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ORIGINAL ARTICLE

Minor stroke in large vessel occlusion: A matched analysis of patients from the German Stroke Registry–Endovascular Treatment (GSR-ET) and patients from the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register (SITS-ISTR)

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Abstract

Background and purpose: Reperfusion treatment in patients presenting with large vessel occlusion (LVO) and minor neurological deficits is still a matter of debate. We aimed to compare minor stroke patients treated with endovascular thrombectomy (EVT) and intravenous thrombolysis (IVT) or IVT alone.

Methods: Patients enrolled in the German Stroke Registry–Endovascular Treatment (GSR-ET) and the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry (SITS-ISTR) between June 2015 and December 2019 were analyzed. Minor stroke was defined as National Institutes of Health Stroke Scale (NIHSS) score ≤5, and LVO as occlusion of the internal carotid, carotid-T, middle cerebral, basilar,

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See commentary by D. J. Seiffge and J. Kaesmacher on page 1565.

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vertebral or posterior cerebral arteries. GSR-ET and SITS-ISTR IVT-treated patients were matched in a 1:1 ratio using propensity-score (PS) matching. The primary outcome was good functional outcome at 3 months (modified Rankin Scale score 0–2).

Results: A total of 272 GSR-ET patients treated with EVT and IVT (age 68.6 ± 14.0 years, 43.4% female, NIHSS score 4 [interquartile range 2–5]) were compared to 272 IVT-treated SITS-ISTR patients (age 69.4 ± 13.7, 43.4% female, NIHSS score 4 [2–5]). Good functional outcome was seen in 77.0% versus 82.9% ($p = 0.119$), mortality in 5.9% versus 7.9% ($p = 0.413$), and intracranial hemorrhage in 8.8% versus 12.5% ($p = 0.308$) of patients in the GSR-ET versus the SITS-ISTR IVT group, respectively. In a second PS-matched analysis, 624 GSR-ET patients (IVT rate 56.7%) and 624 SITS-ISTR patients (IVT rate 100%), good outcome was more often observed in the SITS-ISTR patients (68.2% vs. 80.9%; $p < 0.001$), and IVT independently predicted good outcome (odds ratio 2.16, 95% confidence interval 1.43–3.28).

Conclusions: Our study suggests similar effectiveness of IVT alone compared to EVT with or without IVT in minor stroke patients. There is an urgent need for randomized controlled trials on this topic.

KEYWORDS
minor stroke, stroke, thrombectomy, thrombolysis

INTRODUCTION

Patients with minor ischemic stroke symptoms (National Institutes of Health Stroke Scale [NIHSS] score ≤5, i.e., minor stroke) represent more than 50% of all ischemic strokes [1]. Clinical management of minor stroke varies across stroke centers and countries. Intravenous thrombolysis (IVT) is standard of care for disabling acute ischemic stroke regardless of NIHSS score [2]. Although large vessel occlusion (LVO) typically leads to severe stroke, at least 10–20% of all minor stroke patients present with LVO owing to good collaterals [3,4]. These patients have a substantial risk of poor outcome, with neurological deterioration occurring in up to 20–40% [5–7]. IVT in combination with endovascular thrombectomy (EVT) is currently recommended in LVO patients eligible for IVT and with NIHSS scores >5 [2]. However, the benefit of combined treatment versus IVT alone in patients with NIHSS scores ≤5 is unknown, as few such patients were enrolled in randomized trials [8] and single-center as well as multicenter cohorts reported ambiguous findings [9–11]. A meta-analysis by the HERMES study group did not show an advantage of EVT in patients with NIHSS scores <10 in comparison to standard care including IVT [8,12]. On the other hand, recent observational studies of immediate thrombectomy compared to best medical therapy followed by rescue thrombectomy in deteriorating cases have shown superior outcomes following immediate EVT in minor stroke [13,14]. The aim of this study was to compare the efficacy of EVT with or without IVT versus IVT treatment alone for minor stroke patients with LVO presenting with an NIHSS score ≤5 at baseline using propensity-score (PS) matching.

