N, Nearing K, Belayev A, Doss VT, Elijovich L, Hoit DA, Tsivgoulis G, Alexandrov AV, Arthur AS, et al. Implications of limiting mechanical thrombectomy to patients with emergent large vessel occlusion meeting top tier evidence criteria. *J Neurointerv Surg*. 2017;9:225–228. DOI: 10.1136/neurintsurg-2015-012206.
19. Lopez-Rivera V, Abdelkhaleq R, Yamal J-M, Singh N, Savitz SI, Czap AL, Alderazi Y, Chen PR, Grotta JC, Blackburn S, et al. Impact of initial imaging protocol on likelihood of endovascular stroke therapy. *Stroke*. 2020;51:3055–3063. DOI: 10.1161/STROKEAHA.120.030122.
20. Rothwell PM. External validity of andomized controlled trials: "to whom do the results of this trial apply?". *Lancet*. 2005;365:82–93. DOI: 10.1016/S0140-6736(04)17670-8.
21. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015;16:495. DOI: 10.1186/s13063-015-1023-4.

SUPPLEMENTAL MATERIAL

Table S1. Statistical comparison of clinical characteristics and outcome parameters of stroke patients after selection using the inclusion criteria of the EVT trials MR CLEAN, SWIFT-PRIME and ESCAPE.

	GSR-ET patients (n=2611)	GSR-ET patients after selection according to the criteria of the MR CLEAN trial (n=910)	p-value	GSR-ET patients after selection according to the criteria the of SWIFT – PRIME trial (n=256)	p-value	GSR-ET patients after selection according to the criteria of the ESCAPE trial (n=378)	p-value
Characteristics							
Age, y (IQR)	75 (64–82)	75 (64-81)	n.s.	68 (56-75)	n.s.	74 (63-80)	n.s.
Female, %	50.4	47	n.s.	42	n.s.	45	n.s.
NIHSS, median (IQR)	15 (10–19)	15 (11-19)	n.s.	15 (11-18)	n.s.	15 (11-19)	n.s.
ASPECTS, median (IQR)	9 (7-10)	9 (7-10)	n.s.	9 (8-10)	n.s.	9 (8-10)	n.s.
Medical history, %							
Hypertension	76	73	n.s.	61	n.s.	72	n.s.
Diabetes mellitus	21	20	n.s.	15	n.s.	20	n.s.
Atrial fibrillation	41	43	n.s.	29	n.s.	38	n.s.
Pre stroke of 0 or 1 on modified Rankin scale, %	81	80	n.s.	100	n.s.	100	n.s.
Occluded vessel, %							

Intracranial carotid artery	26	23	n.s.	20	n.s.	25	n.s.
Middle cerebrak artery (M1 segment)	54	54	n.s.	80	n.s.	60	n.s.
Middle cerebral artery (M2 segment)	20	19	n.s.	0	n.s.	15	n.s.
Anterior cerebral artery	3	3	n.s.	0	n.s.	0	n.s.

ASPECTS=Alberta Stroke Program Early CT Score; mRS= modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; TICI = Thrombolysis In Cerebral Infarction Scale; GSR-ET= German Stroke Registry- Endovascular Treatment.

Table S2. Statistical comparison of outcome parameters of GSR stroke patients after selection using the inclusion criteria of the large EVT trials.

	GSR-ET patients (n=2611)	GSR-ET patients after selection according to the criteria of MR CLEAN trial (n=910)	p-Value	GSR-ET patients after selection according to the criteria of the SWIFT-PRIME trial (n=256)	p-Value	GSR-ET patients after selection according to the criteria of the ESCAPE trial (n=378)	p-Value
Outcome							
mTICI grade (anterior circulation), %							
TICI 2b+3	83	85	n.s.	91	n.s.	88	n.s.
Functional outcome after 90 days							
• **Excellent outcome (mRS, 0–1), %**	26	31	n.s.	42	p=0.044	35	p=0.032
• **Good outcome (mRS, 0–2), %**	37	42	n.s.	56	p=0.034	46	p=0.021
• **Death,** %	29	26	n.s.	13	p=0.34	20	n.s.

mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; mTICI = Thrombolysis In Cerebral Infarction Scale; GSR-ET, German Stroke Registry- Endovascular Treatment.