METHODS

Patients from the German Stroke Registry–Endovascular Treatment (GSR-ET; https://www.clinical-trials.gov; NCT03356392) [15,16] and from the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) [17,18] were analyzed. We included patients recorded in the GSR-ET between June 2015 and December 2019 from 25 sites in Germany with acute ischemic stroke due to LVO who initiated mechanical thrombectomy (MT; $n = 6.635$). Of 6635 GSR-ET patients screened, 676 (10.2%) presented with minor stroke with LVO (mean age 69.2 [SD ±13.9] years, median [interquartile range] NIHSS score 4 [2, 5]). IVT was administered in 293 patients (43.3%; Table S1). The GSR-ET is an open-label, academic, industry-independent, prospective, multicenter and observational registry study [15,16]. In GSR-ET, all source data were assessed and rated by the local neurointerventionalists and neurologists. All entered data underwent standardized quality checks that had been programmed to control for consistency, plausibility, and completeness. In cases of inconsistencies or missing data, queries were sent to the local centers. Decisions to perform thrombectomy were based on interdisciplinary assessment by treating physicians using clinical and imaging parameters set according to national and international guidelines [2,19,20]. For the control group, IVT-treated patients recorded in the SITS-ISTR between 6 December 2006 and 1 December 2019 were considered ($n = 171,173$) and only patients with minor stroke symptoms defined as baseline NIHSS score ≤5 were included in this study ($n = 28,646$; 16.7%). We further applied data quality criteria by including centers with a 3-month follow-up rate of ≥70%, which resulted in 1157 patients from 104 centers in 31

countries with 93% of patients from European hospitals, with a total of 0.4% patients from German hospitals. The SITS-ISTR is an ongoing, prospective, academic-driven, multinational register for centers using IVT for the treatment of acute ischemic stroke [17,18]. Stroke severity was assessed using the NIHSS, and degree of dependence or disability was rated using the modified Rankin Scale (mRS) and premorbid mRS (pmRS), respectively.

Definitions

Site of occlusion was determined via computed tomography angiography, magnetic resonance angiography, or angiography. We considered the following sites of occlusions: the internal carotid, carotid-T, middle cerebral (M1 and M2), basilar, vertebral, and posterior cerebral arteries. Successful reperfusion was defined by the modified Thrombolysis in Cerebral Infarction (mTICI) score 2b–3 and complete reperfusion as mTICI score 3 [21]. Based on the data available, admission to hospital was calculated using the arrival to the comprehensive EVT center for the GSR-ER patients, and arrival to the hospital that provided IVT treatment for the SITS-ISTR patients.

Outcomes

The primary outcome was good outcome at 3-month follow-up. Good outcome was defined as mRS scores 0–2. Secondary outcome variables included functional outcome using NIHSS score at 24 h and at discharge, mRS at discharge, (peri-)procedural time intervals, number of days for in-hospital stay, occurrence of intracerebral hemorrhage (ICH) in follow-up imaging, symptomatic ICH (sICH), as well as periprocedural and in-hospital complications and outcome at discharge and follow-up. In the GSR-ET patients, ICH was defined as any hemorrhage in postinterventional imaging after 24 h and sICH as any ICH on follow-up imaging in addition to an increase in NIHSS score of ≥4 points from baseline to 24-h value. In the SITS-ISTR patients, sICH was defined as a local or remote parenchymal hemorrhage type 2 at 22–36-h follow-up radiological examination in addition to a neurological deterioration of ≥4 NIHSS points from baseline or the lowest score during the first 24 h after treatment, or death.

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean and standard deviation (±SD) and non-normally distributed data as median with interquartile range or counts and percentages. We performed univariate comparisons of baseline characteristic between the two populations. Clinical characteristics, imaging data, periprocedural times, and outcome variables were compared among the patients using the Kruskal–Wallis test or median test, as appropriate. Binary logistic regression analysis was performed for good clinical outcome and death at follow-up including variables that presented as significant in the univariate analysis or variables that were known outcome predictors. We used binomial distribution and logit function to compare outcomes. The matched patient set was obtained from the GSR-ET and SITS-ISTR by 1:1 greedy-nearest-neighbor matching using calipers equal to 0.2*SD of the logit of the propensity score, using the software R version 4.0.4, and with matching according to age, sex, baseline NIHSS score, pmRS score and site of occlusion. A first PS-matched set was obtained for GSR-ET patients treated with EVT and IVT (compared to SITS-ISTR patients treated with IVT only), and a second PS-matched set was obtained for GSR-ET patients regardless of IVT treatment (EVT with/without IVT). Comparisons of baseline characteristics between groups were assessed using univariate generalized models (binomial or multinomial distribution) for categorical variables and linear mixed models with matched sets as a random effect for quantitative variables. We used binomial distribution and logit function to compare outcome variables. The outcome analyses were based on PS-matched datasets. For all statistical testing, we used the Statistical Package for Social Science (SPSS Inc., 27.0 for Windows).

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was centrally approved by the Institutional Review Board of the *Ludwig-Maximilians-Universität*, Munich, Germany (protocol no. 689-15). Further approval was obtained from local institutional review boards according to local regulations. The SITS-ISTR was approved by the Research Ethics Committee in Stockholm, Sweden. Requirements for ethical approval and patient consent for participation in the SITS-ISTR differed among participating countries. Ethical approval and patient consent were obtained in countries that required this, while other countries approved the register for use as an anonymized audit.

RESULTS

First PS-matched analysis: EVT and IVT (GSR-ET) vs. IVT alone (SITS-ISTR)

Of 676 GSR-ET patients, 272 (40.2%) were treated with EVT and IVT. These patients were matched in a 1:1 ratio to 272 of 1157 (23.5%) IVT-only-treated SITS-ISTR patients (Figure 1). There were no significant differences between the groups regarding age, sex, vascular risk factors, pre-stroke functional independence, baseline NIHSS score or occlusion site (Table 1). The

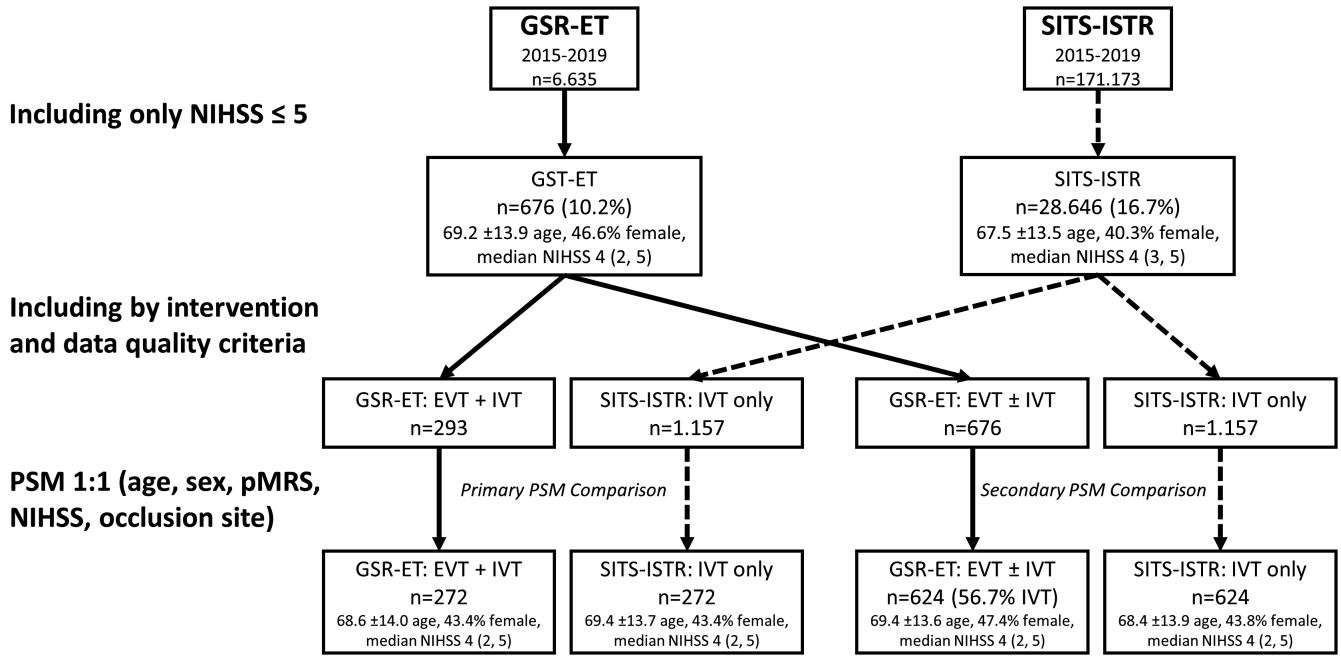

FIGURE 1 Flowchart for the propensity-score matched analysis of large vessel occlusion patients with minor stroke symptoms from the German Stroke Registry–Endovascular Treatment (GSR-ET) and the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register (SITS-ISTR). EVT, endovascular thrombectomy; IQR, interquartile range; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; *n*, number; NIHSS, National Institute of Health Stroke Scale; pmRS, premorbid modified Rankin Scale; PSM, propensity-score matching

median onset to IVT time was 40 min longer in the GSR-ET group compared to the SITS-ISTR group (190 vs. 150 min; $p = 0.010$). GSR-ET patients treated with EVT and IVT had a higher median NIHSS score after 24 h (2 vs. 1; $p < 0.001$) and a longer hospital stay (9.3 ± 6.6 vs. 6.9 ± 6.2 days; $p < 0.001$). Early neurological deterioration (NIHSS score worse by ≥4 points comparing NIHSS score after 24 h to baseline NIHSS score) was seen in 39 (14.3%) versus 20 patients (7.4%) in the GSR-ET and SITS-ISTR, respectively ($p = 0.031$). Both treatment groups had similar rates of any ICH (12.8% vs. 8.8%; $p = 0.308$), but the GST-ET patients included a higher proportion with sICH (4.4% vs. 1.0%; $p < 0.001$). There was no difference in 3-month mortality when comparing GSR-ET to SITS-ISTR patients (7.9% vs. 5.9%; $p = 0.413$), but there was a nonsignificantly higher rate of good outcome in favor of GSR-ET patients as compared to SITS-ISTR patients (82.9% vs. 77.0%; $p = 0.119$ [Figure 2]).

Second PS-matched analysis: EVT with/ without IVT (GSR-ET) vs. IVT alone (SITS-ISTR)

In a second PS-matched analysis we compared 624 GSR-ET patients irrespective of IVT treatment (IVT rate 56.7%) to 624 SITS-ISTR IVT-treated patients (Table 2). No differences between the groups were found regarding age, sex, vascular risk factors, pre-stroke functional independency, or baseline NIHSS score. There were no significant differences regarding occlusion site comparing anterior and/or posterior circulation strokes. However, occlusion of the basilar artery occurred more often in GSR-ET patients (15.1% vs. 10.9%; $p = 0.023$). The median time from onset or last seen well to admission was 105.0 min longer in the GSR-ET group (195 vs. 90 min; $p < 0.001$). At clinical follow-up, GSR-ET patients compared to SITS-ISTR patients had higher NIHSS scores at 24 h (3 vs. 1; $p < 0.001$) and at discharge (2 vs. 1; $p < 0.001$). Comparing GSR-ET and SITS-ISTR patients, 117 (18.8%) versus 50 patients (8.0%), respectively, showed an early neurological deterioration based on NIHSS score at 24 h versus baseline NIHSS score ($p < 0.001$). At 3-month follow-up, good functional outcome was significantly less likely in GSR-ET patients compared to SITS-ISTR patients (68.2% vs. 80.9%; $p < 0.001$). There was no difference in rate of any ICH (9.9% vs. 6.9%; $p = 0.145$) or death by 3-month follow-up (9.4% vs. 7.0%; $p = 0.121$) in the GSR-ET compared to the SITS-ISTR patients (Figure 2). The GSR-ET group included a higher proportion of patients with sICH as compared to the SITS-ISTR group (4.0% vs. 1.0%; $p < 0.001$). Multivariate logistic regression in both PS-matched analyses (EVT and IVT vs. IVT alone, or EVT with or without IVT vs. IVT alone) showed that IVT treatment, age, pmRS and any ICH was associated with good outcome at follow-up (Figure 3).

GSR-ET-related data

Of 382 patients in the GSR-ET group who were not treated with IVT but received EVT, 124 (32%) had a wake-up stroke or unknown symptom onset, 50 patients (13%) had ongoing oral anticoagulant treatment, and 40 patients (10%) had ongoing vitamin K

TABLE 1 Characteristics and comparison of German Stroke Registry–Endovascular Treatment patients, treated with endovascular thrombectomy and intravenous thrombolysis (IVT), and matched Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register patients, treated with IVT only

	GSR-ET Minor strokes *n* = 272	SITS-ISTR Minor strokes *n* = 272	*p* value
Age, years ± SD	68.6 ± 14.0	69.4 ± 13.7	0.591
Sex: female, *n* (%)	118 (43.4)	118 (43.4)	1.000
Etiology, *n* (%)			0.659
Cardioembolic	100 (36.8)	92 (33.8)	
Large artery sclerosis	79 (29.0)	97 (35.7)	
Other determined cause	13 (4.8)	0 (0)	
Stroke of undetermined cause	80 (29.4)	83 (30.5)	
Clinical characteristics at admission			
pmRS score, median (IQR)	0 (0, 0)	0 (0, 0)	0.993
Baseline NIHSS score, median (IQR)	4 (2, 5)	4 (2, 5)	0.591
Time intervals, min (IQR)			
Symptom onset/last seen well to IVT	190.0 (105.0, 304.0)	150.0 (117.8, 215.0)	0.010
Symptom onset/last seen well to flow restoration	280.0 (204.5, 380.3)	/	/
Imaging data, *n* (%)			
Anterior circulation	212 (77.9)	219 (80.5)	1.000
Posterior circulation	60 (22.1)	53 (19.5)	1.000
Site of occlusion, *n* (%)			
Basilar artery	43 (15.8)	35 (12.9)	0.999
Vertebral artery	10 (3.7)	7 (2.6)	1.000
Posterior cerebral artery	18 (6.6)	11 (4.0)	1.000
Carotid-T	6 (2.2)	5 (1.8)	1.000
ICA extracranial	14 (5.1)	23 (8.5)	0.999
MCA M1	87 (32.0)	95 (34.9)	0.999
MCA M2	108 (39.7)	96 (35.3)	0.843
Acute treatment, *n* (%)			
IVT treatment	272 (100)	272 (100)	1.000
MT	272 (100)	0 (0)	/
Periprocedural complications, *n* (%)	57 (21.0)	/	/
Successful reperfusion mTICI score 2b–3, *n* (%)	222 (81.6)	/	/
NIHSS score at 24 h, median (IQR)	2 (1, 5)	1 (0, 3)	<0.001
Outcome at discharge			
NIHSS score, median (IQR)	1 (0, 3)	1 (0, 2)	0.286
mRS score, median (IQR)	1 (0, 3) (available in *n* = 269)	1 (0, 2) (available in *n* = 150)	0.837
Mortality (mRS score 6), *n* (%)	5 (1.8)	10 (3.7)	0.981
ICH (any), *n* (%)	34 (12.5)	24 (8.8)	0.308
sICH, *n* (%)	12 (4.4)	2 (1.0)	<0.001
Hospital stay, days ± SD	9.3 ± 6.6	6.9 ± 6.2	<0.001

Abbreviations: EVT, endovascular thrombectomy; GSR-ET, German Stroke Registry–Endovascular Treatment; ICH, intracerebral hemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; *n*, number; NIHSS, National Institute of Health Stroke Scale; pmRS, premorbid modified Rankin Scale; SICH, symptomatic intracerebral hemorrhage; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register.

antagonist treatment. Of 624 patients in the GSR-ET group with minor stroke symptoms treated with EVT, 243 were referred to an EVT center from another center after initially receiving IVT treatment ("drip and ship"), while 111 patients were admitted directly to the center ("direct to center"). There was no difference in onset to IVT treatment time between drip-and-ship patients compared to direct-to-center patients (190.0 vs. 189.5 min, respectively; $p = 0.385$).

DISCUSSION

Our study, based on multicenter prospective registries of stroke patients treated with reperfusion therapy, aimed to compare the clinical efficacy and safety of IVT combined with EVT versus IVT alone in stroke patients with minor neurological symptoms caused by LVO.

Our main results suggest that for minor stroke patients, defined as those with NIHSS scores ≤5, EVT in combination with IVT compared to IVT alone did not significantly improve functional outcomes. This was despite the fact that successful reperfusion (mTICI scores 2b–3) in EVT- and IVT-treated GSR-ET patients was achieved in 81.6% of patients. On the other hand, patients treated with EVT in combination with IVT had a higher point estimate for sICH in follow-up imaging after 24 h.

Previous retrospective single-center studies in 33 (NIHSS score ≤8, different sites of occlusion), 41 (NIHSS score ≤ 5, M1 occlusions), 88 (NIHSS score ≤ 4, different sites of occlusion) patients

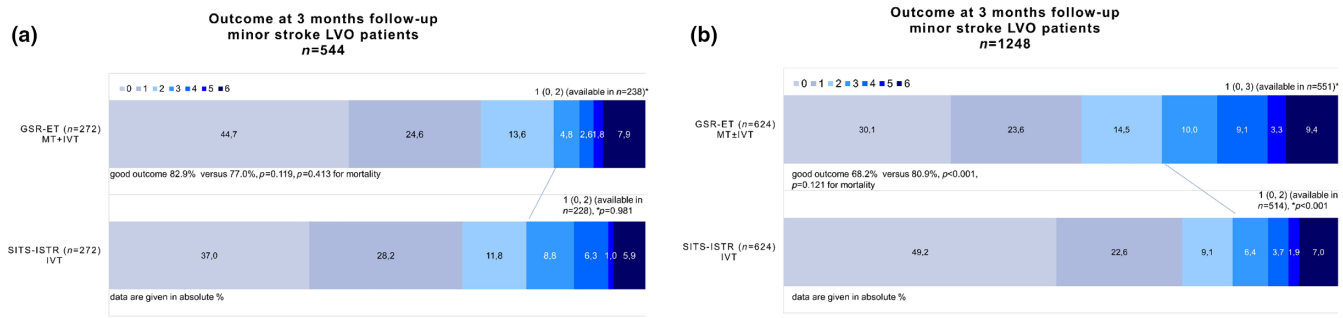

FIGURE 2 Outcome at follow-up comparing (a) German Stroke Registry–Endovascular Treatment (GSR-ET; endovascular thrombectomy [EVT] and intravenous thrombolysis [IVT]) patients versus Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register (SITS-ISTR; IVT-only) patients and (b) GSR-ET (EVT ± IVT) patients versus SITS-ISTR (IVT-only) patients. Abbreviations: EVT, endovascular thrombectomy; IQR, interquartile range; IVT, intravenous thrombolysis; LVO, large vessel occlusion; *n*, number; pmRS, premorbid modified Rankin Scale [Colour figure can be viewed at wileyonlinelibrary.com]

with LVO and minor stroke symptoms showed that thrombectomy could be performed safely and with reasonable rates of good clinical outcomes of 64%, 75% and 60%, respectively, even in longer time windows [9,10,22]. Similar results were shown in a meta-analysis of EVT-treated minor stroke patients [23]. Similarly to these studies, our observational data suggest that EVT with or without IVT was associated with longer hospital stays. Therefore, our data support the hypothesis that EVT is safe and effective regarding successful reperfusion of LVO in those patients, while we did not find higher efficacy of EVT compared to IVT alone.

When comparing EVT with or without IVT to IVT alone, our data showed that patients receiving thrombectomy had a significantly worse functional outcome. Additionally, in follow-up after 24 h, EVT patients tended to have a higher median NIHSS score. The logistic regression analysis confirmed that IVT strongly predicted good outcome, whereas EVT did not. These results are in contrast to those of small former case series where EVT patients had better outcomes than IVT-only patients [6,12] and another case series describing 24 IVT patients compared to 32 interventional patients (19 EVT alone, 13 EVT and IVT) [24]. The latter study confirmed a better NIHSS score shift in the group with endovascular intervention compared to medical treatment. As 40% of the patients who were treated with thrombectomy were ineligible for IVT, there was a clear bias in interpreting these data [24]. In a case series describing 32 patients with thrombectomy, the intervention also led to a greater NIHSS score improvement, where 25% of patients primarily treated with medical therapy did not achieve functional independence at follow-up [6]. A study in 169 patients with M2 occlusion of the middle cerebral artery presenting with minor stroke symptoms compared IVT-only-treated patients versus MT-only-treated patients versus patients treated with the combination of EVT and IVT, and found no differences among the groups in favorable outcome. Considering only patients treated after 2015, there was a significantly improved mRS score shift in the EVT group compared to the IVT-only group [11]. A study including 96 minor stroke patients showed no difference between the IVT group and the standard medical care group regarding the rate of good clinical outcomes. However, patients receiving IVT showed earlier neurological improvement [25]. Existing studies comparing thrombectomy versus IVT in minor stroke LVO patients were based on limited number of patients and comparisons were not matched. To try to overcome these issues, our study used PS matching including the factors age, sex, pmRS score, NIHSS score and especially site of occlusion in patients from two large stroke registries in order to compare the combination of IVT and EVT versus IVT alone.

In addition, good functional outcome in patients with minor stroke symptoms was in the range of 80% and, as expected, was better than in general MT-treated patient cohorts based on data from clinical trials or from large multicenter registries, which found that good outcome was achieved in 37% to 46% of the study populations, respectively [8,16]. This main finding from our data is of importance because, until now, clinical findings from comparisons of EVT and IVT in minor stroke patients were limited to small patient numbers.

In our study we were able to show, in patients treated with IVT (and thus in patients all eligible for IVT treatment), that additional EVT had no further clinical advantage. In contrast, when comparing IVT-only-treated patients with EVT irrespective of additional IVT treatment, IVT-only treated patients showed better functional outcomes. However, there is clearly a bias by indication of EVT in patients without IVT; patients treated with EVT might be patients with clinical deterioration or rescue thrombectomy. We tried to limit the effect of important confounding factors by PS matching, however, our study was observational and our results might nevertheless be biased, especially in patients receiving only EVT due to contraindications for IVT. Data from a multicenter French registry of LVO patients showed that thrombus length was a powerful independent predictor of EVT [26]. In a further analysis, early neurological deterioration of presumed ischemic origin following IVT was predicted by a combination of thrombus length and occlusion site [27]. However, regression analysis showed that IVT was an independent factor for good clinical outcome, leading to a 2.1 higher chance of functional independence at 3-month follow up.

The main strength of our study is the inclusion of the large sample size of minor stroke patients with LVO from prospective

TABLE 2 Characteristics of German Stroke Registry–Endovascular Treatment patients treated with endovascular thrombectomy ± intravenous thrombolysis (IVT), compared to Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register patients treated with only IVT

	GSR-ET Minor strokes *n* = 624	SITS-ISTR Minor strokes *n* = 624	*p* value
Age, years ± SD	69.4 ± 13.6	68.4 ± 13.9	0.181
Sex: female, *n* (%)	296 (47.4)	273 (43.8)	0.213
Etiology, *n* (%)			0.435
Cardioembolic	243 (38.9)	185 (29.6)	
Large artery sclerosis	205 (32.9)	220 (35.3)	
Other determined cause	37 (5.9)	0 (0)	
Stroke of undetermined cause	139 (22.3)	219 (33.5)	
Clinical characteristics at admission			
pmRS, median (IQR)	0 (0, 0)	0 (0, 0)	0.181
Baseline NIHSS score, median (IQR)	4 (2, 5)	4 (2, 5)	0.918
Time intervals, min (IQR)			
Symptom onset/last seen well to admission	195.0 (80.0, 408.0)	90.0 (60.0, 132.8)	<0.001
Symptom onset/last seen well to IVT	190.0 (105.0, 304.0)	160.0 (120.0, 211.0)	0.121
Symptom onset/last seen well to flow restoration	335.0 (220.5, 619.3)	/	/
Imaging data, *n* (%)			
Anterior circulation	487 (78.0)	499 (80.0)	0.468
Posterior circulation	137 (22.0)	125 (20.0)	0.468
Site of occlusion, *n* (%)			
Basilar artery	94 (15.1)	68 (10.9)	0.023
Vertebral artery	30 (4.8)	32 (5.1)	0.871
Posterior cerebral artery	35 (5.6)	25 (4.0)	0.242
Carotid-T	16 (2.6)	7 (1.1)	0.051
ICA extracranial	50 (8.0)	64 (10.3)	0.324
MCA M1	218 (34.9)	204 (32.7)	0.435
MCA M2	220 (35.3)	219 (35.1)	0.706
Acute treatment, *n* (%)			
IVT treatment	354 (56.7)	624 (100)	<0.001
MT	624 (100)	0 (0)	/
Successful reperfusion mTICI score 2b–3, *n* (%)	505 (81.2)	/	/
NIHSS score at 24 h, median (IQR)	3 (1, 6)	1 (0, 3)	<0.001
Outcome at discharge			
NIHSS score, median (IQR)	1 (0, 4)	1 (0, 2)	<0.001
mRS score, median (IQR)	2 (1, 3) (available in *n* = 620)	1 (0, 3) (available in *n* = 339)	<0.001
Mortality (mRS score 6), *n* (%)	26 (4.2)	20 (3.2)	0.250
ICH (any), *n* (%)	62 (9.9)	43 (6.9)	0.145
sICH, *n* (%)	24 (4.0)	6 (1.0)	<0.001
Hospital stay, days ± SD	9.8 ± 7.7	5.9 ± 7.1	<0.001

Abbreviations: EVT, endovascular thrombectomy; GSR-ET, German Stroke Registry–Endovascular Treatment; ICH, intracerebral hemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; *n*, number; NIHSS, National Institute of Health Stroke Scale; pmRS, premorbid modified Rankin Scale; SICH, symptomatic intracerebral hemorrhage; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register.

multicenter registries, reflecting real-life practice. Important clinical confounders were handled using PS matching. Given a lack of published randomized controlled trial results, our study provides valuable observational data on this important clinical topic. Our results suggest that thrombectomy can be performed safely and effectively in minor stroke patients. However, a further clinical benefit of

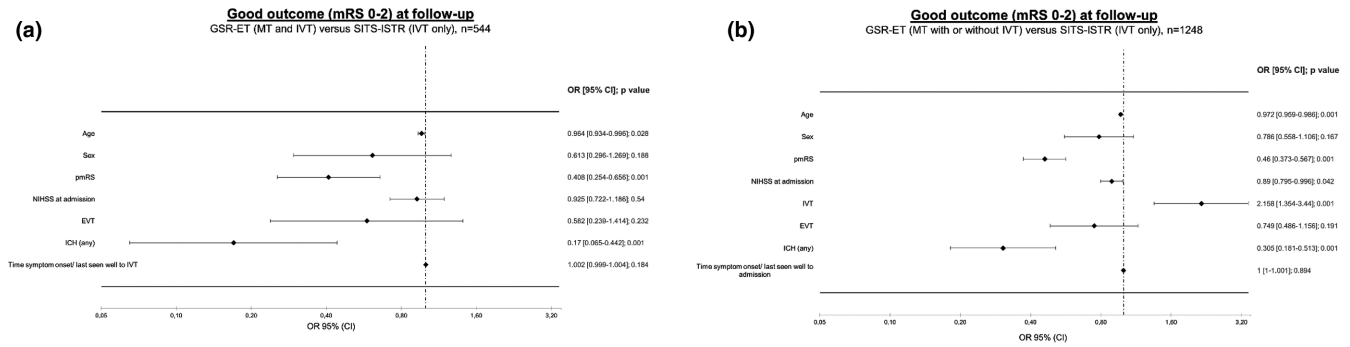

FIGURE 3 Binary logistic regression for good outcome (modified Rankin scale [mRS] score 0–2) at follow-up for (a) in the matched population (German Stroke Registry–Endovascular Treatment [GSR-ET] and Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register [SITS-ISTR]; $n = 544$, propensity-score matching of minor strokes with large vessel occlusion (LVO) comparing GSR-ET (endovascular thrombectomy [EVT] and intravenous thrombolysis [IVT]) versus SITS-ISTR [IVT-only] patients) and (b) in the matched population (GSR-ET and SITS-ISTR; $n = 1248$, propensity-score matching of minor strokes with LVO comparing GSR-ET (EVT with or without IVT) to SITS-ISTR (IVT-only) patients. CI, confidence interval; ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; pmRS, premorbid modified Rankin scale

EVT is not evident from our data. Furthermore, there could be a bias regarding LVO patients that are referred to rescue EVT after deteriorating after IVT treatment or during best medical treatment. From our results, it is not possible to know whether EVT was performed as a primary treatment or after clinical deterioration. In summary, IVT should be promptly applied in otherwise eligible minor stroke patients with LVO and should not be delayed because of possibly indicated MT. To clarify the best acute treatment for patients with LVO with minor stroke, randomized controlled trials are urgently needed. The results from the ongoing ENDOLOW trial are expected to shed further light on this issue (https://clinicaltrials.gov/ct2/show/NCT04167527).

Our results are based on observational data, which are subject to well-known limitations. Firstly, we cannot rule out a selection bias resulting from center-specific standards regarding the treatment of minor stroke patients with LVO. The decision to refer patients for EVT in our study was made by the treating physician, which might have introduced a selection bias. This would particularly apply to minor stroke patients, given the uncertain benefits from EVT for this condition, and this reasoning may also apply to the decision for IVT. Although guidelines recommend IVT in stroke with disabling symptoms, disabling or non-disabling deficits were defined by the treating physician, which may also introduce selection bias. Secondly, we cannot compare the minor stroke patients treated with either with EVT and IVT or IVT alone with patients treated with best medical care. The follow-up rate at 3 months was 85.7% in the GSR-ET and 82.9% in SITS-ISTR groups, which could further lead to a selection bias caused by loss to follow-up. Furthermore, we have no data on whether rescue EVT was performed after clinical deterioration. Finally, due to the available data, sICH definitions differed between GSR-ET and SITS-ISTR patients, which could affect the comparability of these results.

In conclusion, our study found that LVO patients with minor stroke symptoms treated with EVT, with or without IVT, did not have improved chances of good functional outcome compared to IVT treatment alone. EVT appeared safe in these patients but did not provide further clinical improvement, and hospital stay was prolonged in EVT-treated patients. Controlled clinical trials of LVO patients with minor stroke symptoms are urgently needed.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Katharina Feil received funding for research from Boehringer Ingelheim and speaker honoraria from Pfizer outside of this study. Marius Matusevicius, Moriz Herzberg, Steffen Tiedt, Clemens Küpper, Johannes Wischmann, Sonja Schönecker, Annerose Mengel, Jennifer Sartor-Pfeiffer, Konstantin Dimitriadis, Katharina Berger and Marianne Dieterich report no disclosures. Thomas Liebig consults for Stryker Neurovascular GmbH and has received speaker honoraria from Pfizer, Covidien, Phenox and Microvention, outside of this study. Michael Mazya holds a position of Research and Network Executive of SITS International. Niaz Ahmed is the Chairman of SITS International, which receives grants described under funding and has received speaker honoraria from Boehringer Ingelheim. Lars Kellert has received funding for travel or speaker honoraria from Bayer Vital, Boehringer Ingelheim, Bristol-Meyer-Squibb, Daiichi Sankyo and Pfizer, outside of this study, and funding for research from Boehringer Ingelheim.

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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